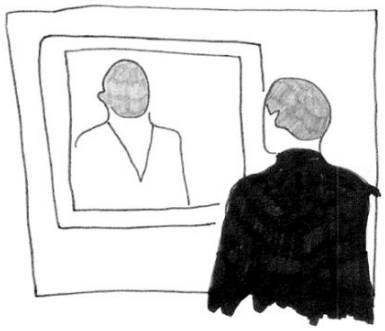

De man in de spiegel staat symbool voor alle patiënten die deelgenomen hebben aan deze studie. De tekening weerspiegelt het contrast tussen het leven van vroeger en nu en de onzekerheid over de toekomst.

GHENT UNIVERSITY

Faculty of Medicine and Health Sciences

Department of Public Health

ADHERENCE TO ORAL ANTICANCER DRUGS

INFLUENCING FACTORS AND UNDERLYING PROCESSES

USUAL CARE AND HEALTHCARE PROFESSIONALS' PERCEPTIONS OF ADHERENCE TO ORAL ANTICANCER DRUGS

Mathieu Verbrugghe

This thesis is submitted in fulfilment of the requirements for the degree of Doctor in Social Health Sciences: Medical-Social Sciences

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Adherence to oral anticancer drugs – Influencing factors and underlying processes, usual care and healthcare professionals' perceptions of adherence to oral anticancer drugs

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Dankbaar,

Omdat we kunnen en mogen zijn,

Omdat vandaag morgen vanzelf weer gisteren wordt,

Zomaar.

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ABBREVIATIONS

ADAGIO	Adherence Assessment with Glivec: Indicators and Outcome
AHT	antihormonal therapy
AIs	aromatase inhibitors
BAAS	Basel Assessment of Adherence Scale
Be	Belgium
BMQ	Beliefs about Medicines Questionnaire
CASP	Critical Appraisal Skills Programme
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CML	chronic myeloid leukemia
GIST	gastrointestinal stromal tumour
HCC	hepatocellular carcinoma
HCP	healthcare provider
IQR	interquartile range
MARS	Medication Adherence Report Scale
MEMS	Medication Event Monitoring System
MPR	Medication Possession Ratio
MRC	Medical Research Council
NL	the Netherlands
NP	nurse practitioners
OACA	oral anticancer agents
OACD	oral anticancer drugs
PAMQ	Perceptions about Adherence Management Questionnaire

PROMs	patient reported outcomes measures
RCC	renal cell cancer
SD	standard deviation
SE	standard error
SDM	shared decision making
SERMs	selective estrogen receptor modulators
TKIs	tyrosine kinase inhibitors
UC	usual care
WHO	World Health Organization

TABLE OF CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

This PhD thesis reports on (1) factors and processes influencing (non-)adherence and (non-)persistence to oral anticancer drugs (OACD), (2) healthcare professionals' perceptions about managing OACD adherence and shared decision making (SDM) and beliefs towards OACD, and (3) usual care in supporting adherence to OACD. The introductory chapter provides a background on (non-)adherence and (non-)persistence in cancer patients treated with OACD. An overview of the conceptual approaches to define patients' medication taking behavior, methods used to assess medication adherence and persistence, prevalence and consequences of non-adherence and non-persistence to OACD, research on factors influencing (non-)adherence and (non-)persistence in patients taking OACD, current knowledge about healthcare professionals' related factors influencing OACD adherence and usual care in supporting adherence to OACD, and OACD adherence enhancing interventions is given. Finally, the outline of this PhD thesis is presented.

ORAL ANTICANCER DRUGS

The use and number of OACD have increased steadily within the last decade (Banna et al., 2010). Almost half of the targeted anticancer drugs developed since 2000 are exclusively administered orally (Ozols et al., 2006; Gralow et al., 2007; Winer et al., 2008). Twenty-five percent of the anticancer drugs can be taken orally (Banna et al., 2010). The shift from intravenous to oral delivery will most likely continue to evolve.

Currently, more than 30 OACD are used for different types of cancer. Most of them are primarily cytostatic in nature and most effective over long periods of time (Foulon et al., 2011). Three major categories of OACD addressed in this PhD thesis are Tyrosine Kinase Inhibitors (TKIs), Selective Estrogen Receptor Modulators (SERMs), and Aromatase Inhibitors (AIs). These categories of OACD were selected because until now, little was known about factors influencing (non-)adherence and (non-)persistence and/or no clear understanding of the complex patterns and dynamics of (non-)adherence and

(non-)persistence existed in patients taking those OACD. Table 1 provides an overview of the substance and brand names of most of the three categories of OACD and the indications they are used for.

Most patients prefer OACD over intravenous anticancer therapy (Liu et al., 1997; Paley et al., 2005; Fallowfield et al., 2006). Reasons are: the convenience of a home-based therapy, the avoidance of an insertion of a central venous catheter, less frequent hospital visits, the feeling of a greater sense of 'control' over their treatment, and previous negative experiences with intravenous therapy (Liu et al., 1997; Paley et al., 2005; Fallowfield et al., 2006). However, the preference for OACD over intravenous anticancer therapy is conditioned by efficacy and toxicity of the treatment (Liu et al., 1997). Only when OACD is no less effective than intravenous anticancer therapy, and toxicity is not worse than expected from intravenous anticancer therapy, patients prefer OACD (Liu et al., 1997; Fallowfield et al., 2006; Pfeiffer et al., 2006). The preference for OACD can also change over time as patients experience more side effects from OACD than expected (Pfeiffer et al., 2006).

Treatment with OACD also poses important challenges for both patients and healthcare professionals. Patients on OACD have to manage their medication more autonomously than intravenous anticancer therapy, time and dosing schedules are often complex, and OACD have to be taken over a long period of time. Many patients believe that OACD are less toxic than intravenous anticancer therapy (Moody et al., 2012). However, patients treated with OACD may also be confronted with severe side effects because chemotherapy medication (both oral and intravenous) often has a narrow therapeutic index (i.e. there is little difference between toxic and therapeutic doses), which increases the risk for harmful side effects (Griffin, 2003; Bartel, 2007; Weingart et al., 2008).

Healthcare professionals are challenged with optimal dose finding, drug interactions, specific education of patients and family, and - above all - the management of toxicity and adherence issues.

Table 1 Tyrosine Kinase Inhibitors, Selective Estrogen Receptor Modulators, and Aromatase Inhibitors and indications for use

Drug classification	Substance name	Brand name	Indication
Tyrosine Kinase Inhibitors (TKIs)	dasatinib	Sprycel® (Bristol-Myers-Squibb)	Chronic Myelogenous Leukaemia (CML)
	erlotinib	Tarceva® (Roche)	Non-small cell lung cancer, pancreatic cancer
	gefitinib	Iressa® (AstraZeneca)	Non-small cell lung cancer
	imatinib	Glivec® (Novartis Pharma)	Chronic Myelogenous Leukaemia (CML), Gastrointestinal stromal tumor (GIST)
	lapatinib	Tyverb® (GlaxoSmithKline)	Breast cancer
	nilotinib	Tasigna® (Novartis Pharma)	Chronic Myelogenous Leukaemia (CML)
	pazopanib	Votrient® (GlaxoSmithKline)	Renal Cell Cancer (RCC)
	sorafenib	Nexavar® (Bayer)	Renal Cell Cancer (RCC), Hepatocellular carcinoma (HCC)
	sunitinib	Sutent® (Pfizer)	Gastrointestinal stromal tumor (GIST), Renal cell cancer (RCC)
Selective Estrogen Receptor Modulators (SERMs)	tamoxifen	Nolvadex® (AstraZeneca, Impexeco, PI-Pharma) Tamizam® (Mithra) Tamoplex® (Teva) Tamoxifen-Mylan (Mylan) Tamoxifen EG® (Eurogenerics) Tamoxifen Sandoz® (Sandoz)	Breast cancer
	fulvestrant	Faslodex® (AstraZeneca)	Breast cancer

Drug classification	Substance name	Brand name	Indication
Aromatase Inhibitors (AIs)	anastrozol	Anastratom® (Mithra)	Breast cancer
		Anastrozole EG® (Eurogenerics)	
		Anastrozole Mylan® (Mylan)	
		Anastrozole Teva® (Teva)	
		Anastrozol Sandoz® (Sandoz)	
		Arimidex® (AstraZeneca)	
	exemestan	Aromasin® (Pfizer)	Breast cancer
		Exemarom® (Mithra)	
		Exemestane Mylan® (Mylan)	
		Exemestane Teva® (Teva)	
		Exemestan Sandoz® (Sandoz)	
	letrozol	Femara® (Novartis Pharma)	Breast cancer
		Femara® (PI-Pharma)	
		Letrozarom® (Mithra)	
		Letrozole Mylan® (Mylan)	
		Letrozole Teva® (Teva)	

Based on: Foulon et al. (2011), BCFI (2013)

TERMINOLOGY AND MEASUREMENT

Different conceptual approaches have been described to define patients' medication taking behavior. The terminology reflects the changing views on medication taking behavior and the changing relationships between patients and healthcare professionals. The terms 'patient compliance', 'medication

adherence', 'concordance', 'persistence', and 'self-management' will be discussed below.

Haynes and colleagues (1979) defined '**patient compliance**' as *"the extent to which the behavior of a patient – with regard to taking medication, following a diet and/or the execution of behavioral changes in lifestyle – is consistent with the recommendations of a specialist"*. This definition shows a clear distinction of roles in which the healthcare professional imposes the therapy and in which the patient follows the imposed therapy. Within this definition, the role of the healthcare professional is a paternalistic one rather than a collaborative one.

In 2003, the World Health Organization (WHO) introduced the term '**adherence**' as "*the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider*" (WHO, 2003). To date, the term 'medication adherence' is more frequently used than 'patient compliance' because this term includes more diverse reasons for patients not following treatment instructions partially or fully (Ngoh, 2009). Other than 'patient compliance', the term 'medication adherence' includes active, voluntary, and collaborative patient involvement (Delamater, 2006). Medication non-adherence is generally believed to have a less judgemental connotation than 'patient non-compliance' (Banna et al., 2010; Foulon et al., 2011) and is more seen as a failure of the health system that has not recognized the patients' needs (EBMT, 2011).

To date, multiple definitions for 'medication adherence' exist (Cramer et al., 2008; Ruddy et al., 2009), but there is still no universally accepted definition (Gebbia et al., 2011). A patient is considered to be fully adherent (100%) when no doses are missed, no more doses are taken than prescribed, and no doses are taken at the wrong time or in the wrong quantity (Cramer et al., 2008; Ruddy et al., 2009; Staddon, 2011). Adherence is mostly measured over a period of time and expressed as a percentage (Cramer et al., 2008). To date, different cut-off rates are used to define medication non-adherence: being ≤80%, ≤90%, ≤100%, or ≥110% adherent over a period of time (Lebovits et al., 1990; Partridge et al., 2003; Kirk and Hudis, 2008; Eliasson et al., 2011; Gebbia et al.,

2011). The cut-off rate of ≤80% is frequently cited in the literature as acceptable or achievable (Sikka et al., 2005; Hess et al., 2006; Simpson et al., 2006). However, until now, little is known about how much adherence to OACD is necessary for optimal treatment effectiveness. Future research is needed to explore more clinically significant and meaningful cut-off rates for the different types of OACD and the different methods to assess non-adherence.

The term '**concordance**' was introduced in 1995 by the Royal Pharmaceutical Society of Great Britain. Concordance is about "*an agreement reached after negotiation between a patient in determining whether, when and how medicines are to be taken*" (Horne, 2006). The term 'concordance' highlights more the relationship between healthcare professionals and patients in which both are equal (Horne, 2006; Bissonnette, 2008).

Bailey and colleagues (2013) introduced a new conceptual model in order to rethink medication adherence: '**medication self-management**'. The conceptual model deconstructs the tasks associated with taking prescription drugs; such as knowledge, skills, and behaviors necessary to take medication correctly. No single clear definition of 'self-management' exists. Barlow and colleagues (2002) define self-management in chronic conditions as "*the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition*". Grypdonck (1999) describes self-management in a broad way with attention to the empowerment of patients and the existential dimension of living with a disease. Grypdonck (1999) defines self-management as the efforts patients make in order to find the best possible compromise between the demands of the disease and the demands of life. From the patient's perspective, self-management is adequate or successful when it leads to goals improving quality of life (Grypdonck in van den Brink et al., 2013). Consequently, choices patients make could be different from those of healthcare professionals.

In the conceptual model introduced by Bailey and colleagues (2013), a series of steps are identified which a patient has to follow to take medication in a safe and effective way within an ambulatory care setting (see figure 1). The conceptual

model particularly attends to the health literacy of patients, or "*the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions*" (Institute of Medicine, 2004; Kutner et al., 2006). This perspective emphasizes the role of health systems and the way in which information is provided to patients (Parker and Ratzan, 2010).

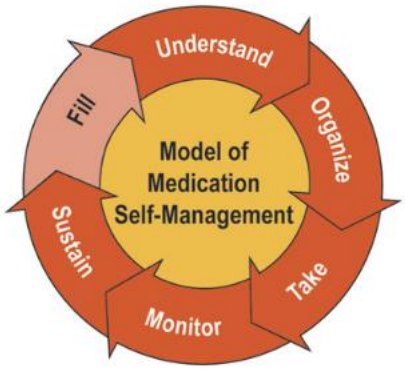

Figure 1. Model of medication self-management (Bailey et al., 2013)

The term '**medication persistence**' describes the duration of time from treatment initiation to discontinuation (Cramer et al., 2008). Medication persistence is considered as being optimal when medication is taken as long as prescribed by the treating physician. The terms 'non-persistence' and 'early discontinuation' are used interchangeably in literature. Medication persistence may be reported as a continuous variable (i.e. number of days therapy), or as a dichotomous variable (i.e. persistent or non-persistent at a predefined period of time) (Cramer et al., 2008; Foulon et al., 2011). To define non-persistence as a dichotomous variable, several different cut-offs in number of days without subsequent refill of pills are used: ≥30, ≥45, ≥60, and ≥180 days (Barron et al., 2007; Darkow et al., 2007; Owusu et al., 2008; Hershman et al., 2010a; Neugut et al., 2011; Nekhlyudov et al., 2011; Streeter et al., 2011).

In sum, an evolution over time can be noticed in conceptualizing patients' medication taking behavior. The term 'compliance' was found to be too paternalistic: patients were expected to take their medication as prescribed by healthcare professionals without participation. To highlight the importance of collaboration between healthcare professionals and patients in decision making processes, the term 'compliance' was replaced by the term 'adherence'. The term 'self-management', which is a further development in thinking about handling prescribed regimens and medication, emphasizes the daily activities a patient has to deal with in order to realize the therapeutic regimen. This way, thinking about medication taking behavior has changed from a paternalistic to an empowering approach in which patients' quality of life plays an important part.

METHODS USED TO ASSESS MEDICATION ADHERENCE AND PERSISTENCE

Different methods are used to assess medication adherence and persistence. No gold standard exists as each method has advantages and limitations (Wagner et al., 2001). The available methods can be divided into direct and indirect methods of measurement (Osterberg and Blaschke, 2005).

Direct methods to assess medication adherence include direct observation, measurement of the level of medicine or metabolite in the blood, and measurement of the biologic blood marker (Foulon et al., 2011). Despite the accuracy of these methods, they are mostly not appropriate to use in routine practice. Direct observation is not feasible to use in an ambulatory setting, and measurement of the level of the medicine or biological marker in the blood is often expensive. Furthermore, for most OACD, measurements of the level of medicine or metabolite in blood is not possible because available markers are not sensitive and reliable enough or not fully validated to assess adherence (Foulon et al., 2011).

Indirect methods to assess medication adherence include pill counts, self-report, electronic medication monitors such as the Medication Event Monitoring System (MEMS©, Aardex), and patient diaries. Pill counts, prescription refills, and self-

report are the most commonly used methods (Ho et al., 2009). Pill counts are easy to perform, however, data can easily be altered by the patient (e.g., pill dumping). Prescription refill rates based on retrospective databases are often used in studies to measure medication adherence (Partridge et al., 2003; Barron et al., 2007; Darkow et al., 2007; Owusu et al., 2008; Kimmick et al., 2009; Nekhlyudov et al., 2011; Neugut et al., 2011; Sedjo and Devine, 2011; Streeter et al., 2011). By using refill data, a Hawthorne effect could be avoided because patients are generally not aware that their refill rates are reviewed (Ruddy et al., 2009). Furthermore, by using refill data, adherence of a large population over a long period of time could be quantified (Ruddy et al., 2009). However, a prescription refill is not equivalent to ingestion of medication, and refill data do not provide information regarding the timing of doses (Osterberg and Blaschke, 2005; Ruddy et al., 2009). Patient self-report is simple, inexpensive, and the more useful method for the clinical setting (Osterberg and Blaschke, 2005). However, measuring adherence by self-report is subject to response bias, with patients often over-reporting adherence rates because of e.g. the desire to please healthcare professionals (Jasti et al., 2006). Numerous self-report adherence scales are available. In a systematic review conducted by Nguyen and colleagues (2014), 43 adherence scales were identified. These scales measure both medication-taking behavior, and/or identify barriers and beliefs associated with adherence (Nguyen et al., 2014). In selecting the 'right' self-report adherence scale, careful consideration is needed of what needs to be measured, and how and in whom the scale has been validated (Nguyen et al., 2014). The Medication adherence report scale (MARS-5) (Horne et al., 2001), a 5-item scale to assess various non-adherent behaviors, and the Morisky and Green test (Morisky et al., 1986), a 4-item test to evaluate attitudes regarding treatment, are two examples of scales used to assess adherence in patients taking OACD (Grunfeld et al., 2005; Marques and Pierin, 2008). A combination of MEMS and self-report questionnaires is found to be the most accurate in measuring medication adherence using indirect methods (Shi et al., 2010).

PREVALENCE AND CONSEQUENCES OF NON-ADHERENCE AND NON-PERSISTENCE TO ORAL ANTICANCER DRUGS

As this PhD thesis mainly focuses on (non-)adherence and (non-)persistence in patients following oral TKI therapy or AHT (SERMs or AIs), only these will be discussed below.

Oral tyrosine kinase inhibitors

Studies on the prevalence of non-adherence and non-persistence with oral TKIs mainly focus on chronic myeloid leukemia (CML) patients. Adherence among CML patients taking oral TKIs vary between 64 and 96.7% (Feng et al., 2006; Tsang et al., 2006; Darkow et al., 2007; Doti et al., 2007; Halpern et al., 2007; Doti et al., 2008; Noens et al., 2009; StCharles et al., 2009; Marin et al., 2010; Wu et al., 2010). In the study by Noens and colleagues (2009), about one-third of the CML patients treated with imatinib were classified as non-adherent as assessed by a structured patient interview. Adherence assessed with pill counts over a 99 days period revealed an adherence rate of 90.9%. In the study by Noens and colleagues (2009), only 14.2% of the patients with CML were 100% adherent. In the study of Marin and colleagues (2010), 14% of the total sample of 87 patients were considered to be non-adherent when using MEMS and a cut-off rate of ≤ 80%. Twenty-three patients (26.4%) were ≤ 90% adherent (Marin et al., 2010). Khandelwal and colleagues (2012) studied adherence in patients with solid tumors (breast, colon) following therapy with oral TKIs sunitinib, sorafenib and erlotinib. They found that 99% were adherent at 1 month, 64% at 3 months, and 43% at 6 months. Non-persistence in this study was 48.8% at 3 months and 76.2% at 6 months. Gebbia and colleagues (2013) studied medication adherence in patients with non-small-cell lung cancer taking the oral TKI erlotinib. They found that 7% of the patients were <90% adherent when using a self-reported questionnaire and 17% when using pill count.

The ADAGIO (Adherence Assessment with Glivec: Indicators and Outcome) study evaluated the impact on outcomes of non-adherence in patients with CML (Noens et al., 2009). The study showed that patients taking 74.0-76.8% of the

prescribed dose had a less good response than patients taking 89.9-92.7% of the prescribed dose (Noens et al., 2009). In this study, suboptimal response was defined at three months as incomplete hematologic response, at six months as less than partial cytogenetic response, and at 18 months as less than major molecular response and, in case of loss of major molecular response, other limitations or other chromosomal abnormalities.[1] Optimal response has been associated with overall and progression-free survival in patients with CML (Druker et al., 2006; Ganesan et al., 2011).

Other studies confirmed that adherence to CML oral anticancer therapies is linked to the achievement of a complete cytogenetic response and a major molecular response (Bazeos et al., 2009; Marin et al., 2010; Ganesan et al., 2011; Ibrahim et al., 2011). Ganesan and colleagues (2011) showed that the estimated 5-year event free survival[2] in non-adherent patients with CML taking imatinib was 59.8% compared with 76.7% in those with no interruptions. In the study of Ibrahim and colleagues (2011) in CML patients on imatinib, 23 patients with an adherence rate ≤85% had a higher probability of losing their complete cytogenetic response at 2 years (26.8% vs. 1.5%) and a lower probability of remaining on imatinib (64.5% vs. 90.6%) compared with the 64 patients with an adherence rate >85%.

[1] Patients with CML respond to treatment in different ways. These are general guidelines for CML drug therapy. Baseline results (test levels at the time of diagnosis) can influence response. The doctor generally work with the following time frame as a guideline to achieve the desired response: *After 3-6 months of therapy*: a complete hematologic response and some cytogenetic improvement, *after 6-12 months of therapy*: a partial cytogenetic response of two-thirds reduction in the number of Ph chromosomes in the marrow, *after 12-18 months of therapy*: a complete cytogenetic response and partial molecular response.

[2] Event free survival was calculated from the date of starting of Imatinib to the occurrence of any one of the following: non-achievement of complete hematological response (CHR) at 6 months, non-achievement of complete cytogenetic response (CCR) at 2 years, loss of cytogenetic response and/or hematological response, progression to accelerated phase/ blast crisis at any point, or death due to any reason.

Antihormonal therapy

Most studies on prevalence and consequences of non-adherence and non-persistence to OACD focus on antihormonal therapy (AHT) in breast cancer (Foulon et al., 2011). Non-adherence and non-persistence rates vary among studies: between 11% and 51% (Güth et al., 2012), between 15% and 50% (Doggrell, 2011) or between 40% and 60% (Fontein et al., 2012). These varying results may be due to different methods used to measure adherence or different definitions used to define (non-)adherence and (non-)persistence (Güth et al., 2012). Non-adherence and non-persistence rates are similar among patients treated with SERMs (tamoxifen), AIs, or with a combination of both (Hershman et al., 2010a; Fontein et al., 2012). In a study by Grunfeld and colleagues (2005), 12% of self-reported non-adherence was found in patients with early stage breast cancer taking tamoxifen. In the study by Waterhouse and colleagues (1993), a combination of methods was used to assess non-adherence in patients taking tamoxifen. A high self-reported adherence was found (97.9%), while adherence was 92.1% assessed by pill counts, and 85.4% by MEMS. In the study conducted by Dezentjé and colleagues (2010), the mean adherence in the first year was 93%, and the mean adherence at the third year was 84%. Sedjo and Devine (2011) studied adherence in patients with breast cancer treated with AIs. Over a one year period, 23% of the patients were non-adherent (<80% medication possession ratio – number of days supply of medication divided by the number of days patient should take the medication).

Non-persistence rates vary between 31% and 34.4% for the five-year treatment (Lash et al., 2006; Güth et al., 2008; Hershman et al., 2010b). In a large study by Barron and colleagues (2007), 21.1% discontinued within the first year of treatment with tamoxifen, 35.2% discontinued within the 3.5 years of treatment. In the study by Henry et al. (2012), 32.6% of the women discontinued the treatment with AIs within the first two years. The median time to treatment discontinuation was 6.1 months (range 0.1-21.2). In the study by Fontein et al. (2012), overall early discontinuation in the treatment with AIs was 18.4%, of which 49.7% discontinued within the first six months of treatment. Non-

adherence and non-persistence increases over time treated with AHT (Barron et al., 2007; Fontein et al., 2012; Huiart et al., 2012). The study by van Herk-Sukel and colleagues (2010) showed that the percentage of continuous users of tamoxifen at 1, 2, 3, 4, and 5 years treatment was 83, 70, 55, 50, and 40%, respectively.

Both non-adherence and non-persistence are associated with an increased risk of recurrence and mortality (Hershman et al., 2010b). In the study by Hershman and colleagues (2010b), the estimated survival at 10 years was 80.7% and 73.6% for women who continued and discontinued AHT, respectively ($p<0.001$). In participants who continued AHT, survival at 10 years was 81.7% in women who were adherent (≥80% medication possession ratio) and 77.8% in women who were non-adherent ($p<0.001$) (Hershman et al., 2010b). After adjusting for clinical and demographic variables, both non-adherence and early discontinuation among those who continued AHT, were independent mortality predictors (Hershman et al., 2010b).

FACTORS INFLUENCING (NON-)ADHERENCE AND (NON-)PERSISTENCE TO ORAL ANTICANCER DRUGS

Factors influencing (non-)adherence and (non-)persistence are complex and interrelated. A frequently used framework to describe the multidimensional phenomenon of adherence, is the WHO framework (WHO, 2003). This framework (figure 2) consists of five dimensions affecting medication adherence: social and economic factors (e.g. medication cost), healthcare team and system-related factors (e.g. provider-patient relationship), condition-related factors (e.g. severity of symptoms), therapy-related factors (e.g. complexity of medication regimen), and patient-related factors (e.g. fear of possible adverse events).

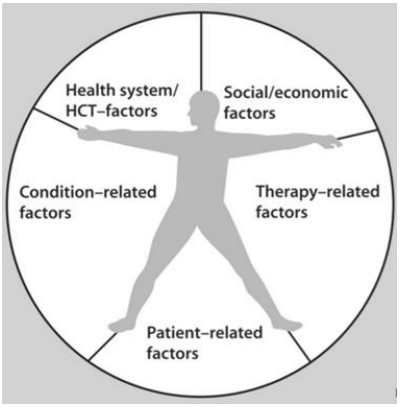

Figure 2: Five dimensions affecting adherence (WHO, 2003)

In patients taking OACD, several factors are found to influence (non-)adherence and (non-)persistence (Ruddy et al., 2009). In a review, Ruddy and colleagues (2009) summarized three interrelated main categories of factors influencing (non-)adherence and (non-)persistence to OACD: personal factors (e.g. emotional state, health beliefs, and social supports), treatment factors (e.g. side effects, and costs), and factors interacting with the system (e.g. satisfaction with care, and relationship with providers).

Most studies determining factors influencing (non-)adherence and (non-)persistence to OACD are conducted in patients with breast cancer. The vast majority of research focusing on factors influencing (non-)adherence and (non-)persistence to OACD is quantitative. Less research is qualitative or mixed methods. Until now, no qualitative research described processes and factors influencing (non-)adherence and (non-)persistence in patients taking different types of oral TKIs. Only one mixed method study was conducted in patients with CML taking the OACD imatinib (Eliasson et al., 2011).

In breast cancer patients taking OACD, only two qualitative studies were conducted focusing on (non-)adherence and (non-)persistence (Pellegrini et al., 2010; Regnier Denois et al., 2011). In the study by Pellegrini and colleagues (2010), the focus was narrowed to the exploration of the relation between

adherence and perceptions of the treatment and experiences of side effects in breast cancer patients taking the SERM tamoxifen. In the qualitative study by Regnier Denois and colleagues (2011) the focus was on behavior and representations of breast cancer patients and oncologists about adherence with OACD. However, Regnier Denois and colleagues (2011) only focused on patients taking capecitabine, an antimetabolite.

Qualitative research could give us insight into the complexity and interrelatedness of factors influencing (non-)adherence and (non-)persistence in patients taking OACD. Qualitative research is more appropriate for studying experiences in the context of an experiential process (Morse and Field, 1996). Furthermore, qualitative research could give us insight into the processes associated with medication (non-)adherence and (non-)persistence to OACD and the meaning of the OACD therapy from the patients' perspective. This is of particular importance to inform patient-tailored interventions to support patients treated with OACD. Qualitative research to different types of OACD is important because OACD groups have different characteristics which influence the experience of the therapy in patients. Oral TKIs, for example, are mainly used in a metastatic setting, and often have a narrow therapeutic index which increases the risk for severe side effects. Qualitative research could also show us how to understand results of quantitative research (Black, 1994), by giving insight into the way several factors found to be associated with (non-)adherence and (non-)persistence contribute to (non-)adherence and (non-)persistence.

HEALTHCARE PROFESSIONALS' RELATED FACTORS INFLUENCING ORAL ANTICANCER DRUGS ADHERENCE AND USUAL CARE IN SUPPORTING ADHERENCE TO ORAL ANTICANCER DRUGS

Healthcare professional-related factors influencing non-adherence in patients with breast cancer taking OACD are e.g. giving too much or too less support than needed by patients (Kahn et al., 2007) and physicians' poor explanation of treatment effects (Kahn et al., 2007). Less participation in decision making than

wanted by patients about OACD therapy was found to be associated with lower adherence in patients with breast cancer (Kahn et al., 2007). The study of Kahn et al. (2007) showed that women with breast cancer who were satisfied about the role they received in the OACD decision-making process, were more likely to continue their therapy (81%) compared to patients receiving a more (73%) or less expanded role (59%) than wanted in the OACD decision-making process. Healthcare professional-related factors influencing adherence in patients with CML taking OACD are e.g. feedback from physicians that seems to reinforce the belief that 'occasional' non-adherence does not matter (Eliasson et al., 2011), and the degree of faith in the physician (Eliasson et al., 2011). In a study by Noens and colleagues (2009), physicians were asked to rate the various WHO categories of adherence influencing factors as contributing or not to non-adherence to imatinib in patients with CML. Therapy-related factors were identified by most of the physicians as determinants of non-adherence (96.1%), followed by patient demographic, social and economic factors (92.1%), the patient-physician relationship (92.1%), disease-related factors (84.3%), physician-related factors (70.6%), and other patient-related variables (70.5%). Within the patient-physician relationship, the communication and interpersonal style of the physician as well as physicians' continuity of care were identified as contributing factors by most of the respondents (both 96.1%), followed by the time physicians spend with patients (91.2%), physicians' empathy and assistance (89.2%), and patient involvement in planning (88.3%). However, most studies researching healthcare professional-related factors are studied from the patient's perspective (Osterberg and Blaschke, 2005). A recently published paper showed that 60% of the physicians did not react to side effects patients experienced (Wuensch et al., 2015). Patients who reported having received detailed answers to their questions were significantly more adherent (Wuensch et al., 2015). Little is known about healthcare professionals' perceptions on OACD adherence and usual care in supporting adherence to OACD. Exploring healthcare professionals' beliefs about OACD and perceptions of OACD adherence, and exploring the current practice of adherence supportive

care is important. Both can offer a point of departure for outlining the aspects of an intervention to support patients following OACD therapy.

ORAL ANTICANCER DRUGS ADHERENCE ENHANCING INTERVENTIONS

Mathes et al. (2014) recently conducted a systematic review on adherence enhancing interventions for OACD. In this systematic review, six studies were included (of which one was an RCT). The methodological quality of the studies was evaluated as moderate to low. Only one study revealed significant results in favor of an adherence intervention (Tschida et al., 2012). In the latter study, a pharmacy program (biweekly to monthly the first three months and then every three months thereafter) was used. The pharmacy program consisted of patient education about medication and comorbidities, a proactive adherence program including refill reminders, and adherence screening. In case of non-adherence, an intervention with the patient and physician was conducted including an oncology clinical management program of telephonic clinical counseling and, the availability of a specialty pharmacist available 24h/7 days a week for questions. In the review of Mathes et al. (2014), two studies showed a tendency in favor of the intervention groups (Simons et al., 2011; Khandelwal et al., 2012). The study of Simons et al. (2011) described a pharmaceutical care intervention including initial patient consultation (median 75 min) and follow-up consultation (at least once during each OACD cycle). In the initial patient consultation, the characteristics of the OACD were explained in detail, education about the importance of adherence was given, a written dosing schedule and a leaflet with information about the prevention and management of adverse effects were provided. The study of Khandelwal et al. (2012) used an oral chemotherapy follow-up management program by an oncology nurse or pharmacist. The program consisted of education, monitoring, and counseling by telephone (day 10 and 20 of the first month of the therapy and monthly thereafter). Furthermore, therapy and side effects were assessed between follow-up visits. When side effects were graded moderate or severe, the prescribing physician was contacted to revise the oral chemotherapy regimen. The results of the systematic review of Mathes et al. (2014) revealed that interventions to improve

adherence to oral anticancer drugs have only shown limited effects. This finding was confirmed in a systematic review on interventions for adherence with OACD in hematological malignancies (Kavookjian and Wittayanukorn, 2014). Of the six studies included in this systematic review, four reported statistically significant improvements in adherence outcomes compared to the control group, only two resulted in improvement in treatment outcomes. The interventions consist of one or more of the following components: general patient education (Levine et al., 1987; Richardson et al., 1990; Doti et al., 2007; Moon et al., 2012), tailored intervention (combinations of patient education and targeted behavior change intervention) (Levine et al., 1987; Richardson et al., 1990; Doti et al., 2007; Moon et al., 2012), and simplification of the dosage/regimen (Doti et al., 2007). However, comparing intervention studies is difficult because of the heterogeneous nature of the different studies (e.g. different content of the adherence enhancing intervention, and differences in adherence definition and measurement) (Kavookjian and Wittayanukorn, 2014; Mathes et al., 2014). Tailored interventions with education and counseling including patient-centered decision-making about treatment choice and adherence support seems to be promising in several studies (Kavookjian and Wittayanukorn, 2014; Mathes et al., 2014). It could be concluded that further high quality intervention studies are needed (Kavookjian and Wittayanukorn, 2014; Mathes et al., 2014).

AIMS AND SCOPE OF THIS THESIS

The general objectives of this PhD thesis are to explore factors and processes influencing (non-)adherence and (non-)persistence in patients taking OACD, explore healthcare professionals' perceptions about managing OACD adherence and SDM and beliefs towards OACD, and usual care in supporting adherence to OACD. We mainly focused on two major categories of OACD: oral TKIs and AHT (both SERMs and aromatase inhibitors). Until now, little was known about factors influencing (non-)adherence and (non-) persistence in patients taking oral TKIs. Much more research was conducted on factors influencing (non-)adherence and (non-)persistence in patients taking AHT. However, in this

group, there was still no clear understanding of the complex patterns and dynamics of (non-)adherence and (non-) persistence. Qualitative research in both patients treated with oral TKIs and AHT was scarce.

Studies exploring adherence issues have predominantly focused on the patient's perspective (Osterberg and Blaschke, 2005). Only few studies focused on the physicians' perspective (Regnier Denois et al., 2010; Kekäle et al., 2014). No studies were conducted including pharmacists, nurses, and physicians. Insight into healthcare professionals' perceptions and beliefs about OACD adherence is important because perceptions and beliefs may influence healthcare professionals' behavior and care (Ajzen, 1991; Valente Teixeira et al., 2012). In turn this may influence patients' adherence behavior (Marteau and Johnston, 1991; Eliasson et al., 2011). Insight into usual care allows to determine areas for improvement.

Van Meijel et al. (2004) constructed a model for the development of evidence-based complex nursing interventions. The model is similar to the 'Framework for development and evaluation of randomized controlled trials for complex interventions to improve health', as published by the Medical Research Council (MRC framework, 2008). The van Meijel model describes four phases: (1) problem definition, (2) building blocks needed for intervention design, (3) intervention design, and (4) intervention validation. The patient's perspective holds a central position in the model. The building blocks needed for intervention design could be derived from this PhD thesis (see figure 1).

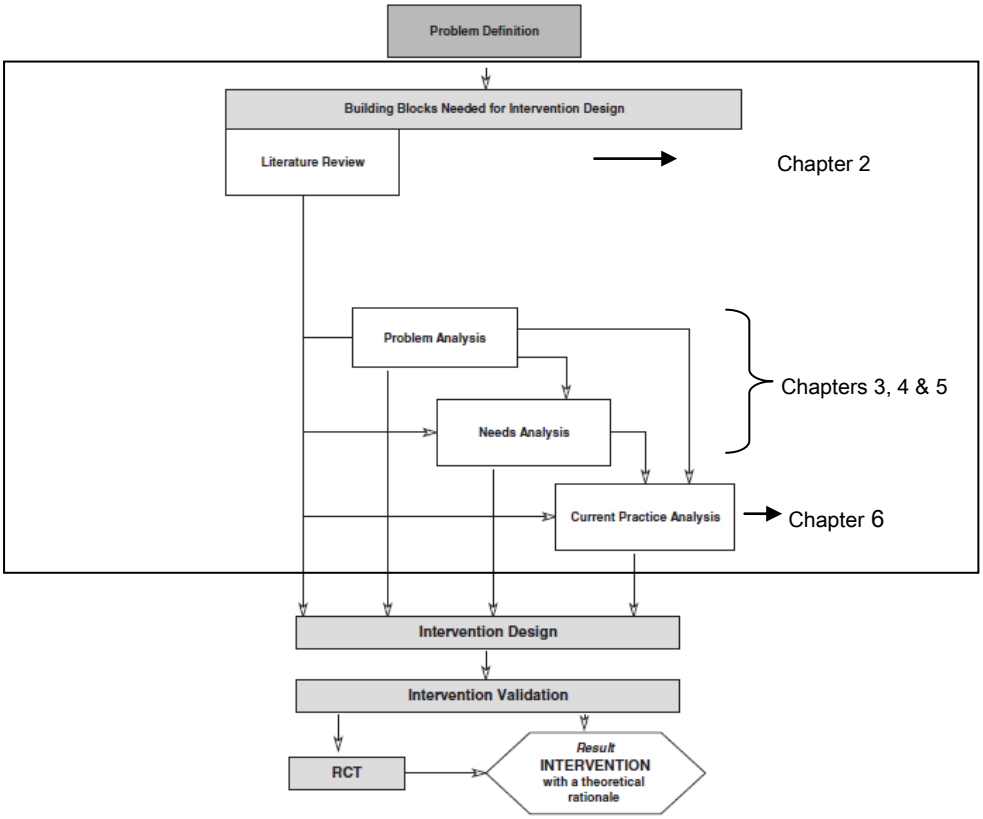

Figure 1: Diagram of developing evidence-based complex nursing interventions (Van Meijel et al., 2004)

Information about interventions and their effectiveness is an important part of a thorough literature review to inform intervention design (van Meijel et al., 2014). In this PhD thesis, we did not evaluate the effectiveness of adherence interventions in patients taking OACD because Mathes et al. (2014) recently conducted a systematic review on adherence enhancing interventions for OACD (see chapter oral anticancer drugs adherence enhancing interventions).

First, a systematic review was conducted to provide an updated overview of determinants and associated factors of medication (non-)adherence and (non-)persistence in patients taking OACD. In the systematic review, all types of OACD were considered.

Second, a qualitative research on factors influencing (non-)adherence in patients taking oral TKIs was conducted to explore processes and factors influencing (non-)adherence to oral TKIs, and to get insight into the interrelatedness of influencing factors.

Third, a qualitative research on factors influencing (non-)adherence and (non-)persistence in breast cancer patients with adjuvant AHT was conducted to explore processes and factors influencing (non-)adherence and (non-)persistence to AHT, and to get insight into the interrelatedness of influencing factors.

Fourth, a quantitative study was conducted to get insight into healthcare professionals' perceptions about managing OACD adherence, beliefs towards OACD, and perceptions towards SDM, which is known to be an adherence influencing factor from the patients' perspective (Kahn et al., 2007).

Fifth, a quantitative study was conducted to get insight into usual care in supporting adherence to OACD in (hemato-)oncology settings in Belgium and the Netherlands.

The results of the studies conducted in the context of this PhD thesis could help healthcare professionals to understand why patients taking oral TKI's or AHT do not adhere or persist to their therapy. Insight into the patients' experiences could help to inform the development of patient tailored interventions to support patients following oral anticancer therapy. Insight into the attitudes and beliefs of healthcare professionals about medication (non-)adherence in patients taking OACD could help to develop interventions tailored to healthcare professionals' perceived capacity to support patients taking OACD. Insight into usual care could give a point of departure for outlining aspects of an intervention to support patients taking OACD.

In summary, the outline of this PhD thesis is as follows:

- Chapter 1: General introduction
- Chapter 2: Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review
- Chapter 3: Factors influencing adherence in cancer patients taking oral tyrosine kinase inhibitors: a qualitative study
- Chapter 4: Factors influencing the process of medication (non-)adherence and (non-)persistence in breast cancer patients with adjuvant antihormonal therapy: a qualitative study
- Chapter 5: Adherence to oral anticancer agents: healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands
- Chapter 6: Adherence to oral anticancer agents: healthcare providers' perceptions and usual care in Belgium and the Netherlands
- Chapter 7: General discussion

REFERENCES

Ajzen I.The theory of planned behavior. *Organizational Behavior and Human Decision Processes* 1991;**50**:179-211.

Bailey SC, Oramasionwu CU, Wolf MS. Rethinking adherence: a health literacy-informed model of medication self-management. *Journal of Health Communication* 2013;**18**:20-30.

Banna GL, Collova E, Gebbia V, Lipari H, Giuffrida P, Cavallaro S, et al. Anticancer oral therapy: emerging related issues. *Cancer Treatment Reviews* 2010;**69**:595-605.

Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. *Patient Education and Counseling* 2002;**48**(2):177-187.

Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: a lesson for oncologists. *Cancer* 2007;**109**(5):832-839.

Bartel, S.B. (2007). Safe practices and financial considerations in using oral chemotherapeutic agents. *American Journal of Health-System Pharmacy* 2007*,***64**(9, Suppl. 5), S8–S14.

Bazeos A, Khorashad J, Mahon FX, Eliasson LL, Milojkovic D, Bua M, et al. Long term adherence to imatinib therapy is the critical factor for achieving molecular responses in chronic myeloid leukemia patients. *ASH Annual Meeting Abstracts* 2009;**114**:3290.

BCFI. Gecommentarieerd Geneesmiddelen repertorium 2013.

Bissonnette JM. Adherence: a concept analysis. *Journal of Advanced Nursing* 2008;**63**:634-643.

Black N. Why we need qualitative research. *Journal of Epidemiology and Community Health* 1994;**48**:425-426.

Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. *Value Health* 2008;**11**:44-47.

Darkow T, Henk HJ, Thomas SK, Feng W, Baladi JF, Goldberg GA, Hatfield A, Cortes J. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukemia. *Pharmacoeconomics* 2007;**49**:22-30.

Delamater AM. Improving patient adherence. *Clinical Diabetes* 2006;**24**:71-77.

Dezentjé VO, van Blijderveen NJ, Gelderblom H, Putter H, van Herk-Sukel MP, Casparie MK, et al. Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. *Journal of Clinical Oncology* 2010;**28**(14):2423-2429.

Doti C, Stemmelin G, Shanley C, et al. Cytogenetic response in relation to the adherence to treatment with Imatinibmesylate: a case control study. *Blood* 2007;**110**(11):4553.

Doti C, Stemmelin G, Shanley C, Ceresetto J, Rabinovicj O, Moiraghi B, Flores MG, Garcia JJ, Bullorsky E. Cytogenetic response in relation to the adherence to treatment with imatinibmesylate: a case control study. *Blood* 2007;**110**:4553.

Doti CA, Stemmelin G, Moiraghi EB, Flores MG, Garcia JJ, Murro H, Bullorsky EO. Adherence to imatinibmesylate treatment: two years follow up. *Blood* 2008;**112**:4267.

Doggrell S. Adherence to oral endocrine treatments in women with breast cancer: can it be improved? *Breast Cancer Research and Treatment* 2011;**129**:299-308.

Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *The New England Journal of Medicine* 2006;**355**(23):2408-2417.

Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leukemia Research* 2011;**35**:626-630.

European Group for Blood and Marrow Transplantation Swiss Nurses Working Group. (2011) Adherence to oral anti-tumor therapies.

Fallowfield L, Atkins L, Catt S, Cox A, Coxon C, Langridge C, Morris R, Price M. Patients' preferences for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Annals of Oncology* 2006;**17**:205-210.

Feng W, Henk H, Thomas S, Baladi J, Hatfield A, Goldberg GA, Cortes J. Compliance and persistency with imatinib. *Journal of Clinical Oncology* 2006;**24**:6038.

Fontein D, Nortier J, Liefers G, Putter H, Kranenbarg E, van den Bosch J, Maartense E, Rutgers E, van de Velde C. High non-compliance in the use of letrozole after 2,5 years of extended adjuvant endocrine therapy. Results from the IDEAL randomized trial. *The Journal of Cancer Surgery* 2012;**38**:110-117.

Foulon V, Schöffski P, Wolter P. Patient adherence to oral anticancer drugs: an emerging issue in modern oncology. *Acta Clinica Belgica* 2011;**66**(2):85-96.

Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S, et al. Non-adherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *American Journal of Hematology* 2011;**86**(6):471-474.

Gebbia V, Bellavia M, Banna GL, Russo P, Ferraù F, Tralongo P, Borsellino N. Treatment monitoring program for implementation of adherence to second-line erlotinib for advanced non-small cell lung cancer. *Clinical Lung Cancer* 2013;**2013**:390-398.

Gebbia V, Bellavia G, Ferraù F, Valerio MR. Adherence, compliance and persistence to oral antineoplastic therapy: a review focused on chemotherapeutic and biologic agents. *Expert Opinions on Drug Safety* 2011;**11**(S1):S49-59.

Gralow J, Ozols RF, Bajorin DF, Cheson BD, Sandler HM, Winer EP, Bonner J, Demetri GD, et al. Clinical cancer advances 2007: major research advances in cancer treatment, prevention, and screening—a report from the American Society of Clinical Oncology. *Journal of Clinical Oncology* 2008;**26**:313-325.

Griffin E. Safety considerations and safe handling of oral chemotherapy agents. *Clinical Journal of Oncology Nursing* 2003;**7**(6, Suppl.), 25–29.

Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling*2005;**59**:97-102.

Grypdonck M. (1999). *Het leven boven de ziekte uittillen. De opdracht van de Verpleegkunde en de Verplegingswetenschap voor chronisch zieken.* Amsterdam: SMD.

Güth U, Huang DJ, Schötzau A, Zanetti-Dällenbach R, Holzgreve W, Bitzer J, Wight E. Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. *British Journal of Cancer* 2008;**99**:428-433.

Güth U, Myrick ME, Kilic N, Eppenberger-Castori S, Schmid SM. Compliance and persistence of endocrine adjuvant breast cancer therapy. *Breast Cancer Research and Treatment* 2012;**131**:491-499.

Halpern R, Barghout V, Williams D, Compliance with imatinibmesylate associated with lower health resource utilization and costs for patients with CML and GIST. *Blood* 2007;**110**:5159.

Haynes RB, Taylor DW, Sacket DL.(1979) Compliance in healthcare: Johns Hopkins University Press.

Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *Journal of Clinical Oncology* 2012;**30**:936–942.

Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai W, Fehrenbacher L, Gomez SL, Miles S, Neugut AI. Early discontinuation and non-adherence to adjuvant hormonal therapy in a cohort of 8769 early-stage breast cancer patients. *Journal of Clinical Oncology* 2010a;**28**(27):4120-4128.

Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, Kwan M, Gomez SL, Neugut AI. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Research and Treatment* 2010b;**126**:529-537.

Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Annals of Pharmacotherapy* 2006;**40**:1280-1288.

Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;**119**:3028-3035.

Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006;**130**:65S-72S.

Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a measurement tool for audit and research. *International Journal for Quality in Healthcare* 2001;**10**:135-140.

Huiart L, Bouhnik A, Rey D, Tarpin C, Cluze C, Bendiane MK, Viens P, Giorgi R. Early discontinuation of tamoxifen intake in younger women with breast cancer: Is it time to rethink the way it is prescribed? *European Journal of Cancer* 2012;**11**:1939-1946.

Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood* 2011;**117**(14):3733–3736.

Institute of Medicine.(2004). Health literacy: a prescription to end confusion. Washington, DC: National Academies Press.

Jasti S, Siega-Riz AM, Cogswell ME, Hartzema AG. Correction for errors in measuring adherence to prenatal multivitamin/mineral supplement use among low-income women. *Journal of Nutrition* 2006;**136**:479-483.

Kahn KL, Schneider EC, Malin JL, Adams JL, Epstein AM. Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Medical Care* 2007;**45**:431-439.

Kavookjian J, Wittayanukorn S. Interventions for adherence with oral chemotherapy in hematological malignancies: a systematic review. *Research in Social and Administrative Pharmacy* 2014 [In press].

Khandelwal N, Duncan I, Ahmed T, Rubinstein E, Pegus C. Oral chemotherapy program improves adherence and reduces medication wastage and hospital admissions. *Journal of the National Comprehensive Cancer Network* 2012;**10**:618-625.

Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *Journal of Clinical Oncology* 2009;**27**(21):3445-51.

Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clinical Breast Cancer* 2008;**8**(2):155-161.

Kutner M, Greenberg E, Jin Y, Paulsen C, White S. The health literacy of America's adults: results from the 2003 National assessment of adult literacy. Washington, DC: National Center for Education Statistics: US Department of Education, 2006.

Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course.*Breast Cancer Research and Treatment* 2006;**99**(2):215-20.

Lebovits AH, Strain JJ, Schleifer SJ, Tanaka JS, Bhardway S, Messe MR. Patient noncompliance with self-administered chemotherapy. *Cancer* 1990;**65**:17-22.

Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. *Journal of Clinical Oncology* 1987;**5**(9):1469-1476.

Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *Journal of Clinical Oncology* 1997;**15**:110-115.

Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *Journal of Clinical Oncology* 2010;**28**:2381-2388.

Marques PAC, Pierin AMG.Factors that affect cancer patient compliance to oral anti-neoplastic therapy. *ActaPaulista de Enfermagem* 2008;**21**(2):323-329.

Marteau TM, Johnston M. Health professionals: a source of variance in health outcomes. *Psychology & Health* 1991;**5**:47-58.

Mathes T, Sunya-Lee A, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: A systematic review. *Cancer Treatment Reviews* 2014;**40**(1):102-108.

Moody M, Jackowski J. Are patients on oral chemotherapy in your practice setting safe? *Clinical Journal of Oncology Nursing* 2010;**14**:339-346.

Moon JH, Sohn SK, Kim SN, et al. Patient counseling program to improve the compliance to imatinib in chronic myeloid leukemia patients. *Medical Oncology* 2012;**29**(2):1179-1185.

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care* 1986;**24**(1):67-74.

Morse J, Field PA. (1996). Nursing Research. The application of qualitative approaches. Cheltenham UK: Stanley Thornes (Publishers) Ltd.

Nekhlyudov L, Li L, Ross-Degnan D, Wagner AK. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. *Breast Cancer Research and Treatment* 2011;**130**:681-689.

Neugut AI, Subar M, Wilde ET, Stratton S, Brouse CH, Hillyer GC, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *Journal of Clinical Oncology* 2011;**29**(18-):2534-42.

Ngoh LN. Health literacy: a barrier to pharmacist-patient communication and medication adherence. *Journal of American Pharmacists Association 2003;***49**(5):e132–46;quiz e147–9.

Nguyen T-M-U, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring? A systematic review. *British Journal of Clinical Pharmacology* 2014;**77**(3):427-445.

Noens L, van Lierde MA, Bock R, Verhoef G, Zachèe P, Benerman Z. Prevalence, determinants and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* 2009;**113**:5401-5411.

Osterberg L, Blaschke T. Adherence to medication. *The New England Journal of Medicine* 2005;**353**(5):487-497.

Owusu C, Buist DS, Field TS, Lash TL, Thwin SS, Geiger AM, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. *American Society of Clinical Oncology* 2008;**26**(4):549-555.

Ozols RF, Herbst RS, Colson YL, Gralow J, Bonner J, Curran Jr WJ, Eisenberg BL, Ganz PA, et al. Clinical cancer advances 2006: major research advances in cancer treatment, prevention, and screening – a report from the American Society of Clinical Oncology. *Journal of Clinical Oncology* 2010;**25**:146-162.

Paley M, Love N, Carlson R, Tripathy D, Kaderman R, Paley D, Dvorkin J, Ziel K. Preferences for oral, parenteral antitumor therapy: a survey of 260 patients with metastatic breast cancer. *Journal of Clinical Oncology* 2005;**23**(16s):619.

Parker R, Ratzan SC. Health literacy: a second decade of distinction for Americans. *Journal of Health Communication* 2010;**15**(2):20-33.

Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology* 2003;**21**(4):602-606.

Pellegrini I, Sarradon-Eck A, Soussan PB, Lacour A-C, Largillier R, Tallet A, et al. Women's perceptions and experience of adjuvant tamoxifen therapy account for their adherence: brest cancer patients' pint of view. *Psycho-Oncology* 2010;**19**:472-479.

Pfeiffer P, Mortensen JP, Bjerregaard B, Eckhoff L, Schønnemann K, Sandberg E, Aabo K, Jakobsen A. Patient preference for oral or intravenous chemotherapy: a randomized cross-over trial comparing capecitabine and Nordic fluorouracil/leucovorin in patients with colorectal cancer. *European Journal of Cancer* 2006;**42**:2739-2743.

Regnier Denois V, Poirson J, Nourissat A, Jacquin J-P, Guastalla JP, Chauvin F. Adherence with oral chemotherapy: results from a qualitative study of the behavior and representations of patients and oncologists. *European Journal of Cancer Care* 2010;**20**:520-527.

Richardson JL, Shelton DR, Krailo M, et al. The effect of compliance with treatment on survival among patients with hematologic malignancies. *Journal of Clinical Oncology* 1990;**8**(2):356-364.

Royal Pharmaceutical Society of Great Britain. From compliance to concordance: towards shared goals in medicine taking. London: RPS, 1997.

Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA: Cancer Journal for Clinicians* 2009;**59**(1):56-66.

Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Research and Treatment* 2011;**125**(1):191-200.

Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health Quality Life Outcomes* 2010;**8**(99).

Sikka R, Xia F, Aubert RE. Estimation medication persistency using administrative claims data. *The American Journal of Managed Care* 2005;**11**:449-457.

Simons S, Ringsdorf S, Braun M, et al. Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. *Support Care Cancer* 2011;**19**(7):1009-1018.

Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA.A meta-analysis of the association between adherence to drug therapy and mortality. *British Medical Journal* 2006;**333**:15-20.

Staddon A. Challenges of ensuring adherence to oral therapy in patients with solid malignancies. *Community Oncology* 2011;**8**(6):254-262.

StCharles M, Bollu VK, Hornyak E, Coombs J, Blanchette CM, De Angelo DJ. Predictors of treatment non-adherence in patients treated with imatinibmesylate for chronic myeloid leukemia. *Blood* 2009;**14**:2209.

Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *Journal of Oncology Practice* 2011,**7**(3S):46s-51s.

Tsang J, Rudychev I, Pescatore SL. Prescription compliance and persistency in chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST) patients on imatinib. *Journal of Clinical Oncology* 2006;**24**:6119.

Tschida SJ, Aslam S, Lal LS, et al. Outcomes of a specialty pharmacy program for oral oncology medications. *The American Journal of Pharmacy Benefits* 2012;**4**(4):165-174.

van den Brink R, Timmermans H, Havers J, van Veenendaal H. (2013). *Ruimte voor regie – Pioniers over zelfmanagement in de zorg.* Alphen aan den Rijn: Vakmedianet Management B.V.

Van Herk-Sukel M, van de Poll-Franse L, Voogd A, Nieuwenhuijzen G, Coebergh JW, Herings R. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis. *Breast Cancer Research and Treatment* 2010;**122**:843-851.

van Meijel B, Gamel C, van Swieten-Duijfjes B, Grypdonck MHF. The development of evidence-based nursing interventions: methodological considerations. *Journal of Advanced Nursing* 2004;**48**(1):84-92.

Valente Teixeira F, Pais-Ribeiro JL, Pinho da Costa Maia ÂR. Beliefs and practices of healthcare providers regarding obesity: a systematic review. *Revista da Associação Médica Brasileira*2012;**58**:254-262.

Wagner JH, Justice AC, Chesney M, Sin-clair G, Weissman S, Rodriguez-Barradas M. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. *Journal of Clinical Epidemiology* 2001;**54**:Suppl 1:S91-S98.

Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology* 1993;**11**:1189-1197.

Weingart SN, Brown E, Bach PB, Eng K, Johnson SA, Kuzel TM, Langbaum TS, Leedy D, et al. NCCN task force report: oral chemotherapy. *Journal of National Comprehensive Cancer Network* 2008;**6**(Suppl. 3):S1-S14.

Winer E, Gralow J, Diller L, Karlan B, Loehrer P, Pierce L, Demetri G, Ganz P, et al. Clinical cancer advances 2008: major research advances in cancer treatment, prevention, and screening—a report from the American Society of Clinical Oncology. *Journal of Clinical Oncology* 2009;**27**:812-826.

World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva: WHO, 2003.

Wu EQ, Johnson S, Beaulieu N, Arana M, Bollu V, Guo A. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Current Medical Research and Opinion* 2010;**26**:61-69.

Wuensch P, Hahne A, Haidinger R, Meiβler K, Tenter B. Discontinuation and non-adherence to endocrine therapy in breast cancer patients: is lack of communication the decisive factor? *Journal of Cancer Research and Clinical Oncology* 2015;**141**:55-60.

CHAPTER 2

DETERMINANTS AND ASSOCIATED FACTORS INFLUENCING MEDICATION ADHERENCE AND PERSISTENCE TO ORAL ANTICANCER DRUGS: A SYSTEMATIC REVIEW

Based on the article of Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treatment Reviews* 2013; **39**(6): 610-621.

ABSTRACT

Background and aims

The use of oral anticancer drugs has increased in modern oncology treatment. The move from intravenous treatments towards oral anticancer drugs has increased the patients' own responsibility to take oral anticancer drugs as being prescribed. High rates of non-adherence to oral anticancer drugs have been reported. A systematic literature review was conducted to gain insight into determinants and associated factors of non-adherence and non-persistence in patients taking oral anticancer drugs.

Review methods

PubMed, Cochrane, Web of Science and Cinahl were systematically searched for studies focusing on determinants and associated factors of medication non-adherence and non-persistence to oral anticancer drugs. The methodological quality of the included studies was assessed by two independent reviewers. No studies were excluded based on the quality assessment.

Results

Twenty five studies were included and systematically reviewed. The quality of the studies was moderate. Associated factors influencing medication non-adherence and non-persistence to oral anticancer drugs are multifactorial and interrelated. Older and younger age, and the influence of therapy related side effects were found to be predominant factors.

Conclusion

Non-adherence and non-persistence to oral anticancer drug therapy are complex phenomena. More qualitative research is needed to facilitate the development of patient tailored complex interventions by exploring patients' needs and underlying processes influencing medication non-adherence and non-persistence to oral anticancer drugs.

INTRODUCTION

The use and the number of different oral anticancer drugs (OACD) have increased in modern oncology (Banna et al., 2010). Currently, 25% of the cancer chemotherapy in development can be taken orally (Banna et al., 2010). Many of the available OACD are primarily cytostatic in nature and most effective when given over long-term periods (Foulon et al., 2011). OACD such as imatinib, has transformed chronic myeloid leukemia (CML) from a lethal to a chronic disease (Eliasson et al., 2011). The use of OACD improves the quality of life of cancer patients by reducing hospital stay and give them a greater sense of control over their treatment while guaranteeing the treatment efficacy (Regnier Denois et al., 2010), however, also poses important challenges such as managing side effects, the prolonged treatment period and adherence issues.

Several studies show that most patients (range 54% to 89%) prefer to be on an oral therapy compared to intravenous therapy (Liu et al., 1997; Paley et al., 2005; Fallowfield et al., 2006; Wojtacki et al., 2006); this mainly because medication can be taken at home and no needle has to be placed (Liu et al., 1997; Fallowfield et al, 2006; Simchowitz et al., 2010). The shift from intravenous treatments towards OACD therapy increases patients' responsibility to take their OACD rigorously as being prescribed by their physician (Foulon et al., 2011). Because of the association between adherence and treatment success, concerns about non-adherence to OACD therapy have become an increasingly important issue in oncology (Partridge et al., 2002; Foulon et al., 2011; Gebbia et al., 2011).

Until now, multiple definitions of medication (non-)adherence exist (Cramer et al., 2008; Ruddy et al., 2009) but there is no universally accepted definition (Gebbia et al., 2011). For this review, non-adherence has been operationalized based on the definition by Ruddy et al. (2009), who consider a patient to be non-adherent if "doses are missed, extra doses are taken or doses are taken in the wrong quantity or at the wrong time". This definition was chosen because of its concreteness. Non-persistence occurs when patients "do not take their

medication as long as prescribed" (Ruddy et al., 2009). The terms non-persistence and early discontinuation are used interchangeably in the literature.

A literature review by Foulon et al. (2011) reports on OACD therapy non-adherence rates between 0% and 84%. The variation is mainly related to (1) differences in the type of OACD therapy (e.g. side effects, complexity of regimen), (2) differences in the definition of adherence being applied in the primary studies, and (3) differences in the assessment of medication adherence. OACD therapy non-adherence rate in breast cancer patients was found to be as high as 23% over a one year period (Sedjo and Devine, 2011). Treatment discontinuity was found in 17% of the patients after two years (Fink et al., 2004); and even in 31% after five years (Lash et al., 2006). Marin et al. (2010) reported that 26.4% of the CML patients was ≤ 90% adherent with their prescribed OACD therapy. Similar results have been found in a Belgian setting (Noens et al., 2009). One third of the patients with CML appeared to be non-adherent with their treatment; only 14.2% was found to be completely adherent (Noens et al., 2009).

Non-adherence and non-persistence significantly reduce the efficacy of OACD therapies (Foulon et al., 2011). Non-adherent patients with CML, treated with the OACD imanitib, were less likely to achieve complete cytogenetic responses (CCyR), resulting in a reduced success rate (Marin et al., 2010; Ganesan et al., 2011; Ibrahim et al., 2011). In the study by Noens et al. (2009), patients taking 74.0% to 76.8% of the prescribed dose had a less good response than patients taking 89.9% to 92.7% of the prescribed dose. In breast cancer patients, lower survival rates were found for patients being < 80% adherent to the oral drug tamoxifen (McCowan et al., 2008). Non-adherence to OACD therapy was also related to higher healthcare costs due to the increased number of doctor visits, longer hospital stays and more frequent hospitalizations (Darkow et al., 2007; Wu et al., 2010).

Given the magnitude and consequences of non-adherence in patients on an OACD therapy, an exploration of associated factors and underlying processes of medication non-adherence is needed. Factors influencing medication non-

adherence and non-persistence are complex due to the multifactorial and interrelated character (WHO, 2003). Understanding the complexity of non-adherence and non-persistence to OACD is important as it can inform the development of an intervention to enhance adherence and persistence with this type of medication. A literature review is therefore a crucial step in the development of such interventions (Van Meijel et al., 2004).

Literature reviews on medication non-adherence or non-persistence with OACD therapy are often not conducted and/or reported in a rigorous systematic way (Ruddy et al., 2009; Moore, 2010; Foulon et al., 2011). To our knowledge, only one systematic review including literature up until 2002 on non-adherence and non-persistence in patients taking OACD, has been conducted (Partridge et al., 2002). In the latter review different OACD have been considered.

The aim of our review is to provide an updated overview of determinants and associated factors of medication (non-)adherence and (non-)persistence in patients taking different types of OACD.

METHODS

Search strategy

Four electronic databases were searched: PubMed, the Cochrane database, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy consisted of MeSH terms and free text words subsequently combined (see table 1).

All titles and abstracts were screened independently by two reviewers (MV & KL). If the abstract did not provide enough information to decide upon inclusion/exclusion, the full paper was retrieved for further screening. Disagreements about inclusion or exclusion were discussed between the reviewers until consensus was reached. The reference lists of the included articles were reviewed and additional articles were considered if appropriate.

Selection criteria

Articles were included if they addressed OACD therapy, focused on determinants and associated factors of medication adherence/compliance and/or medication persistence of patients aged 18 and older, and were evaluated as being of strong or moderate methodological quality. Factors considered to evaluate methodological quality for quantitative studies were: the presence of selection bias, allocation bias, confounders, study design, blinding, data collection methods, withdrawals and drop-outs, and the appropriateness of the analysis to the research question (Vyncke et al., 2013). For qualitative studies, methodological quality was evaluated considering clear statement of the aims, the relationship between researcher and participants, ethical issues, rigorousness of the data analysis, clear statements of the findings, value of the study, appropriate methodology, design, recruitment strategy and data collection (Public Health Resource Unit, 2006).

The primary outcomes of the primary studies had to be (non-)adherence and (non-)persistence to OACD therapy to be eligible for inclusion. Only original research articles published between 1990 and April 2012 and written in English, French, German or Dutch were included. Study design was not used as a selection criterion. Studies conducted in developing countries were excluded because of the different context and differences in healthcare delivery systems.

Quality assessment

The methodological quality of each study was independently evaluated by two reviewers (MV & KL) using (1) the Quality Assessment Tool developed by Vyncke et al. (2013) for quantitative studies, and (2) the Critical Appraisal Skills Programme (CASP) developed by the Public Health Resource Unit, National Health Service, England (2006) for qualitative studies.

The Quality Assessment Tool of Vyncke et al. (2013) is based on a tool developed by the Effective Public Health Practice Project (Thomas et al., 2004) and used by Mirza et al. (2007). This tool was chosen because of (1) the extensiveness of the assessment of methodological quality and, (2) the usability

for quality assessment of different quantitative research designs. The tool considers presence of selection bias and confounders, study design, blinding, data collection methods, withdrawals and drop-outs, appropriateness of the analysis to the research question, and the integrity of the intervention. The item on integrity of the intervention was not applicable for this review. For each item, two reviewers (MV & KL) assigned a rating of strong, moderate or weak based on the evaluation criteria of the quality assessment tool. Discrepancies in the reviewers' evaluations were discussed until consensus was reached.

The CASP includes 10 questions to assess (1) rigorousness, (2) credibility and, (3) relevance of the qualitative study by answering yes/no for each question. The first two questions are general screening questions considering whether the goal of the study is clear, and whether a qualitative methodology is appropriate for the study. When both questions are positively answered, it is worth proceeding to the remaining detailed questions to consider methodological quality (Public Health Resource Unit, 2006).

Data abstraction and synthesis

Two reviewers (MV and KL) independently extracted the data from each article. Findings were summarized using a data extraction sheet (table 2). This sheet included the following items: author(s) and publication date, research focus, design, the definition of medication non-adherence and non-persistence, measurement, participants (n), factors associated with medication non-adherence or higher adherence, and factors associated with medication non-persistence or higher persistence. Inconsistencies in data extraction were discussed until consensus was reached.

RESULTS

Selection of the articles

The literature search resulted in 3351 articles. Duplicates (n=485) were excluded. Based on the selection criteria, 85 full texts were retrieved and reviewed; resulting in 25 articles for inclusion. No relevant articles were added

after reviewing the reference list of the included articles. A flow chart of the search strategy is presented in figure 1.

Methodological quality of the included studies

Details on the quality assessment of the included studies are presented in table 3 for studies with a quantitative approach, and in table 4 for studies with a qualitative or mixed method approach. In general, the overall methodological quality of the quantitative studies was moderate. None of the studies mentioned the influence of confounders on the results. For all studies, the method for the assessment of medication adherence was clearly indicated. Few studies reported on power calculations (n=1) (Noens et al., 2009) and on how they handled missing data (n=1) (Lebovits et al., 1990) and drop-outs (n=2) (Güth et al., 2008; Kirk and Hudis, 2008). None of the studies with a qualitative design adequately described the relationship between researcher and participants. However, the methodology, design, and data collection were evaluated as being appropriate. Consequently, none of the studies were excluded after considering methodological quality.

Study characteristics

An overview of the study characteristics, determinants and factors associated with medication (non-)adherence and (non-)persistence to OACD therapy is presented in Table 2.

Different study designs were used: retrospective study designs (n=12), prospective study designs (n=6), cross-sectional study designs (n=5), a qualitative study design (n=1), and a mixed method design (n=1). Sample size ranged from small studies (n=21) to large studies (n=13593). The majority of the studies (n=17) were conducted in the United States of America. The remaining studies were conducted in Europe (n=7) and Brazil (n=1).

Eleven studies focused on medication (non-)adherence, nine studies on medication (non-)persistence or early discontinuation and five studies on both (non-)adherence and (non-)persistence with OACD. Most of the studies (n=20) focused on patients with breast cancer and often included a secondary

characteristic (age, stage of the disease or a combination of both). The other studies focused on (non-)adherence and (non-)persistence in patients with CML (n=3), and in patients with different types of cancer (n=2).

Definition and assessment of medication (non-)adherence and (non-)persistence

A wide variation was found regarding the criteria for defining medication (non-)adherence and (non-)persistence and methods for assessment.

Criteria used for defining medication non-adherence were taking less (< 80% [Partridge et al., 2003; Partridge et al., 2010], < 90% [Lebovits et al., 1990; Eliasson et al., 2011], < 100% [Kirk and Hudis, 2008]) or more of the prescribed dose (> 110% [Lebovits et al., 1990]), lower scores on the Medication Adherence Report Scale (MARS-5) (Grunfeld et al., 2005), having a Medication Possession Ratio (MPR) ≤ 80% (Kimmick et al., 2009; Hershman et al., 2010; Nekhlyudov et al., 2011; Neugut et al., 2011; Sedjo and Devine, 2011), having ≤ 3 points on the Morisky and Green Test (Marques and Pierin, 2008), or having ≥ 1 positive answer on the Basel Assessment of Adherence Scale (Noens et al., 2009). The definition of medication non-persistence included different cut-off rates in number of days with a discontinued intake of OACD (≥ 30 [Darkow et al., 2007], ≥ 45 [Neugut et al., 2011], ≥ 60 days [Owusu et al., 2008; Nekhlyudov et al., 2011] and ≥ 180 days [Barron et al., 2007; Hershman et al., 2010).

The methods used to assess medication adherence and persistence in patients taking OACD were pharmacy refill data extracted from pharmacy records and medical claims (n=11) (Partridge et al., 2003; Barron et al., 2007; Darkow et al., 2007; Kirk and Hudis, 2008; Ma et al., 2008; Owusu et al., 2008; Kimmick et al., 2009; Nekhlyudov et al., 2011; Neugut et al., 2011; Sedjo and Devine, 2011; Streeter et al., 2011), self report (n=10) (Demissie et al., 2001; Fink et al., 2004; Grunfeld et al., 2005; Atkins and Fallowfield et al., 2006; Lash et al., 2006; Kahn et al., 2007; Güth et al., 2008; Kirk and Hudis, 2008; Marques and Pierin, 2008; Regnier Denois et al., 2010) or a combination of both (n=2) (Lebovits et al., 1990; Noens et al., 2009). Only two studies used a Medication Event Monitoring System (MEMS) (Eliasson et al., 2011; Partridge et al., 2010), an electronic monitoring system to compile the dosing histories, including one study using a

combination of MEMS and self report. No objective methods such as biological markers were used in the included studies.

Determinants and associated factors of medication (non-)adherence and (non-)persistence to oral anticancer drugs

This review shows that (non-)adherence and (non-)persistence to OACD therapy are influenced by different factors (see table 2). A distinction is made between factors influencing medication (non-)adherence and factors influencing medication (non-)persistence. Determinants and associated factors of (1) (non-)adherence and (non-)persistence and (2) higher adherence and higher persistence will be structured according to the five categories suggested by the World Health Organization (WHO, 2003) framework of factors influencing medication adherence.

Patient- related factors

Several patient-related factors were found to be associated with medication non-adherence in patients taking OACD. They can be divided into intentional non-adherence and unintentional non-adherence. Lower perceived necessity by the patient for taking the drug (n=1) (Grunfeld et al., 2005), perception of no benefit to be gained from taking the drug (n=1) (Grunfeld et al., 2005), concerns about symptoms (n=1) (Noens et al., 2009), the opinion that missing a dose makes no difference (n=1) (Eliasson et al., 2011), and lower perceived quality of life (n=1) (Eliasson et al., 2011) were found as intentional patient-related factors associated with medication non-adherence in patients on an OACD therapy. Forgetting (n=2) (Kirk and Hudis, 2008; Eliasson et al., 2011) and accidentally taking too much of the prescribed drug (n=1) (Eliasson et al., 2011) were found to be the most common patient-related factors being associated with unintentional medication non-adherence. Self-efficacy (n=1) (Noens et al., 2009) and the belief that medication intake as being prescribed would help to cure from cancer (n=1) (Grunfeld et al., 2005) were reported as important patient-related factors associated with higher adherence to OACD therapy. Having neutral or negative beliefs about the value of the drug (n=1) (Fink et al., 2004) was found to be a patient-related factor associated with non-persistence.

Therapy-related factors

Treatment related side effects are the most frequently reported therapy-related factors associated with non-adherence to OACD therapy (n=5) (Grunfeld et al., 2005; Atkins and Fallowfield, 2006; Kirk and Hudis, 2008; Regnier Denois et al., 2010; Eliasson et al., 2011). The study by Grunfeld et al. (2005) reported that 46% of the non-adherent breast cancer patients mentioned side effects as primary reasons for non-adherence to tamoxifen. The main side effects reported were hot flashes (32%), night sweats (24%), concentration or memory difficulties (22%), sleep problems (16%), emotional problems (anxiety, panic, depression; 15%), weight gain (15%), and loss of libido (12%). Treatment related side effects were also reported as the primary reason (70%) for medication non-adherence in the study by Kirk and Hudis (2008). OACD side effects were not associated with a specific type of drug in this study. Atkins and Fallowfield (2006) found also a significant association (p=0.001) between disliked aspects (e.g. side effects, difficulties swallowing tablets and inconvenience) of oral anti-tumoral medication in breast cancer patients (e.g. side effects) and non-adherence. Treatment related side effects were also reported as underlying factors for non-adherence in the two qualitative studies.[3;4] One of these two studies focused on CML patients (Eliasson et al., 2011) and the other study focused on different types of cancer (metastatic breast, metastatic colon, and adjuvant colon) (Regnier Denois et al., 2010).

Other therapy-related factors of medication non-adherence included longer duration of therapy (n=3) (Partridge et al., 2003; Marques and Pierin, 2008; Noens et al., 2009), having a mastectomy rather than breast-conserving treatment (n=2) (Partridge et al., 2003; Partridge et al., 2010), starting with a higher dose of OACD (n=2) (Darkow et al., 2007; Noens et al., 2009), changed doses (n=1) (Eliasson et al., 2011), type of drug (mercaptopurine, dexamethasone, thalidomide, and hormone therapy drugs) (n=1) (Marques and Pierin, 2008), having a lumpectomy (n=1) (Hershman et al., 2010), and variation in timing for medication intake (e.g. before or after meals) (n=1) (Regnier Denois et al., 2010).

Side effects (n=3) (Demissie et al., 2001; Lash et al., 2006; Kahn et al., 2007), increased number of prescriptions (n=3) (Barron et al., 2007; Neugut et al., 2011; Streeter et al., 2011), having a mastectomy rather than breast-conserving surgery (lumpectomy) and radiation (n=1) (Ma et al., 2008), and the type of drug (imatinib, sorafinib, sunitinib, erlotinib, lapatinib versus capecitabine) (n=1) (Streeter et al., 2011) were associated with non-persistence in patients taking OACD. Having a lumpectomy rather than having a mastectomy (n=1) (Hershman et al., 2010) was found to be associated with higher non-persistence in one study.

Having a higher number of medication prescriptions at baseline was found to be associated with higher persistence in one study (Lash et al., 2006). Women needing to take more medications during follow-up were more likely to discontinue the OACD therapy. Longer intervals between two prescriptions (n=1) (Hershman et al., 2010), more medications to be taken daily (n=1) (Lash et al., 2006), and patients who had radiotherapy before (n=1) (Hershman et al., 2010) were factors associated with higher medication persistence in patients on an OACD therapy.

Disease-related factors

Co-morbidities (n=2) (Hershman et al., 2010, Sedjo and Devine, 2011), unknown tumor size (n=1) (Hershman et al., 2010), and having a node-positive disease (n=1) (Partridge et al., 2010) were associated with medication non-adherence in patients on an OACD therapy. However, co-morbidities were also found to be associated with higher persistence in one study (Kimmick et al., 2009).

Disease-related factors associated with non-persistence to OACD were similar to those associated with non-adherence. However, other factors associated with medication non-persistence were history of antidepressant use (n=1) (Barron et al., 2007), ductal pathology (n=1) (Ma et al., 2008) and negative and unknown hormone receptor status (n=1) (Kahn et al., 2007).

Healthcare system factors

Shorter duration of treatment follow-up visits (n=1) (Noens et al., 2009), prescribing errors (n=1) (Eliasson et al., 2011), and conflicting information regarding consequences (n=1) (Eliasson et al., 2011) were associated with non-adherence in patients on an OACD therapy. Different doctors responsible for follow-up (n=1) (Kahn et al., 2007), and follow-up by a primary physician rather than an oncologist (n=2) (Güth et al., 2008; Neugut et al., 2011) were associated with medication non-persistence in patients taking OACD. Not previously being informed about side effects (n=1) (Kahn et al., 2007), less patient participation in decision making than wanted (n=1) (Kahn et al., 2007), and receiving too much or too less support than needed (n=1) (Kahn et al., 2007) were also factors associated with medication non-persistence in these patients.

Enhanced knowledge of the disease and treatment (n=1) (Noens et al., 2009), having consulted an oncologist in the year before beginning tamoxifen therapy (n=1) (Partridge et al., 2008), longer duration of the first visit with a patient newly diagnosed with CML (n=1) (Noens et al., 2009), and physicians' higher number of CML patients seen in the past year (n=1) (Noens et al., 2009) were associated with higher medication adherence in patients taking OACD.

Social and economic factors

Younger age (n=3) (Partridge et al., 2003; Atkins and Fallowfield, 2006; Sedjo and Devine, 2011), older age (n=3) (Partridge et al., 2003; Noens et al., 2009; Neugut et al., 2011), and higher out-of-pocket costs (n=3) (Kirk and Hudis, 2008; Neugut et al., 2011; Sedjo and Devine, 2011) were associated with non-adherence in patients taking OACD. Younger age was defined as ≤45 (Partridge et al., 2003; Sedjo and Devine, 2011), older age as ≥85 (Partridge et al., 2003), and higher out-of-pocket costs as ≥$30 (Sedjo and Devine, 2011). A higher educational level (n=1) (Noens et al., 2009) was associated with higher adherence in patients taking OACD.

Older age (n=6) (Barron et al., 2007; Kahn et al., 2007; Owusu et al., 2008; Hershman et al., 2010; Nekhlyudov et al., 2011; Neugut et al., 2011) was also

found to be associated with lower persistence of the OACD treatment. Higher out-of-pocket costs (n=2) (Neugut et al., 2011; Streeter et al., 2011), younger age (n=2) (Ma et al., 2008; Hershman et al., 2010), lower income (n=2) (Nekhlyudov et al., 2011; Streeter et al., 2011), and female gender (n=1) (Darkow et al., 2007) were also influencing medication non-persistence. Married status was found to be associated with higher persistence (n=1) (Hershman et al., 2010).

DISCUSSION

The aim of this review was to determine factors associated with medication (non-)adherence and (non-)persistence in patients taking OACD. This review suggests that (non-)adherence and (non-)persistence in this patient group is multi-factorial, complex and influenced by patient-related, therapy-related, disease-related, healthcare system and social-economic factors. However, generalizations require caution as the included studies used different definitions, methods for assessing medication adherence, and cut-off rates for defining medication adherence.

Methodological quality of the included studies

In general, methodological quality of the included studies was moderate. No studies were excluded after considering methodological quality. The most common methodological limitations were the absence of clear data on withdrawals or drop-out, the absence of a power calculation, and not taking into account possible confounders in the analysis. Further, the self-report questionnaires used in the included studies to assess medication non-adherence were often self-constructed and not always tested for validity and reliability. Only in a few studies, validated self-report questionnaires were used (Grunfeld et al., 2005; Marques and Pierin, 2008; Noens et al., 2009). Future studies need to address these issues, as they can influence the validity of the study findings.

Study characteristics

Twelve studies used a retrospective study design. This design has several limitations: (1) it often only includes data that are necessary for administrative statistical purposes (Güth et al., 2008), (2) it is often limited to specific patient populations and thus findings from these studies may have limited generalizability, and (3) it cannot report on unintentional non-adherence. Causal relationships between non-adherence or non-persistence and determinants of medication non-adherence can also not be detected by using a retrospective design.

In studies with a cross-sectional (n=5) or prospective study design (n=6), the risk of a sample bias has to be considered due to the voluntary character of study participation (Mann et al., 2003). Prospective study designs are more appropriate to study determinants of medication non-adherence or non-persistence in patients taking OACD than cross-sectional designs due to the longitudinal character (Noens et al., 2009). One study used a qualitative approach and one study a mixed method approach. It seems that qualitative study designs are scarce in our review and in adherence research. This is remarkably as qualitative study designs possess the ability to apprehend an overall view of underlying factors and processes associated with medication non-adherence or non-persistence in order to explain these phenomena (Black, 1994). Qualitative research is essential and more appropriate to explore the influence of interpersonal relation aspects in medication adherence and persistence with OACD. These aspects have been identified as important factors influencing medication adherence in other pathologies, but are underexplored in the included studies (Vervoort et al., 2007; Stavropoulou, 2011; Van Hecke et al., 2011).

Definition and assessment of medication (non-)adherence and (non-)persistence

To date there is no universally accepted definition of medication adherence nor an appropriate method to optimally assess medication adherence and persistence (Gebbia et al., 2012). To define medication non-adherence and non-persistence, different cut-off rates were used. Based on the extracted data from

databases, the number of days covered by filled prescriptions or the MPR were often calculated with a cut-off ≤ 80% to define non-adherence. This cut-off rate is frequently cited in the literature as achievable or acceptable (Sikka et al., 2005; Hess et al., 2006; Simpson et al., 2006). For MEMS, a cut-off for non-adherence was set on ≤ 80% in oral adjuvant chemotherapy in breast cancer patients (Partridge et al., 2010) and ≤ 90% in CML patients taking imatinib (Eliasson et al., 2011). The rate of ≤ 90% is identified as the most important factor for an adequate molecular response with imatinib (Marin et al., 2010). In defining medication non-persistence, several different cut-offs in number of days without subsequent refill of pills were used (Barron et al., 2007; Owusu et al., 2008; Neugut et al., 2011; Streeter et al., 2011). There is a need to further explore clinically significant cut-off rates when measuring (non-)adherence to increase comparability in research.

Existing methods to assess medication adherence and persistence include objective methods such as the measurement of metabolites of the medication in body fluids, and subjective methods such as counting tablets, self report and MEMS. In this review, only subjective methods were used, mainly self-report questionnaires or self report in patient interviews (Lebovits et al., 1990; Demissie et al., 2001; Fink et al., 2004; Grunfeld et al., 2005; Atkins and Fallowfield, 2006; Lash et al., 2006; Kahn et al., 2007; Güth et al., 2008; Kirk and Hudis, 2008; Marques and Pierin, 2008; Noens et al., 2009; Eliasson et al., 2011). However, patient self reported medication adherence or persistence is often overestimated because of psychological reasons (fear to be considered unreliable and willingness to please healthcare providers) (Gebbia et al., 2012), and because patients may not be fully aware of their lapses in doses (Gebbia et al., 2012). In measuring adherence, a Hawthorne effect must be taken into account (Ruddy et al., 2009) as patients might be aware that their adherence or persistence is being studied. MEMS was used in two studies (Partridge et al., 2010; Eliasson et al., 2011). This method has previously showed to be more accurate than self report or pill counts (Arnsten et al., 2001), but measuring adherence by using MEMS is expensive and not always feasible in daily practice (Shi et al., 2010). A combination of MEMS and self-report questionnaires, is found to be most

accurate in measuring medication adherence (Shi et al., 2010). The combination of these methods was only used in one study (Eliasson et al., 2011). Other data were obtained from retrospective databases such as pharmacy or insurance records with refill data (Sedjo and Devine, 2011; Darkow et al., 2007; Güth et al., 2008; Partridge et al., 2003; Hershman et al., 2010; Kimmick et al., 2009; Nekhlyudov et al., 2011; Neugut et al., 2011; Owusu et al., 2008; Barron et al., 2007; Ma et al., 2008; Streeter et al., 2011). None of the included studies defined non-adherence as doses being taken at the wrong time. Despite, this might be a critical factor in treatment effectiveness (Ruddy et al., 2009). Future research should also focus on this type of non-adherence and take into account the specific margin of the OACD whereas in between the OACD needs to be taken without losing efficacy of the treatment.

Determinants and associated factors of medication (non-)adherence and (non-)persistence to oral anticancer drugs

Treatment related side effects are predominant factors associated with non-adherence and non-persistence in patients on an OACD therapy. Being inadequately informed about side effects in advance is found to be a factor associated with increased medication non-persistence (Kahn et al., 2007), while a better knowledge of the disease and therapy is associated with a higher adherence (McPherson et al., 2001; Gysels and Higginson, 2007; Noens et al., 2009). The study by Kirk and Hudis (2008) showed that understanding the clinical importance of OACD is helpful for 90% of the patients to adhere to their therapy. The majority of the patients in the study of Kirk and Hudis (2008) also indicated an appropriate management of treatment-related side effects as an important factor influencing medication adherence. These findings support the need for patient tailored educational support (Vermeire et al., 2001; Hartigan, 2003; Moore, 2007) and management of symptoms during follow-up (Kav et al., 2008).

Both younger and older age, were major factors associated with non-adherence and non-persistence in patients taking OACD. This association was primarily found in breast cancer patients. Several studies indicate that younger women do

not adjust to breast cancer as well as older women, affecting their medication adherence (Ganz, 1994; Wenzel et al., 1999). The study by Compas et al. (1999) suggests that younger women with breast cancer are more affectively distressed and tend to cope with stressors in a less adaptive way. However, the reasons for non-adherence and non-persistence in this group of patients remain unclear. A factor that may increase non-adherence and non-persistence in younger women with breast cancer is that younger women are more likely to undergo early menopause caused by breast cancer treatment (Petrek et al., 2006), which may affect women's child wish. Older patients are often more influenced by polypharmacy for comorbidities and chronic conditions, physical challenges, psychosocial issues (e.g. decreased social support), and increasing incidence of memory problems (Balkrishnan, 1998; Chia et al., 2006). These factors can also impede medication adherence and persistence.

Implications for practice

The findings from this review provide insight into the complexity of determinants associated with (non-)adherence to OACD in cancer patients. An important finding from the review is that patients taking OACD differ widely (e.g. age, disease entity, co-morbidities, and severity of side effects) underlining the need for different and tailored approaches in support, depending on their preferences, age, therapeutic regimen, disease entity, and severity of side effects. Clinicians should help patients to understand that early recognition of treatment related side effects can be of great benefit to them (Hartigan, 2003). Further, patients should be well informed about the long-term benefits of the treatment and how treatment related side effects could be managed in daily life. This education should be tailored and based on patient preferences instead of being uniformly organized (McPherson et al., 2001). This tailored approach should be performed in a context of reciprocity between the physician and the patient, so patients' expectations and individual beliefs could be discussed and patients could become active actors of their therapy.

Limitations

Some limitations of this review need to be considered. Generalizations require caution as the data obtained from the studies are difficult to compare due to their specific focus (different types of drugs, disease entities, and design), and the different cut-off rates and methods for assessing non-adherence and non-persistence. Only two studies used MEMS to assess non-adherence, so the results should be interpreted with caution.

Performing a meta-analysis to generalize results and compare subgroups of cancer patients taking OACD was not possible due to the heterogeneity of the studies.

Most of the studies focus on breast-cancer patients (80%) so the conclusions from this study are mainly relevant for this group. Data on other types of cancer are scarce, for example research in patients taking oral tyrosine kinase inhibitors is limited to the three included studies with CML patients. Therefore, further research should pay more attention to other types of cancer.
In studies using a retrospective design based on pharmaceutical or commercial databases (n=8), and in articles written by authors supported by pharmaceutical grants (n=6), a potential conflict of interest needs to be considered (Boyd et al., 2003).

CONCLUSION

This systematic review gives an updated overview of the literature on associated factors and determinants of medication (non-)adherence and (non-)persistence in patients on an OACD therapy. Older and younger age, and the influence of therapy related side effects are predominant factors associated with medication adherence and persistence to OACD therapy. However, influencing factors to medication adherence and persistence to OACD therapy are multifactorial and interrelated. Caution is needed in the interpretation and with the generalizability of the results as the studies differ widely in study focus, definitions and measurements of medication adherence and persistence. Qualitative research

could facilitate the development of patient tailored complex interventions by exploring patients' needs and underlying processes influencing medication adherence and persistence to OACD.

Table 1. Search strategy with MeSH terms and free text words

	OR	OR	OR
MeSH terms	Medication adherence	Administration, oral	Neoplasms
	Patient compliance	Antineoplastic agents	
Related terms	Medication compliance	Oral drug administration	Tumor
	Medication persistence	Antitumor drugs	Cancer
	Medication non-adherence	Antitumor agents	
	Medication non-compliance	Antineoplastic drugs	
	Patient adherence	Antineoplastics	
	Patient cooperation		
	Patient non-compliance		
	Patient non-adherence		
	Concordance		
	Non-persistence		
	Early discontinuation		
	Early discontinuance		
	Treatment discontinuation		
	Treatment discontinuance		
	Treatment interruptions		
	Pill discontinuation		
	Pill discontinuance		
	Abandonment		
	AND	**AND**	

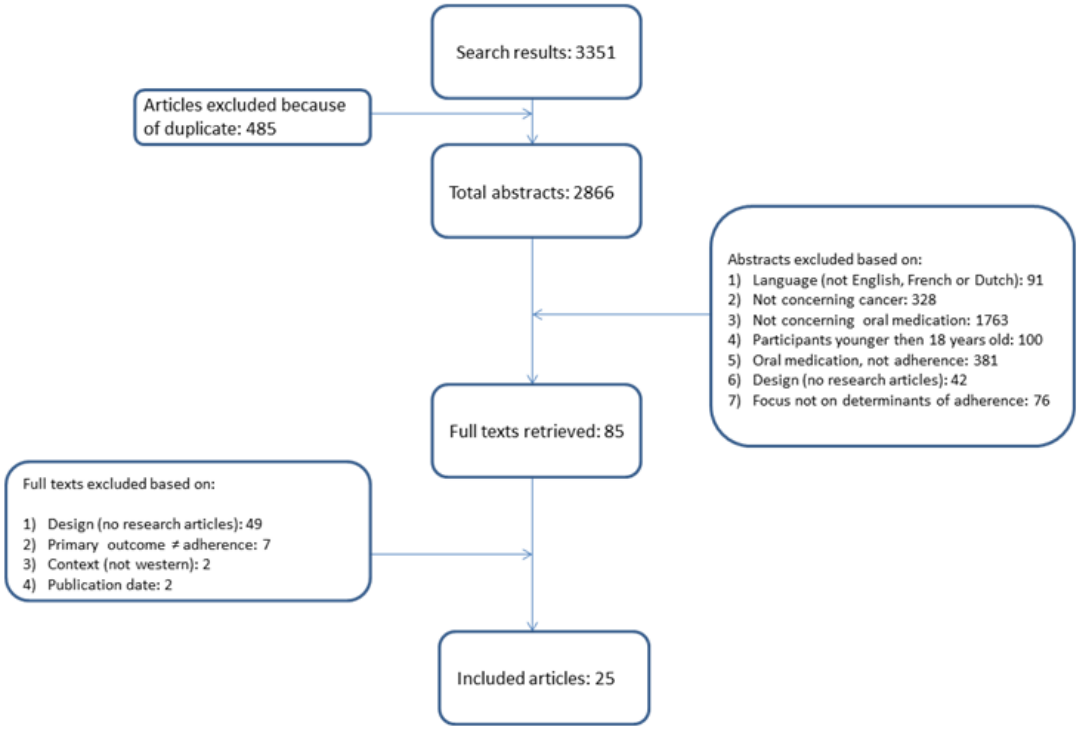

Figure 1. Results of the search strategy

Table 2. Study characteristics, determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Lebovits et al. (1990)	Patient non-compliance with self-administered chemotherapy	Prospective cohort study	Taking < 90% or taking >110% of oral anticancer drugs	(1) Percentage of drug missed during 26 weeks of treatment, (2) self-report in interview based on direct questioning how many pills have been taken during the preceding week of the interview	Patients with breast cancer (51)	(-) treatment location (private and clinic settings rather than academic setting), lower income (and lower socioeconomic status)	NA
Demissie et al. (2001)	Predictors of use, side effects, and discontinuation of adjuvant tamoxifen	Prospective cohort study	Discontinuation (not further specified)	Self-report by computer-assisted telephone interviews at second follow-up, asking detailed questions (not specified) about discontinuance of oral anticancer drug	Older women with breast cancer (303)	NA	(-) Side effects (depression, nausea, vision problems, and vaginal bleeding) (+) patients who were estrogen receptor-positive
Partridge et al. (2003)	Non-adherence to adjuvant tamoxifen therapy	Retrospective analysis of data	Taking < 80% of the doses of prescribed tamoxifen	Refill data (dosage, quantity dispensed, and number of days supplied) extracted from the paid claims from the New Jersey Medicaid program and the New Jersey Pharmaceutical Assistance to the Aged and Disabled (PAAD) program	Women with primary breast cancer (2378)	(-) ≤ 45 years old, ≥ 85 years old, nonwhite subjects, longer duration of therapy, patients who had had a mastectomy (rather than breast-conserving surgery) (+) patients who had a consultation with a medical oncologist before initiation of tamoxifen	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Fink et al. (2004)	Patient beliefs about risks and benefits of tamoxifen therapy and tamoxifen discontinuance	Prospective cohort study	Discontinuation (not further specified)	Self-report by telephone interviews at 3, 6, 15 and 27 months by asking whether women discontinued tamoxifen	Older women with estrogen receptor-positive breast cancer (597)	NA	(-) Having neutral or negative beliefs about the value of tamoxifen, having positive nodes
Grunfeld et al. (2005)	Adherence beliefs about taking tamoxifen	Cross-sectional	(1) Answering "no" on the self-reported question; (2) lower scores (without a cut-off score) on the Medication Adherence Report Scale (MARS-5)[1] indicating non-adherence	(1) Self-report with a single question: "In the past week, have you taken your tamoxifen everyday?", (2) MARS-5	Women with breast cancer aged 35-65 years old (110)	(-) lower perceived necessity for tamoxifen and no benefit to be gained from taking tamoxifen, side effects (hot flashes, night sweats, concentration or memory difficulties, sleep problems, emotional problems, weight gain, and loss of libido) (+) the belief that taking tamoxifen would stop the patients from developing breast cancer	NA
Atkins & Fallowfield (2006)	Intentional and non-intentional non-adherence to oral anticancer drugs	Cross-sectional	Anwering 'occasionally', 'sometimes', 'quite often', or 'very often' on 2 questions assessing intentional and non-intentional non-adherence	Self-report on 2 questions: "How often do you forget to take your tablets?" and "How often do you choose not to take your tablets?"	Women with breast cancer (131)	(-) younger age, disliking aspects of medication (side effects, inconvenience, difficulties swallowing tablets)	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Lash et al. (2006)	Adherence to tamoxifen over the five-year course	Prospective cohort study	Discontinuation (not further specified) by self-report in interviews	Self report by telephone interviews at 3, 6, 15, 27, 39, 51, and 63 months after surgery (questions not specified)	Older women with breast cancer (462)	NA	(-) having or developed initial severe side effects (+) more prescription medications at baseline
Barron et al. (2007)	Early discontinuation of tamoxifen	Retrospective analysis of data	Non-persistence: ≥180 consecutive days of no tamoxifen supply without alternative hormonal therapy during that time	Refill data (number of days supply, quantity and dosage of tamoxifen) extracted from the Irish Health Services Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy database	Women with breast cancer aged 35 years or older (2816)	NA	(-) history of antidepressant use (use in the year preceding the tamoxifen initiation), age (older than 75, between 35 and 44), increased number of prescriptions per month/year before starting tamoxifen
Darkow et al. (2007)	Treatment interruptions and non-adherence with imatinib	Retrospective analysis of data	(1) Treatment interruptions: failure to refill imatinib within 30 days from the end of supply of the prior prescription (2)< 50% low MPR[2]; 50-90% intermediate MPR, 90-95% high MPR, > 95% very high MPR	Refill data from an anonymous database including electronic pharmacy records and medical claims	Patients with CML (267)	(-) increased amount of different medication, starting with higher dose imatinib (≥ 600mg), high cancer complexity (difficulty of managing the patient because of e.g. comorbidities), female gender	(-) female gender, high cancer complexity

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Kahn et al. (2007)	Patient centered experiences in breast cancer - predicting long-term adherence to tamoxifen use	Prospective cohort study	Persistence not specified	Patient self-report survey. Question(s) about non-persistence: not specified	Breast cancer patients (881)	NA	(-) older age (>65), severe side effects, negative and unknown hormone receptor status, no single doctor mainly responsible for follow-up, less participation in decision making than wanted, receiving too much or too less support than needed from caregivers, not previously informed about side effects
Güth et al. (2008)	Non-adherence with adjuvant endocrine therapy	Retrospective analysis of data	Discontinuation (not further specified)	Self-report during follow-up (not further specified)	Postmenopausal patients with invasive breast cancer (325)	NA	(-) Patients who did not have follow-up in an oncologic unit but rather with a general practitioner
Kirk & Hudis (2008)	Barriers in adherence to oral hormonal therapy	Cross-sectional	Taking < 100% of oral anticancer drugs	Self-reported internet survey with 30 questions about intake of oral anticancer drugs as directed	Patients with breast cancer (328)	(-) treatment related side effects, cost of the medication, forgetfulness, constant reminder of cancer diagnosis	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Ma et al. (2008)	Non-compliance with adjuvant radiation, chemotherapy, or hormonal therapy	Retrospective analysis of data	Stop or refuse to take tamoxifen within the 1st year of treatment (if not stopped on the advice of a physician)	Data not further specified on discontinuation of tamoxifen - extracted from the breast cancer database of the senior author including data from the registry as well as electronic medical data used in a retrospective chart review	Women with breast cancer (788)	NA	(-) younger (mean of 54 versus 59 years old), white, larger ductal cancers, treated with mastectomy rather than lumpectomy and radiation, ductal pathology
Marques & Pierin (2008)	Factors affecting cancer patient compliance to oral anti-neoplastic therapy	Cross-sectional	≤3 points on Morisky and Green Test[3]	Morisky and Green Test	Cancer patients under anti-neoplastic oral therapy in a private hospital (61)	(-) longer treatment time, type of medication (mercaptopurine, dexamethasone, thalidomide, and hormone therapy drugs), patients who had alternative treatment (massage) (+) patients who previously had radiotherapy	NA
Owusu et al. (2008)	Predictors of tamoxifen discontinuation	Retrospective analysis of data	Discontinuation: ≥ 60 days discontinuing tamoxifen during 5 years after initial tamoxifen prescription	Refill data (date of initial tamoxifen prescription and date of discontinuation) extracted from cancer register, administrative, and clinical databases	Older women with estrogen receptor-positive breast cancer (961)	NA	(-) Older age (>75), increasing comorbidities, indeterminate estrogen receptor status, have had breast-conserving surgery without radiotherapy

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Kimmick et al. (2009)	Adjuvant hormonal therapy use among insured, low-income women with breast cancer	Retrospective analysis of data	(1) Adherence by MPR ≤ 80%, (2) non-persistence as a 90-day gap in prescription fill	Refill data extracted from the North Carolina Central Cancer Registry (CCR) and North Carolina Medicaid Claims administrative database	Insured, low-income women with breast cancer (1491)	(+) nonmarried status	(+) nonmarried status, having more comorbidities (Charlson comorbidity index[4] of 3 compared with 0), regional rather than local stage of tumor
Noens et al. (2009)	Prevalence, determinants, and outcomes of non-adherence to imatinib therapy	Prospective observational study	(1) patient Visual Analog Scale (VAS) rating, (2) ≥ 1 positive answers on the Basel Assessment of Adherence Scale (BAAS)[5], (3) pill count: other dose taken than prescribed during 90-day period	BAAS scale, VAS rating the overall adherence, pill counts	Patients with CML (169)	(-) bothersomeness of symptoms, number of symptoms, number of adverse events, third person perceptions of adherence, higher age[6], longer time since CML diagnosis[6], living alone[6], male sex[6], longer time on imatinib[6], imatinib dose more than or equal to 600 mg/day[6], higher degrees of chronic care received[6], higher (self-)reported functional status and quality of life[6], shorter median duration of treatment follow-up visits (presumably a proxy of vigilance)[6], years of physicians' professional experience[6]	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
						(+) knowledge of disease and treatment[6], more medications to be taken daily[6], secondary school or higher education[6], self-efficacy in long-term medication behavior[6], physicians' higher number of active patients with CML seen in the past year[6], median duration of the first visit with a patient newly diagnosed with CML[6], (practicing in a university or teaching hospital[6], holding specialization in hematology[6])	
Hershman et al. (2010)	Early discontinuation and non-adherence to adjuvant hormonal therapy	Retrospective analysis of data	(1) Non-adherence by MPR < 80%, (2) early discontinuation if 180 days elapsed from the prior prescription without a refill	Refill data (date of prescription and date of refill) from the pharmacy information management system from the Kaiser Permanente of Northern California	Early stage breast cancer patients (8769)	(-) African American race, lumpectomy, unknown tumor size, lymph node involvement, comorbidities	(-) younger (<50 years old) or older age (≥65 years old), lumpectomy (v mastectomy, comorbidities (+) married status, receipt of chemotherapy or radiotherapy, longer prescription refill interval

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Partridge et al. (2010)	Adherence and persistence with oral adjuvant chemotherapy	Cross-sectional	MEMS < 80%	MEMS	Older women with early-stage breast cancer (161)	(-) having node-positive disease, received partial mastectomy/lumpectomy/excisional biopsy	NA
Regnier Denois et al. (2010)	Behavior and representations of patients and oncologists on adherence with oral chemotherapy	Qualitative study design	Occasionally forget intake of oral anticancer drug	Self-report in patient interviews and focus group interviews	Patients with breast cancer (42)	(-) change in routine (town visits, visiting friends, going on holiday), not understand prescriptions, side effects, changes in timing for taking the treatment in terms of meal times	NA
Eliasson et al. (2010)	Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed	Mixed method study design	MEMS (Medication Event Monitoring System) ≤ 90%	(1) Answering "yes" in a patient interview on the question: "It is common that patients at times miss a few doses, for a whole range of reasons. Thinking just of the past 7 days have you missed any doses?", (2) data from a previous quantitative study measuring adherence by MEMS	Patients with CML (21)	(-) (1) Unintentional non-adherence (forgetting, accidentally taking too much, prescribing error, no imatinib available at pharmacy), (2) intentional non-adherence (attributable to side effects, socializing/dining out/drinking alcohol, travelling, diversion from planned activities, temporary illness	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
						(cold), risk of pregnancy, negative emotions and feelings, "no real reason/lack of discipline", bad taste, changed doses), (3) consequences of non-adherence (perceived consequences, conflicting information regarding consequences, "getting away with it", reliance on monitoring and health care providers to detect and relay changes in clinical parameters, do not think missing the odd dose make a difference)	

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Nekhlyudov et al. (2011)	Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence	Retrospective analysis of data	(1) Adherence by MPR ≤ 80%, (2) non-persistence by having a gap between two consecutive prescriptions of at least 60 days	Refill data extracted from claims submitted to Harvard Pilgrim Health Care, a non-profit health plan in Massachusetts	Women with early stage breast cancer (2207)	NA	(-) elderly women (>70 years old at diagnosis - compared to younger than 50 years old), lower income neighbourhood (associated factor only during first year of treatment)
Neugut et al. (2011)	Compliance with adjuvant hormonal therapy	Retrospective analysis of data	(1) Non-adherence: MPR < 80%, (2) Non-persistence: presciption supply gap ≥ 45 days without subsequent refill	Refill data extracted from an anonymous Information Warehouse database of medication prescriptions	Women with early stage breast cancer (8110)	(-) higher out-of-pocket cost, older age	(-) prescription not by oncologist (by primary care physician), 10 or more other prescriptions, higher out-of-pocket cost, older than 85 years
Sedjo & Devine (2011)	Predictors of non-adherence to aromatase inhibitors	Retrospective analysis of data	MPR < 80%	Refill data extracted from the MarketScan® Commercial Claims and Encounters Databases from Thomson Reuters	Commerciall y insured women with breast cancer (13593)	(-) younger age (<45 years old), out-of-pocket costs ≥$30 per prescription, no mastectomy, higher Charlson Comorbidity Index	NA

Author (publication date)	Research focus	Design	Defining non-adherence and non-persistence	Measurement of (non-)adherence and (non-)persistence	Participants (N)	Factors associated with (-) non-adherence or (+) higher adherence	Factors associated with (-) non-persistence or (+) higher persistence
Streeter et al. (2011)	Factors affecting abandonment of oral oncolytic prescriptions	Retrospective analysis of data	Abandonment (reversal of an adjudicated pharmacy claim without a subsequent paid claim for oncolytic within the ensuing 90 days)	Refill data extracted from administrative claims from the Wolter Kluwer Dynamic Claims Lifecycle Database (pharmacy utilization data)	Cancer patients (10508)	NA	(-) high cost, increased prescription activity, lower income, type of drug (imatinib, sorafenib, sunitinib, erlotinib, lapatinib compared with capecitabine)

[1] *Medication Adherence Report Scale (MARS-5)* is a scale with 5 items to assess various non-adherent behaviours including how often patients have deliberately not taken their medicines and forgotten to take them. All questions are answered on a five point Likert-scale, resulting in a range from 5 to 25 point, with higher scores indicating greater adherence / [2] M*edication Possession Ratio* (MPR) is a formula used to determine adherence that is measured from the first to the last prescription, with the denominator being the duration from index to the exhaustion of the last prescription and the numerator being the days supplied over that period from first to last prescription / [3]*Morisky and Green test* evaluates attitudes regarding treatment and is made up of four questions / [4] *Charlson Comorbidity Index* predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned with a score of 1,2,3 or 6 depending on the risk of dying associated with this condition. Then the scores are summed up and given a total score which predicts mortality / [5] *Basel Assessment of Adherence Scale (BAAS)* is a 4-question clinical interview guide questioning adherence behavior / [6] not independent factors and should be interpreted as part of a canonical model of multiple complementary variables

Table 3. Summary of the quality assessment of the included quantitative studies (23)

	Selection bias	Allocation bias	Confounders	Data collection methods	Withdrawals and drop-outs	Analysis					
						Q1[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]
Lebovits et al.	Moderate	Moderate	Weak	Strong	Weak	N[7]	P[8]	Y[9]	Y	Y	Y
Demissie et al.	Moderate	Moderate	Weak	NA[10]	Weak	N	Y	Y	Y	NR[11]	Y
Partridge et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	N	Y	NR	Y
Fink et al.	Weak	Moderate	Weak	NA	Weak	N	Y	Y	Y	NR	Y
Grunfeld et al.	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Atkins & Fallowfield	Moderate	Moderate	Weak	NA	Weak	N	Y	Y	Y	NR	Y
Lash et al.	Moderate	Moderate	Weak	Strong	Weak	N	P	Y	Y	NR	Y
Barron et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Darkow et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kahn et al.	Moderate	Moderate	Weak	Moderate	Weak	N	Y	Y	Y	NR	Y
Güth et al.	Weak	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kirk & Hudis	Moderate	Moderate	Weak	Moderate	Moderate	N	Y	Y	Y	NR	Y
Ma et al.	Moderate	Moderate	Weak	NA	Moderate	N	P	Y	Y	NR	Y
Marques & Pierin	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Owusu et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Kimmick et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Noens et al.	Moderate	Moderate	Weak	Strong	Strong	Y	Y	Y	Y	NR	Y

	Selection bias	Allocation bias	Confounders	Data collection methods	Withdrawals and drop-outs	Analysis					
						Q1[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]
Hershman et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Partridge et al.	Weak	Moderate	Weak	Strong	Weak	N	Y	Y	Y	NR	Y
Nekhlyudov et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Neugut et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Sedjo & Devine	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y
Streeter et al.	Moderate	Moderate	Weak	NA	Moderate	N	Y	Y	Y	NR	Y

[1]sample size or power calculation / [2]characteristics of study participants extensively described / [3]main results of statistical analysis unambiguously described / [4]statistical methods appropriate / [5]missing data handled in an appropriate way / [6]result section report on all outcome measures mentioned in method-section / [7]No / [8]Partially / [9]Yes / [10]Not applicable /[11]Not Reported

Table 4. Summary of the quality assessment of the mixed method study and qualitative study (2)

	Clear statement of the aims	Appropriate methodology	Appropriate design	Appropriate recruitment strategy	Appropriate data collection	Consideration relationship between researcher and participants	Consideration ethical issues	Rigorousness data analysis	Clear statement of findings	Valuability of the study
Eliasson et al.	+	+	+	-	+	-	+	+	+	+
Regnier Denois et al.	+	+	+	+	+	-	+	-	+	+

+ = yes, - = no

[1]Mixed method study

REFERENCES

Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang C-J, Buono D, Eckholdt H, Howard AA, Schoenbaum EE. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *HIV//AIDS* 2001; **33**: 1417-1423.

Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer* 2006; **42**: 2271-2276.

Balkrishnan R. Predictors of medication adherence in the elderly. *Clinical Therapeutics* 1998; **20**: 764-771.

Banna LG, Collovà E, Gebbia V, Lipari H, Giuffrida P, Cavallaro S, Condorelli R, Buscarino C, Tralongo P, Ferraù F. Anticancer oral therapy: emerging related issues. *Cancer Treatment Reviews* 2010; **69**: 595-605.

Barron TI, Connolly RM, Bennett K, Feely J, Kennedy JM. Early discontinuation of tamoxifen. *American Cancer Society* 2007; **109**(5):832-839.

Black N. Why we need qualitative research. *Journal of Epidemiology and Community Health* 1994; **48**: 425-426.

Boyd EA, Cho MK, Bero LA. Financial conflict-of-interest policies in clinical research: issues for clinical investigators. *Academic Medicine* 2003; **78**(8): 769-774.

Chia LR, Schlenk EA, Dunbar-Jacob J. Effect of personal and cultural beliefs on medication adherence in the elderly. *Drugs and Aging* 2006*;* **23**: 191-202.

Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MH, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. *Value in Health* 2008; **11**(1): 44-47.

Compas B, Stoll M, Thomsen A, et al. Adjustment to breast cancer: age-related differences in coping and emotional distress. *Breast Cancer Research and Treatment* 1999; **54**: 195-203.

Darkow T, Henk HJ, Thomas SK, Feng W, Baladi J-F, Goldberg GA, et al. Treatment interruption and non-adherence with imatinib and associated healthcare costs – a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics* 2007; **25**(6): 481-496.

Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. *Journal of Clinical Oncology* 2001; **19**(2): 322-328.

Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leukemia Research* 2011; **35**: 626-630.

Fallowfield L, Atkins L, Catt S, Cox A, Coxon C, Langridge C, Morris R, Price M. Patients' preferences for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Annals of Oncology* 2006; **17**: 205-210.

Fink AK, Gurwitz J, Rakowski W, Guadagnoli E, Silliman RA. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology* 2004; **22**(16): 3309-3315.

Foulon V, Schöffski P, Wolter P. Patient adherence to oral anticancer drugs: an emerging issue in modern oncology. *Acta Clinica Belgica* 2011; **66**(2): 85-96.

Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *American Journal of Hematoly* 2011; **86**(6):471-4.

Ganz P. Breast cancer in older women: quality-of-life considerations. *Cancer Control* 1994; **1**: 372-379.

Gebbia V, Bellavia G, Ferraù F, Valerio MR. Adherence, compliance and persistence to oral antineoplastic therapy: a review focused on

chemotherapeutic and biologic agents. *Expert Opinion on Drug Safety* 2012; 11(1): S49-S59.

Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling* 2005; **59**: 97-102.

Güth U, Huang DJ, Schötzau A, Zanetti-Dällenbach R, Holzgreve W, Bitzer J, Wight E. Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. *British Journal of Cancer* 2008; **99**: 428-433.

Gysels M, Higginson IJ. Interactive technologies and videotapes for patient education in cancer care: systematic review and meta-analysis of randomized trials. *Support Cancer Care* 2007; **15**: 7-20.

Hartigan K. Patient education: the cornerstone of successful oral chemotherapy treatment. *Clinical Journal of Oncology Nursing* 2003; **7**: 21-24.

Hershman DL, Kushi LH, Sha T, Buono D, Kershenbaum A, Tsai W-Y, Fehrenbacher L, Gomez LS, Miles S, Neugut AI. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *Journal of Clinical Oncology* 2010; **28**(27): 4120-4128.

Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *The Annals of Pharmacotherapy* 2006; **40**: 1280-1288.

Ibrahim AR, Eliasson L, Apperley JF, Milojkovic D, Bua M, Szydlo R et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood* 2011;**117**(14): 3733-6.

Kahn KL, Schneider EC, Malin JL, Adams JL, Epstein AM. Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Medical Care* 2007; **45**(5): 431-439.

Kav S, Johnson J, Rittenber C, Fernadez-Ortega P, Suominen T, Olsen PR, Patiraki E, Porock D, Dahler A, Toliusiene J, Tadic D, Pittayapan P, Roy V, Wang Q, Colak M, Saca-Hazboun H, Makumi D, Kadmon I, Ben Ami S, Anderson E, Clark-Snow R. Role of the nurse in patient education and follow-up of people receiving oral chemotherapy treatment: an international survey. *Support Care Cancer* 2008; **16**: 1075-1083.

Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *Journal of Clinical Oncology* 2009; **27**(21): 3445-3451.

Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clinical Breast Cancer* 2008; **8**(2):155-161.

Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat* 2006**; 99**(2): 215-220.

Lebovits AH, Strain JJ, Schleifer SJ, Tanaka JS, Bhardway S, Messe MR. Patient noncompliance with self-administered chemotherapy. *Cancer* 1990; **65**: 17-22.

Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *Journal of Clinical Oncology* 1997; **15:** 110-5.

Ma AMT, Barone J, Wallis AE, Wu NJ, Garcia LB, Estabrook A, Rosenbaum-Smith SM, Tartter PI. Noncompliance with adjuvant radiation, chemotherapy or hormonal therapy in breast cancer patients. *The American Journal of Surgery* 2008; **196**: 500-504.

Mann CJ. Observational research methods. Research design II: cohort, cross-sectional, and case-control studies. *Emergency Medicine Journal* 2003; **20**: 54-60.

Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *Journal of Clinical Oncology* 2010; **28**(14): 2381-8.

Marques PAC, Pierin AMG. Factors that affect cancer patient compliance to oral anti-neoplastic therapy. *Acta Paulista de Enfermagem* 2008; **21**(2): 323-329.

McCowan C, Shearer J, Donnan PT, Dewar JA, Crilly M, Thompson AM et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *British Journal of Cancer* 2008;**99**(11):1763-8.

McPherson CJ, Higginson IJ, Hearn J. Effective methods of giving information in cancer: a systematic literature review of randomized controlled trials. *Journal of Public Health Medicine* 2001; **23**(3): 227-234.

Mirza M, Fitzpatrick-Lewis D, Thomas H: Is there a relationship between food insecurity and overweight/obesity? Hamilton, ON: Ontario Public Health Research, Education and Development: Effective Public Health Practice Project; 2007

Moore S. Facilitating oral chemotherapy treatment and compliance through patient/family-focused education. *Cancer Nursing* 2007; **30:** 112-122.

Moore S. Nonadherence in patients with breast cancer receiving oral therapies. *Clinical Journal of Oncology Nursing 2010;* **14**(1): 41-47.

Nekhlyudov L, Li L, Ross-Degnan D, Wagner AK. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. *Breast Cancer Research and Treatment* 2011; **130**: 681-589.

Neugut AI, Subar M, Wilde ET, Stratton S, Brouse CH, Hillyer GC, Grann VR, Hershman DL. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *Journal of Clinical Oncology* 2011; **29**(18): 2534-2542.

Noens L, van Lierde M-A, De Bock R, Verhoef G, Zachée P, Berneman Z, Martiat P, Mineur P, Van Eygen K, MacDonald K, De Geest S, Albrecht T, Abraham I. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* 2009; **113**(22): 5401-5411.

Owusu C, Buist DSM, Field TS, Lash TL, Thwin SS, Geiger AM, Quinn VP, Frost F, Prout M, Ulcickas Yood M, Wei F, Silliman RA. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. *American Society of Clinical Oncology* 2008; **26**(4): 549-555.

Paley M, Love N, Carlson R, et al. Preferences for oral, parenteral antitumor therapy: a survey of 260 patients with metastatic breast cancer. *Proceedings of the American Society of Clinical Oncology* 2005; **23**:619.

Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. *Journal of the national cancer institute* 2002; **94**(9):652-661.

Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology* 2003; **21**(4): 602-606.

Partridge AH, Archer L, Kornblith AB, Gralow J, Grenier D, Perez E, Wolff AC, Wang X, Kastrissios H, Berry D, Hudis C, Winer E, Muss H. Adherence and persistence with oral adjuvant chemotherapy in older women with early-stage breast cancer in CALGB 49907: adherence companion study 60104. *Journal of Clinical Oncology* 2010; **28**(14): 2418-2422.

Petrek J, Naughton M, Case, et al. Incidence, time course, and determinates of menstrual bleeding after breast cancer treatment: a prospective study. *Journal of Clinical Oncology* 2006; **24**: 1045-1051.

Public Health Resource Unit *(*2006*)* Critical Appraisal Skills Programme (CASP) Making Sense of Evidence, 10 Questions to Help Make Sense of Qualitative Research*. Retrieved from* http://www.sph.nhs.uk/sph-files/casp-appraisal-tools/Qualitative%20Appraisal%20Tool.pdf *on 16th April 2012.*

Regnier Denois V, Poirson J, Nourissat A, Jacquin J-P, Guastalla JP, Chauvin F. Adherence with oral chemotherapy: results from a qualitative study of the behaviour and representations of patients and oncologists. *European Journal of Cancer Care* 2010; **20**: 520-527.

Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA: a Cancer Journal for Clinicians* 2009; **59**(1):56-66.

Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Research and Treatment* 2011; **125**(1): 191-200.

Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health and Quality Life Outcomes* 2010; **8**(99).

Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *American Journal of Managed Care* 2005; **11**: 449-457.

Simchowitz B, Shiman L, Spencer J, Brouillard D, Gross A, Connor M, Weingart SN. Perceptions and experiences of patients receiving oral chemotherapy. *Clinical Journal of Oncology Nursing* 2010; **14**(4): 447-453.

Simpson SH, Eurich DT, Majumdar SR et al. A meta-analysis of the association between adherence to drug therapy and mortality. *British Medical Journal* 2006; **333**: 15-20.

Stavropoulou C. Non-adherence to medication and doctor-patient relationship: evidence from a European survey. *Patient Education and Counseling* 2011; **83**: 7-13.

Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *Journal of oncology practice* 2011; **7**(3S): 46s-51s.

Thomas BH, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: Providing the research evidence for public health nursing interventions. *Worldviews on Evidence Based Nursing* 2004; **1**(3):176-184.

Van Hecke A, Verhaeghe S, Grypdonck M, Beele H, Defloor T. Processes underlying adherence to leg ulcer treatment: A qualitative field study. *International Journal of Nursing Studies* 2011; **48**(2): 145-155.

Van Meijel B, Gamel C, Swieten-Duijfjes B, Grypdonck MH. The development of evidence-based nursing interventions: methodological considerations. *Journal of Advanced Nursing* 2004; **48:** 84-92.

Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy Therapy* 2001; **26:** 331-342.

Vervoort S, Borleffs J, Hoepelman A, Grypdonck M. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS* 2007; **21**: 271-281.

Vyncke V, Stevens V, De Clercq B, Ieven A, Hrafn Jonsson S, Darias Curvo S, et al. Does neighborhood social capital make a difference for levelling the health gradient in children? A literature review. *BMC Public Health* 2013; **13**:65.

Wenzel L, Fairclough D, Brady M, et al. Age-related differences in the quality of life of breast carcinoma patients after treatment. *Cancer* 1999; **86**: 1768-1774.

Wojtacki J, Wiraszka R, Rolka-Stempniewicz G, et al. Breast cancer patients' preferences for oral versus intravenous second-line anticancer therapy. *European Journal of Cancer* 2006; **159**: abstr 381.

World Health Organization. Adherence to long-term therapies, evidence for action. *Geneva* 2003.

Wu EQ, Guerin A, Yu AP, Bollue VK, Guo A, Griffin JD. Retrospective real-world comparison of medical visits, costs, and adherence between nilotinib and dasatinib in chronic myeloid leukaemia. *Current Medical Research Opinion* 2010; **26**(12): 2861-2869.

CHAPTER 3

FACTORS INFLUENCING (NON-)ADHERENCE IN CANCER PATIENTS TAKING ORAL TYROSINE KINASE INHIBITORS: A QUALITATIVE STUDY

Based on the article of Verbrugghe M, Duprez V, Beeckman D, Grypdonck M, Quaghebeur M, Verschueren C, Verhaeghe S, Van Hecke A. Factors influencing (non-)adherence in cancer patients taking oral tyrosine kinase inhibitors: a qualitative study. Accepted for publication in *Cancer Nursing.*

ABSTRACT

Background

Non-adherence in cancer patients taking oral anticancer drugs is common. Reasons for non-adherence are still not really understood as influencing factors are often complex, dynamic and interrelated.

Objective

A qualitative study was conducted to gain insight into (non-)adherence behavior in patients taking oral tyrosine kinase inhibitors by exploring (1) processes and factors influencing (non-)adherence, and (2) their interrelatedness.

Methods

Semi-structured interviews were held with 30 patients of different ages and with different types of cancer. A grounded theory approach was used.

Results

Three foci were found when dealing with oral tyrosine kinase inhibitors: (1) a focus on survival, (2) a focus on quality of life, and (3) a balance between survival and quality of life. The process of adherence was determined by a set of complex and interrelated influencing factors: treatment related side effects, hope, anxiety, trust, and feedback mechanisms.

Conclusion

This qualitative study gives insight into processes and factors influencing (non-)adherence behavior in patients taking oral tyrosine kinase inhibitors. The results of this study can help healthcare professionals understand why patients taking oral tyrosine kinase inhibitors do not always adhere to their therapy.

Implications for practice

Conditions should be created by which patients get maximum opportunity to establish a balance between survival and quality of life. An open climate and a trust based relationship should be established in which patients feel comfortable to openly discuss their therapy and the difficulties they experience.

INTRODUCTION

There is a steady increase in the availability and use of oral anticancer drugs (OACD) in the treatment of cancer (Banna et al., 2010). Currently, 25% of the anticancer drugs can be taken orally and this will continue to rise in the future (Banna et al., 2010). Tyrosine kinase inhibitors (TKIs) are one type of OACD. Tyrosine kinase inhibitors allow target-specific therapy for selected malignancies (Arora and Scholar, 2005). Most TKIs have to be taken for long periods of time and have palliative rather than curative properties. Eleven registered oral TKIs are used in the targeted treatment of specific cancers (Levitzki, 2013). Imatinib, for example, is used for the treatment of chronic myeloid leukemia (CML), and sunitinib for the treatment of renal cell carcinoma, gastrointestinal stromal tumors, and neuroendocrine tumors.

For treatment effectiveness, optimal adherence to OACD is considered important (Noens et al., 2009; Marin et al., 2010; Xu et al., 2012). A patient is considered to be non-adherent when doses of the prescription to which the patient has consented are skipped, extra doses are taken or doses are taken in the wrong quantity or at the wrong time (Ruddy et al., 2009). Non-adherence rates in patients taking OACD range from 0 to 84% (Foulon et al., 2011) depending on (1) the definition of non-adherence, (2) the tool used to measure non-adherence, and (3) the type of OACD therapy (e.g. therapy complexity and side effects). Adherence studies in patients taking OACD mainly focus on hormone therapy in breast cancer patients (Partridge et al., 2010; Nekhlyudov et al., 2011; Neugut et al., 2011). Adherence studies in patients taking oral TKIs mainly focus on patients with CML taking imatinib (Darkow et al., 2007; Noens et al., 2009; Marin et al., 2010; Eliasson et al., 2011; Jönsson et al., 2012). Studies reporting on adherence in other malignancies treated with oral TKIs are scarce.

Mainly quantitative studies are conducted to explore influencing factors of non-adherence in patients taking OACD. Patient, therapy, disease, healthcare system, and social and economic characteristics are found to influence adherence in patients taking OACD (Verbrugghe et al., 2013). The influence of therapy related side effects (Grunfeld et al., 2005; Atkins and Fallowfield, 2006;

Kirk and Hudis, 2008; Regnier Denois et al., 2010; Eliasson et al., 2011), and older (Partridge et al., 2003; Noens et al., 2009; Neugut et al., 2011) or younger age (Partridge et al., 2003; Neugut et al., 2011; Sedjo and Devine, 2011) are found to be predominant factors associated with non-adherence in patients taking OACD. However, despite many quantitative studies, reasons for non-adherence in patients taking OACD are still not fully understood as influencing factors of non-adherence are often complex, dynamic and interrelated (Verbrugghe et al., 2013). The lack of a clear understanding may partly explain the still high prevalence of non-adherence to oral TKIs to date (Anderson et al., 2014; Kekäle et al., 2014). Qualitative research could give insight into the complexity and interrelatedness of factors influencing medication (non-)adherence and is more appropriate than quantitative research to discover underlying processes (Black, 1994). A better understanding of (non-)adherence in patients taking oral TKIs could, in turn, inform patient tailored interventions. Furthermore, qualitative research is more appropriate than quantitative research to explore the influence of interpersonal relational aspects, known to be important factors in medication adherence in other diseases (Vervoort et al., 2007; Stavropoulou, 2011; Van Hecke et al., 2011).

To date, qualitative studies in adherence research in patients taking OACD are scarce. In a recent systematic review of determinants and associated factors influencing adherence to OACD (Verbrugghe et al., 2013), only one qualitative study in patients with breast cancer (Kirk and Hudis, 2008) and one mixed methods study in patients with CML (Eliasson et al., 2011) were found among the 25 included studies. To our knowledge, no qualitative research describes processes and factors influencing (non-)adherence in different types of oral TKIs.

This study aims to give insight into (non-)adherence behavior in patients taking oral TKIs by exploring (1) processes and factors influencing (non-)adherence, and (2) their interrelatedness.

METHODS

A grounded theory approach (Glaser and Strauss, 1967) was used in this study because it allowed for understanding patients' behaviors and actions and provided guidance for studying complex and dynamic phenomena (Brown et al., 2002) such as (non-)adherence behavior. A grounded theory approach is a qualitative systematic research method to inductively derive a theoretical framework from a systematic, interactive process of data collection and analysis (Charmaz, 2006; Threlfall et al., 2007).

Setting and sample

Patients were recruited in five hospitals in Belgium: two university and three regional hospitals. The sample consisted of native Dutch speaking patients, ≥ 18 years old, diagnosed with different types of cancer, and treated with an oral TKI. Patients in a palliative care stage (prognosis of <6 months survival) were excluded, as previous research demonstrated that other factors sometimes get more attention than taking OACD (Krouse et al., 2004; Irshad and Maisey, 2010). In selecting patients, diversity regarding for instance age, time since diagnose, and pathology was taken into account (purposive sampling). Ultimately, thirty-one patients were asked to participate, one refused because of the progression of the disease. Table 1 shows the participants' demographic, disease, and treatment-related characteristics. The age varied between 36 and 88 years. Most participants were men (n=18). Participants had been diagnosed between 4 months and 8.8 years previously, most with renal cell cancer or CML. For most of the participants (n=21) it was the first treatment with OACD since the start of oral anticancer treatment. Most participants lived together with a partner (n=21) and had children (n=25).

Data collection

A designated healthcare professional in the hospital contacted potential participants and provided oral information about the study. When patients agreed to participate, a researcher contacted the patient to make an appointment for the interview.

Interviews were held at a location of their choice, to encourage openness and in-depth conversations. Twenty-seven interviews took place at the patients' home and three interviews took place at the outpatient department in the hospital. The interviews were semi-structured and informed by topics (Table 2) from a recent review of determinants and associated factors influencing (non-)adherence in patients taking oral anticancer drugs (Verbrugghe et al., 2013). The interviews started with an open question to encourage patients to tell their story: "You received an oral treatment for cancer, could you tell me what your life has been like these last few months?". Demographic data were collected at the end of each interview in order not to disturb the flow of the interview. As the process of data collection and data-analysis evolved, the topic list was adjusted with more specific subtopics to enrich the process of data collection. New subtopics were: (1) the desire to have a normal life, (2) the meaning of feedback from medication, follow-up examinations, and healthcare professionals, (3) locus of control, (4) the meaning of the unpredictability of side effects and the acceptability of side effects, and (5) anxiety and hope.

The interview style generally became more structured as the number of interviews progressed. During and after the interviews, the researcher wrote down relevant observations concerning the context of the interview. Observations were included in the analysis.

Data collection took place between May 2012 and November 2013. All interviews were conducted by the first author (M.V.). Interviews were tape-recorded, transcribed verbatim by a third person, and verified for transcription accuracy by the first author. Interviews lasted on average 52 minutes (range 15-88). During 9 of the 30 interviews, a third person was present (often the patient's partner) for all or a part of the interview.

This study was approved by the Ethical Review Committee of Ghent University Hospital and by the local committees of the participating hospitals (B670201212975). All participants were given detailed information (written and verbal) about the study and signed an informed consent. Possible identifiers

were removed from the transcripts. The audio documents were deleted at the end of the study.

Data analysis

The themes were developed based on discussion by the three main researchers (M.V., A.V.H. & V.D.). Each new insight emerging from the group discussion was checked against the other data. The analytical process revealed new subtopics to include in the following interviews.

The transcripts were coded and themes were described. Data were entered into a software program for qualitative data analysis (NVivo 10, QRS International Pty. Ltd.). A coding tree was developed. After 15 interviews, three foci reflecting the patients' basic stance towards their treatment with oral TKIs were developed (theoretical framework). After specific recruitment (theoretical sampling) and a thorough discussion of the emerged themes, we got a clearer picture of how the patients' focus interacted with factors influencing adherence behavior. All the transcripts were reread several times to trace how the themes were represented in the interviews.

In the initial phase of data collection, purposive sampling was used in order to assure the representativeness of participants with different ages, different social situations, different diagnoses (and type of oral TKIs). By using purposive sampling, which is the selection of information-rich cases related to the phenomenon of interest (Palinkas et al., 2013), we aimed to have a broad exploration of the experiences of patients taking oral TKIs. As soon as patients' foci in dealing oral TKI therapy were developed (after 15 interviews), theoretical sampling (Stavropoulou, 2011) was used. Patients were then recruited to further explore factors influencing the foci: patients who stopped treatment on their own initiative, patients who were less directly faced with the life-threatening nature of the disease, and patients for whom the oral TKI was no longer effective. The new data contributed to the further development and refinement of the theoretical framework developed in this study.

After 27 interviews, data saturation was reached in accordance with the constant comparison analyzing aspect of grounded theory (altering process of data collection and data-analysis in a cyclic way until new interviews no longer contribute to the further refinement of the theoretical framework) (Boeije, 2002). Three additional interviews were conducted, but revealed no additional information.

To improve the quality of the data collection, a supervisor (A.V.H.) gave feedback on the interview style and data analysis. Analysis was validated by the process of researcher triangulation. A second researcher (V.D.) followed the process closely, read all the transcripts, assisted with the coding, and frequently discussed the coding and themes that emerged from the analysis. Additionally, a group of five experts met five times in order to discuss the results of the data analyses in order to optimize the quality. The five experts were selected because of their expertise in qualitative research and/or relevant work experience. Two of them were oncology nurse specialists. They read some of the interviews and performed their own analysis. These analyses were discussed in group.

RESULTS

In dealing with oral TKI therapy, three foci were developed (theoretical framework): (1) a focus on survival, (2) a focus on quality of life, and (3) a balance between survival and quality of life. The focus was influenced by a set of complex and interrelated factors. The intensity and quantity of side effects was found to be a crucial factor. Foci were not static: they could shift over time. The figure gives an overview of the influencing factors and the three foci.

Three foci

Within *a focus on survival,* treatment got the highest priority. In patients with this focus, treatment with oral TKI was often seen as the last chance to survive. Many of these patients had recently received bad news, for example that surgical treatment was not an option anymore. For some patients starting oral

TKI therapy meant that they had moved on from a curative to a chronic, palliative treatment and this confronted them with the non-curable and life-threatening nature of the disease. These patients often reported enduring side effects without complaining and reported a low quality of life. They felt a great responsibility for their survival. They often did not report side effects to healthcare professionals out of the fear for a dose reduction and a concomitant decrease in efficacy of the treatment. They often believed that bearing side effects would lead to better results, as they assumed the prescribed oral TKI and dose would lead to higher survival. This putted them at risk for an adverse drug reaction (toxicity), which could, in turn, endanger their chances of prolonging life. When patients with a focus on survival accidentally forgot to take their medication, they often panicked and feared this would reduce their chance to survive. A focus on survival was frequently present in the initial phase of the oral anticancer treatment.

> *"The oncologist said that surgery was not an option anymore, that they only could give medication. That was terrible for me. The day after, I started with that medication. And then I thought: "I have to make sure that the tumor will shrink." This medication must must must work. (…) It's hard because it makes me so sick. (…) Even when side effects are so intense, I wait to report them to the hospital until I really can't hold on anymore."*

When the *focus* was *on quality of life*, patients often experimented with their medication to make quality of life acceptable: they took drug holidays, reduced the dosage or deviated from instructions given by healthcare professionals. These adjustments mostly happened on their own initiative and without consulting their healthcare professionals. These patients frequently reported having limited knowledge about their medication. They often did not know the rationale for the instructions that were given to them, for example the reason for a 12 hour interval between a first and second oral TKI dose. As a result, they sometimes made decisions in handling their oral TKI therapy which could endanger the effectiveness of the therapy. These patients often reported not

having an open relationship with their healthcare professionals. They sometimes felt they were not being heard by healthcare professionals.

> *"The doctor didn't give me much information about the medication. He just said I had to leave 12 hours between the first and the second dose. But for me, that's hard because there are not 12 hours between my breakfast and my dinner. I often sleep a little longer. Now there is often only seven hours between the two doses. I don't care. It was only in the beginning he gave that instruction and he never brought it up again. I think it's because I see that nothing happens when I don't leave 12 hours in between."*

Patients *balancing between survival and quality of life* reported a sufficient quality of life without deviating from medication instructions provided by healthcare professionals. These patients often made some adjustments in dealing with their medication based on a sound knowledge and in consultation with their healthcare professionals; for example, they took the medication in the evening instead of in the morning. They often reported to have a trust based and open relationship with healthcare professionals. Within this relationship, they often could combine their outlook on life and experiences with the therapy with the medical instructions they received from healthcare professionals. Most often they reported side effects and other problems more easily, which allowed healthcare professionals to manage side effects in a better way. In general, they had a good basic knowledge of their medication, allowing them to make adequate decisions in dealing with their therapy. They were informed as to why, for example, it was important to leave 12 hours between the first and second dose for some treatments.

Focus shifts

Patients shifted foci over time as a result of events or changes in perception.

Patients shifted, for example, from a focus on survival to a balance between focus on survival and focus on quality of life when they came to accept in some

way the palliative (and non-curative) character of their therapy whereby space was created for quality of life.

For some patients experiencing intense and severe side effects and low support from healthcare professionals, finding a balance between survival and quality of life was often difficult. They shifted from a focus on survival to a focus on quality of life, and back. They often endured side effects until they reached their physical and mental limit, and then used all kinds of mechanisms to decrease side effects as quickly as possible, e.g. by taking drug holidays.

> "*I continued to take the oral TKI, but after a while I had no appetite anymore, I could not eat and drink anymore, It was terrible. Every afternoon I had to lie on my bed because I was running on the end of my strength. I had no life anymore. I was completely burned out. And then I decided to stop the therapy because It became traumatic."*

When side effects became less severe, patients often started taking their medication again. Restarting was often initiated by (1) hope for a prolonged life and sometimes hope of being cured of the cancer, and (2) the fear that they would not survive without taking the oral TKI.

Factors influencing foci in dealing oral TKI therapy

Several factors influencing the focus in dealing oral TKI therapy were found. A selection of important influencing factors is presented below: side effects, hope, anxiety, trust, and feedback mechanisms. This selection of influencing factors was made because of their relevancy to the aim of this study and/or because they have received little attention in literature. Other influencing factors found in this study (social support, medication reminder tools, routine, self-efficacy, and perception of the medication properties) are not described in this paper as they have already been studied in other adherence research in patients taking OACD (Verbrugghe et al., 2013).

Side effects

Side effects, which can be severe in oral TKI treatment, had a major influence on the quality of life of patients. For some patients, life became almost unbearable due to the intense side effects.

> *"I always have to rub ointment on me. And I have enormous acid reflux. And my mucous membranes are affected too. I suffered a lot from that. I've also been burnt by the oral TKI treatment. On my eyelids, I even had second degree burns. It was really heavy. It should diminish, if not, I cannot hold on any longer. I really try to endure, but life should still be worth living. Right now, the margin is very narrow."*

On the other hand, some patients could lead a normal life to some extent. Side effects and their influence on quality of life were important factors influencing the patients' focus. Avoiding side effects in order to maintain an acceptable quality of life was the main reported reason why patients did not adhere to the prescribed regimen to which they had committed themselves.

Influence of side effects

Oral TKI side effects could suddenly appear and could become more intense. This made it often difficult for patients to plan in advance and raised a constant fear that side effects could emerge. This fear often affected their quality of life. The more side effects, the greater their intensity, and the more unpredictable their occurrence, the greater the impact was on their quality of life. This made it more difficult for most patients to deal with their oral TKI treatment, and increased the risk for non-adherence behavior in patients with a focus on quality of life.

Two perceptions of side effects were reported. Some participants indicated that side effects were probably unavoidable. They perceived side effects as a sign that the treatment worked. Hence, they were willing to accept them up to a certain extent. For others, strong side effects were a sign that the treatment was too strong for them. Patients with a focus on survival often endured side effects, while patients with a focus on quality of life more often stopped the treatment

and took drug holidays until side effects decreased and quality of life was acceptable again. Side effects becoming less severe and disappearing to some extent, often made it easier to start taking their medication again. Drug holidays often became more attractive when side effects decreased quickly.

Being informed about side effects

Participants indicated that knowing in advance which side effects would occur was reassuring because then they could recognize symptoms as being side effects of their therapy. When they experienced side effects, they were reassured that nothing else was the matter, such as a progression of their disease. Participants reported that they were not always well informed about (1) the importance of reporting side effects and (2) the normal course of side effects (i.e. the increase or decrease of side effects over time). Some participants endured side effects and suffered a low quality of life because they thought that side effects would become less severe over time after their body got used to the oral TKI. However, this was not always the case. In some participants, oral TKI side effects accumulated over time.

Hope

Many participants tried to retain hope. For participants, hope seemed to involve keeping in mind a positive outcome in an uncertain situation, even if they were well informed by healthcare professionals about their medical prognosis. They needed hope to: (1) stand the multitude of uncertain situations with which they were confronted (e.g. How long will the medication work?, How long will my body endure the medication?, How long can I live with the medication?, and What are the alternatives if the medication does not work?), and (2) continue their therapy while they experienced a low quality of life. The more intense the side effects and the lower the quality of life, the more they needed hope to continue their therapy.

To maintain hope, four strategies were reported. The first strategy was creating the mental perspective of a medication-free period. Due to the intensity of side-effects, the experienced quality of life was in great contrast with the quality of life

they had before the disease. Small things before the disease, associated with normal daily life, were no longer possible due to medication prescriptions (such as using alcohol) or side effects (such as working in the garden). Participants often felt an intense desire for these 'unreachable daily life things'. Therefore, several participants hoped for a medication-free period without side effects in which they could do the things they did before. This perspective gave them courage to endure their therapy with often intense side effects.

> *"I don't know how long I have to take this medication. The doctor said lifelong, but if my next CT scan is positive, I'll inquire whether I can stop the treatment for one or two months during the summer. Then I could enjoy a barbecue and drink a glass of wine. Now, I'm often so tired and side effects are so intense. I just want to have a normal life again for a while."*

The second strategy was looking for illustrations of the outcomes participants hoped for. Several participants looked e.g. for stories of patients undergoing oral TKI therapy for a long time without becoming resistant to the oral TKI or patients who had been cured of cancer with oral TKI. Another strategy was expressing their belief in scientific progress. Several patients hoped that medication would become available that would cure their cancer and that would not be harmful to other organs. The last strategy was hoping for a positive outcome. Some patients indicated that keeping in mind a positive outcome such as the oral TKI being effective or being the exceptional patient who survived and was cured of the cancer gave them courage to endure the therapy or start to take their oral TKI again after a drug holiday or after a medication free period.

Participants were often driven by hope when they started to take their oral TKI again after a longer drug holiday. After side effects were mitigated by taking a drug holiday, patients regained courage and started to take their oral TKI again.

When hope was undermined by healthcare professionals who emphasized medical reality or negated hopeful reactions, participants often lost their trust in these healthcare professionals. By withdrawing their trust, they often decreased the importance of what healthcare professionals said.

> *"When I said I felt the medication was working, the doctor said I would never be cured again from the cancer. I think that's a wrong reaction. Instead, they should encourage patients. I do not listen anymore to what she (the doctor) says. My body tells me that the medication works."*

Several participants reported they felt discouraged by such reactions from healthcare professionals. As a result, some of the participants no longer reported side effects and started to experiment with their oral TKI themselves in order to improve their quality of life. This increased the risk of non-adherence behavior.

Anxiety

Many participants experienced anxiety when being treated with oral TKIs. They were anxious and uncertain about the future, they often feared that the medication would lose its effectiveness and that their body would become resistant to the oral TKI. Participants were often aware of the vital role of oral TKI intake. Many described taking the treatment as 'having no choice'. Participants described anxiety about dose reductions, the amount of medication, and when confronted with other health problems.

Anxiety about a dose reduction

Some participants feared that a dose reduction would decrease their survival time. As a result, they often did not report side effects. Especially patients with a focus on survival held a strong belief that they were ultimately in control of the success of the treatment by enduring and often postponed reporting side effects. When doses were reduced as a result of reporting side effects, some participants experienced this as a personal failure: they failed to endure the side effects.

> *"The doctor questioned my quality of life because I'm so sick from this medication. She wanted to give me a lower dose: 25mg instead of 37.5mg, but I refused. I'll hold on. It's the only option if I want to have a chance. It's very very hard, but I have to go on, I have to go on. I just don't have any other choice."*

Some healthcare professionals communicated to patients that the oral TKI was the last treatment option. Furthermore they sometimes communicated that further treatment with the oral TKI would only be considered if the oral TKI showed significant positive results within a certain period of time, as the treatment was very costly (to society). This often made patients fearful and reluctant to report side effects, especially patients with a focus on survival.

Anxiety about the amount of medication

Beside the oral TKI, patients often had to take other medications to treat side-effects or comorbidities. They often feared that the amount and combination of different medications would affect their body. Several patients worried about this, which made the treatment even more burdensome for them.

> *"It's hard, I have to take (counts aloud) 3, 6, 11 pills. Eleven pills, that's almost a meal. I never had to take any medication in the past and now suddenly I have to take 11 pills and I was not a pill taker. I think it will affect my stomach because I'm not used to taking so many pills. This really worries me."*

Anxiety when confronted with other health problems

Several participants indicated that they feared that their body could not bear side effects when they were confronted with other health problems (for instance flu). Due to the additional health problem, patients often felt exhausted and no longer had the capacity to endure side effects. As a result, some patients stopped (temporarily) taking the oral TKI.

> *"When you feel so sick and miserable [due to the combination of the side effects from the oral TKI treatment and flu], you just can't think about tomorrow. Then you just want the misery to end. "*

Trust

A relationship based on trust with healthcare professionals increased the likelihood of finding a balance between survival and quality of life. Such a relationship made most patients feel more comfortable about reporting side

effects and able to be honest about their quality of life and about the difficulties they experienced in dealing with their oral TKI. Within a relationship of trust, most patients were confident that the best was being done for them. They often did not feel they were undermining their chances of survival by being open with healthcare professionals.

Participants reported a relationship based on trust as a result of a supportive approach by healthcare professionals. This approach gave them the feeling they were treated as a person and not only as a patient. They felt supported and were reassured that the best was being done for them.

> *"If you have any questions, they are there. You never feel alone. I think that's very important to many patients. You do not have the feeling to be just one of many and if you have any questions, you also get the chance to talk about it."*

From the patients' perspective, elements that contributed to a trusting and supportive relationship were: (1) openness, (2) taking time, (3) an informative approach, (4) support in treating side effects, (5) accessibility and continuous availability of healthcare professionals, (6) seeing patients on a regular basis, and (7) signs of a good multidisciplinary collaboration between healthcare professionals.

Feedback mechanisms

Feedback mechanisms from medication, healthcare professionals, and follow-up examinations played an important role in adherence behavior.

Some participants expected feedback from their *body* by a physical reaction when they were non-adherent to their treatment regimen. Some participants expected that 'something' would happen, for instance that side effects would become more severe and intense. When physical reactions did not clearly occur, this risk for non-adherence behavior in the future increased.

> *"The first time I forgot to take the medication, I thought something was going to happen such as a reaction in my blood, or side effects that would increase. But that was not so. Nothing happened."*

Participants did not always receive feedback on their behavior from *healthcare professionals*. When participants forgot to take their oral TKI, and reported it to healthcare professionals, they received the feedback that forgetting one time is not harmful. This often reinforced non-adherence behavior. They learned that occasionally forgetting to take the oral TKI was not that bad. When they forgot to take the oral TKI a second time, they often did not report it anymore to healthcare professionals.

Blood tests and scans provided participants with feedback on their behavior. At that point, they received feedback about the progression of the disease and the impact of the medication on the disease. Positive scan results were often a motivation to continue therapy. Some participants with a focus on survival saw the positive results as a reward for their efforts: enduring the side effects led to the results they hoped for.

DISCUSSION

This study shows that in dealing with oral TKI therapy, three foci can be defined: a focus on survival, a focus on quality of life, and a balance between survival and quality of life. The foci (theoretical framework) developed in this study help to explain how non-adherence behavior arises, which increases the understanding of the phenomenon of non-adherence to oral TKIs. A complex and interrelated set of factors was found to influence the patients' focus. Researching processes and factors influencing (non-)adherence by means of qualitative research instead of quantitative research made it possible to explain how e.g. side effects, hope, and anxiety contribute to adherence or non-adherence behavior in these patients. The influence of hope, anxiety, trust, and feedback mechanisms on adherence behavior have received little attention in literature until now.

Treatment related side effects were found to be a crucial factor influencing (non-)adherence in patients taking oral TKIs in this study. This corroborates other research findings on factors associated with non-adherence to OACD

(Grunfeld et al., 2005; Kirk and Hudis, 2008; Regnier Denois et al., 2010; Eliasson et al., 2011).

Patients focusing on survival often do not report side effects, fearing a dose reduction and a decrease in efficacy of the treatment. This has been reported previously (Regnier Denois et al., 2010). Based on in-depth analyses of our interviews, three interrelated mechanisms could explain this finding. First, some patients believe that bearing the side effects will lead to better results, as they assume the prescribed oral TKI and dose will lead to higher survival rates. Second, some patients might have a high internal locus of control (i.e. the belief to be personally responsible for the own health) (Wallston et al., 1978). They act as if they believe they are ultimately in control of the success of the treatment by enduring and often not reporting side effects. Third, some patients are not adequately informed about (1) the course of side effects (i.e. the increase or decrease of side effects over time), and (2) the importance of reporting side effects.

Hope was found to be an important influencing factor in this study. This confirms other studies' findings in cancer patients (McMillan and Weitzer, 1998; Thorne et al., 2008). Hope is crucial for patients to cope with their disease and treatment. The meaning of hope for patients often contrasts with the meaning of hope for healthcare professionals. For patients, hope is a mechanism to stand the disease and the therapy and is a necessity for living (Thorne et al., 2007). For healthcare professionals, hope is often the objective chance for a positive outcome (such as survival rates) (Thorne et al., 2006). Healthcare professionals can undermine hope by emphasizing medical reality, for example by quoting statistical information on prognosis (Thorne et al., 2006). Undermined hope is found to be associated with emotional distress, problematic coping or poor disease management (Thorne et al., 2007). Undermined hope leads to a reduced capacity to continue to engage with life (Elliot and Olver, 2006; Kim et al., 2006). Our study adds that undermining hope may affect the relationship between healthcare professionals and patients. As a result, patients may no longer report side effects and may start to experiment with their oral TKI without

consulting healthcare professionals. Consequently, the choices patients make are not always based on sound knowledge and could endanger the effectiveness of the therapy, the quality of life, and could increase the risk for toxicity.

Implications for practice and future research

The results of this study could help healthcare professionals to deal in a more nuanced way with the non-adherence behavior of patients taking oral TKIs. Patients could have good reasons to be non-adherent to the oral TKI therapy. Healthcare professionals should be aware that an oral TKI regimen is stressful (severity, intensity and unpredictable character of side effects) and strongly impacts quality of life, as previously reported by Philips and colleagues (2013). Healthcare professionals should take care that adherence does not become the sole focus, but should also take into account the patients' perspectives of quality of life, since a balance between quality of life and survival makes the therapy more feasible for patients. A patient's motivation and energy to endure therapy may be reduced by the demands of the disease and therapy, referred to as ego depletion (Baumeister et al., 1998; Baumeister, 2003). In patients experiencing severe side effects, healthcare professionals should be aware that each new demand may lead to ego depletion, which can result in decreased quality of life and a decreased adherence to medical recommendations (Solberg Nes et al., 2013).

Conditions should be established by which patients get maximum opportunity to establish a balance between survival and quality of life. An open climate and a trust based relationship should be created so that patients can report side effects without the fear of undermining their chance of survival. Reporting side effects enables healthcare professionals to support patients in dealing with side effects or changing a dosage or medication in order to make quality of life as acceptable as possible. The association between trust and adherence behavior has previously been studied in other pathologies (Van Hecke et al., 2011). Based on the results of our study, a relationship based on trust could be established by (1) not undermining patients' hope, (2) interpersonal competence

(active listening, caring, empathy, providing information and answering questions), (3) regular contacts, (4) accessibility of healthcare professionals (e.g. by telephone permanence), and (5) sufficient time during appointments to listen to the patients' experience of the treatment and the disease. Not undermining patients' hope and interpersonal competence were also found to contribute to a relationship based on trust in other studies (Benzein and Saveman, 1998; Mechanic and Meyer, 2000). However, our study adds to the literature how undermining hope could withdraw trust and may, in turn, lead to non-adherence behavior.

Furthermore, patients should be guided in making adequate decisions regarding their therapy by: (1) patient-centered education about (the development of) side-effects to set realistic expectations, (2) informing patients as to how medication works and why it is important to follow instructions, and (3) discussing the possible ways of incorporating the regimen adequately into daily life.

Methodological considerations and limitations

Despite the heterogeneity of the sample (i.e. different types of cancer and different oral TKIs), data saturation was reached for the study population. The reported findings apply to blood cancers as well as solid tumors and their treatments with different oral TKIs.

The study was conducted in Belgium so the results of this study should be interpreted in the context of Western European healthcare systems. Caution should be used when generalizing the findings to other countries as cultural differences may influence illness experience and healthcare practice (Kleinman and Benson, 2006).

In 9 of the 30 interviews, a third person was present (mostly the patient's partner) for all or part of the interview at the request of the patient. In some interviews, the third person answered a part of the questions. The perspective of the third person however, may be different from the patient's perspective. Despite the interview techniques employed to create openness, the patients' openness may have been affected by the presence of a family member in some

of the interviews. Patients may have avoided a discussion of fears and concerns in order to protect their family members (Leydon et al., 2000; Bachner and Carmel, 2009).

Despite emphasizing anonymity before the start of each interview and the encouragement to be open, it was still possible that some participants did not felt comfortable talking openly about non-adherence. Talking about non-adherence could have created feelings of guilt or patients could have been afraid to be stigmatized as a non-adherent patient. To promote a climate of comfort to talk about (non-)adherence, special attention was paid to the use of non-threatening and non-judgmental questions such as: “For some patients, it is hard to take their medication as prescribed because of various reasons. How is that for you?”.

CONCLUSION

This qualitative study gives insight into the processes and factors influencing (non-)adherence in patients taking oral TKIs and their interrelatedness. Three foci, determined by a set of influencing factors on adherence in patients taking oral TKIs is presented. A focus on survival, a focus on quality of life, and a balance between survival and quality of life were found. Treatment related side effects, hope, anxiety, trust, and feedback mechanisms were found to be major influencing factors. The results of this study may help healthcare professionals to understand why patients taking oral TKIs do not always adhere to their therapy and aid them in developing interventions to support these patients in coming to a balance between survival and quality of life.

Table 1: Demographic-, Disease-, and Treatment-related Characteristics of the Participants

		Mean (SD)	Range
Age			
	Men (n=18)	58.1 (12.2)	36-79
	Women (n=12)	60.5 (13.0)	42-88
	Total	59.1 (12.3)	36-88
Years since diagnosis		3.7y (1.9y)	4m – 8.8y
		n	
Current social situation			
	Living with a partner	21	
	Living alone	9	
Children			
	Yes	25	
	No	5	
Number of OACD since start oral therapy			
	1	21	
	2	6	
	3	2	
	≥4	1	
Diagnosis			
	RCC[a]	12	
	CML[b]	8	
	Breast cancer	4	
	Skin cancer	3	
	GIST[c]	1	
	HCC[d]	1	
	Non-small cell lung cancer	1	

[a]Renal Cell Cancer, [b]Chronic Myeloid Leukemia, [c]Gastrointestinal Stromal Tumour, [d]Hepatocellular Carcinoma

TABLE 2: *Topic List*

Patients' attitude towards the medication regimen
Perceptions about the medication
Worries about the medication
Trust and belief
Expectations
Barriers and facilitators of medication adherence
Principles of self-management
Fit medication into daily life
Adherence
Coping with the therapy and its consequences
Information
Information from healthcare professionals
Information seeking
Understanding and evaluation of received information
Social support
Side effects

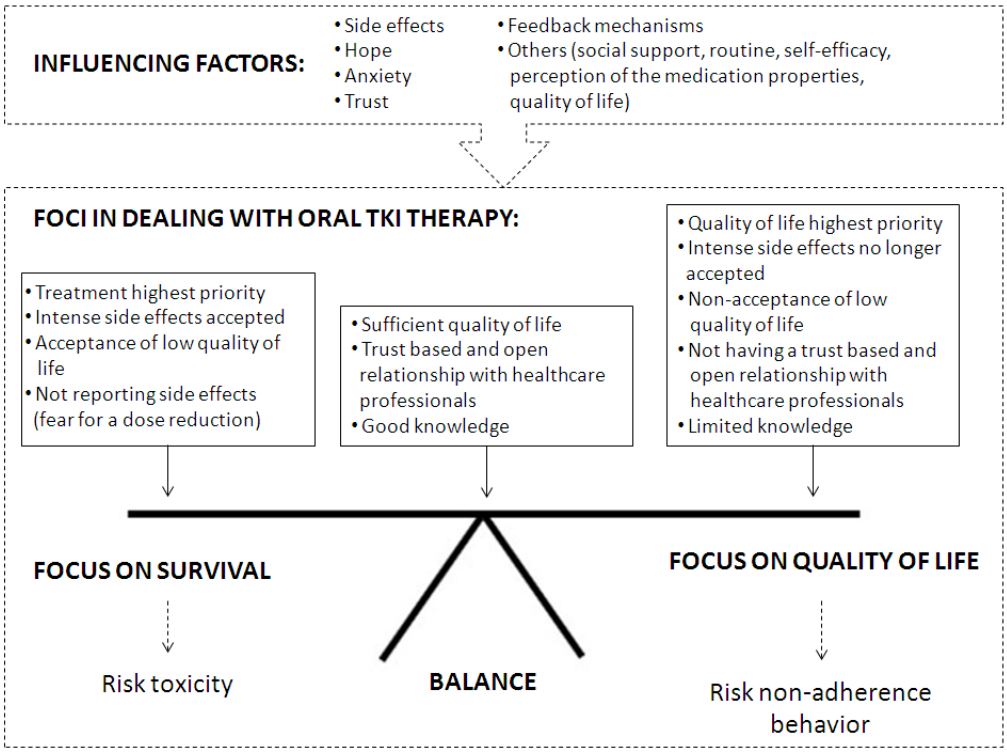

Figure. Foci in dealing with oral TKI therapy

REFERENCES

Anderson KR, Chambers CR, Lam N, et al. Medication adherence among adults prescribed imatinib, dasatinib, or nilotinib for the treatment of chronic myeloid leukemia. *Journal of Oncology Pharmacy Practice.* 2014.

Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. *Perspectives in Pharmacology.* 2005;315(8):971-979.

Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *Eur J Cancer.* 2006;42:2271-2276.

Bachner YG, Carmel S. Open communication between caregivers and terminally ill cancer patients: the role of caregivers' characteristics and situational variables. *Health Communication.* 2009;24:524-531.

Banna LG, Collovà E, Gebbia V, Lipari H, et al. Anticancer oral therapy: emerging related issues. *Cancer Treat Rev.* 2010;69:595-605.

Baumeister RF, Bratslavsky E, Muraven M, et al. Ego depletion: Is the active self a limited resource? *J Pers Soc Psychol.* 1998;74(5):1252-65.

Baumeister RF. Ego depletion and self-regulation failure: a resource model of self-control. *Alcohol Clin Exp Res.* 2003;27(2):281-284.

Benzein E, Saveman B-I. Nurses' perception of hope in patients with cancer: a palliative care perspective. *Cancer Nurs.* 1998;21(1):10-16.

Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality and Quantity.* 2002;36:391-409.

Brown SC, Stevens RA, Troiano PF, et al. Exploring complex phenomena: grounded theory in student affairs research. *Journal of College Student Development.* 2002;43(2):173-183.

Black N. Why we need qualitative research. *J Epidemiol Community Health.* 1994;48:425-426.

Charmaz, K. (2006). Constructing grounded theory: A practical guide through qualitative analysis. London: Sage.

Darkow T, Henk HJ, Thomas Sk, et al. Treatment interruption and non-adherence with imatinib and associated healthcare costs – a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics.* 2007;25(6):481-496.

Eliasson L, Clifford S, Barber N, et al. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res.* 2011;35:626-630.

Elliot JA, Olver IN. Hope and hoping in the talk of dying cancer patients. *Soc Sci Med.* 2006; 64:138-149.

Foulon V, Schöffski P, Wolter P. Patient adherence to oral anticancer drugs: an emerging issue in modern oncology. *Acta Clin Belg.* 2011;66(2):85-96.

Glaser BG, Strauss A. *The Discovery of Grounded Theory*. Chicago: Adline Atherton; 1967.

Grunfeld EA, Hunter MS, Sikka P, et al. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Educ Couns.* 2005;59:97-102.

Irshad S, Maisey N. Considerations when choosing oral chemotherapy: identifying and responding to patient need. *European Journal of Cancer Care.* 2010;19:5-11.

Jönsson S, Olsson B, Söderberg J, et al. Good adherence to imatinib therapy among patients with chronic myeloid leukemia – a single-center observational study. *Ann Hematol.* 2012; 91(5):679-685.

Kekäle M, Talvensaari K, Koskenvesa P, et al. Chronic myeloid leukemia patients' adherence to peroral tyrosine kinase inhibitors compared with adherence as estimated by physicians. *Patient Preferences and Adherence.* 2014;8:1619-1627.

Kim DS, Kim HS, Schwartz-Barcott D, et al. The nature of hope in hospitalized chronically ill patients. *Int J Nurs Stud.* 2006;43:547-556.

Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clin Breast Cancer.* 2008;8(2):155-161.

Kleinman A, Benson P. Cultural, moral experience and medicine. *The Mount Sinai Journal of Medicine.* 2006;73(6):834-839.

Krouse RS, Rosenfeld KE, Grant M, et al. Palliative care research: issues and opportunities. *Cancer Epidemiol Biomarkers Prev.* 2004;13:337-339.

Levitzki A. Tyrosine kinase inhibitors: views of selectivity, sensitivity, and clinical performance. *Annu Rev Pharmacol Toxicol.* 2013; 53:161-185.

Leydon GM, Boulton M, Moyniham C, et al. Cancer patients' information needs and information seeking behaviors: in depth interview study. *BMJ.* 2000;320, 909-913.

Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol.* 2010;28(14):2381-2388.

McMillan SC, Weitzer M. Quality of life in cancer patients: use of a revised Hospice index. *Cancer pract.* 1998;6:282-288.

Mechanic D, Meyer S. Concepts of trust among patients with serious illness. *Soc Sci Med.* 2000;51(5):657-668.

Nekhlyudov L, Li L, Ross-Degnan D, et al. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. *Breast Cancer Res Treat.* 2011;130:589-681.

Neugut A, Subar M, Wilde ET, et al. Association between prescripton co-payment amount and compliance with adjuvant hormonal therapy in

women with early-stage breast cancer. *J Clin Oncol.* 2011; 29(18):2534-2542.

Noens L, van Lierde M-A, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood.* 2009;113(22):5401-5411.

Palinkas LA, Horwitz SM, Green CA, et al. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health.* 2013.

Partridge AH, Wang PS, Winer EP, et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol.* 2003;21(4):602-606.

Partridge AH, Archer L, Kornblith AB, et al. Adherence and persistence with oral adjuvant chemotherapy in older women with earl-stage breast cancer in CALGB 49907: adherence companion study 60104. *J Clin Oncol.* 2010;28(14):2418-2422.

Phillips KM, Pinilla-Ibarz J, Sotomayor E, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. *Support Care Cancer.* 2013;21:1097-1103.

Regnier Denois V, Poirson J, Nourissat A, et al. Adherence with oral chemotherapy: results from a qualitative study of the behavior and representations of patients and oncologists. *Eur J Cancer Care.* 2010;20:520-527.

Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA: Cancer J Clin.* 2009;59(1):56-66.

Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Res Treat.* 2011;125(1):191-200.

Solberg Nes L, Ehler SL, Patten CA, et al. Self-regulatory fatigue in hematologic malignancies: impact on quality of life, coping, and adherence to medical recommendations. *International Journal of Behavioral Medicine.* 2013;20:13-21.

Stavropoulou C. Non-adherence to medication and doctor-patient relationship: evidence from a European survey. *Patient Educ Couns.* 2011;83:7-13.

Thorne S, Hislop TG, Kuo M, et al. Hope and probability: patient perspectives of the meaning of numerical information in cancer communication. *Qualitative Health Research.* 2006;16(3):318-336.

Thorne S, Oglov V, Armstrong E-A, et al. Prognosticating futures and the human experience of hope. *Palliative and Supportive Care.* 2007;5:227-239.

Thorne SE, Hislop TG, Armstrong E-A, et al. Cancer care communication: The power to harm and to power to heal? *Patient Education and Counseling.* 2008;71:34-40.

Threlfall AG, Milsom KM, Hunt M, et al. Exploring the content of the advice provided by general dental practitioners to help prevent caries in young children. *British Dental Journal.* 2007;202:E9.

Van Hecke A, Verhaeghe S, Grypdonck M, et al. Processes underlying adherence to leg ulcer treatment: a qualitative field study. *Int J Nurs Stud.* 2011;48(2):145-155.

Verbrugghe M, Verhaeghe S, Lauwaert K, et al. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treat Rev.* 2013;39:610-621.

Vervoort S, Borleffs J, Hoepelman A, et al. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS.* 2007;21:271-281.

Wallston KA, Wallston BS, de Vellis R. Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Educ Monogr.* 1978;6:160-170.

Xu S, Yang Y, Tao W, et al. Tamoxifen adherence and its relationship in mortality in 116 men with breast cancer. *Breast Cancer Res Treat*. 2012;136(2):495-502

CHAPTER 4

FACTORS INFLUENCING THE PROCESS OF MEDICATION (NON-)ADHERENCE AND (NON-)PERSISTENCE IN BREAST CANCER PATIENTS WITH ADJUVANT ANTIHORMONAL THERAPY: A QUALITATIVE STUDY

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ABSTRACT

Non-adherence and non-persistence in breast cancer patients taking antihormonal therapy is common. However, the complex patterns and dynamics of adherence and persistence are still not fully understood. This study aims to give insight into the process of (non-)adherence and (non-)persistence by researching influencing factors and their interrelatedness in breast cancer patients taking antihormonal therapy by means of a qualitative study with semi-structured interviews. The sample consisted of 31 breast cancer patients treated with antihormonal therapy. Purposive and theoretical sampling and the constant comparison method based on a grounded theory approach were used. Expectations regarding the impact of antihormonal therapy, social support from family and friends, and recognition from healthcare professionals were found to influence the process of non-adherence and non-persistence. The results of this study can help healthcare professionals understand why breast cancer patients taking antihormonal therapy do not always adhere to or persist in taking the therapy and may facilitate patient-tailored interventions.

INTRODUCTION

Breast cancer is the most prevalent cancer in women (Brennan and Houssami, 2011). In approximately 75%, the cancer is oestrogen-receptor positive (Anderson, 2002). Most of the breast cancer patients with oestrogen-receptor positive breast cancer cells receive adjuvant antihormonal therapy (AHT) to reduce the risk of recurrence (Early Breast Cancer Trialists' Collaborative Group, 2011). Two main types of AHT are currently used in the treatment of breast cancer: aromatase inhibitors and selective estrogen receptor modulators (SERMs). A treatment regimen of at least five years with tamoxifen, a SERM, is the most commonly prescribed AHT for patients with oestrogen-receptor positive breast cancer. A five year regimen with adjuvant tamoxifen has been shown to reduce the recurrence risk by 46% and the breast cancer mortality risk by 26% (Early Breast Cancer Trialists' Collaborative Group, 1998).

For optimal treatment effectiveness, adherence to AHT and persistence are important (Early Breast Cancer Trialists' Collaborative Group, 1992). Adherence is the extent to which patients follow the instructions on taking their medication (Osterberg and Blaschke, 2005). Optimal persistence is the time period during which patients continue to take their medication as prescribed (Ruddy et al., 2009). In literature, early discontinuation is often used as a synonym for non-persistence. Non-adherence to AHT ranges from 11 to 60% (Doggrell, 2011; Fontein et al., 2012; Güth et al., 2012), depending on (1) the tool used to measure non-adherence, and (2) the definition of non-adherence (Güth et al., 2012). Non-persistence rates for the five-year course of AHT ranges from 31 to 34% (Lash et al., 2006; Güth et al., 2008; Hershman et al., 2010). Non-adherence and non-persistence rates increase with time treated with AHT (Barron et al., 2007; Fontein et al., 2012). In a study by Herk-Sukel et al. (2010), the cumulative percentage of patients discontinuing tamoxifen was 17% in the first year, 30% in the second year, 45% in the third year, 50% in the fourth year and 60% in the fifth and last year.

Factors associated with non-adherence and non-persistence in breast cancer patients taking AHT are complex and interrelated (Ruddy et al., 2009; Verma et

al., 2011; Verbrugghe et al., 2013). Treatment related side effects, longer duration of therapy, and younger- and older age are found to be predominant factors associated with non-adherence in breast cancer patients taking AHT (Verbrugghe et al., 2013). In a study by Grunfeld et al. (2005), 46% of the non-adherent patients taking AHT reported side effects as the primary reasons for non-adherence to tamoxifen. The main side effects reported in that study were hot flashes, cognitive disfunctions, night sweats, emotional problems, sleep problems, weight gain, and loss of libido. Predominant factors associated with non-persistence in breast cancer patients taking AHT are older age, younger age, and treatment-related side effects (Verbrugghe et al., 2013).

Extensive quantitative research has been conducted to explore factors associated with non-adherence and non-persistence in breast cancer patients taking AHT (Verbrugghe et al., 2013). However, the complex patterns and dynamics of (non-)adherence and (non-)persistence in breast cancer patients taking AHT are still not fully understood. A qualitative study can give us insight into the process of (non-)adherence and (non-)persistence to AHT as qualitative research is more appropriate for the study of experiences in the context of an experiential process (Morse and Field, 1996). Furthermore, qualitative research can show us how to understand the findings of quantitative research by providing insight into the way several factors found to be associated with (non-)adherence and (non-)persistence contribute to the process of (non-)adherence and (non-)persistence. To our knowledge, only one qualitative study on (non-)adherence with AHT has been conducted, focusing exclusively on (non-)adherence in breast cancer patients taking tamoxifen (Pellegrini et al., 2010). However, in the study by Pellegrini et al. (2010), the focus was narrowed to the exploration of the relation between adherence and perceptions of the treatment and experienced side effects.

This study aims to give insight into the process of (non-)adherence and (non-)persistence by researching influencing factors and their interrelatedness in breast cancer patients taking AHT (both SERMs and aromatase inhibitors).

METHODS

A qualitative study based on principals of grounded theory, e.g. purposive and theoretical sampling and the constant comparison method (Glaser and Strauss, 1967) was used.

Setting and sample

In total, thirty-one patients were recruited in a university hospital in Belgium. Inclusion criteria were: diagnosed with breast cancer within the last six years, receiving AHT, ≥ 18 years old, and Dutch speaking.

In the initial phase of data collection, participants with different characteristics were recruited, with the aim of broadly exploring the experience of breast cancer patients treated with AHT. Purposive sampling was used to assure the representativeness of participants who had been on AHT for different periods of time. As soon as influencing factors of (non-)adherence and (non-)persistence to AHT were found from the initial data, theoretical sampling was used in order to elaborate, refine and test the discovered influencing factors and their interrelatedness (Coyne, 1997). Patients with suspected non-adherence to the AHT, those in a further stage of the AHT treatment, and those who had stopped the treatment, were recruited. The new data furthered insight into the process of (non-)adherence and (non-)persistence.

Data collection

A team consisting of a clinical nurse specialist and breast cancer nurses working in the university breast clinic contacted potential participants and informed them about the study. If patients wanted to take part in the study, a researcher contacted the patients to give them further information and to make an appointment for the interview.

Semi-structured interviews were held at the place of preference of the participants. The interview topics included the care provided, the received information about AHT, the use and perception of AHT, adherence, social support, and patients' needs. The interviews started with the open question:

“How have you experienced the antihormonal therapy so far?”, to encourage the participants to tell their story in their own words. Demographic data were collected at the end in order not to interrupt the narrative flow of the interview.

Data collection was part of a cyclic process of data collection and analysis. As the process of data collection and analysis advanced, the topic list was adjusted and new topics were added to the topic list. New topics were: perceptions on finishing the five year AHT, coping with side effects of the AHT in daily life, (evolution of) social support, the influence of feeling supported by healthcare workers, and the influence of information on and expectations about the impact of the AHT. As the insight into the process of (non-)adherence to AHT and (non-)persistence progressed, a more structured interview style was used.

Interviews were held between November 2011 and May 2014. All the interviews were conducted by two researchers. Every interview was audio taped, transcribed verbatim, and verified for transcription accuracy. After the interviews, memos on the context and reflections on the interpretation of themes were made. The interviews took on average 44 minutes (range 14-125).

Data analysis

The interviews were read and re-read in order to become familiar with the data. The factors influencing (non-)adherence to AHT and (non-)persistence were developed based on thorough discussion among five researchers. Every new insight that emerged from the group discussion was compared to the data. The analytical process revealed new topics to be included in the following interviews.

Data were entered into NVivo 10 (QRS International Pty. Ltd.). A code tree was developed. After 9 interviews, factors were distilled out of the data. After specific recruitment (e.g. patients who had stopped AHT) and a thorough discussion, we were able to see how the factors were related and how they influenced (non-)adherence behavior and (non-)persistence. All the transcripts were reread with the identified factors to trace how they were represented in the interviews.

Data collection and analysis took place iteratively. Data were analyzed based on the constant comparison analyzing aspect of grounded theory (Boeije, 2002)

until theoretical saturation was achieved. This means that new interviews no longer furthered the refinement of the theoretical framework (the process of (non-)adherence and (non-)persistence).

Validity

To enhance the validity of the interpretations, researcher triangulation was used in all the phases of the study. To improve the quality of data collection, two supervisors (A.V.H. & E.D.) gave feedback on the interview style, the codes and data analysis. Additionally, an expert in qualitative research (S.V.) who was not previously involved in the data analysis, verified the data analysis by reading several interviews and discussing the analyses on two occasions at the end of the study.

Ethical considerations

The study was approved by the Ethical Review Committee of the participating hospital. All participants were given written and verbal information about the study and gave informed consent to participate. Identifiable information was removed from the transcripts. Audio files were deleted at the end of the study.

RESULTS

First demographic data will be presented. Second, a selection of the most important factors influencing the process of (non-)adherence and (non-)persistence will be presented (experiences with the previous trajectory, expectations regarding the impact of AHT, impact of the AHT and the experience of the follow-up period, perceptions of AHT, social support, and support by healthcare professionals). Third, the way influencing factors lead to (non-)adherence or (non-)persistence, will be presented (theoretical framework). The second part is mainly the result of purposive sampling and analysis aiming at the broad exploration of the experiences of breast cancer patients treated with AHT. The third part is mainly the result of theoretical sampling and analysis aiming to get insight into the interrelatedness of the influencing factors

(experiences) until theoretical saturation was achieved. In the third part, the findings presented in part two are combined and presented in a theoretical framework: the process of (non-)adherence and (non-)persistence.

Demographic data

Table 1 shows the demographic and treatment-related characteristics of participants. Most participants were > 50 years old (n=21), married (n=20) with children (n=23). Almost all participants previously received surgery (n=30), and received chemotherapy (n=22) and/or radiotherapy (n=23). Fourteen participants were treated with an aromatase inhibitor, while 17 participants were treated with tamoxifen. The time participants were on AHT was equally distributed over the five years of AHT treatment. Two participants were interviewed after the five year treatment period had ended.

Factors influencing the process of (non-)adherence and (non-)persistence

Experience with the previous trajectory: the context for antihormonal therapy

The way participants experienced the previous trajectory (from cancer diagnosis until the start of the AHT), influenced the way they gave meaning to the AHT.

Participants often compare the AHT with previous treatments (chemotherapy, radiotherapy, surgery, targeted therapy). Previous treatment was perceived as very intense, both physically and psychologically.

During previous trajectory, they generally felt well supported and recognized by family, friends, and healthcare professionals. Most participants felt to be intensively managed and well informed by healthcare professionals about the treatment and the impact thereof. This often made participants less anxious, as it helped them to prepare for what to expect in the near future.

Expectations regarding the impact of antihormonal therapy

Expectations regarding the impact of the AHT are strongly influenced by the information given to the participants by healthcare professionals (mostly physicians). Being poorly informed about the possible impact of the AHT strengthens the expectation that the AHT is not a difficult regimen to follow.

Patients may also expect that the impact of the AHT will be limited because they believe that AHT could not be any worse than the previous treatment. They expect to be able to resume their normal lives after chemotherapy or radiation therapy ended. Participants often attached most importance to the information they received from the physician, especially when they felt they had been well informed and supported during the previous treatment.

> *"The physician only told me I had to take the AHT medication and that I didn't have any other choice than taking the AHT. She didn't say much about side effects. She said that side effects were different for every person and that I would find out."*

Impact of the antihormonal therapy and the experience of the follow-up period

How the AHT affects someone's life depends on the seriousness of side effects, the psychological and social consequences of these side effects, and on the contrast between life with AHT and life before the disease.

Side effects such as fatigue impede participants in performing their normal daily activities. Physical changes such as weight gain and vaginal dryness constantly confront participants with the fact that they are not the same person anymore, and perhaps will never be again.

> *"After the previous treatments, I wanted to put it out of my head and go on with my life. But when I buy new clothes, I have to buy a bigger size, which confronts me with that goddamn disease. I want to leave this chapter behind and be like before. I do not think I will ever be the same again, and that is very hard to accept."*

The impact of side effects also depends on the phase of life. For premenopausal women, taking AHT means they almost immediately go into menopause, while this process otherwise takes years. This makes the contrast with the past suddenly very large and irreversible. It often entails a further perceived loss of their femininity (after e.g. mastectomy) over which they have no control or influence. As a result of the sudden, irreversible and uncontrollable change, participants feel alienated from themselves and their future.

Participants for whom the impact of the AHT is high, often feel compromised in their roles as mother, partner, housewife, and friend. Due to the side effects they can no longer fulfill these roles as before. Because of fatigue, for example, participants are not able to see friends the way they were used to, or they are not able to do as much housework. Faced with side effects such as vaginal dryness and a strong reduction of libido, participants have less sexual intercourse with their partner, which can make them feel inferior as a woman and as a partner. The discrepancy between the participants' desire and their abilities makes them feel frustrated, helpless and worthless. In the interviews, the participants suggest feeling inadequate and guilty towards their partner, family and friends. In sum, they feel permanently a cancer patient. Because of feelings of inferiority and shame, some participants hardly go outside and isolate themselves.

> *"In the beginning, it was very difficult for me that my husband had to clean the house and I could only look on. I sat there crying because I like to clean the house and I could do nothing."*

> *"For him, I regret. I do not feel the desire to have sex anymore. That is over. And then I think: "He is normal". I do not feel normal anymore. I do not feel like a woman anymore."*

In the follow-up period, participants are anxious that the breast cancer will recur. This anxiety makes them hyper alert to bodily sensations. They feel as if their body has let them down, which makes it difficult for them to normalize bodily sensations. This increases the need for a framework in which they can check the normality of bodily sensations and in which they can find reassurance.

> *"I have lost the ignorance of childhood. When I become aware of a bodily sensation, I always think it is cancer. The least thing I become aware of, I think it's a tumor."*

Perceptions of the antihormonal therapy

Perceptions of the AHT are closely related to the impact of the AHT. Perceptions of the AHT treatment like 'AHT is just taking a pill' or 'AHT is insignificant

compared to previous treatment' start to change as soon as they are confronted with side effects of the AHT. When participants experience the impact of AHT physically, mentally, and in relation to others, they are forced to adjust their perceptions of the AHT.

Taking the pills reminds participants that the cancer fight is not over yet. Even participants who experienced fewer side effects and who return to their 'normal life', are reminded by the daily intake that cancer is an unfinished chapter. Further, as the AHT should be taken for at least five years, the end of the treatment seems far away for patients, in contrast with the previous treatment. In the participant's experience, this is not just taking a pill but a five-year cure for cancer.

> *"Everyone acts like the treatment is over. It does not feel like the treatment is over. As long as I have to take this medication, I am not like before."*

Taking AHT gives participants the feeling that they have extra protection against a recurrence of breast cancer. This makes them feel they have control over their health. The perception of protection and control is more pronounced in participants experiencing a low impact of side effects. For them, the benefits of the therapy (protection against recurrence and feeling of a sense of control) exceed the harms (moderate side effects, confrontation with cancer). It makes them feel safe as long as they take their AHT medication. These participants are often grateful that medication exists that helps them to protect against recurrence. For participants not experiencing many side effects, it is more difficult when the end of the therapy approaches. They are anxious about recurrence when the protection of the AHT stops, which makes them feel they are losing control.

> *"The AHT is a protection against cancer. I think it will be hard for me the day I have to stop the medication. Suppose I relapse when I am no longer taking that medication. Now the medication gives me the feeling I am protected against recurrence."*

Taking the AHT is perceived as compulsory; the patient has no choice in the matter. This perception is more pronounced in participants for whom the impact of the AHT is high. They take the AHT medication because they feel responsible towards themselves, their family and friends to take care of their health. Not taking the medication as prescribed could result in feelings of guilt if they were to relapse. Also out of respect for the expertise of the physician who prescribed the AHT, participants feel as if they have no other choice than to take the AHT. The fact that AHT makes relapse less likely makes it difficult to downplay the importance of the AHT.

> *"I know I have no other choice than taking the AHT medication. It protects me against cancer and we can be reasonably sure that there will be no relapse if I take this medication for five years. I have to continue now because there is always a little voice that says: "You have had cancer."*

Social support

Social support is about an understanding attitude by family and friends towards participants for the impact they experience. A distinction is made between the social support participants receive from family and friends, and social support from peers.

Social support from family and friends

Family and friends are often the main sources of social support. Social support helps participants deal with the difficulties they encounter and makes them feel less alone.

For participants experiencing little social support from family, it is harder. They often feel they are not understood and bother others when they vent about their difficulties and concerns. Some participants mention that it seems like their partner and/or children are acting as if nothing is wrong during the phase of AHT. Participants have the feeling that their family has the idea that the AHT is something ordinary, which makes participants feel forced to resume 'normal life'.

> *"Everyone seems to think that, in the end, I've gotten off rather easy: "You've only got one pill left to take, no more chemotherapy, no more radiotherapy. The worst is behind you.". It's all minimized. They consider me to have had only half, or even quarter of a cancer. I have some issues with this. I did have the side-effects of the AHT. I felt impaired in my femininity. The fact that people then minimized it all, that was the most difficult to deal with."*

Others' expectations that one can resume 'normal life', makes it difficult for participants to talk about their problems. As a result, participants often remain silent about the way they really feel. In this way they try to avoid the incomprehension that disappoints them and makes them feel alone. Some participants hardly go outside in order to avoid confrontation with others (and incomprehension) as much as possible.

> *"You always have the same complaints and you always have to repeat them, but you can't do this at home. When you always repeat the same complaints to your husband like: "I have got this again, or that again", after a while they say: "Can you ever stop complaining?" or "God, you are a selfish person." The children would say: "You always have to complain and whine.". I really don't do that anymore, I do not talk about it anymore."*

Social support from peers

Peers are considered as equals and the only ones who can really understand participants as they have been through similar experiences. With peers, participants feel understood and supported. Sharing with peers makes them feel normal and not exceptional. They look for peers with similar bodily sensations and experiences. Participants also find reassurance regarding the cause of a bodily sensation by exchanging experiences about side effects. When participants identify with peers however, it is very confrontational if a peer suffers a relapse. As a result, the fear of being faced with bad news themselves often increases.

Support by healthcare professionals

The need to be reassured

Participants experiencing physical symptoms are often worried about the source of these symptoms *(cfr. Impact of antihormonal therapy)*. They are anxious and look for reassurance that the symptoms are side effects from the AHT and not signs of a relapse. The need to be reassured is especially high for participants who were not well informed in advance about the possible side effects of the AHT. Participants expect that physicians will discuss in detail the symptoms they may experience and take time to listen to them, support them, and help them to deal with the impact of the AHT. Participants experiencing that that healthcare professionals ignore or skim over the difficulties they mention (e.g. by saying that they need to learn to live with side effects), makes them even more worried and anxious about the origin of the experienced bodily sensations. Participants often start to doubt themselves, wondering whether they are just imagining side effects, and they start to feel like they are being particularly bothersome as a result of not feeling understood. Consequently, participants often stop sharing their experiences during follow-up period and stop reporting side effects.

As a result of experiencing not getting satisfactory answers from healthcare professionals, they often start their own search for answers and ways to handle their side effects. This is often a lonely search, looking for answers and reassurance by reading brochures, looking on the internet and talking to peers.

> *"I read the patient information leaflet and look for testimonials on the internet from women who have the same side effects as I have. When I find an answer, I feel reassured. I regret I do not find reassurance and answers with my physician."*

The need to be recognized

Participants need to be recognized for the difficulties they experience. Feeling recognized is about an understanding attitude from healthcare professionals, by which the patient feels heard. Participants report not feeling recognized when follow-up examinations feel rushed, when side effects are minimized or brushed

aside, or when self-discovered solutions to deal with side effects are not taken seriously. As a result of not feeling recognized, they become hurt, disappointed and angry because they feel misunderstood. To avoid the confrontation with disbelief and incomprehension, they often do not report their difficulties anymore, which places them in a lonely position.

> *"When I mentioned side effects I got the reaction: "You have to accept you are getting older." At that point I disconnected myself from the conversation; there was no longer any point in talking to this person. I was furious, but you can't do anything with that furiousness, and I didn't want to do anything with it anymore… At that moment you collapse and you think: "It doesn't make sense anymore to say anything".*
>
> *"I would like to say to the physicians who work by appointment, to take a little more time and to listen a little better. I had the feeling that I could not be outside fast enough. I was not dressed yet and he was already writing a prescription. That hurts."*

Feeling recognized is also about being valued as an individual by the physician. Participants feel a human approach from healthcare professionals when attention is paid to non-somatic issues and also when physicians can admit that for certain problems there is no direct solutions. Such a relationship is experienced as respectful, equal and non-intimidating. The feeling of being approached as a human being strengthens the confidence in healthcare workers and gives participants the courage to continue the therapy.

> *"It's not about the almighty physician, but about admitting that they do not know everything. And that physician admitted it and then you feel treated in a human way and then that's ok for me. That is all I need in order to continue, then I can be much more accepting."*

The process of (non-)adherence and (non-)persistence

Figure 1 (theoretical framework: process of (non-)adherence and (non-)persistence) shows how factors contribute to (non-)adherence and (non-)persistence/early discontinuation. The term 'process' was chosen to

describe the interrelatedness of experiences over time leading to non-adherence or non-persistence/early discontinuation.

A distinction is made between participants experiencing a low impact and a high impact of the AHT on their lives. The impact is the result of side effects, the psychological and social consequences of side effects, and the contrast with life before the disease.

Participants experiencing a low impact

Participants experiencing moderate or acceptable side effects and for whom the contrast with life before the disease is limited, do not need to adjust their perceptions of the impact of AHT because it is often close to their expectations. In general, these participants attach less importance to the fact they were not well informed about side effects. For them, following the prescribed therapy is often self-evident because the benefits (protection against recurrence and the feeling of a sense of control) exceed the harms.

Participants experiencing a high impact

Participants experiencing a high impact of the AHT, the weight of the therapy is determined by a balance between the burden of the AHT and the participants' capacity to deal with this burden. When expectations concerning the impact contrast with the actual impact and when patients do not feel recognized by healthcare professionals, the burden is heavier.

Participants for whom the impact is high and who are not informed in advance about the possible impact of the AHT, have a hard time when faced with its impact. They experience side effects of the AHT they did not expect and notice that the contrast with life before the disease remains or even increases. Because they did not expect the impact, they could not prepare for it. They are often disappointed because they have to adjust their perception of AHT, which is experienced as emotionally very exhausting. This affects the trust relationship with the physician. They feel misled by believing that the AHT regimen would not be hard to follow. The contrast makes it more difficult to be open and report side effects to healthcare professionals in the future. Consequently, participants have

the feeling of standing alone, making them even feel more anxious about the source of the symptoms they experience.

> *"I think they have explained too little about side effects. They have actually minimized them, which makes them worse than I imagined them to be. Now I have to learn to deal with it after I have experienced them and this is very difficult."*

> *"I was prepared for anything, except the fact that I would go into menopause from one day to the next. Nobody had informed me about it. I was very, very disappointed and saddened. People say it had to happen, which is true, but that was the furthest thing from my mind. You are losing part of your femininity. For me that was the most difficult part of the entire treatment… I did have everything, but that was the worst for me. And maybe because they did not inform me in advance."*

The degree of recognition participants receive from healthcare professionals increases or reduces the burden of the AHT. When they do not feel recognized, the burden of the AHT is heavier, making it more difficult to continue to take their AHT adherently or to persevere.

The capacity to deal with the burden of the AHT is determined by the presence of personal coping resources and the degree of social support. The degree of social support counteracts the burden of the AHT. When the degree of social support is low, this makes it more difficult to bear the burden. It makes patients feel even lonelier in dealing with the difficulties they encounter and in their struggle to continue the therapy.

In most cases, participants develop strategies to cope with the impact and the burden of the AHT. When the balance tilts to the burden side, in order to be able to continue the AHT, they resort to strategies such as:

- Relativize experienced difficulties by putting them into the perspective of other life issues and by comparing themselves with patients who are experiencing more difficulties than they are, which helps them to continue the AHT.

"I am more fatigued, but that's due to the aging. Every normal person gets more tired by the evening."

- Rationalizing experienced shortcomings in relation to healthcare professionals. They indicate, for example, that physicians have little time during consultations to talk in detail about the difficulties patients experience. This way they try to avoid the feeling of being disappointed. The more shortcomings they experience, the more difficult it is to rationalize these away.
- Seeking social support with peers when to compensate the lack of social support from family and friends.
- Creating one's own perspective to be able to continue therapy when the impact of the AHT is high. Having a known ending date gives participants courage to continue the therapy. Some participants make an agreement with their physicians to continue therapy for a shorter period than five years in order to create a less distant perspective. Some participants create a perspective for themselves by dividing the treatment period into shorter periods.

  "I hope that those five years will pass quickly. In September it will be two years, then another half year and then I am halfway. Once I am halfway, it will pass more quickly, so I will be glad to be halfway."

- Adapting expectations of life and future to the AHT (e.g. activity level and goals). The extent to which patients succeed is often related to age. The younger and/or the more active participants are, the more their life is changed with respect to the life they had before the disease and the more difficult it seems to adapt life to the treatment.

The extent to which participants succeed in finding effective strategies to cope with the impact and the burden of the AHT determines whether participants continue AHT. When the balance remains tilted towards the burden side, participants think about quitting therapy. When considering giving up therapy,

they are often doubtful because of the fear they might relapse, making them feel guilty towards themselves, family and friends. When the potential higher risk of a relapse does not outweigh the low quality of life they are experiencing, they stop the AHT temporarily (non-adherence) or permanently (non-persistence/early discontinuation).

When participants stop the treatment, they try to legitimize their decision and to convince themselves it was the right thing to do. In this way, they try to counter the feeling of guilt in case of a relapse. Participants use arguments such as: 'I have been taking AHT for four years; one year will not make a difference', 'research is still under development; they do not know if it helps or not' or 'A friend died from breast cancer, she also took AHT and did not survive anyway'.

In some cases, however, patients restart the treatment or shift to another because the physician was able to persuade them to start again and because they were afraid of relapse.

DISCUSSION

The aim of this study was to gain insight into the process of (non-)adherence and (non-)persistence in breast cancer patients with AHT by researching influencing factors and their interrelatedness. This study shows how factors such as expectations regarding the impact of treatment, information, recognition and social support contribute to the process of (non-)adherence and (non-)persistence in breast cancer patients with AHT.

The process of (non-)adherence and (non-)persistence presented in this study facilitate the interpretation of factors influencing (non-)adherence and (non-)persistence found in quantitative studies. Our study highlights the interrelatedness of influencing factors and reveals processes underlying factors frequently found in quantitative studies. Side effects, for example, are the most commonly found predictors of non-adherence and non-persistence in breast cancer patients taking AHT (Kirk and Hudis, 2008; Grunfeld et al., 2005; Atkins and Fallowfield, 2006; Lash et al, 2006; Demissie et al., 2001). This study adds

that not only the impact of side effects per se, but also expectations regarding the impact of the AHT and feeling recognized by healthcare professionals contribute to the process of (non)-adherence and (non)-persistence.

For participants experiencing side effects they did not expect, the burden of the AHT is heavier, which increases the risk of non-adherence and non-persistence. Kahn and colleagues (2007) also found that breast cancer patients taking tamoxifen who experienced side effects that they were not told about in advance, were less likely to continue tamoxifen in comparison to patients who did know what side effects they could expect (62% vs. 85%, $p<0.001$). Side effects that affect the quality of life of patients taking AHT are usually not life-threatening, and may therefore differ from those side effects that physicians are mostly concerned about (Fellowes et al., 2001). As a result, such side effects may not be discussed with patients or only to a limited extent and may not be recognized as affecting patients' quality of life. Our study shows that this reinforces the idea that AHT is not a hard regimen to follow, leading to feelings of disappointment when patients are confronted with unexpected side effects resulting in a greater emotional and physical burden.

The degree of recognition participants receive from healthcare professionals increases or reduces the burden of AHT. In this way, recognition can act as an important buffer against the impact of the AHT. Kahn and colleagues (2007) found that patient-centered care processes and behavior were associated with better adherence, even in patients experiencing a high impact of the AHT. Patient-centered care processes and behavior included, amongst other things, caring interactions with patients, involving patients in decision-making and counseling patients about (potential) side effects. The qualitative study of Burkitt Wright and colleagues (2004) showed that physicians were valued the most when they were technical experts, formed individual relationships with them, and respected them. When patients thought that they had been misled as a result of poor communication, the trust in the physician was irretrievable. Our study adds that the feeling of being misled makes patients disappointed, puts them in a lonely position, and makes the burden of the AHT heavier for them. This mostly

affects patients who lack sufficient personal coping resources and enjoy less social support.

Implications for practice

The results of our study highlight the patients' need to be clearly informed about the impact of the AHT in order not to raise false expectations. Being well informed helps patients to prepare for what is coming and to avoid expectations that need to be adjusted afterwards, which is perceived as emotionally very exhausting. This study also emphasizes the need for patient centered care with regular follow-up consultations over the total course of AHT, during which patients are given sufficient space to express their difficulties and worries. An equal relationship in which they are being taken seriously by healthcare professionals encourages them to express their difficulties and feelings. Further, patients need to be supported in dealing with the impact of AHT by helping them manage the side effects and giving them psychological support and recognition. Therefore, a multidisciplinary approach during follow-up should be implemented and healthcare professionals should be sensitized about the importance of recognizing patients and trained to do this in an appropriate way. Reassuring patients about the cause of bodily sensations is an ongoing duty of healthcare professionals. As this study also highlights the importance of social support, it is recommended to inform family and friends about the possible impact of the AHT and involve them in patient care during the follow-up period with AHT. Contact between patients should be encouraged during follow-up as this study highlights the importance of social support from peers.

Strengths and limitations

This is the first qualitative study giving insight into the processes of (non-)adherence and (non-)persistence in breast cancer patients considering both SERMs and aromatase inhibitors. Despite the strengths, some limitations need to be addressed.

Saturation was achieved early in the study for some of the influencing factors. This may be the result of recruiting in one hospital. Consequently, it is likely that

care was perceived as similar which could have led to a selection bias. Future research could be conducted in more additional settings in order to explore generalization of the study findings.

Participants who had received chemotherapy may experience more late side effects of the chemotherapy during follow-up period with AHT than other participants. In this study, late side effects of the chemotherapy may also have influenced the impact of the therapy and contributed to the process of (non-)adherence and (non-)persistence. In future research, the consequences of side effects of previous chemotherapy could be more taken into account.

CONCLUSION

This qualitative study gives insight into the process of (non-)adherence and (non-)persistence in breast cancer patients taking AHT. Expectations regarding the impact of AHT, social support from family and friends, and recognition from healthcare professionals were found to influence (non-)adherence and (non-)persistence. The results of this study can help healthcare professionals understand why breast cancer patients taking AHT do not always adhere to or persist in taking the therapy and may facilitate patient tailored interventions.

Table 1. Demographic and treatment-related characteristics

	Characteristics	N
Age (years)		
	30-39	2
	40-49	8
	50-59	11
	60-69	8
	70-79	2
Married		
	Yes	20
	No	11
Children		
	Yes	23
	No	8
Working		
	Yes	14
	No	17
Level of education		
	Secondary	16
	Tertiary	15
Previous treatment		
	Surgery	30
	Chemotherapy	22
	Radiotherapy	23
	Targeted therapy	6
Antihormonal medication		
	Aromatase inhibitor	14
	Tamoxifen	17
Time on antihormonal therapy (years)		
	< 1	5
	1-2	7
	2-3	5
	3-4	5
	4-5	7
	>5	2

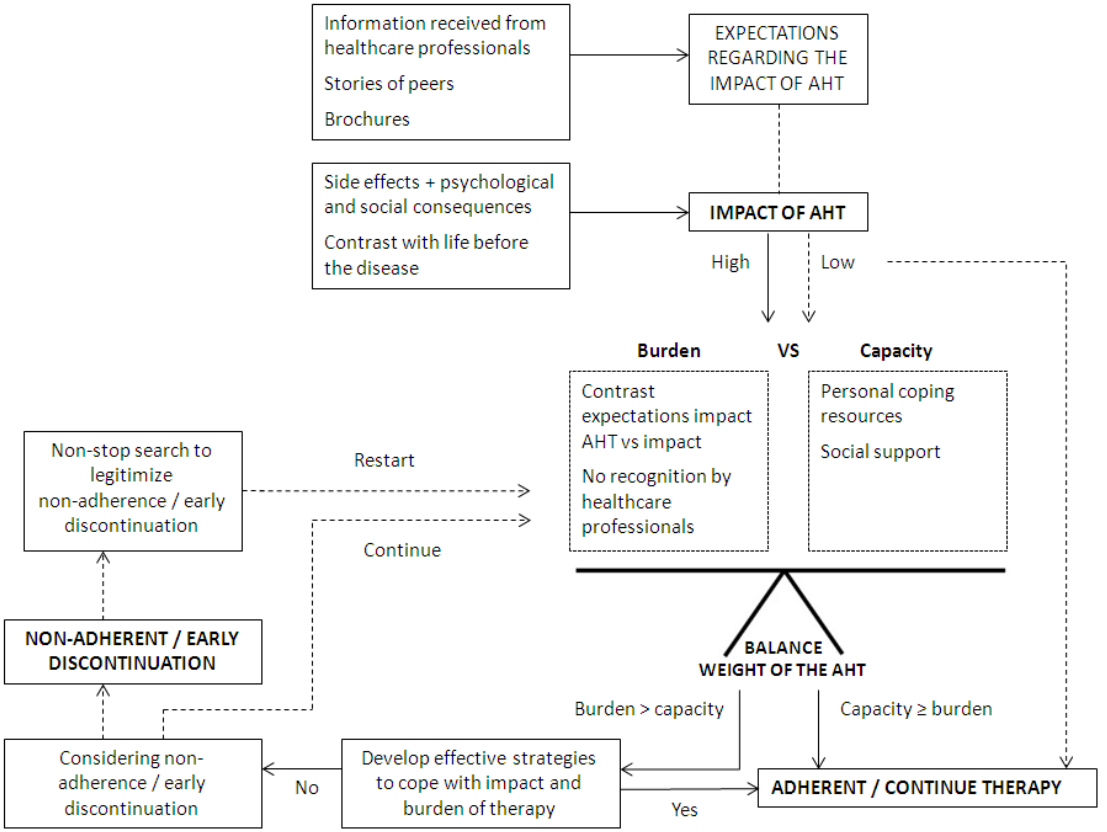

Figure 1. Theoretical framework: the process of (non-)adherence and (non-)persistence

REFERENCES

Anderson E. (2002) The role of oestrogen and progesterone receptors in human mammary development and tumorigenesis. Breast Cancer Research, 4(5), 197-201.

Atkins, L., Fallowfield, L. (2006) Intentional and non-intentional non-adherence to medication amongst breast cancer patients. European Journal of Cancer, 42, 2271-2276.

Barron, T.I., Connolyy, R.M., Bennett, K., Feely, J., Kennedy, J.M. (2007) Early discontinuation of tamoxifen. American Cancer Society, 109(5), 832-839.

Boeije, H. (2002) A purposeful approach to the constant comparative method in the analysis of qualitative interviews. Quality and Quantity, 36, 391-409.

Brennan, M.E., Houssami, N. (2011) Overview of long term care of breast cancer survivors. Maturitas, 69, 106-112.

Burkitt Wright, E., Holcombe, C., Salmon, P. (2004) Doctors' communication of trust, care, and respect in breast cancer: qualitative study. British Medical Journal, 328, 864.

Coyne, I.T. (1997) Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? Journal of Advanced Nursing, 26(3), 623-630.

Demissie, S., Silliman, R.A., Lash, T.L. (2001) Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. Journal of Clinical Oncology, 19(2), 322-328.

Doggrell, S. (2011) Adherence to oral endocrine treatments in women with breast cancer: can it be improved? Breast Cancer Research and Treatment, 129, 299-308.

Early Breast Cancer Trialists' Collaborative Group. (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant

tamoxifen: patient-level meta-analysis of randomised trials. Lancet, 378, 771–784.

Early Breast Cancer Trialists' Collaborative Group. (1998) Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet, 351, 1451-1467.

Early Breast Cancer Trialists' Collaborative Group. (1992) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. Lancet, 339(8784), 1-15.

Fellowes, D., Fallowfield, L.J., Saunders, C.M., Houghton, J. (2001) Tolerability of hormone therapies for breast cancer: How informative are documented symptom profiles in medical notes for 'well-tolerated' treatments? Breast Cancer Research and Treatment, 66, 73-81.

Fontein, D., Nortier, J., Liefers, G., Putter, H., Kranenbarg, E., van den Bosch, J., et al. (2012) High non-compliance in the use of letrozole after 2,5 years of extended adjuvant endocrine therapy. The Journal of Cancer Surgery, 38, 110-117.

Glaser BG & Strauss A. (1967) The Discovery of Grounded Theory. Chicago: Adline Atherton.

Grunfeld, E.A., Hunter, M.S., Sikka, P., Mittal, S. (2005) Adherence beliefs among breast cancer patients taking tamoxifen. Patient Education and Counseling, 59, 97-102.

Güth, U., Myrick, M.E., Kilic, N., Eppenberger-Castori, S., Schmid, S.M. (2012) Compliance and persistence of endocrine adjuvant breast cancer therapy. Breast Cancer Research and Treatment, 131, 491-499.

Güth, U., Huang, D.J., Schötzau, A., Zanetti-Dällenbach, R., Holzgreve, W., Bitzer, J., et al. (2008) Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. British Journal of Cancer, 99, 428-433.

Hershman, D.L., Shao, T., Kushi, L.H., Buono, D., Tsai, W.Y., Fehrenbacher, L., et al. (2010) Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Research and Treatment, 126, 529-537.

Kahn, K.L., Schneider, E.C., Malin, J.L., Adams, J.L., Epstein, A.M. (2007) Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. Medical Care, 45(5), 431-439.

Kirk, M.C., Hudis, C.A. (2008) Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. Clinical Breast Cancer, 8(2), 155-161.

Lash, T.L., Fox, M.P., Westrup, J.L., Fink, A.K., Silliman, R.A. (2006) Adherence to tamoxifen over the five-year course. Breast Cancer Research and Treatment, 99(2), 215-220.

Morse, J., Field, P.A. (1996) Nursing Research. The application of qualitative approaches. Cheltenham UK: Stanley Thornes (Publishers) Ltd.

Osterberg, L., Blaschke, T. (2005) Adherence to medication. The New England Journal of Medicine, 353(5), 487-497.

Pellegrini, I., Sarradon-Eck, A., Soussan, P.B., Lacour, A-C, Largillier, R., Tallet, A., et al. (2010) Women's perceptions and experience of adjuvant tamoxifen therapy account for their adherence: breast cancer patients' point of view. Psycho-Oncology, 19, 472-479.

Ruddy, K., Mayer, E., Partridge, A. (2009) Patient adherence and persistence with oral anticancer treatment. CA: A Cancer Journal for Clinicians, 59(1), 56-66.

van Herk-Sukel, M.P., van de Poll-Franse, L.V., Voogd, A.C., Nieuwenhuijzen, G.A., Coebergh, J.W., Herings, R.M. (2010) Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a populations-based analysis. Breast Cancer Research and Treatment, 122(3), 843-851.

Verbrugghe, M., Verhaeghe, S., Lauwaert, K., Beeckman, D., Van Hecke, A. (2013) Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. Cancer Treatment Reviews, 39(6), 610-621.

Verma, S., Madarnas, Y., Sehdev, S., Martin, G., Bajcar, J. (2011) Patient adherence to aromatase inhibitor treatment in the adjuvant setting. Medical Oncology, 18(1), 3-9.

CHAPTER 5

ADHERENCE TO ORAL ANTICANCER AGENTS: HEALTHCARE PROVIDERS' PERCEPTIONS, BELIEFS AND SHARED DECISION MAKING IN BELGIUM AND THE NETHERLANDS

Based on the article of Verbrugghe M, Timmers L, Boons C, van den Bemt B, Hugtenburg J, Van Hecke A. (2015). Adherence to oral anticancer agents: healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands. *Under review.*

ABSTRACT

Background

Little is known about healthcare providers' perceptions of adherence management of oral anticancer agents. The study aims to explore healthcare providers' perceptions of oral anticancer agents and adherence.

Methods

A cross-sectional, multi-center observational study among healthcare providers in hemato-oncology settings in Belgium and the Netherlands was conducted. Physicians, nurse practitioners, nurses and pharmacists were asked to complete questionnaires on their perception of patient adherence and its management (PAMQ) and their beliefs about oral anticancer agents (BMQ-Specific). Physicians were also asked to complete a questionnaire on their perception of shared decision making (SDM-Q-Doc).

Results

The sample consisted of 254 healthcare providers. 56, 50, 28 and 23% of respectively physicians, nurse practitioners, nurses and pharmacists reported to know the level of adherence of their patients and 59, 53, 43 and 10% think that patients discuss adherence with them. 70, 82, 63 and 62% and 78, 87, 76 and 80% of physicians, nurse practitioners, nurses and pharmacists reported to have knowledge of causes respectively consequences of non-adherence. 81, 92, 83 and 67% of physicians, nurse practitioners, nurses and pharmacists felt able to influence adherence. Lower concerns about oral anticancer agents were associated with a higher total score on the PAMQ (β[SE]= -.85[.24]; CI -1.33 to -.38). Physicians scored a mean of 75 on the SDM-scale.

Conclusion

A considerable part of the healthcare providers states they do not know the adherence of their patients, nor do they think patients discuss adherence with them. However, they feel to have knowledge of adherence and perceive to be able to influence adherence of their patients.

INTRODUCTION

Non-adherence to oral anticancer agents (OACA) is complex and determinants are interrelated (Verbrugghe *et al*, 2013). For OACA treatment effectiveness, optimal adherence is considered important (e.g. better clinical response, survival) (Noens *et al*, 2009; Marin *et al*, 2010; Xu *et al*, 2012). A patient is considered optimally adherent (100%) to the agreed prescribed therapy when no doses have been missed, no more doses have been taken than prescribed, and doses have not been taken at the wrong time or wrong quantity (Ruddy *et al*, 2009; Staddon, 2011).

The framework suggested by the World Health Organization (WHO, 2003) is frequently used to describe the multidimensional phenomenon of medication adherence. It includes five interacting dimensions influencing adherence: social and economic factors, condition-related factors, therapy-related factors, patient-related factors, and healthcare provider (HCP) and system-related factors. HCP-related factors found to influence OACA (non-)adherence were observed in patients with breast cancer on chronic endocrine therapy (e.g. a poor physician's explanation of treatment effects) (Kahn *et al*, 2007) and in patients with chronic myeloid leukemia (CML) on long-term imatinib (e.g. feedback from physicians that seems to reinforce the belief that 'occasional' non-adherence does not matter) (Eliasson *et al*, 2011). Shared decision making was found to influence persistence to OACA in breast cancer patients in a prospective cohort study (Kahn *et al*, 2007). Women who were satisfied about the role they played in the OACA therapy decision making process, were more likely to continue their therapy (81%) as compared to patients playing a more (73%) or less expanded role (59%) than wanted regarding the decision making process (Kahn *et al,*2007). Studies on HCP- related factors influencing non-adherence in patients treated with short-term OACA (e.g. erlotinib, sunitinib) are scarce (Timmers *et al* 2014, Timmers *et al* 2015).

Studies exploring adherence issues have predominantly focused on the patient's perspective (Osterberg and Blaschke, 2005). Beliefs about medicines have previously been shown to influence adherence in patients taking OACA

(Grunfeld *et al*, 2005; Bhattacharya *et al*, 2012). However, insight into HCPs' beliefs about OACA and perceptions about OACA adherence are also important because perception and beliefs may influence HCPs' behavior and care (Ajzen, 1991; Valente Teixeira *et al*, 2012). In turn, this may influence patients' adherence behavior (Marteau and Johnston, 1991; Eliasson *et al*, 2011). Until now, HCPs' perceptions about OACA adherence, HCPs' beliefs about OACA and the physicians' perceptions towards the shared decision making process in OACA therapy have hardly been explored. Insight into these topics may inform the development of interventions targeted to HCPs' capacity to counsel patients taking OACA.

The present study aims to (1) explore HCPs' perceptions about OACA adherence management and beliefs towards OACA, (2) explore the physicians' perceptions towards the shared decision making process, and (3) report on factors influencing HCPs' perceptions about OACA adherence management.

METHODS

Design

A cross-sectional, multi-center observational study among HCPs working in hemato-oncology settings in Dutch-speaking Belgium and the Netherlands was performed. This paper reports on one part of a larger study. The other paper describes usual care activities in adherence care provided in the same settings (Adherence to oral anticancer agents: HCPs' perceptions and usual care in Belgium and the Netherlands).

Setting and sample

The study was conducted between April and October 2014. HCPs were included if they met the following criteria: being a medical oncologist, hematologist, nurse, nurse practitioner, or pharmacist; working in a hemato-oncology setting, in Dutch-speaking Belgium or the Netherlands.

Data collection procedure

Participants were informed about the study by their professional associations in Belgium and the Netherlands. An e-mail with information and an invitation to complete the online questionnaire was sent to all members of professional associations involved. After the initial invitation, one or two reminders were sent. Additional recruitment took place by distributing the online questionnaire within the authors' network, and by handing out a paper version of the questionnaire at a scientific meeting where HCPs from the targeted groups were present.

Measurements

A composite electronic questionnaire starting with demographic characteristics like profession, number of years employed, gender, type of hospital, and specialization (hematology or medical oncology) was used.

Five items on HCPs' perceptions of management of adherence (Perceptions about Adherence Management Questionnaire - PAMQ) were developed by a team consisting of a medical oncologist, hematologist, three pharmacists, and three researchers (nurse, psychologist, health scientist) with experience in the field of medication adherence in oncology and hematology. The five items were: knowing the level of adherence of all my patients, thinking that patients discuss non-adherence with me, being able to influence adherence behavior of my patients, having sufficient knowledge about consequences of non-adherence, and having sufficient knowledge about causes on non-adherence to discuss this with patients. Each item was scored on a 5-point Likert scale, ranging from strongly disagree (1) to strongly agree (5). The scores agree (4) and strongly agree (5) were dichotomized into yes (1) and the other scores (1-3) into no (0). A total score (ranging from zero to five) was calculated by summing the five dichotomized items. A higher total score on the PAMQ indicated a higher number of perceptions about managing adherence the HCP agree with.

The Shared Decision Making Questionnaire – physician version (SDM-Q-Doc) was used to assess the shared decision making process in medical consultation from the physician's perspective (Scholl et al, 2012). The SDM-Q-Doc has

shown to be a well-accepted and reliable instrument (Scholl et al, 2012). Items were rated on a 6-point Likert scale from zero (absolutely inappropriate) to six (absolutely appropriate). A sum score of the nine items was made (range 0 to 45). This sum score was standardized using a linear transformation into a scale from 0 to 100 as recommended by Scholl et al (2012), in order to facilitate interpretation. A higher score on the SDM-Q-Doc indicated perceptions of more shared decision making. The SDM-Q-Doc was only assessed by physicians because treatment-decisions primarily occur at the physicians' level.

Beliefs about OACA were assessed by using the Beliefs about Medicines Questionnaire (BMQ-Specific) (Horne *et al*, 1999). The BMQ-Specific has been validated in different populations including patients with a chronic disease or a malignancy (Horne *et al*, 1999; Horne and Weinman, 1999). The BMQ-HCP version was translated in Dutch following the inverse translation method (Koller *et al*, 2007) by CB and LT and authorized by R. Horne, the main author of the BMQ-Specific (Horne *et al*, 1999). The BMQ-Specific consists of two scales: a 5-item necessity scale assessing beliefs about the necessity of the medication to control the disease and a 5-item concerns scale assessing concerns about the potential negative impact of the medication (Horne *et al*, 1999). Items were rated on a 5-point Likert scale ranging from strongly disagree to strongly agree. Individual scores obtained from each 5-item scale were summed (range 5 to 25). Higher scores on the BMQ-necessity indicate stronger beliefs in the necessity of OACA to control the disease, higher scores on the BMQ-concerns indicate stronger concerns about the potential negative impact of OACA (Horne and Weinman, 1999; Horne *et al*, 1999). A cutoff score of 15 or above was used to determine low/high necessity or concerns (Van Steenis *et al*, 2014). Four profiles of HCPs representing HCPs' beliefs were created based on scores of the BMQ-Specific necessity/concerns scales (Menckeberg *et al*, 2008; Mann *et al*, 2009; Van Steenis *et al*, 2014): indifferent (low necessity, low concerns), skeptical (low necessity, high concerns), accepting (high necessity, low concerns), and ambivalent (high necessity, high concerns). A necessity-concerns differential score was calculated to assess the relative importance of the medication by subtracting the concerns-scale from the necessity-scale

(range -20 to 20). A positive differential score indicates stronger necessity beliefs than concerns.

Validation of the questionnaire

The questionnaire was pilot-tested by nine HCPs in the Netherlands and Belgium (i.e. three pharmacists, three nurses, one hematologist, one medical oncologist, and one general practitioner). In individual interviews with HCPs, it was explored whether the items were understood as intended.

Ethics

The study procedure was approved by the Ethical Review Committee of the Ghent University Hospital (Belgium) and assessed not governed by the Dutch Medical Research Involving Human Act by the Medical Ethics review board of the VU University Medical Center in Amsterdam (the Netherlands).

Statistical analysis

Descriptive data were presented as frequencies (percentages) and means (standard deviations [SD]). Differences between groups were tested by means of the Pearson Chi-square test, the unpaired t-test, and one-way Anova test. The Pearsons correlation coefficient was used to test the association between continuous data. For statistical analyses, the professions hematologists and medical oncologists were merged into the group ‘physicians’.

To identify associated factors of HCPs’ perceptions about adherence management, linear regression analysis was performed with the total PAMQ-score as dependent variable and potential predictors as independent variables. Variables with a value $p<0.25$ were entered in a multiple linear regression model to evaluate the associations’ independency. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses.

RESULTS

Demographic characteristics

In total 329 HCPs initiated the online questionnaire, of which 236 completed the demographic characteristics and at least one section with questions. Recruitment at the conference yielded 18 additional questionnaires. In total, 254 questionnaires were used for the analysis. Demographic characteristics of participants are shown in Table 1. The median number of years employed was 14 years (IQR= 7-25). Most participants were female (73.2%) and 51.2% worked in the Netherlands. The sample consisted of 23.6% pharmacists, 29.9% nurses, 15% medical oncologists, 16.5% hematologists, and 15% nurse practitioners working in different hospitals (n=106). The majority of the HCPs worked in the field of medical oncology (70.5%) in a non-academic hospital (67.6%).

HCPs' perceptions about adherence management (PAMQ)

In total, 254 HCPs completed the PAMQ. An overview of the perceptions about adherence management according to profession, gender, country, type of hospital, and specialization is presented in Table 2. Slightly more than half of the physicians and half of the nurse practitioners indicated to know the level of adherence of their patients (56% and 50% respectively) and perceived that patients discuss adherence with them (59% and 53% respectively). Most HCPs (especially physicians [81.3%], nurse practitioners [92.1%] and nurses [82.9%]) indicated to be able to influence adherence behavior of their patients. Most HCPs thought to have sufficient knowledge about the consequences of non-adherence (79.1%), less HCPs indicated to have sufficient knowledge about the causes of non-adherence to discuss this with patients (67.7%).

For the total PAMQ-score, both physicians and nurse practitioners scored significantly higher than nurses (unpaired t-test; $p=0.022$ and $p=0.008$ respectively) and pharmacists (both $p<0.001$). No significant difference was found between physicians and nurse practitioners.

A supplementary analysis was performed to determine significant differences between the subgroups of physicians (medical oncologists vs. hematologists).

More medical oncologists than hematologists indicated to know the level of adherence of all their patients (Pearson Chi-square; n[%] = 27[71%] vs. 18 [43%]; p=0.011) and thought that patients discussed non-adherence with them (n[%] = 28[74%] vs. 19 [45%]; p=0.01).

Beliefs about OACA (BMQ)

The BMQ-Specific was completed by 222 HCPs. An overview of the necessity and concerns scale and the differential score according to profession, gender, country, type of hospital, and specialization, is presented in Table 2. The necessity-scale and the concerns-scale were normally distributed. The mean score on the BMQ-necessity was 18.3 (SD=2.94), the mean score on the BMQ-concerns was 13.5 (SD=2.57). The strongest necessity beliefs were found for the items “My patients’ health, at present, depends on these medicines” (Mean [SD]=3.97[.49]), “The future health of my patients will depend on these medicines” (Mean [SD]=3.9[.77]), and “These medicines protect my patients from becoming worse” (Mean[SD]=3.79[.76]). The strongest belief about concerns was found for the item “I sometimes worry about the long-term effects of these medicines” (Mean [SD]=3.34[.98]).

The BMQ-necessity score was significantly higher among physicians than nurses (unpaired t-test; p=0.005) and nurse practitioners (p=0.046); pharmacists scored significantly higher than nurses (p=0.010). Necessity beliefs and concerns about OACA scores were significantly higher among Belgian HCPs than among Dutch HCPs. The BMQ-necessity was significantly higher among HCPs in hematology than HCPs in oncology. The association between the differential score and number of years employed was found to be significant (r= -0.13, p=0.045), indicating the longer HCPs are employed, the higher concerns compared to necessity beliefs. When considering HCPs’ profiles, 56.8% are accepting, 33.3% ambivalent, 7.7% indifferent, and 2.3% skeptical towards OACA. No significant differences between professions, gender, countries, number of years employed, and types of hospital were found.

Shared decision making (SDM)

In total, 95 of the 99 physicians, completed the SMQ-Q-Doc. Table 2 shows the SDM-Q-Doc scores according to gender, country, type of hospital, and specialization. The mean sum score (scale 0 to 100) was 75.53 (SD=19.26).The lowest scores on item level were found for the items “I wanted to know exactly from the patient how he/she wants to be involved in making the decision” (Mean [SD]=3.39[1.21]) and “My patient and I selected a treatment option together” (Mean [SD]=3.36[1.41]). The highest scores were found on the items “I precisely explained the advantages and disadvantages of the treatment options to my patient” (Mean [SD]=4.15[1.07]), “I helped my patient understand all the information” (Mean [SD]=4.11[.79]), and “My patient and I reached an agreement on how to proceed” (Mean[SD]=4.08[1.13]). No significant differences were found for profession (hematologists vs. oncologists), gender, country, specialization, and type of hospital. No significant association was found for the number of years employed.

Factors influencing HCPs’ perceptions about adherence management

The independent associations between the total PAMQ-score and other factors are presented in Table 3. No multi-collinearity was observed among the independent variables (Spearmans’ρ<0.60). Univariate analysis showed that being a nurse or pharmacist, and having higher concerns beliefs was associated with lower total PAMQ-scores. The multivariate analysis showed that being a pharmacist was associated with lower total PAMQ-scores. No significant associations were found between BMQ-Specific profiles and total PAMQ-score. When comparing the two most common profiles (accepting vs. ambivalent) at PAMQ item-level, more accepting HCPs thought to know the level of adherence of all their patients (Pearson Chi-square; n[%] = 58[46%] vs. 22 [30%]; p=0.028) and felt able to influence adherence behavior of their patients (n[%] = 110[87%] vs. 53 [73%]; p=0.009). A higher sum score on the SDM-Q-Doc (more shared decision making) was independently associated with a higher total PAMQ-score (p=.019; β [SE] = .017[.007]; 95% confidence interval: 0.003 to 0.031).

DISCUSSION

The results of the present study showed that only slightly more than half of the physicians thought to know the level of adherence of their patients and supposed that patients discussed non-adherence with them. In line with these results, patients reported that physicians do not always discuss OACA (non-)adherence (Eliasson *et al,* 2011). Underlying reasons may be the assumptions that patients are highly adherent due to the severity of the disease and that the relationship of confidence physicians have with their patients naturally leads to adherence (Regnier Denois *et al,* 2011). Talking about non-adherence has also been considered detrimental to the unspoken contract of trust in the therapeutic relationship (Regnier Denois *et al,* 2011). Openness to talk about adherence should be established. To be able to talk about adherence, an open and trust-based relationship and providing patients with a knowledge base of why it is important to be open about adherence behavior is important (Verbrugghe et al., 2015).

An interesting finding was that all HCPs felt able to influence adherence of their patients and have sufficient knowledge of causes and consequences of non-adherence. Even if we leave out of account to what extent these HCPs counsel their patients about adherence, this finding is at least a ground for the performance of adherence support programs. In the second part of this study, which we will publish separately, we will report the actual adherence care which is provided by these HCPs.

Pharmacists had lower scores on the perceptions about adherence management. A likely explanation is that pharmacists have generally less contact with patients taking OACA and also have a less active role in counseling these patients. Few pharmacists indicated items implying face-to-face contact with patients (i.e. know the level of adherence and think that patients discuss non-adherence with them), while most of them indicated to have sufficient knowledge about the consequences of non-adherence and the causes to discuss this issue with patients.

Scores on beliefs about the necessity of OACA were higher than scores on concerns about the potential negative impact of OACA among all professions (positive necessity-concerns differential scores). HCPs are perhaps indeed quite aware of the necessity of OACA treatment and its effectiveness or may be, despite the increasing attention for quality of life, more focused on survival and the continuation of treatment until there is no more treatment to offer (Keating *et al,* 2010).

Comparing HCPs' beliefs about OACA with patients' beliefs reported in literature, the mean necessity-concerns differential score in the present study was lower than a comparable score of patients taking the OACA capecitabine (4.8 vs. 7.8) (Bhattacharya *et al,* 2012). However, in both studies the necessity-concerns differential scores were positive indicating that on average the beliefs of patients and HCPs in necessity outweigh concerns about the potential negative impact of OACA treatment.

Nurses scored lower on the necessity-concerns differential than physicians, nurse practitioners and pharmacists. Nurses appear to express more worries about the use of OACA than physicians, nurse practitioners and pharmacists. Nurses have more frequent and intense contact with patients taking OACA when they are hospitalized, mostly as a result of severe and intense side effects or disease progression. Seeing patients suffering is confrontational and may be emotionally demanding (Corner, 2002).

We also found that HCPs who were accepting (high necessity beliefs, low concerns) considered themselves more able to influence adherence and thought to have a better notion of patient adherence than HCPs who were ambivalent towards OACA (high necessity, high concerns). Patients with a chronic non-oncological disease being accepting towards medicines were previously found to have the highest adherence levels (Tibaldi *et al*, 2009). In future research, the association between (1) HCPs' perceptions about OACA adherence management, beliefs about OACA, and usual care, and (2) patients' adherence levels should be studied.

Particularly the SDM scores of items with regard to giving patients a good knowledge base about their treatment options (explaining advantages and disadvantages of the treatment options and helping to understand all information), were considered high. The high score on the item "My patient and I reached an agreement on how to proceed" indicates that physicians are willing to give patients a role in the decision making process. However, the lowest mean score was found for the item regarding involvement of patients in the final decision making ("my patient and I selected a treatment option together"). This is very likely as in current practice the physician is often the person to finally select the treatment option. As patients who were assigned a more extensive role than wanted in the decision-making process, appeared to be less adherent to their OACA (Kahn *et al,* 2007), physicians should firstly discuss whether patients want a role in the decision making process and secondly, discuss which role would be fitting.

Limitations and methodological considerations

This study was the first to explore perceptions about adherence management and beliefs about OACA of different HCPs involved in the care for patients taking OACA in Belgium and the Netherlands. Despite the strengths, some limitations need to be addressed.

One limitation is the method of recruitment. The questionnaire was sent out by several professional associations and distributed in the own network (snowball sampling). We could not calculate response rates. Furthermore, we assume that particularly HCPs who are affiliated with the research topic, have completed the questionnaire. Presumable, this has influenced our results. The results of the recruitment at the meeting (with HCPs assumable more affiliated with the topic) were not significantly different from the results from the recruitment by professional associations (online questionnaire). This may indicate the presence of selection bias in the sample recruited by professional associations. Nevertheless, this study provides an interesting insight in HCPs' views upon adherence to OACA. Furthermore, the sample in this study was not truly random, so statistical significance should be interpreted with caution.

Another limitation is that the questionnaire is not specified to specific patient groups. HCPs could have kept in mind patients treated with long-term or short-term OACA. It is possible that differences between HCPs (e.g. hematologists vs. medical oncologists) could be partly explained by specific properties associated to one of both groups of OACA.

CONCLUSION

A considerable part of the HCPs states they do not know the adherence of their patients, nor do they think their patients discuss adherence with them. However, they feel to have knowledge of adherence and perceive to be able to influence adherence of their patients. There seems to be a good basis for adherence supportive care. Their statements about the care they provide will be published separately.

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Table 1 Demographic characteristics of participants

		Total n=254 (%)	Median (IQR)
Number of years employed			14 years (7-25 years)
Gender	Male	68 (26.8%)	
	Female	186 (73.2%)	
Profession	Medical oncologist	38 (15%)	
	Hematologist	42 (16.5%)	
	Nurse	76 (29.9%)	
	Nurse practitioners	38 (15%)	
	Pharmacist	60 (23.6%)	
Country	Belgium	124 (48.8%)	
	The Netherlands	130 (51.2%)	
Specialization	Hematology	70 (29.5%)	
	Medical oncology	167(70.5%)	
Type of hospital	Academic	81 (32.4%)	
	Non-academic	169 (67.6%)	

IQR: Interquartile Range

Table 2 Results on the Perceptions about Adherence Management Questionnaire (PAMQ), Beliefs about Medicines Questionnaire (BMQ-Specific) and Shared Decision Making Questionnaire (SDM-Q-Doc) according to profession, gender, country, type of hospital, and specialization

	TOTAL	PROFESSION					GENDER			COUNTRY			TYPE OF HOSPITAL			SPECIALIZATION		
	N=254	Physician N=80	Nurse practitioner N=38	Nurse N=76	Pharmacist N=60		Male N=68	Female N=186		The Netherlands N=130	Belgium N=124		Academic N=81	Non-academic N=169		Hematology N=70	Medical oncology N=167	
		n(%)	n(%)	n(%)	n(%)	Pearson Chi-square	n(%)	n(%)	Pearson Chi-square	n(%)	n(%)	Pearson Chi-square	n(%)	n(%)	Pearson Chi-square	n(%)	n(%)	Pearson Chi-square
PAMQ																		
I know the level of adherence of all my patients	98 (38.6%)	45 (56.3%)	19 (50%)	21 (27.6%)	14 (23%)	**<.001***	31 (44.9%)	68 (36.6%)	.22	54 (41.2%)	45 (36.3%)	.42	32 (39.5%)	65 (38.2%)	.85	27 (38.6%)	66 (39.3%)	.92
I think that patients discuss non-adherence with me	106 (41.7%)	47 (58.8%)	20 (52.6%)	33 (43.4%)	6 (10%)	**<.001**	30 (44.1%)	76 (40.9%)	.64	57 (43.8%)	49 (39.5%)	.48	30 (37%)	74 (43.8%)	.31	31 (44.3%)	69 (41.3%)	.67
I am able to influence the adherence behavior of my patients	203 (79.9%)	65 (81.3%)	35 (92.1%)	63 (82.9%)	40 (66.7%)	**.014**	59 (86.8%)	144 (77.4%)	.10	110 (84.6%)	93 (75%)	.056	67 (82.7%)	133 (78.7%)	.46	60 (85.7%)	129 (77.2%)	.14
I have sufficient knowledge about the consequences of non-adherence	201 (79.1%)	62 (77.5%)	33 (86.8%)	58 (76.3%)	48 (80%)	.60	51 (75%)	150 (80.6%)	.33	99 (76.2%)	102 (82.3%)	.23	66 (81.5%)	132 (78.1%)	.54	53 (75.7%)	132 (79%)	.57
I have sufficient knowledge about the causes of non-adherence to discuss this with patients	172 (67.7%)	56 (70%)	31 (81.6%)	48 (63.2%)	37 (61.7%)	.15	51 (75%)	121 (64.7%)	.12	88 (67.7%)	84 (67.2%)	.93	56 (68.3%)	113 (66.9%)	.82	44 (62.9%)	117 (70.1%)	.28
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	ANOVA F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)
Total PAMQ-score[a]	3.07 (1.39)	3.44 (1.39)	3.63 (1.26)	2.93 (1.33)	2.4 (1.28)	**<.001**	3.25 (1.23)	3.01 (1.45)	.22	3.13 (1.39)	3.01 (1.39)	.48	3.10 (1.39)	3.05 (1.39)	.81	3.07 (1.39)	3.07 (1.43)	.98
SDM-Q-Doc[b]	75.53 (19.26)	75.53 (19.26)	n/a	n/a	n/a	n/a	80.06 (14.29)	72.64 (21.47)	.07	73.50 (21.61)	80.15 (11.36)	.12	77.68 (17.82)	74.73 (20.02)	.53	76.73 (18.59)	73.82 (20.85)	.50

	TOTAL	PROFESSION					GENDER			COUNTRY			TYPE OF HOSPITAL			SPECIALIZATION		
	N=254	Physician N=80	Nurse practitioner N=38	Nurse N=76	Pharmacist N=60		Male N=68	Female N=186		The Netherlands N=130	Belgium N=124		Academic N=81	Non-academic N=169		Hematology N=70	Medical oncology N=167	N=254
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	ANOVA F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)	Mean (SD)	Mean (SD)	t-test F (p-value)
BMQ-Specific																		
Specific-Necessity[c]	18.30 (2.94)	18.86 (2.50)	17.69 (3.33)	17.52 (2.90)	18.96 (3.00)	**.010**	18.65 (2.91)	18.16 (2.95)	.25	17.83 (2.84)	18.81 (2.97)	**.013**	18.28 (2.85)	18.29 (2.96)	.98	18.97 (2.73)	17.94 (2.99)	**.02**
Specific-Concerns[c]	13.50 (2.57)	13.14 (2.88)	13.17 (2.44)	13.98 (2.37)	13.60 (2.42)	.23	13.35 (2.67)	13.56 (2.54)	.57	13.06 (2.60)	13.96 (2.47)	**.009**	13.87 (2.62)	13.33 (2.56)	.15	13.97 (2.77)	13.37 (2.42)	.12
NC/diff[d]	4.82 (3.66)	5.71 (3.49)	4.63 (3.82)	3.53 (3.32)	5.37 (3.79)	**.003**	5.30 (3.33)	4.62 (3.78)	.21	4.81 (3.72)	4.84 (3.61)	.94	4.41 (3.47)	4.99 (3.76)	.28	5.00 (3.68)	4.59 (3.65)	.46

PAMQ, Perceptions about Adherence Management Questionnaire; SDM-Q-Doc, Shared Decision Making Questionnaire; BMQ-Specific, Beliefs about Medicines Questionnaire (necessity and concerns about medicines) [a]Scores range 0 to 5 - a higher score on the PAMQ indicates a higher number of perceptions about managing adherence the HCP agree with; [b]Scores range 0-100 – physician version, a higher score indicates perceptions of more shared decision making; [c]Scores range 5 to 25 – higher scores indicates stronger beliefs of necessity or concerns; [d]Necessity-concerns differential score (range -20 to 20) – a positive differential score indicates stronger necessity beliefs than concerns; *The bold values indicate statistical significance at the p<*0.05 level*

Table 3 Regression analysis with the Perceptions about Adherence Management Questionnaire (PAMQ) – total score as dependent variable and potential predictors as independent variables

	Univariate			Multivariate		
Variable	**β (SE)**	**95% CI**	**P-value**	**β (SE)**	**95% CI**	**P-value**
Profession[a]						
Nurse practitioner	.19 (.26)	-.32 to .71	.46	.33 (.28)	-.22 to .88	.24
Nurse	-.50 (.21)	-.92 to -.085	**.019***	-.38 (.24)	-.84 to .09	.11
Pharmacist	-1.04 (.23)	-1.48 to -.59	**<.001**	-.85 (.24)	-1.33 to -.38	**<.001**
Gender[b]	.25 (.20)	-.14 to .63	.22	.26 (.20)	-.14 to .66	.20
Number of years employed	-.008 (.01)	-.024 to .007	.30			
Country[c]	.12 (.18)	-.22 to .47	.48			
Type of hospital[d]	.05 (.19)	-.32 to .42	.81			
Specialization[e]	.006 (.20)	-.39 to .40	.98			
Necessity-scale	.006 (.03)	-.056 to .068	.86			
Concerns-scale	-.08 (.04)	-.15 to -.011	**.024**	-.07 (.03)	-.13 to -.003	.060
NC/diff[f]	.046 (.025)	-.003 (.096)	.066			

SE = standard error; CI = confidence interval; [a]Reference category is physician; [b]Reference category is female; [c]Reference category is Belgium; [d]Reference category is non-academic hospital; [e]Reference category is medical oncology; [f]Necessity-concerns differential score; *The bold value indicates statistical significance at the p<0.05 level.

REFERENCES

Ajzen I (1991) The theory of planned behavior. *Organizational Behavior and Human Decision Processes* **50**: 179-211

Bhattacharya D, Easthall C, Willoughby KA, Small M, Watson s (2012) Capecitabine non-adherence: exploration of magnitude, nature and contributing factors. *J Oncol Pharm Pract* **18**: 333-342

Corner J. (2002) Nurses' experiences of cancer. *Eur J Cancer Care* **11**: 193-199

Eliasson L, Clifford S, Barber N, Marin D (2011) Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leukemia Res* **35**: 626-630

Grunfeld EA, Hunter MS, Sikka P, Mittal S (2005) Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Educ Couns* **59**: 97-102

Horne R, Weinman J, Hankins M (1999) The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health* **14**: 1-24

Horne R, Weinman J (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* **47**:555–567

Kahn KL, Schneider EC, Malin JL, Adams JL, Epstein AM (2007) Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Med Car* **e45**: 431-439

Keating NL, Landrum MB, Rogers Jr. SO, Baum SK, Virnig BA, Huskamp HA, Earle CC, Kahn KL (2010) Physician factors associated with discussions about end-of-life care. *Cancer* **116**: 998-1006

Koller M, Aaronson NK, Blazeby J, Bottomley A, Dewolf L, Fayers P, Johnson C, Ramage J, Scott N, West K, EORTC Quality of Life Group (2007)Translation procedures for standardised quality of life

questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach. *Eur J Cancer* **43**: 1810-1820

Mann DM, Ponieman D, Leventhal H, Halm EA (2009) Predictors of adherence to diabetes medications: the role of disease and medication beliefs. *J Behav Med* **32**: 278-284

Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, Apperley JF, Szydlo R, Desai R, Kozlowski K, Paliompeis C, Latham V, Foroni L, Molimard M, Reid A, Rezvani K, de Lavallade H, Guallar C, Goldman J, Khorashad JS. (2010) Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* **28**: 2381-2388

Marteau TM, Johnston M(1991) Health providers: a source of variance in health outcomes. *Psychology & Health* **5**: 47-58

Menckeberg TT, Bouvy ML, Bracke M, Kaptein AA, Leufkens HG, Raaijmakers JA, Horne R (2008) Beliefs about medicines predict refill adherence to inhaled corticosteroids. *Journal of Psychosomatic Research* **64**: 47-54

Noens L, van Lierde M-A, De Bock R, Verhoef G, Zachée P, Berneman Z, Martiat P, Mineur P, Van Eygen K, MacDonald K, De Geest S, Albrecht T, Abraham I (2009) Prevalence, determinants, and outcomes of non-adherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* **113**:5401-5411

Osterberg L, Blaschke T (2005) Adherence to medication. NEJM **353**: 487-497

Regnier Denois V, Poirson J, Nourissat A, Jacquin JP, Guastalla JP, Chauvin F (2011) Adherence with oral chemotherapy: results from a qualitative study of the behavior and representations of patients and oncologists. *Eur J Cancer Care* **20**: 520-527

Ruddy K, Mayer E, Partridge A (2009) Patient adherence and persistence with oral anticancer treatment. *CA: Cancer J Clin* **59**: 56-66

Scholl I, Kriston L, Dirmaier J, Buchholz A, Härter M (2012) Development and psychometric properties of he Shared Decision Making Questionnaire – physician version (SDM-Q-Doc). *Patient Educ Couns* **88**: 284-290

Staddon A (2011) Challenges of ensuring adherence to oral therapy in patients with solid malignancies. *Community Oncology* **8**: 254-262

Tibaldi G, Clatworthy J, Torchio E, Argentero P, Munizza C, Horne R (2009) The utility of the necessity-concerns framework in explaining treatment non-adherence in four chronic illness groups in Italy. *Chronic Illness* **5**: 129-133

Timmers L, Boons CCLM, Kropff F, Van De Ven PM, Swart EL, Smit EF, Zweegman S, Kroep JR, Timmer-Bonte JNH, Boven E, Hugtenburg JG (2014) Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncologica* **53**: 259-267.

Timmers L, Boons CCLM, Moes-ten Hove J, Smit EF, van de Ven PF, Aerts JG, Eleonora LS, Boven E, Hugtenburg JG (2015) Adherence, exposure and patients' experiences with the use of erlotinib in non-small cell lung cancer. *J Cancer Res Clin Oncol* [Accepted for publication]

Valente Teixeira F, Pais-Ribeiro JL, Pinho da Costa Maia ÂR (2012) Beliefs and practices of healthcare providers regarding obesity: a systematic review. *Revista da Associação Médica Brasileira* **58**: 254-262

Van Steenis MNA, Driesenaar JA, Bensing JM, Van Hulten R, Souverein P, Van Dijk L, De Smet P, Van Dulmen A (2014) Relationship between medication beliefs, self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. *Patient Prefer Adher* **8**: 83-91

Verbrugghe M, Verhaeghe S, Lauwert K, Beeckman D, Van Hecke A (2013) Determinants and associated factors influencing medication adherence and persistence to oral anticancer agents: a systematic review. *Cancer Treat Rev* **39**: 610-621

World Health Organization (2003) Adherence to long-term therapies: Evidence for action. WHO: Geneva

Xu S, Yang Y, Tao W, Song Y, Chen Y, Ren Y, Liu P, Pang D (2012) Tamoxifen adherence and its relationship in mortality in 116 men with breast cancer. Breast *Cancer Res Treat* **13**: 495-502

CHAPTER 6

ADHERENCE TO ORAL ANTICANCER AGENTS: HEALTHCARE PROVIDERS' PERCEPTIONS AND USUAL CARE IN BELGIUM AND THE NETHERLANDS

Based on the article of Timmers L, Boons C, Verbrugghe M, van den Bemt B, Van Hecke A., Hugtenburg J. (2015). Adherence to oral anticancer agents: healthcare providers' perceptions and usual care in Belgium and the Netherlands. *Under review.*

ABSTRACT

Purpose: The objective of this study was to assess current practice of adherence supportive care provided to patients using oral anticancer agents (OACA) in Belgium and the Netherlands and to explore how healthcare providers' (HCPs) perceptions of and beliefs about OACA are related to the provided adherence care.

Methods: A cross-sectional, observational study among HCPs, with the profession of oncologist, haematologist, nurse practitioner, nurse or pharmacist, in (haemato)-oncology settings in Belgium and the Netherlands was conducted by means of a questionnaire. Adherence supportive care activities were collected by means of a literature search and input of healthcare providers (HCPs) and experts and pilot tested in HCPs.

Results: 208 HCPs (53% male) participated, of whom 107 respectively 101 work in 51 hospitals in the Netherlands respectively 26 hospitals in Belgium. A total of 47 care activities were listed and categorised in eight domains. The median scores per care activities domain for respectively all HCPs, physicians, nurse practitioners (NPs), nurses and pharmacist were: Knowledge: 79, 86, 100, 71 and 29%; Awareness: 75, 75, 75, 63 and 0%; Social influence: 67, 67, 67, 67 and 0%; Self-efficacy: 40, 60, 80, 50 and 0%; Intention formation: 67, 67, 100, 83 and 50%; Action control: 25, 25, 50, 25 and 0%; Adverse event management: 100, 100, 100, 100 and 29%; Facilitation: 64, 64, 73, 55 and 27%.

Conclusion: Activities aimed at patients' knowledge and adverse event management were reported most frequently whereas activities aimed at self-efficacy and the use of cues were reported less frequently. The provided care differs between the professions involved in OACA adherence, with NPs the most active and pharmacists reporting the least adherence care. As compared to Belgium, in the Netherlands physicians reported less care activities whereas nurses and pharmacists report more activities. HCPs' perceptions of adherence management were strongly related to the adherence care they report.

INTRODUCTION

The issue of non-adherence is a rather new phenomenon in oncology. For decades, chemotherapy was predominantly administered intravenously (IV). During the last years, a substantial and rapidly growing number of oral anticancer agents (OACA) has been introduced (O'Neill and Twelves, 2002; Timmers et al., 2012). Oral administration may improve quality of life by its convenience and ease of use. Most patients prefer oral administration being ensured that OACA's efficacy is at least similar to that of IV treatment (Liu et al., 1997; Borner et al., 2001; Fallowfield et al., 2006). With the growing use of OACA, the relevance of medication adherence has become more urgent in oncology.

Non-adherence with medication is a complex and multidimensional healthcare problem. Adherence is defined as the extent to which a patient follows agreed recommendations for prescribed treatments (Sabaté, 2003). Patients may intentionally or non-intentionally be non-adherent during different stages of their treatment (Vrijens et al., 2012; Hugtenburg et al., 2013). Adherence to long-term therapies is estimated 50-70% (Sabaté, 2003; Osterberg and Blaschke, 2005; Vrijens et al., 2012; Hugtenburg et al., 2013). It has been shown that adherence to OACA can also be a problem; adherence and persistence rates with OACA between 16% and 100% are reported (Ruddy et al., 2009).

Consequences of non-adherence can be tremendous for the individual patient (e.g. lack of efficacy or increased toxicity) and society (increased healthcare costs). The minimum level of adherence which is necessary for clinical outcome, varies by drug and is often not exactly known. Research on adherence to tyrosine kinase inhibitors in the treatment of chronic myeloid leukaemia (CML) revealed a strong relationship between the missing of some intakes per month and clinical response (Marin et al., 2010).

Factors influencing non-adherence are complex. The World Health Organization has developed a framework which describes the multidimensional phenomenon of medication adherence (Sabaté, 2003). It includes five interacting dimensions

influencing adherence: social and economic factors, condition-related factors, therapy-related factors, patient-related factors, and healthcare provider (HCP) and system-related factors. Studies exploring adherence issues have predominantly focused on the patient (Osterberg and Blaschke, 2005; Verbrugghe et al., 2013). Few research is published on HCP-related factors influencing medication adherence.

HCP-related factors were found to influence OACA (non-)adherence. In patients with breast cancer on chronic endocrine therapy, a poor physician's explanation of treatment effects seemed related to non-adherence (Kahn et al., 2007). In addition, patients with CML on long-term imatinib reported that positive feedback from physicians reinforced the belief that 'occasional' non-adherence does not affect response (Eliasson et al., 2011). HCPs' perceptions of and beliefs about OACA may influence their behaviour and care which in turn may influence patients' adherence behaviour (Eliasson et al., 2011). In the paper reporting about the first part of this study (Adherence to oral anticancer agents: healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands), we assessed the beliefs of HCPs about OACA and their perceptions of management of adherence. Most HCPs indicated to have enough knowledge of causes and consequences of adherence and felt to be able to influence adherence of their patients. However, many of them, especially nurses and pharmacists, reported not to know the adherence of their patients, nor did they think their patients discuss adherence with them. It is not known how these results are related to their actual performed adherence care.

The present study focused on the current practice of adherence supportive care provided in (haemato-) oncology in Belgium and the Netherlands.

METHODS

Study design

An international cross-sectional observational study was conducted between April 2014 and October 2014 in the Netherlands and Belgium. HCPs with the

profession of oncologist, haematologist, nurse practitioner, nurse or pharmacist, and providing patient care in a (haemato-) oncology settings in the Netherlands or Dutch-speaking part of Belgium, were asked to fill out a questionnaire. The study was assessed not governed by the Dutch law on Medical Research in Humans by the Medical Ethics review board of VU University Medical Center (VUMC, Amsterdam, the Netherlands) and was approved by the Ethical Review Committee of the Ghent University Hospital (Belgium).

Data collection procedure

HCPs were invited to fill out an electronic questionnaire by their professional association. The questionnaire was available by an internet-link. After two-four weeks one or two reminders were sent to stimulate response. Additional recruitment took place by distributing the link to the online questionnaire within the authors' network, and by handing out a paper version of the questionnaire at a scientific meeting about 'adherence with oral anticancer agents', held on the 14th of October 2014 in Brussels.

Questionnaire

A composite questionnaire was used. At the start, the following characteristics of the respondents were collected: profession, gender, number of years employed, type of hospital (academic or non-academic) and specialization. Respondents were asked to fill out the questionnaire with in mind the patient group which they treated most.

The questionnaire consisted of four parts:

1. HCPs' perceptions of management of adherence

   Five questions, developed by the research team, were used to assess HCPs' perceptions of adherence management (PAMQ, HCP's Perceptions of Adherence Management Questionnaire): *Insight in adherence*: I know the level of adherence of all my patients; *Patients' communication*: I think that patients discuss non-adherence with me, *Capability to influence:* I am able to influence adherence behavior of my patients, *Consequences*: I have sufficient knowledge about the

consequences of non-adherence, and *Causes:* I have sufficient knowledge about the causes of non-adherence to discuss this with patients. The answers were assessed on a 5-point Likert scale: strongly disagree, disagree, neutral, agree, and strongly agree. The answers 'agree' and 'strongly agree' were dichotomised into 'yes'. The total PAMQ-score (ranging from zero to five) was calculated by summing the five dichotomised items. A higher total score on the PAMQ indicated a higher number of perceptions about managing adherence the HCP agree with.

2. Shared Decision Making

   To assess the style of SDM, the validated Shared Decision Making Questionnaire – physician version (SDM-Q-Doc), in the authorised Dutch translation, was used (Scholl et al., 2012). The questionnaire consists of 9 items that are rated on a 6-point Likert scale (absolutely inappropriate to absolutely appropriate, scored with 0 to 5). A sum score was made (range 0 to 45), and linear transformed into a scale from zero to 100 to facilitate interpretation as recommended by Scholl et al. (2012). A higher score indicates a higher level of acceptance towards shared-decision making.

3. Beliefs about OACA

   The validated Beliefs about Medicines Questionnaire (BMQ-Specific) (Horne et al., 1999; Horne et al., 2013), was used to assess beliefs about the necessity of the medication to control the disease and the concerns about the potential negative impact of the medication. The BMQ-Specific consists of twice 5 items for the subscale 'Concerns' respectively 'Necessity', which are scored on a 5-point Likert scale ('strongly disagree' to 'strongly agree', scored from 1 to 5) resulting in a score for the subscales ranging from 5 to 25. BMQ-Specific was adapted for use in HCPs by Lesius at al (unpublished) and was translated into Dutch following the inverse translation method (Koller et al., 2007) by CB and LT. The Dutch HCPs-version was authorised by the original first

author R. Horne. HCPs were profiled in four groups: accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), indifferent (low necessity, low concerns) and sceptical (low necessity, high concerns) with the scale midpoint of 15 used as a cut-off to divide low and high (Menckeberg et al., 2008).

4. Usual care activities

   To assess usual care (UC) in supporting adherence to OACA, a list of care activities used in adherence supportive care was prepared. The list was based on the Quality of Standard Care questionnaire as used by de Bruin et al. to assess UC in supporting patients to adhere to HAART-therapy (de Bruin et al., 2009; de Bruin et, 2010). The list was adapted to oncology by the research team consisting of a haematologist, a medical oncologist, three pharmacists, and three researchers [nurse, psychologist, health scientist] with expertise in the field of medication adherence in oncology and haematology. Items were sorted in three parts: activities carried out at the start-up of therapy, activities carried out during follow-up appointments, and activities which were not connected to specific time-points. For each item, HCPs had to indicate whether they delivered the UC activity during the last six months for the majority of their patients (yes or no).

The complete questionnaire was pilot-tested by nine HCPs (i.e. three pharmacists, three nurses, one haematologist, one medical oncologist, and one general practitioner) in Belgium and the Netherlands. During individual interviews, it was explored whether the items were understood as intended. Furthermore HCPs were asked about items of supportive adherence care and to add items if anything was missing. After processing the comments, the final version of the questionnaire was defined.

Categorising items in domains

Items were categorised in eight domains. Seven domains are based on the categorization as developed by de Bruin et al. (2009): Knowledge, Awareness,

Self-efficacy, Intention formation, Social influence, Action control and Facilitation. One additional domain was developed: Adverse events management. Each member of the research group independently categorised the care activities into one of the domains. Then, the categorization of these items into the domains was discussed in the group in two rounds until consensus was reached. Table 1 gives an overview of the domains, its definitions, and typically used techniques of activities within the domain.

Statistics

Respondent descriptive data were analysed as frequencies (percentages) for categorical variables and as the median and interquartile range (IQR) for continuous data. The UC sum score of HCPs in the Netherlands and the UC sum score of HCPs in Belgium were compared for all professions by means of the non-parametric Chi^2-test for nurse practitioners (NP) and the T-test for all other professions (normally distributed scores). Associations between respondent characteristics and the sum score of care activities were assessed in univariate linear regression analyses in which UC sum score was taken as the dependent variable. A multivariate linear regression was performed using all characteristics which had a $p<0.25$ in the univariate analyses. For all analyses, a two-tailed significance level of 0.05 was used. *P*-values below this level were considered statistically significant. Statistical analysis was performed with SPSS 22.0 for Windows (IBM Corp, Armonk, NY, USA).

RESULTS

Respondent characteristics

A total of 208 HCP (53% male) were included, of whom 107 worked in 51 hospitals the Netherlands and 101 were employed in 26 hospitals in Belgium. Characteristics of the HCPs are shown in Table 2. The scores of the HCPs on PAM-Q, SDM-Q-doc, and BMQ are also listed in Table 2. Detailed results and discussion about these topics are reported in the paper ‘Adherence to oral

anticancer agents: healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands (submitted)'.

Usual Care in adherence supportive care

Table 3 depicted how many HCPs performed one or more of 47 predefined care activities in the last six months for the majority of their patients. The items are categorised in domains and scores are shown for all HCPs as well as for professions separately. Most activities were reported by 50-75% of respondents. Activities within the domain Self-efficacy were reported less often (by 45-50% of HCPs) while most activities within the domain Adverse event management were provided by 75-85% of HCPs. The use of a medication electronic monitoring system (MEMS) was reported by only 5% of HCPs. The median and interquartile range per domain is listed for all HCPs together and by profession in Table 4. As the domains consist of a different number of items; the range per domain varies.

In figure 1, the maximum score of all domains is presented as 100%. The median scores per domain for respectively all HCPs, physicians, NP, nurses and pharmacist are: Knowledge: 79, 86, 100, 71 and 29%; Awareness: 75, 75, 75, 63 and 0%; Social influence: 67,67,67, 67 and 0%; Self-efficacy: 40, 60, 80, 50 and 0%; Intention formation: 67, 67, 100, 83 and 50%; Action control: 25, 25, 50, 25 and 0%; Adverse event management: 100, 100, 100, 100 and 29%; and Facilitation: 64, 64, 73, 55 and 27%.

Belgium versus the Netherlands

Table 5 shows the UC sum scores of HCPs and by profession for the Netherlands and Belgium separately. Belgian physicians had a higher UC sum score compared to their Dutch colleagues (31.0 versus 27.0). Whereas Dutch nurses and pharmacists had a higher UC sum score than their Belgian colleagues (35.0 vs 28.0 for nurses and 18.5 versus 3.0 for pharmacists).

Associations with Usual Care in adherence supportive care

Univariate associations of UC sum score are presented in Table 6. The sum score of NP were higher than physicians and the sum score of pharmacists were

significantly lower. The perceptions of adherence management were significantly related to the UC sum score. Higher scores on the scales 'Insight in adherence', 'Patients' communication', 'Capability to influence' and 'Causes' were significantly related with a higher UC sum score. In the multivariate analyses the following HCPs' characteristics were significantly associated with the UC sum score: Profession (p<0.001), Country (OR -3.95; 95%CI: -6.59 to - 1.30, p<0.001) and Total PAMQ- score (OR 2.21; 95%CI: 1.25 – 3.80, p<0.001).

DISCUSSION

The assessment of adherence supportive care revealed a wide range of UC activities provided in the Netherlands and Belgium. Activities aimed at adverse event management were reported most frequently; most physicians, NP, and nurses provided all activities within this domain. The attention which is given to adverse events management in supportive care for OACA does not surprise, as in oncology adverse events occur very often and can be serious. Adverse events may have great impact on patients' quality of life (Verbrugghe et al., 2015) and have shown to be related to non-adherence and early discontinuation of OACA-treatment (Verbrugghe et al., 2013; Timmers et al., 2014; Wouters et al., 2014). All physicians reported to inquire after experienced adverse events and the severity of the adverse events. For several OACA the dosing regimen is individually adjusted by the physician in case of adverse events, especially in case of grade II-IV. Therefore, information about adverse events is essential for physicians.

Although many UC activities are performed by all HCPs in our study, UC activities related to the self-efficacy domain seemed to be less common. Less than 50% of HCPs performed care activities related to self-efficacy. However, self-efficacy is known to be an important factor influencing adherence and adequate self-management, addressed in theoretical behavioral frameworks (Bandura, 2004) as well as in medication adherence oncology research (Noens et al., 2009; Wouters et al., 2014). Also the domain Action control received

relatively little attention. The care activities within this domain focus on cues which are especially relevant to avoid unintentional non-adherence. As we know that adherence decreases during time (Partridge et al., 2003), supportive adherence care as included in the domain Action Control is especially relevant for OACA which are planned to be used for longer periods.

The reported provided care differed between professions and countries. The role of the different professions did not seem to vary much per domain. Nurse practitioners provided the widest range of care activities. They were more active within all domains of care compared to the other HCPs. This might be due to their specialization, training in education and focus on self-management support and the time spent on patient-contact. The positive impact of NPs in quality of care in oncology was demonstrated before (van Hezewijk et al., 2011; McCorkle et al., 2012). Pharmacists provided significantly less care activities compared to the other HCPs. In four out of eight domains they usually did not provide any care activity at all.

HCPs in the Netherlands and Belgium seem to have organised the care in different ways. The role of the various HCPs seemed different in both countries. Whereas the physician performed more adherence care activities in Belgium, in the Netherlands a higher percentage of nurses and pharmacists were involved in UC activities related to medication adherence. Striking is the difference in reported adherence supportive care between Dutch and Belgian pharmacists. In Belgium, OACA are delivered by the pharmacist working in a hospital pharmacy. In the Netherlands OACA are delivered from the hospital as well, but most hospitals organise this from a pharmacy specialised in outpatients. This pharmacy is equipped for direct patient contact. Furthermore, all Dutch pharmacists have access to patients' list of (co-)medication due to electronic services. This might contribute to the differences in the level of provided pharmaceutical care. Nevertheless, the role of pharmacists in management of adherence to OACA is low in both countries compared with the other HCPs.

There is a strong relationship between the perceptions of adherence management and the number of adherence care activities provided. HCPs who

scored higher on the statements about insight and knowledge to manage adherence actually performed more adherence care activities. However, remarkable is the discrepancy of the PAMQ-score and UC sum score for pharmacists: though they stated to have enough insight and knowledge and felt able to influence patients' adherence, they did not provide many care activities. Probably within the multidisciplinary team, involvement of pharmacists might be optimised as they have a unique contribution in medication therapy management (Mancini, 2012).

Research on current practice of care to support adherence to OACA in Spain, Japan and the USA, revealed great variation. A survey of 647 nurses in the USA in 2014 revealed that about half of them worked in practices without specific policies and procedures to support patients using OACA and inadequate interdisciplinary communication (Roop and Wu, 2014). The results of a nurse-based survey in Japan in 2014 indicated that practices varied, but nurses were less likely to ask adherence-related questions to patients in follow-up than in new patients (Komatsu et al., 2014). In Spain a study among oncology pharmacists in 2013 found that the majority of responding hospitals had safety and adherences practices for oral OACA. However, the level of these practices varied and they reported significant opportunities for improvement, monitoring OACA-adherence (Conde-Estevez et al., 2013).

There are strengths and limitations to discuss. This study provides an extensive survey of care activities provided by HCPs (physicians, as well as NPs, nurses as pharmacists) in supporting adherence to OACA. The list of 47 items was literature based and adjusted and supplemented with input from oncologists, haematologists, NPs, nurses, pharmacists and researchers specialised in adherence with OACA from two different countries. We expect our list to be by itself of value for HCPs and researchers working with OACA. Three main limitations of the study need to be mentioned. First, the reported adherence care is not specified to specific patient groups. It might be that adherence care provided to patients using long-term medication consists of different activities compared to care provided to patients with an expected short-term treatment.

This paper gives a general overview of UC in (haemato-) oncology. The second limitation of this study is the selection bias. Though we recruited respondents from 87 different hospitals, the questionnaire might be filled out mainly by HCPs interested in adherence care. Furthermore, answers may be overstated as people tend to give socially desirable information. It is not unlikely that the adherence care is less extensive in daily practice. It would be interesting to study the provided care by using video observations in daily practice, which has shown to be a reliable and valid method (Ram et al., 1999). Third, the sample in this study was not truly random, so statistical significance should be interpreted with caution.

CONCLUSION

In conclusion, we provide a unique and complete list of 47 items of care activities provided by HCPs in supporting adherence to OACA, which we expect to be of value for HCP as well as researchers.

The assessment of adherence supportive care revealed a wide range of UC activities provided in the Netherlands and Belgium. The extent of UC activities provided differs by profession; NPs are the most active, pharmacists provide least adherence care. For all HCPs, activities aimed at increasing patients' knowledge and adverse event management were reported most frequently whereas activities aimed at self-efficacy and action control were performed less. We advise to focus on these latter domains when developing interventions to support patients taking OACA and enhance quality of care as self-efficacy and action control have shown to be associated with higher adherence to medication.

There is a strong relationship between the perceptions of adherence management and the number of reported adherence care activities that are provided. The provided care differs between the professions that are involved in OACA adherence and also by country. This confirms that in intervention

research, a clear description of which care is provided in the reference group is obligated.

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Table 1. Domains of Usual Care activities in adherence supportive care

Domain	Definition	Typically used technique(s)
Knowledge	Usual care activities focussing on the knowledge of patients about their diseases and the medicines used for treatment, excluding knowledge related to adverse events.	- providing information - increase patient understanding
Awareness	Usual care activities aimed to increase the awareness of patients with respect to non-adherence to treatment and consequences of non-adherence	- risk communication - giving feedback on patients' behaviour
Self-efficacy	Usual care activities that focus on self-efficacy; a patient's belief in her/his ability in succeeding to adhere to treatment	- the planning of coping responses like discussing adherence barriers and finding ways to overcome barriers
Intention Formation	Usual care activities which focus on fostering the intention to adhere by planning how and when to take the medication	- the development of a tailored medication schedule
Social Influence	Usual care activities that provide patients with professional social support with respect to the correct use of their medication	- organising social support
Action Control	Usual care activities which focus on the effective implementation of the intended use of medication	- stimulating the use of cues
Adverse Events Management	Usual care activities which focus on patients' management of adverse events	- providing information - coping with adverse events
Facilitation	Usual care activities which facilitate a correct use of medication and which are not categorised in one of the other domains	- reducing environmental barriers

Table 2. Basic characteristics

N = 208	All	NL	Be
	N = 208	N = 107	N = 101
Gender (%)			
male	29.3	33.6	24.8
female	70.7	66.4	75.2
Profession (%)			
oncologist	15.9	10.3	21.8
hematologist	15.9	26.2	5.0
NPs	16.8	17.8	15.8
nurse	28.8	21.5	36.6
pharmacist	22.6	24.3	20.8
Work experience (yr)			
median	16	16	17
range	1-46	2-46	1-40
Type of hospital (%)			
academic	29.6	22.4	37.4
non-academic	70.4	77.6	62.6
Number of different hospitals	87	51	36
Specialisation (%)			
hematology	30.6	38.0	22.6
oncology	69.4	62.0	77.4
Adherence (PAMQ) (%)			
Insight in adherence	41.8	43.9	39.6
Patients' communication	43.8	45.8	41.6
Capability to influence	82.2	86.0	78.2
Consequences	78.8	75.7	82.2
Causes	68.3	69.2	67.3
Total PAMQ-score (0-5)			
- median	3.0	3.0	3.0
- IQR	2.0-4.0	2.0-4.0	2.0-4.0
SDM*-score (0-100)	82.2	84.4	80.0
BMQ-group (%)			
accepting	58.3	61.3	55.0
ambivalent	31.1	24.5	38.0
indifferent	8.3	11.3	5.0
sceptical	2.4	2.8	5.0

Abbreviations: NL, the Netherlands; Be, Belgium; NPs, nurse practitioners;

yr, year; IQR, interquartile range; SDM-score, sum score of the Shared

Decision Making-doc-Questionnaire – a higher sum scores indicates perceptions of more

shared decision making; PAMQ, HCP's Perceptions of Adherence Management Questionnaire – a higher score on the PAMQ indicates a higher number of perceptions about managing adherence the HCP agree with; BMQ, Beliefs about Medicines Questionnaire. * - higher scores indicates stronger beliefs of necessity or concerns; SDM only assessed for physicians (N=66).

Table 3. Usual care activities in supporting adherence

	*N**	all HCPs 208*	physician 66*	NPs 35*	nurse 60*	pharmacist 47*
		%	%	%	%	%
Knowledge						
Provide information on the disease	208	74.0	100.0	100.0	75.0	17.0
Provide information on the expected effect(s) of the drug	206	73.3	100.0	88.2	69.5	29.8
Discuss the action of the drug	206	72.3	95.5	88.2	61.0	42.6
Hand out brochures or written information about the disease and/or medication used for treatment	205	69.3	67.2	91.2	66.7	59.6
Discuss when the first effect of the medication can be expected	206	64.1	100.0	76.5	50.8	21.3
Monitor and/or discuss possible interactions with other medicines or foods	204	77.0	84.4	93.9	66.7	68.1
Discuss (changes in) sexuality	197	32.5	32.3	66.7	39.3	0.0
Awareness						
Discuss the importance of treatment adherence	200	76.0	85.9	87.9	80.7	47.8
Discuss the consequences of non-adherence (to treatment)	199	57.8	71.4	69.7	59.6	28.3
Ask the patient if he/she has missed one or more doses	198	56.6	65.1	81.8	66.1	15.2
Discuss the use and results of the Medication Event Monitoring System (MEMS)	195	4.6	4.9	6.3	5.4	2.2
Social influence						
Involve partner and/or relatives in the treatment	199	71.9	85.9	87.5	82.5	28.3
Encourage patients to organise social support	197	40.1	49.2	54.5	52.6	2.2
Refer a patient to a patients' association	198	36.4	54.0	60.6	30.4	2.2
Self-efficacy						
Encourage patients to timely plan the intake of medicines during holidays and weekends	197	43.7	53.2	57.6	42.9	21.7
Discuss potential barriers regarding treatment adherence	198	49.0	55.6	62.5	52.6	26.1
Discuss possible ways to overcome potential barriers regarding treatment adherence (at start of the treatment)	199	50.3	57.1	69.7	49.1	28.3
Inquire after barriers regarding treatment adherence	198	49.5	58.7	75.8	50.0	17.4
Discuss ways to overcome potential barriers regarding treatment adherence (at follow-up)	197	45.7	56.5	69.7	42.9	17.4

		all HCPs	physician	NPs	nurse	pharmacist
	*N**	208*	66*	35*	60*	47*
		%	%	%	%	%
Intention formation						
Discuss the scheduled duration of medication treatment	206	70.9	100.0	91.2	57.6	31.9
Explain how often the medicine should be taken. If necessary, explain the treatment schedule	205	90.2	96.9	97.1	90.0	76.6
Discuss the intake of the medicines relative to that of meals and why	202	81.2	72.6	97.0	88.3	72.3
Discuss what to do if there is vomiting shortly after ingestion of the medicine	203	64.0	60.3	91.2	76.3	34.0
Explain what to do if a dose is missed	198	67.2	61.9	97.0	75.0	43.5
Development of an individual written medication schedule	195	43.1	27.9	81.3	50.0	28.3
Action control						
Identify daily routines and encourage patients to align the taking of medicines with their routines	199	58.8	55.6	90.9	71.9	23.9
Encourage patients to use a seven day pillbox	197	27.9	17.5	50.0	35.7	17.4
Encourage patients to use the Medication Event Monitoring System (MEMS)	194	5.2	5.0	9.4	3.6	4.3
Encourage patients to use alarm devices for properly timing their medication intake	196	22.4	11.3	48.5	26.8	13.3
Adverse events management						
Discuss the common side effects of the drug	207	83.6	97.0	94.1	83.3	57.4
Discuss options to mitigate the impact of side effects (at start of treatment)	205	77.6	81.3	97.1	85.0	48.9
Discuss the possibility of dose adjustment if side effects occur	205	66.8	90.8	73.5	67.8	27.7
Inquire after (perceived) side-effects of treatment	198	84.3	100.0	100.0	85.7	50.0
Inquire after the severity of the side-effects	198	82.3	100.0	97.0	87.5	41.3
Discuss options to mitigate the impact of side effects (during treatment)	198	77.3	92.1	93.9	80.4	41.3
Give the patient a telephone number and tell who to contact in the case of side-effects	195	70.8	85.0	97.0	80.4	21.7
Facilitation						
Explain how and where the product is available	204	76.0	83.1	91.2	70.7	61.7
Discuss drug storage recommendations	200	61.0	33.3	72.7	64.9	85.1

		all HCPs	physician	NPs	nurse	pharmacist
	*N**	208*	66*	35*	60*	47*
		%	%	%	%	%
Give feedback about treatment efficacy	198	60.1	100.0	67.7	48.2	13.0
Inquire after positive effects of treatment	198	69.2	96.8	78.8	69.6	23.9
Ensure the timely transfer of medication information to other health care providers	197	61.9	80.6	59.4	40.4	65.2
Call the patient after the start of treatment to ask about experiences	194	22.7	8.5	51.5	35.7	4.3
Give the patient a telephone number and tell who to contact in case of problems with treatment adherence	196	59.2	67.2	87.9	62.5	23.9
Inform the patient about 24 hour availability of assistance	197	67.5	85.2	81.8	73.7	26.1
Intensify the number of follow-up visits if patients have problems with treatment adherence	197	30.5	38.7	51.5	26.8	8.7
Refer patients to another healthcare provider for (co-)treatment (e.g. in the case of adverse events)	198	48.5	60.3	63.6	42.9	28.3
Refer to another healthcare provider in case of (suspected) psychosocial problems	197	61.4	77.4	81.8	76.9	6.5

Abbreviations: HCPs, healthcare providers; NPs, nurse practitioners

* Note: missings excluded from analyses

Table 4 Usual Care Domain-scores

		Knowledge	Awareness	Social Influence	Self-efficacy	Intention Formation	Action Contol	Adverse Events Management	Facilitation
range:		(0-7)	(0-4)	(0-3)	(0-5)	(0-6)	(0-4)	(0-7)	(0-11)
All HCPs	N	194	195	195	195	190	193	194	191
median		5.5	2.0	2.0	2.0	4.0	1.0	7.0	7.0
IQR		3-6	1-3	1-2	0-5	3-6	0-2	5-7	4-8
Physicians	N	59	61	61	61	58	60	59	58
median		6.0	3.0	2.0	3.0	4.0	1.0	7.0	7.0
IQR		5-6	2-3	1.5-2	1-5	3-5	0-1	6-7	6-8
NPs	N	33	32	32	32	31	32	33	32
median		7.0	3.0	2.0	4.0	6.0	2.0	7.0	8.0
IQR		6-7	2-3	2-3	1.3-5	6-6	1-3	6-7	7-10
Nurses	N	56	56	56	56	55	56	56	55
median		5.0	2.5	2.0	2.5	5.0	1.0	7.0	6.0
IQR		3-6	1-3	1-2	0-5	3-6	1-2	5.3-7	4-9
Pharmacists	N	46	46	46	46	46	45	46	46
median		2.0	0.0	0.0	0.0	3.0	0.0	2.0	3.0
IQR		0-3.3	0-2	0-1	0-2	1-4	0-1	0-6	1-6

Abbreviations: HCPs, healthcare providers; IQR, interquartile range; NPs, nurse practitioners.

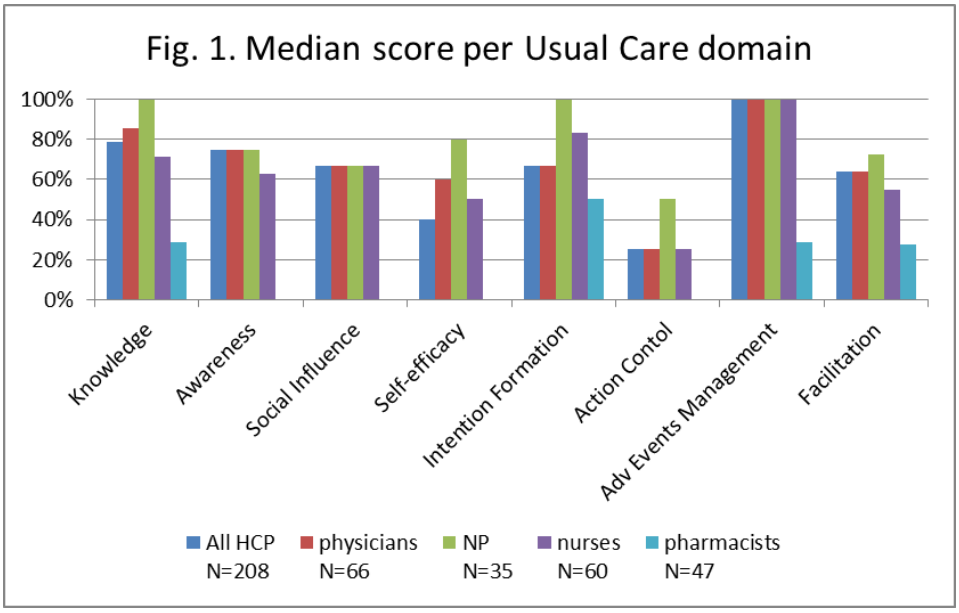
Fig. 1. Median score per Usual Care domain
100%
80%
60%
40%
20%
0%
Knowledge
Awareness
Social Influence
Self-efficacy
Intention Formation
Action Contol
Adv Events Management
Facilitation
All HCP N=208
physicians N=66
NP N=35
nurses N=60
pharmacists N=47

Table 5. Total score Usual Care NL vs Be

	NL		Be		NL vs Be	
	N	UC-sum	N	UC-sum	*p*	
Physician	27	27,0	25	31,0	0.043	*
NPs	13	38,0	16	36,5	0.307	
Nurse	17	35,0	37	28,0	<0.001	*
Pharmacist	24	18,5	21	3,0	0.026	*

Abbreviations: NL, the Netherlands; Be, Belgium; vs, versus; UC-sum, usual care activities sum score; HCPs, healthcare providers; NPs, nurse practitioners.

Table 6. Univariate associations with Usual Care sum score
N=180

	OR	95% CI	*p*-value	
Gender (male)	1.97	-1.35 - 5.28	0.244	
Profession			<0.001	*
Physician as reference:				
- Nurse Practioner	4.19	0.38 - 8.01	0.031	*
- Nurse	-1.60	-4.80 - 1.59	0.324	
- Pharmacist	-12.69	-16.04 - -9.34	<0.001	*
Work experience (yr)	-0.03	-0.17 - 0.11	0.673	
Type of hospital (academic)	-3.20	-6.45 - 0.06	0.054	
Specialisation (oncology)	-2.36	-5.80 - 1.09	0.178	
Country (the Netherlands)	-2.51	5.50 - 0.48	0.100	
Adherence (PAMQ)				
Insight in adherence	6.80	3.93 - 9.68	<0.001	*
Patients' communication	9.32	6.62 - 12.01	<0.001	*
Capability to influence	5.78	2.08 - 9.47	0.002	*
Consequences	3.60	-0.04 - 7.24	0.053	
Causes	3.70	0.59 - 6.81	0.020	*
Total PAMQ-score	3.23	2.26 - 4.19	<0.001	*
SDM*-score	-0.00	-0.09 - 0.09	0.973	
BMQ-group			0.972	
Accepting as reference:				
- Ambivalent	-3.34	.-3.72 - 3.05	0.844	
- Indifferent	0.32	-5.45 - 6.08	0.866	
- Sceptical	-2.22	-12.55 - 8.11	0.680	

Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval, yr, year; SDM-score, sum score of the Shared Decision Making-doc-Questionnaire; *, SDM only assessed for physicians (N=66); BMQ, Beliefs about Medicines Questionnaire.

REFERENCES

Bandura A: Health promotion by social cognitive means. *Health Educ Behav* 2004;**31**:143-164.

Borner M, Scheithauer W, Twelves C, et al. Answering patients' needs: oral alternatives to intravenous therapy. *Oncologist* 2001;**6**(4):12-16.

Conde-Estevez D, Salas E, Albanell J. Survey of oral chemotherapy safety and adherence practices of hospitals in Spain. *Int J Clin Pharm* 2013;**35**:1236-1244.

de Bruin M, Viechtbauer W, Hospers HJ, et al. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. *Health Psychol* 2009;**28**:668-674.

de Bruin M, Viechtbauer W, Schaalma HP, et al. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. *Arch Intern Med* 2010;**170**:240-250.

Eliasson L, Clifford S, Barber N, et al. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. *Leuk Res* 2011;**35**:626-630.

Fallowfield L, Atkins L, Catt S, et al. Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol* 2006;**17**:205-210.

Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health* 1999;**14**:1-24.

Horne R, Chapman SC, Parham R, et al. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a

meta-analytic review of the Necessity-Concerns Framework. *PLoS One* 2013;**8**:e80633.

Hugtenburg JG, Timmers L, Elders PJ, et al. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient Prefer Adherence* 2013;**7**:675-682.

Kahn KL, Schneider EC, Malin JL, et al. Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Med Care* 2007;**45**:431-439.

Koller M, Aaronson NK, Blazeby J, et al. Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach. *Eur J Cancer* 2007;**43**:1810-1820.

Komatsu H, Yagasaki K, Yoshimura K. Current nursing practice for patients on oral chemotherapy: a multicenter survey in Japan. *BMC Res Notes* 2014;**7**:259.

Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;**15**:110-115.

Mancini R. Implementing a standardized pharmacist assessment and evaluating the role of a pharmacist in a multidisciplinary supportive oncology clinic. *J Support Oncol* 2012;**10**:99-106.

Marin D, Bazeos A, Mahon F, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* 2010;**28**:2381-2388.

McCorkle R, Engelking C, Lazenby M, et al. Perceptions of roles, practice patterns, and professional growth opportunities: broadening the scope of advanced practice in oncology. *Clin J Oncol Nurs* 2012;**16**:382-387.

Menckeberg TT, Bouvy ML, Bracke M, et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. *J Psychoso Res* 2008;**64**:47-54.

Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* 2009;**113**:5401-5411.

O'Neill VJ, Twelves CJ. Oral cancer treatment: developments in chemotherapy and beyond. *Br J Cancer* 2002;**87**:933-937.

Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487-497.

Partridge AH, Wang PS, Winer EP, et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol* 2003;**21**:602-606.

Ram P, Grol R, Rethans J, et al. Assessment of general practitioners by video observation of communicative and medical performance in daily practice: issues of validity, reliability and feasibility. *Medical education* 1999;**33**, 447-454.

Roop JC, Wu HS. Current practice patterns for oral chemotherapy: results of a national survey. *Oncol Nurs Forum* 2014;**41**:185-194.

Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin* 2009;**59**:56-66.

Sabaté E (2003). Adherence to long-term therapies. Evidence for action., in . Geneva, World Health Organization.

Scholl I, Kriston L, Dirmaier J, et al. Development and psychometric properties of the Shared Decision Making Questionnaire--physician version (SDM-Q-Doc). *Patient Educ Couns* 2012;**88**:284-290.

Timmers L, Beckeringh JJ, Herk-Sukel MPP, et al. Use and costs of oral anticancer agents in the Netherlands in the period 2000-2008. *Pharmacoepidemiol Drug Saf* 2012;**21**:1036-1044.

Timmers L, Boons CC, Kropff F, et al. Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncol* 2014;**53**:259-267.

van Hezewijk M, Ranke GM, van Nes JG, et al. Patients' needs and preferences in routine follow-up for early breast cancer; an evaluation of the changing role of the nurse practitioner. *Eur J Surg Oncol* 2011;**37**:765-773.

Verbrugghe M, Verhaeghe S, Lauwaert K, et al. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: A systematic review. *Cancer Treat Rev* 2013;**39**:610-621.

Verbrugghe M, Duprez V, Beeckman D, et al. Factors influencing adherence in cancer patients taking oral tyrosine kinase inhibitors. *Cancer Nursing.* [Accepted for publication].

Vrijens B, De GS, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;**73**:691-705.

Wouters H, Stiggelbout AM, Bouvy ML, et al. Endocrine therapy for breast cancer: assessing an array of women's treatment experiences and perceptions, their perceived self-efficacy and nonadherence. *Clin Breast Cancer* 2014;**14**:460-467.

CHAPTER 7

GENERAL DISCUSSION

The aims of this PhD thesis were (1) exploring factors and processes influencing (non-)adherence and (non-)persistence to oral anticancer drugs (OACD), (2) exploring healthcare professionals' perceptions about managing OACD adherence and shared decision making (SDM) and beliefs towards OACD, and (3) exploring usual care in supporting adherence to OACD. In chapter 2, a systematic literature review on associated factors of (non-)adherence and (non-)persistence in patients taking OACD was described. Chapter 3 and 4 described two qualitative studies giving insight into influencing factors and processes underlying (non-)adherence and (non-)persistence in patients taking oral tyrosine kinase inhibitors (TKIs) and antihormonal therapy (AHT). Chapter 4 and 5 described two quantitative studies exploring healthcare professionals' perceptions about managing OACD adherence and SDM and beliefs towards OACD, and usual care.

In the general discussion, four main issues will be addressed. First, adherence and self-management support: a complex intervention design will be addressed. The building blocks needed for a complex intervention design which could be derived from this PhD thesis will be discussed (literature review, problem and needs analysis, and current practice analysis). Second, some methodological considerations will be provided. Third, implications for practice will be provided and fourth, recommendations for future research will be outlined.

ADHERENCE AND SELF-MANAGEMENT SUPPORT: A COMPLEX INTERVENTION DESIGN

Our study showed that factors influencing (non-)adherence and (non-)persistence in patients taking OACD are multifaceted. Several OACD (non-)adherence and (non-)persistence influencing factors were found to interact with each other. Also the importance of the patients' perspective, patients' experiences and needs were highlighted. Furthermore, the importance of not solely focusing on adherence and persistence to OACD, but also on taking into account the patients' perspectives of quality of life was emphasized. Based on our findings, we could conclude that (non-)adherence and (non-)persistence in

patients taking OACD are complex phenomena. Consequently, facilitating adherence and persistence in patients taking OACD and supporting them in ongoing self-management require a complex intervention. Based on the previous findings, the complex intervention should consist of a number of components. First, a clustering of different components to address the different influencing factors should be included. Second, interventions should not be aimed at all patients taking OACD but should be tailored to the specific needs of the patients. Third, multiple intervention outcomes should be evaluated (e.g. adherence, quality of life, self-management).

To develop complex interventions, the van Meijel model is appropriate (van Meijel et al., 2004). The model describes a planned and systematic approach for the development of complex nursing interventions. A strong emphasis is placed on patients' experiences and perspectives. The building blocks needed for intervention design (van Meijel et al., 2004) could be derived from this PhD thesis. Within this chapter, the discussion of our study findings will be structured according to these building blocks: literature review (chapter 2), problem and needs analysis (chapter 3, 4, and 5), and current practice analysis (chapter 6).

Literature review

A thorough literature review is the starting point of complex intervention development (van Meijel et al., 2004). In this phase, information is needed to inform the intervention development. It is explored whether there is sufficient knowledge about factors influencing OACD (non-)adherence and (non-)persistence, patients' needs and problems, and interventions to support patients in adhering to OACD (see chapter 1: general introduction).

In chapter 2, an overview was given of factors influencing (non-)adherence and (non-)persistence in patients taking different types of OACD. Factors positively and negatively associated with adherence and persistence were described. Influencing factors were structured according to the five categories suggested by the World Health Organization framework of factors influencing medication

adherence (WHO, 2003). Patient-related, therapy-related, disease-related, healthcare system-related, and social-economic factors were found to influence (non-)adherence and (non-)persistence. Side effects, younger and older age, longer duration of therapy, increased number of prescriptions, co-morbidities, and higher out-of-pocket costs were found to be associated with non-adherence and non-persistence in multiple studies included in the systematic review.

The systematic review revealed that much of the research on factors influencing (non-)adherence and (non-)persistence to OACD was conducted from a reductionist perspective (Gater et al., 2012). However, complex behavioral phenomena such as adherence and persistence to OACD could not be reduced to its constituent elements. For example, the focus on objective assessment of (factors influencing) adherence by reviewing retrospective databases supports the reductionist perspective assertion (Gater et al., 2012). In retrospective research, factors that may predict adherence are often limited to demographic, disease or treatment-related factors as found in our systematic review. These factors may be considered as 'weak' predictors of (non-)adherence (McHorney, 2009). For patient demographic variables, the lack of a consistent relationship with adherence is well documented (Dimatteo, 2004). Age, for example, which is frequently found to be associated with (non-)adherence and (non-)persistence to OACD, could be interpreted as a 'distal' predictor. Our systematic review highlighted the need for exploration of underlying processes influencing adherence and persistence to OACD, and to get more insight into the needs and problems from the patients' perspective to inform patient-tailored interventions.

Problem and needs analysis

The literature review (chapter 2) showed that the complex patterns and dynamics of (non-) adherence and (non-)persistence in patients taking OACD are still not fully understood. More insight was needed into the patients' needs and the interrelatedness of influencing factors and underlying processes of (non-)adherence and (non-)persistence from the patients' perspective.

Therefore, two qualitative studies were conducted to get insight into patients' needs and experiences in an open and inductive manner. Insight into underlying processes was revealed and some new influencing factors were found.

The literature review showed that side effects, for example, are a predominant factor associated with (non-)adherence and (non-)persistence in patients taking OACD. In the qualitative studies, important factors were found to be related to side effects such as the information patients received about side effects and the normal course of side effects, perceptions and expectations about side effects, the discrepancy with normal daily life, the healthcare professionals' recognition (for difficulties such as side effects), and the need to be reassured that side effects of the OACD are not signs of a relapse. A recently published paper showed that 60% of the physicians did not react on side effects patients experienced (Wuensch et al., 2015). Patients who reported having received detailed answers to their questions were significantly better adherent (Wuensch et al., 2015). Our study showed that in patients taking AHT who felt well informed about side effects and feel recognized for the difficulties they experienced, the burden was lower. In contrast, patients who did not feel recognized when they mentioned side effects, often did not report their difficulties anymore in order to avoid the confrontation with disbelief and incomprehension. This placed them in a lonely position, which made the burden of the AHT higher and made it more difficult to adhere/persist to the therapy. Previous results show that multiple factors influenced (non-)adherence. Consequently, only reducing side effects may not lead to improved adherence.

Recently published studies show that, in spite of the current (mostly quantitatively based) knowledge, non-adherence to OACD is still high (Kekäle et al., 2014; Anderson et al., 2015). Non-adherence is especially high in patients treated for a malignancy with a chronic character such as chronic myeloid leukemia (CML), using long-term OACD. Adherence rates to OACD in patients treated for a cancer type with a more acute, life threatening character, such as renal cell cancer with short-term OACD seems to be higher (Wolter et al., 2012; Timmers et al., 2014; Timmers et al., 2015). Despite the lack of extensive

research in the latter type of cancer, our study could offer an explanation for the higher adherence rates found in patients treated with short-term OACD. In the oral TKI study (chapter 3), patients treated with OACD for a cancer type with a more acute, life threatening character considered treatment with oral TKI often as the last chance to survive. For some patients, starting oral TKI therapy meant that they had moved on from a curative to a chronic, palliative treatment. This confronted them with the non-curable and life-threatening nature of the disease. These patients reported to be highly adherent to their therapy. For these patients, treatment mostly got the highest priority (focus on survival). They often felt a great responsibility for their survival and often did not report side effects to healthcare professionals out of the fear for a dose reduction and a concomitant decrease in efficacy of the treatment. These study findings could also reveal a plausible explanation on how overadherence (Allen & Williamson, 2014), which is taking more medication than prescribed to OACD, arises. Patients with a focus on survival could be at risk for overadherence.

In literature, a distinction is often made between unintentional and intentional non-adherence. Unintentional non-adherence is often seen as the result of a lack of capacity and resource (e.g. forgetting, not knowing exactly how to use medicines), while intentional non-adherence is often seen as more deliberate and associated with patient motivation (Clifford et al., 2008). Both types of non-adherence were found and discussed during the interviews. However, our results mainly report on the understanding of intentional non-adherence. We have chosen to highlight this type of non-adherence because this seems to be the most complex and interrelated phenomenon and therefore the most difficult to intervene on. However, unintentional and intentional non-adherence are not entirely independent. Forgetting, for example, is more likely when motivation for medication is low.

In chapter 5, healthcare professionals' perceptions about managing OACD adherence, SDM and beliefs towards OACD were explored. Few studies focused on the physicians' perspective (Regnier Denois et al., 2010; Kekäle et al., 2014). No studies reported on perspectives of pharmacists, nurses, and

physicians simultaneously. The study by Kekäle et al. (2014) compared CML patients' adherence with adherence as estimated by their physicians. The physicians' estimate of adherence was too optimistic in 73% of the cases. In our study, significantly more medical oncologists indicated to know the level of adherence of all their patients and thought patients discussed non-adherence with them compared to hematologists. As stated earlier, adherence is especially low in patients treated for a malignancy with a chronic character such as the hematologic malignancy CML, using long-term OACD and mostly treated by hematologists (Kekäle et al., 2014; Anderson et al., 2015). Adherence rates to OACD in patients treated for a cancer type treated with short-term OACD in the field of medical oncology, seems to be higher (Timmers et al., 2014; Timmers et al., 2015). It is plausible that in patients treated with short-term OACD, medical oncologists may assume that patients are highly adherent given the acute and life-threatening character of the disease, which might have been reflected in the higher scores of medical oncologists. Also, both medical oncologists and hematologists might be aware of the different adherence rates of their patient population in literature which might influence their perception of adherence in their patients.

In our study, necessity beliefs about OACD outweighed concerns among all studied healthcare professionals. However, extensively emphasizing the importance of taking the OACD could make patients feel responsible for their own survival. The qualitative study in patients taking oral TKIs showed that patients with a focus on survival, as a result, did not report side effects out of the fear of a dose reduction, which put them at risk for an adverse drug reaction (toxicity). Healthcare professionals mainly focusing on necessity of OACD and patients focusing on survival could reinforce each other in persevering OACD therapy while suffering a low quality of life and being at risk of toxicity.

The problem and needs analysis showed that oral TKI and AHT regimen may strongly impact on patients' quality of life. The importance of taking into account patients' experiences and needs in following OACD therapy to inform complex intervention development was emphasized in the two qualitative studies. From

the healthcare professionals perspective, a considerable part stated they do not know the adherence of their patients and do not think patients discuss adherence with them indicating little openness to talk about adherence. Based on the problem and needs analysis, patient tailored counseling, supporting ongoing self-management, recognition for the difficulties patients experience, and establishing a trust-based and open relationship are key elements to inform complex intervention development.

Current practice analysis

Current practice analysis is the last building block to inform the development of a complex intervention to support patients following OACD therapy, according to the model of van Meijel (2004). In chapter 6, usual care activities in supporting adherence to OACD in (haemato-) oncology in Belgium and the Netherlands among different healthcare professionals were explored. A wide range of care activities were revealed. The extent of usual care activities provided differs by profession; nurse practitioners are the most active, pharmacist provided least adherence care. For all healthcare professionals, activities in the domain Knowledge and Adverse Event Management were reported most frequently whereas activities of the domains Self-efficacy, Social influence and Action Control are performed less. Most physicians, nurse practitioners, and nurses provided all activities within the domain Adverse Event Management. In oncology, adverse events occur very often and can be serious. Physicians need to know the occurrence and the grade of adverse events to determine the dosing of OACA. Furthermore adverse events have great impact on patients' quality of life as shown in our two qualitative studies. The attention which is giving to adverse events management in supportive care for OACA is justified. However, in complex intervention development, an emphasis should be placed on the domains Self-efficacy, Social influence and Action Control and the interrelatedness of the different domains to support adherence and enhance quality of care and life. More attention is needed for organizing social support

and self-efficacy increasing interventions in the context of ongoing self-management support.

METHODOLOGICAL CONSIDERATIONS

In the systematic review we aimed at providing an updated overview of determinants and associated factors of medication (non-)adherence and (non-)persistence in patients taking different types of OACD. Therefore, both qualitative as quantitative research were considered. However, in this systematic review, we did not consider the strength of the associations of the different determinants in relation to (non-)adherence and (non-)persistence in the quantitative studies.

By using both qualitative and quantitative research, it was possible to compare findings from the quantitative studies from healthcare professionals' perspectives to patients' perspectives from the qualitative studies. Furthermore, it enabled us to detect contradictions between the qualitative and quantitative studies and provide explanations for this.

In both qualitative studies, it was possible that some participants did not feel totally comfortable talking openly about non-adherence and non-persistence. Patients who were non-adherent could have felt guilty about their non-adherence. For example, as found in the study in patients taking AHT, the fact that the OACD makes relapse less likely makes it difficult to downplay the importance of AHT. Admitting that they did not take the medication as prescribed could have resulted in feelings of guilt if they were to relapse. Furthermore patients could have been afraid to be stigmatized as a 'bad' patient. To promote openness, the interviewer explained the importance of being open to understand what patients are going through and emphasized anonymity. To promote a climate of comfort to talk about non-adherence and non-persistence, special attention was paid to the use of non-threatening and non-judgmental questions.

In the quantitative studies, the role of different healthcare professionals was explored. Until now, only a small number of studies focused on the role of

specific professions (mostly nurses and pharmacists) to support adherence in patients taking OACD. However, we did not study the integral interdisciplinary support given to patients taking OACD. In the quantitative studies, the role of the psychologist was not studied in relation to adherence care. Yet, the qualitative studies showed the great psychological demands associated with the cancer trajectory and the treatment with OACD. Furthermore, the questionnaire used in the quantitative studies did not allow e.g. to explore how coordination occurs between healthcare professionals, and to explore the consistency of the provided information to patients by different healthcare professionals.

IMPLICATIONS FOR PRACTICE

As described in the introductory chapter, interventions including a tailored approach seem to be promising (Kavookjian and Wittayanukorn, 2014; Mathes et al., 2014). However, more high quality intervention studies are needed. Emphasis must be placed on the patients' experience to understand (non-)adherence and (non-)persistence and to inform tailored interventions to support patients taking OACD. On the hospital level, the patient's perspective should be essential in the strategic choices hospitals make.

Healthcare professionals should create conditions wherein patients get maximal chances to come to a balance between surviving and quality of life (see chapter 3). Interventions should be discussed with the patient so that it fits the patients' life and needs. For example, healthcare professionals should not give a standard tool such as a mobile phone reminder to prevent unintentional non-adherence, but should discuss the patients' needs and habits and discuss what could be particularly helpful for them.

Patients should be provided with ongoing self-management and care support. Supporting patients to adequate self-management means that patients should be empowered to find the best possible compromise between the demands from life and the demands of the disease as defined by Grypdonck (1999). In

addition, patients should be supported to prevent inadequate self-management. Based on the results of our study, the following should be addressed:

- Support of adequate self-management (including the support of self-efficacy)
- Support patients to be open about side effects and to handle side effects
- Patient tailored counseling and the understanding of the patient's knowledge, beliefs and concerns
- Recognition for the difficulties patients experience
- Providing an individualized knowledge base about medication, disease, therapy, and adherence tailored to the patients' needs and level of understanding to increase insightful knowledge about the treatment and side effects. Without insightful knowledge, patients could not make well-informed decisions. This could increase the risk of inadequate decisions, which may (unnecessary) affect the efficacy of the treatment or the patients' quality of life.
- Enhancing social support (family/friends/peers)
- Communication and sufficient time taking during contacts
- A trust-based relationship
- Not undermining patients' hope
- Regular contacts (e.g. by means of telephone follow-up)
- Permanence and an accessible trust contact person
- Interdisciplinary approach

Healthcare professionals should be careful that adherence does not become the sole focus, but should also take into account the patients' perspectives of (quality of) life. A distinction should be made between health coaching and life coaching. Health coaching mainly focuses on improving health, while life coaching more broadly focuses on the patients' life and wellness rather than

pathology (Ammentorp et al., 2013). Life coaching could be recommended as a complementary strategy to support patients, starting from their values, needs, and priorities. Consequently, a well informed and supported patient, who decides to stop the treatment in favor of quality of life, should not be categorized as being non-persistent. When this decision is well-informed, this could be described as an act of adequate self-management.

Our study showed that a trust based relationship is crucial to make patients feel comfortable about reporting side effects and reporting on quality of life and experienced difficulties. Reporting side effects enables healthcare professionals to support patients in dealing with side effects or changing of dosage or medication in order to make quality of life as acceptable as possible. Based on the qualitative study in patients taking oral TKIs, a practice with sufficient space for individual, regular and easy accessible consultations could be recommended to increase the likelihood of establishing a trust-based relationship. Furthermore, healthcare professionals' interpersonal skills play an important role in establishing a relationship of trust (Burkitt Wright et al., 2004; Kahn et al., 2007). Authentic, open communication and a supportive, proactive and encouraging attitude are important to ensure that the patient is comfortable to share information that might cause feelings of having done something wrong, fear of reprimand, or feelings of embarrassment. The qualitative study on AHT highlighted the importance of recognizing patients for the experienced difficulties and valuing patients as an individual. The qualitative study on AHT also stressed the importance of active listening, an empathic attitude, and patient-centered communication. Additionally, the importance of a communication style reinforcing adequate behavior and not undermining patients' hope was highlighted in the oral TKI study.

Based on the results of our study, an interdisciplinary approach to support patients in adequate self-management could be recommended. The qualitative study in patients taking oral TKIs showed that signs of a good interdisciplinary collaboration (for example, when patients noticed that healthcare professionals exchanged information with each other and no conflicting advice was provided)

increased trust. The emphasis on productivity in physicians could make it difficult to provide sufficient time for patient tailored education, follow-up and adequate self-management support. The qualitative study in AHT indicated that patients do not expect this from physicians. Therefore, nurse practitioners/clinical nurse specialists could play an important role by communicating, educating, and supporting patients in ongoing self-management. Research in chronically ill patients also indicated that involvement of nurse practitioners increased patient's self-efficacy (Richardson et al., 2014; Broderick et al., 2014), which is an important factor in medication adherence and adequate self-management. The quantitative study of usual care showed that nurse practitioners are the most active in providing usual care activities, especially in the domains self-efficacy, knowledge, intention formation, adverse event management, and facilitation. A strong nurse-patient relationship with individualized education has previously shown to be crucial for successful management of adherence to OACD (Wood, 2012). Nurse practitioners/clinical nurse specialists could play a key role in augmenting the patient-provider interaction and further adherence within a trust based relationship. Identification of a single nurse practitioner/clinical nurse specialist as a point of contact besides the physician may promote trust in patients and increase openness to express the experienced difficulties. Given the important role of nurse practitioners/clinical nurse specialists for the support of patients following OACD therapy, a nomenclature for nurse consultations may be developed. This may enable hospitals to increase patient tailored care by nurse practitioners/clinical nurse specialists.

Nurses may have (had) more frequent and intense contact with the patient and/or may have built a trust and open relationship with the patient during hospitalizations. Therefore, nurses could have an important signal function (for example about (the impact of) side effects, the patients' needs, concerns and support) within an interdisciplinary team. Furthermore, nurses may be important to provide psycho-social support to patients.

The study in patients taking oral TKIs showed that patients are often anxious about the amount of medication they have to take. Pharmacists could have an

important role as an expert in medication review. Pharmacists could support patients or other healthcare workers by clarifying information about the medication, interactions, administration, and side effect management.

General practitioners could play an important role as being a confidant for some patients. General practitioners could act as intermediate between patient and hospital. However, therefore transmural care should be supported and general practitioners should be involved standard from the beginning of the trajectory. A central contact person (e.g. nurse practitioner/clinical nurse specialist) could be indicated to facilitate communication in both ways.

Involvement of different healthcare professionals (e.g. pharmacists and general practitioners) could be optimized when electronic health records are made more accessible for different healthcare professionals. This way, patient-centered care and integrated care could be supported.

The qualitative studies showed that the disease and the OACD therapy are often very stressful and demanding and strongly impacts on quality of life. Therefore, every healthcare worker should provide psychosocial support. Yet, for some patients, a psychologist may be an important actor for psychological help and the enhancement of coping abilities. However, previous studies showed that some patients may be reluctant to appeal on a psychologist because they fear that their positive attitude that they consider important to stand the therapy, may be threatened (Maher and De Vries, 2011; Matthews et al., 2003). Therefore, a psychologist should be integrated in an interdisciplinary team approach. Team members could reduce barriers towards psychological help by emphasizing the normality of psychosocial needs and by transferring trust when referring to a psychologist (Daem et al., 2013).

FUTURE PERSPECTIVES

In a future study, a complex patient tailored intervention following the van Meijel model (2004), could be developed based on the results of our findings to support adherence and self-management in cancer patients taking OACD. In

constructing and evaluating the intervention, patient reported outcomes measures (PROMs) should be included (e.g. quality of life). Non-adherence and non-persistence are multidimensional complex phenomena so interventions should include multiple components as described above. In annex, components for an intervention are provided based on our study findings. This may provide a point of departure for the construction of an intervention in a specific setting. A future implementation study is needed to validate the intervention in a specific setting.

The intervention should be evaluated by using a cyclical procedure of trying out, evaluating, and revising (Van Meijel et al., 2004) on multiple levels: patients (e.g. self-management, adherence, quality of life), healthcare professionals (e.g. counseling skills), and organization (e.g. appropriateness and feasibility of the intervention). To ensure high quality reporting of studies on the development and evaluation of complex interventions, a set of 16 criteria for reporting complex interventions in healthcare (CReDECI) could be used (Möhler et al., 2012). The criteria list is categorized into three stages, according to the British Medical Research Counsil's framework on the development and evaluation of complex interventions (MRC): development (e.g. description of underlying theoretical considerations), feasibility and piloting (e.g. information on pilot-testing), and introduction of the intervention and evaluation (e.g. description of the control intervention). By using the CReDECI criteria, more transparent and comprehensive reporting of complex interventions could be established (Möhler et al., 2012).

Both qualitative studies showed the importance of social support in patients taking OACD. The quantitative usual care study showed that partners and/or relatives are mostly involved in the treatment. However, few patients seem to be encouraged to organize social support and referred to a patients' association. In future research, the role of family members and/or relatives, as well as the role of peers in supporting patients taking OACD should be studied to get more insight into their roles from their perspective and the patients' perspective.

As stated in the methodological considerations, we did not study the integral interdisciplinary support given to patients taking OACD. More insight is needed in how to organize the support of self-management and adherence of patients taking OACD from an integral interdisciplinary approach. Furthermore, the role of the psychologist into the interdisciplinary team supporting patients taking OACD should be taken into account in future research.

REFERENCES

Allen J, Williamson S. Over compliance with capecitabine oral chemotherapy. *Int J Clin Pharm* 2014;**36**:271-273.

Ammentorp J, Uhrenfeldt L, Flemming A, et al. Can life coaching improve health outcomes? – A systematic review of intervention studies. *BMC Health Services Research* 2013;**13**:428.

Anderson KR, Chambers CR, Lam N, et al. Medication adherence among adults prescribed imatinib, dasatinib, or nilotinib for the treatment of chronic myeloid leukemia. *Journal of Oncology Pharmacy Practice* 2015;**2**(1):19-25.

Broderick JE, Keefe FJ, Bruckenthal P, Junghaenel DU, Schneider S, Schwartz JE, Kaell AT, Caldwell DS, McKee D, Reed S, Gould E. Nurse practitioners can effectively deliver pain coping skills training to osteoarthritis patients with chronic pain: A randomized, controlled trial. *Pain* 2014;**155**(9):1743-54.

Burkitt Wright E, Holcombe C, Salmon P. Doctors' communication of trust, care, and respect in breast cancer: qualitative study. *British Medical Journal* 2004;**328**:864.

Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the necessity-concerns framework. *J Psychosom Res* 2008;**64**:41-46.

Daem M, Verbrugghe M, Schrauwen W, Leroux S, Decoene E, Verhaeghe S, Van Hecke A, Beeckman D, Grypdonck M. (2013). Psychosociale zorg voor patiënten met kanker: een gedeelde opdracht. Brussel: Vlaamse Liga tegen Kanker.

Dimatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004;**42**(3):200-209.

Gater A, Heron L, Abetz-Webb L, Coombs J, Simmons J, et al. Adherence to oral tyrosine kinase inhibitor therapies in chronic myeloid leukemia. *Leukemia Research* 2012;**36**:817-825.

Grypdonck M. (1999). *Het leven boven de ziekte uittillen. De opdracht van de Verpleegkunde en de Verplegingswetenschap voor chronisch zieken.* Amsterdam: SMD.

Kahn KL, Schneider EC, Malin JL, Adams JL, Epstein AM. Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Med Care* 2007;**45**:431-439.

Kavookjian J, Wittayanukorn S. Interventions for adherence with oral chemotherapy in hematological malignancies: a systematic review. *Research in Social and Administrative Pharmacy* 2014 [In press].

Kekäle M, Talvensaari K, Koskenvesa P, Porkka K, Airaksinen M. Chronic myeloid leukemia patients' adherence to peroral tyrosine kinase inhibitors compared with adherence as estimated by their physicians. *Patient Preference and Adherence* 2014;**8**:1619-1627.

Maher K, De Vries K. An exploration of the lived experiences of individuals with relapsed Multiple Myeloma. *European Journal of Cancer Care* 2011;**20**(2):267-275.

Mathes T, Antoine S-L, Pieper D, Eikermann M. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treatment Reviews* 2014;**40**:102-108.

Matthews AK, Corrigan PW, Rutherford JL. Mental illness stigma as a barrier to psychosocial services for cancer patients 2003;**1**:375-379.

McHorney CA. The adherence estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin* 2009;**25**(1):215-238.

Möhler R, Bartoszek G, Köpke S, Meyer G. Proposed criteria for reporting the development and evaluation of complex interventions in healthcare

(CReDECI): guideline development. *International Journal of Nursing Studies* 2012;**49**:40-46.

Regnier Denois V, Poirson J, Nourissat A, Jacquin J-P, Guastalla JP, Chauvin F. Adherence with oral chemotherapy: results from a qualitative study of the behavior and representations of patients and oncologists. *Eur J Cancer Care* 2010;**20**:520-527.

Richardson GC, Derouin AL, Vorderstrasse AA, Hipkens J, Thompson JA. Nurse practitioner management of type 2 diabetes. *Perm J.* 2014;**18**(2):e134-40.

Timmers L, Boons CCLM, Kropff F, Van De Ven PM, Swart EL, Smit EF, Zweegman S, Kroep JR, Timmer-Bonte JNH, Boven E, Hugtenburg JG. Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncologica* 2014*;* **53**: 259-267.

Timmers L, Boons CCLM, Moes-ten Hove J, Smit EF, van de Ven PF, Aerts JG, Eleonora LS, Boven E, Hugtenburg JG. Adherence, exposure and patients' experiences with the use of erlotinib in non-small cell lung cancer. *J Cancer Res Clin Oncol* 2015 [Accepted for publication]

van Meijel B, Gamel C, van Swieten-Duijfjes B, Grypdonck MHF. The development of evidence-based nursing interventions: methodological considerations. *Journal of Advanced Nursing* 2004;**48**(1):84-92.

Wolter P, Hendrickx T, Renard V, et al. Adherence to oral anticancer drugs (OAD) in patients (pts) with metastatic renal cancer (mRCC): First results of the prospective observational multicenter IPSOC study (Investigating Patient Satisfaction with Oral Anti-cancer Treatment). *J Clin Oncol* 2012;**30**(suppl): Abstract 4622.

Wood L. A review on adherence management in patients on oral cancer therapies. *European Journal of Oncology Nursing* 2012;**16**(4):432-438.

World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva: WHO, 2003.

Wuensch P, Hahne A, Haidinger R, Meiβler K, Tenter B. Discontinuation and non-adherence to endocrine therapy in breast cancer patients: is lack of communication the decisive factor? *J Cancer Res Clin Oncol* 2015;**141**:55-60.

APPENDIX

COMPONENTS FOR AN INTERVENTION

KEY PRINCIPLES

- ✓ **The patients' perspective and experience** (Chapter 3 & 4)

  The perspective and experience of the patient (e.g. perception and experience of the disease and the current and past therapies, the influence on quality of life, perceptions about side effects and the impact of the therapy) is the key point of departure for counseling and supporting patients starting or following OACD therapy.

- ✓ **An open and trust-based relationship** (Chapter 3 & 4)

  An open and trust-based relationship makes most people more comfortable to be honest about side effects, their adherence behavior and the difficulties they experience during the OACD treatment period. This increases the likelihood of finding a balance between survival and quality of life in patients taking oral TKIs. In both patients taking AHT and TKIs, this makes the burden of the therapy lower.

  Elements contributing to the establishment and maintenance of an open and trust-based relationship are:

  - Taking time during appointments to listen to how patients are doing, how they experience the therapy and their quality of life
  - Accessibility and continuous availability (e.g. by telephone permanence)
  - Having contact with patients on a regular basis, preferable the same contact person in order to establish and maintain the trust relationship (e.g. pro-active telephone contact on a regular basis between two follow-up appointments to ask how patients are doing)
  - Signs of a good multidisciplinary collaboration between HCPs (e.g. when it is clear that healthcare professionals exchange information with each other and no conflicting advice is provided)

- Encouragement to express difficulties and worries
- Recognition for the patients' situation and experienced difficulties
- Not undermining patients' hope, hope is an important coping strategy for patients
- Interpersonal competence (active listening, caring, empathy, providing information and answering questions)
- Honesty and clarity about side effects and the possible impact of the therapy in order not to create false expectations and disappointments

✓ **Self-management support** (Chapter 3 & 4)

Patients should be supported in adequate self-management. They should be guided in making adequate decisions regarding their therapy by:

- Patient-centered education about (the development of) side-effects to set realistic expectations
- Informing patients as to how medication works and why it is important to follow instructions. Different methods can be used in order to inform patients adequately (e.g. verbal and written information, a visual scheme, e-health).
- Explain to patients why side effects may occur
- Discussing the possible ways to incorporate the regimen into daily life
- Specific interventions to improve self-management (e.g. assist the patient in addressing self-identified barriers and help them to deal with it). For example: discuss with patients whether they expect instructions will be difficult to follow. Search for solutions together that fits the patients' life and needs and do not provide standard tools. For example, for some patients a reminder on the mobile phone could be very effective to prevent unintentional non-adherence, for others, the intake of the OACD could be combined with daily habits. Supporting

patients taking OACD requires a high degree of knowledge and experience of HCPs, therefore, training of HCPs might be necessary.

- ✓ **Social support** (Chapter 3, 4 & 6)

  Social support helps patients to deal with the difficulties they encounter and makes them feel less alone. Therefore, it is important to **involve family members and/or friends** in the therapy. A knowledge base about the therapy and the consequences should also be provided to them. Family members should be informed about the ongoing burden of cancer therapy to counteract false expectations (such as resuming normal life in the period of AHT). Family members could be asked which role would be suitable within the informal care and what difficulties they expect. In patients having little social support (e.g. older patients), the general practitioner and the home nurse could be more involved. The possibility of having **contact with peers** (cancer peer support group) could also be discussed (e.g. in patients experiencing difficulties where there is not a direct solution for). However, for some patients this might be too confrontational (e.g. the possible confrontation with peers suffering a relapse). Patients could also be referred to a **patients' association**.

- ✓ **Self-efficacy** (Chapter 2, 3, 4 & 6)

  The patient's belief in his/her ability in succeeding to follow treatment instructions to which he/she consented is an important adherence influencing factor. However, in usual care, too little attention is paid to self-efficacy. When patients do not believe to be able to follow certain instructions, things that helped the patients in the past could be explored and patients could be asked if this could be helpful to them now. Furthermore, small and achievable goals could be set in the beginning. When patients succeed in these goals, this should be reinforced positively. Supporting patients' self-efficacy requires a high degree of knowledge and experience of HCPs, therefore, training of HCPs might be necessary.

OACD THERAPY INITIATION

- ✓ The physician may introduce the team and emphasizes the **interdisciplinary collaboration**. Signs of a good interdisciplinary collaboration between healthcare professionals increase trust (Chapter 3). The physician may introduce the nursing consultations and a **nurse practitioner/clinical nurse specialist as a point of contact** besides the physician. For some patients the **general practitioner** might be an important confidant. Therefore, the relationship with the general practitioner should be questioned in the beginning of the trajectory and the general practitioner should be involved in the trajectory.
- ✓ **Knowledge base** (chapter 3 & 4): Patients should receive an individualized knowledge base about disease, medication, therapy, follow-up, and adherence. A good knowledge base is important to support **patients' self-management**, allowing them to make adequate decisions in dealing with their therapy. Education (and the amount of information) should be tailored to the patients' needs and level of understanding to increase insightful knowledge. Special attention should be paid to e.g. older patients and patients with low education. Information should be dosed according to the needs of the patient at that specific moment. For example, extensive or difficult information should not be provided after patients have received bad news.
    - Ask patients about their perceptions of the disease, the therapy and their quality of life.
    - Ask if they have already heard of the medication or they know people taking this type of OACD and what they expect from the OACD. This way, (true/false) **perceptions** could be detected and the patient could be informed adequately.
    - Explain **how medication works** and why it is important to follow instructions (e.g. why it is important to leave a certain time between the first and second dose).

- Be **careful with reporting about treatment options and evaluations**. Communicating that further treatment with a type of OACD would be considered if the OACD showed significant positive results within a certain period of time, makes patients fearful and reluctant to report side effects. Therefore, HCPs could explain that finding the right OACD and the right dose is often the result of a search.
- Explain **what to do in case of (unintentional) deviating from the treatment instructions (e.g. in case of forgetting a dose).**
- Explain the importance of **finding a balance between the therapeutic effect and quality of life.**
- Discuss **which side effects** could occur (the most important side effects could be given in order not to overwhelm patients with information – provide patients with additional accessible information of all other possible side effects and refer to the continuous availability of HCPs by giving a contact card). Being informed about side effects is important because it reassures patients that nothing else is the matter, such as a progression of their disease. Involve family members as described in the general principles (cfr. social support).
- Explain **what to do in case of side effects**. For example, a simple scheme with instructions in case side effects occur could be provided so that patients could differentiate harmful from not-harmful side effects and know what to do in case of side effects (i.e. what they could do themselves, when they should contact the general practitioner or the hospital), which is reassuring.
- Give patients **realistic information** about the intensity, severity and normal course of side effects (i.e. increase or decrease of side effects over time). Realistic information is important to prepare patients for what to expect (possible impact) of the therapy. This way, disappointments could be avoided as this increase the burden

of the therapy and affects the relationship with HCPs, which makes it more difficult to continue OACD therapy.

- Make sure the **information** is provided **in a uniform way amongst the different HCPs** to avoid confusion in patients, which could affect their trust in HCPs and the therapy.
- Explain patients **why it is important to be honest about experienced side effects**, this way patients could be supported in coming to a balance between surviving and quality of life. This is particularly important for patients who are being confronted with the non-curable and life-threatening nature of the disease (greater chance of coming to a focus on survival and not reporting side effects).
- For patients taking **multiple medications**, reassure them that this is being monitored carefully. Here, a pharmacist could have an important role.

✓ **Shared decision making** (chapter 5 & 6): ask whether patients want to have a role in the decision making process. Discuss which role would be fitting.

BETWEEN FOLLOW-UP CONSULTATIONS

✓ **Contact patients** (e.g. the nurse practitioner/clinical nurse specialist) by phone and ask how they are doing and whether they have any questions (create openness and establish trust – see chapter 3 & 4). Contact could be intensified at the start of a (new) OACD therapy or when patients experience difficulties during the follow-up period. In current practice, this requires special attention (chapter 6).

✓ **Accessibility and continuous availability** (e.g. by telephone permanence, e-mail, e-health platform) (chapter 3 & 4)

OACD FOLLOW-UP CONSULATIONS

✓ **Side effects and the impact of the therapy** (chapter 2, 3 & 4)

- Ask patients **how they experience the therapy and how this impacts on their quality of life and their roles and stimulate expressions of difficulties/worries**. Give patients sufficient space to express their difficulties, worries and perceptions. Provide recognition for the patients' situation and experienced difficulties.
- Ask **which side effects they experienced, create openness to mention side effects and listen** how patients are doing, how they experience the therapy and their quality of life.
- Ask **what they tried themselves to reduce side-effects** and whether this was effective, give positive reinforcement. Provide them with knowledge and tools to reduce side effects.
- **Reassure patients** that symptoms are side effects from the OACD and not signs of a relapse or a progression of the disease.
- **Give patients answers about side effects**, otherwise they might start a search on their own, which is often a lonely search and affects the relationship with the HCP. Provide patients with reliable information and links to websites (e.g. in the patient brochure).
- Be **honest about difficulties where there is not a direct solution for**. For patients, admitting there is not a direct solution (e.g. in patients taking AHT) is often a sign of a human approach, which strengthens the relationship. However, in the case there is not a solution for a problem, HCPs could intensify contact (e.g. by telephone or e-mail) and follow how patients further deal with this. Establishing contact with peers could be useful for some patients.

✓ **Perspectives and hope** (chapter 3 & 4)

- **Ask for the perspectives patients have**. Having or creating perspectives is of great importance for patients to be able to continue therapy.

- Patients' **hope may not be undermined** by negating hopeful reactions or emphasizing medical reality after a hopeful reaction. Patients need hope to stand the multitude of uncertain situations they are confronted with and to continue therapy while sometimes experiencing a low quality of life. Hope is particularly needed to be able to continue therapy in patients experiencing a low quality of life and intense side effects. When hope is undermined, patients feel discouraged. As a result, some patients will no longer report side effects and start to experiment themselves with their therapy to improve quality of life, which increases the risk of inadequate self-management and/or non-adherence behavior.

✓ **Dose reduction/change of OACD** (chapter 3)

- Be aware that patients are often **anxious that a dose reduction or change of OACD would decrease their survival time**. As a result, patients with a focus on survival may not report side effects.
- Consider **how patients perceive a dose reduction or change of OACD.**
- **Explain why a dose reduction or change of OACD is necessary** and the best solution. Normalize this change and use objective parameters such as liver and kidney values to demonstrate that a dose reduction is necessary.
- A **follow-up screening** could be planned **as soon as possible** after a dose reduction, so the period of uncertainty about the effectiveness of the medication, is as short as possible. However, a certain period between a dose reduction or change of OACD might be necessary to assess effectiveness by screening. Inform patients why it is not useful to evaluate earlier.

✓ **Adherence** (chapter 2, 3, 4, 5 & 6)

- **Discussing adherence openly** is important. A lot of HCPs state they do not know the adherence of their patients nor do they think their

patients discuss adherence with them. Supporting and discussing patients' adherence requires a high degree of knowledge and experience of HCPs, therefore, training of HCPs might be necessary. To be able to talk about adherence, an open and trust-based relationship and a knowledge base of why it is important to be open about adherence behavior is necessary. Be aware that for some patients, it is difficult to talk about adherence. To create openness, it is important to **ask non-threatening questions** for example: 'For some patients it is hard to take every day there medication consequently, how is this for you?' or 'Could you describe how you take your medication and how this goes?'.

- **Feedback mechanisms** play an important role in adherence behavior. When patients report non-adherence (e.g. forgetting to take the OACD), be careful with the feedback that forgetting one time is not harmful, this might reinforce non-adherence behavior.
- **Special attention** (e.g. intensified follow-up appointments or telephonic contacts or support/tools) **is required for**:
    - patients with other health problems
    - in case of daily routine interruptions (e.g. going on holiday)
    - patients experiencing a lot of difficulties
    - patients experiencing difficulties where there is not a direct solution for
    - patients taking multiple medications
    - patients having little social support
    - patients longer on OACD therapy
    - patients of whom the contrast with the life before the disease is high
    - patients with history of antidepressant use

SUMMARY

The availability and use of oral anticancer drugs (OACD) in the treatment of cancer has steadily increased. The management of adherence and persistence to OACD has become a key challenge in modern oncology treatment. Adherence and persistence in cancer patients OACD are complex phenomena. This doctoral thesis aims to get insight into factors and processes influencing (non-)adherence and (non-)persistence in patients taking OACD, explore healthcare professionals' (HCPs) perspectives and usual care in supporting adherence to OACD.

In the first phase of this thesis, a systematic literature review was conducted on associated factors of (non-)adherence and (non-)persistence in patients taking OACD. Twenty-five studies were included and systematically reviewed. Factors positively and negatively associated with adherence and persistence were found and structured according to the five categories suggested by the World Health Organization (2003): patient-related, therapy-related, disease-related, healthcare system-related, and social-economic factors. Older and younger age, and the influence of side effects were found to be predominant factors. The systematic review suggested that (non-)adherence and (non-)persistence to OACD are multi-factorial, complex and interrelated. The need for qualitative studies to explore underlying processes influencing adherence and persistence was highlighted.

Second, a qualitative study was conducted to get insight into influencing factors and processes underlying (non-)adherence and (non-)persistence in patients taking oral tyrosine kinase inhibitors (TKIs). Semi-structured interviews were held with 30 patients of different ages and with different types of cancer. A grounded theory approach was used. Three foci were found when dealing with oral TKIs: (1) a focus on survival, (2) a focus on quality of life, and (3) a balance between survival and quality of life. The process of adherence was determined by a set of complex and interrelated factors: treatment related side effects, hope, anxiety, trust, and feedback mechanisms.

Third, a qualitative study was conducted to get insight into influencing factors and processes underlying (non-)adherence and (non-)persistence in breast

cancer patients taking antihormonal therapy (AHT). Semi-structured interviews were held with 31 patients. Data collection and analysis were based on a grounded theory approach. Expectations regarding the impact of AHT, social support from family and friends, and recognition from HCPs were found to influence the process of (non-)adherence and (non-)persistence.

Fourth, a quantitative study was conducted aiming to explore HCPs' perceptions about adherence management (PAMQ) and beliefs towards OACD adherence (BMQ), PAMQ influencing factors, and physicians' shared decision making (SDM). A cross-sectional, multi-center observational study among HCPs in hemato-oncology settings in Belgium and the Netherlands was conducted. The sample consisted of 254 HCPs. A considerable part of HCPs does not know the adherence of their patients, nor do they think their patients discuss adherence with them. However, they have knowledge of adherence and perceive to be able to influence adherence of their patients. Nurses and nurse practitioners/clinical nurse specialists had lower necessity concerns differentials than the other HCPs. Lower concerns beliefs were associated with a higher total PAMQ-score. SDM was considered high among physicians.

Fifth, within the same quantitative study, usual care in supporting adherence to OACD was explored. Two hundred and eight HCPs completed the usual care part. The assessment of usual care in the Netherlands and Belgium reveals a wide range of care activities provided. Activities in the domain Knowledge and Adverse Event Management were reported most frequently whereas activities of the domains Self-efficacy and Action Control were reported less. The reported provided care differs between the professions that are involved in OACD adherence (with nurse practitioners the most active and pharmacists providing the least adherence care) and also by country. There is a strong relationship between the perceptions about adherence management and the adherence care activities that are provided.

The results of this PhD study emphasize the importance of the patients' experience to understand (non-)adherence and (non-)persistence to OACD. A complex patient tailored intervention informed by our study findings could be

developed to support adherence and self-management in cancer patients taking OACD.

SAMENVATTING

De behandeling van kanker gebeurt in toenemende mate door middel van orale antitumorale medicatie (OAM). Therapieontrouw en het vroegtijdig beëindigen van de behandeling komen vaak voor. De factoren die therapie(on)trouw bij OAM beïnvloeden zijn complex en multifactorieel. Dit doctoraatsonderzoek beoogt inzicht te krijgen in beïnvloedende factoren en processen van therapie(on)trouw en het vroegtijdige beëindiging van de behandeling met OAM, het exploreren van hulpverlenersperspectieven en van de huidige zorg met betrekking tot therapietrouw-ondersteuning bij patiënten behandeld met deze medicatie.

In deel één werd een systematische literatuurstudie uitgevoerd naar beïnvloedende factoren en processen van therapie(on)trouw en het al dan niet vroegtijdig beëindigen van de behandeling met OAM. De review toonde zowel positief als negatief beïnvloedende factoren, onder te brengen in de vijf categorieën van de WHO (2003): patiënt-gerelateerde, sociale en economisch-gerelateerde, ziekte-gerelateerde, behandeling-gerelateerde factoren en gezondheidszorgsysteem. Oudere en jongere leeftijd, en de invloed van bijwerkingen waren vaak voorkomende factoren geassocieerd met therapieontrouw en het vroegtijdig beëindigen van de behandeling. De systematische literatuurstudie toonde aan dat beïnvloedende factoren van therapie(on)trouw en het al dan niet vroegtijdig beëindigen van de behandeling met OAM multifactorieel, complex en onderling gerelateerd zijn.

In het tweede deel werd een kwalitatief onderzoek uitgevoerd om inzicht te verkrijgen in beïnvloeden factoren en onderliggende processen van therapie(on)trouw in de behandeling met orale tyrosine kinase inhibitoren (TKI's). Door middel van de 'grounded theory' benadering werden 30 semi-gestructureerde interviews met patiënten die orale TKI's nemen, geanalyseerd. De resultaten toonden drie focussen bij patiënten behandeld met orale TKI's: (1) een focus op overleven, (2) een focus op kwaliteit van leven en (3) patiënten die tot een evenwicht (proberen) komen tussen overleven en kwaliteit van leven. Het onderzoek toonde eveneens een complexe en onderling gerelateerde set

aan beïnvloedende factoren: nevenwerkingen, hoop, angst, vertrouwen en feedback mechanismen.

In het derde deel vond een analoog kwalitatief onderzoek plaats om inzicht te verkrijgen in beïnvloeden factoren en onderliggende processen van therapie(on)trouw en het al dan niet vroegtijdig beëindigen van de behandeling met orale antihormonale therapie (AHT), bij 31 patiënten behandeld met AHT. Verwachtingen met betrekking tot de impact van de AHT, sociale steun van familie en vrienden, en erkenning van hulpverleners werden gevonden als beïnvloedende factoren van therapie(on)trouw en het al dan niet vroegtijdig beëindigen van de behandeling met AHT.

Een cross-sectionele multicentrische observationele studie bij 254 hulpverleners werkzaam in de hemato-oncologie in België en Nederland, brengt de percepties van hulpverleners met betrekking tot het managen van therapietrouw (PAMQ) en hun percepties met betrekking tot de noodzaak van en zorgen over OAM (BMQ) en gedeelde besluitvorming (SDM) in beeld (deel 4). Een aanzienlijk deel van de hulpverleners geeft aan de therapietrouw van hun patiënten niet te kennen en denken ook niet dat patiënten therapietrouw met hen bespreken. Wel geven ze aan kennis te hebben van therapietrouw en zien ze zichzelf in staat om therapietrouw te beïnvloeden. Verpleegkundigen en verpleegkundig specialisten vertoonden een lagere differentiaalscore (noodzaak/zorgen) dan andere hulpverleners. Minder zorgen met betrekking tot OAM was geassocieerd met een hogere PAMQ-totaal score. SDM werd hoog geacht bij artsen.

Hetzelfde kwantitatief onderzoek exploreerde de gebruikelijke zorg met betrekking tot therapietrouw bij OAM bij 208 hulpverleners (deel 5). De resultaten toonden een brede range aan zorgactiviteiten in zowel België als Nederland. De mate waarin activiteiten werden uitgevoerd verschilde erg naargelang het land en de beroepsgroep; verpleegkundig specialisten deden het meest aan de therapietrouw zorgactiviteiten, apothekers het minst. De domeinen kennis en management van bijwerkingen werden het meest uitgevoerd bij alle hulpverleners; eigeneffectiviteit, sociale invloed en action control het minst. De resultaten toonden een sterk verband tussen het aantal uitgevoerde

zorgactiviteiten en de percepties met betrekking tot het managen van therapietrouw.

De resultaten van dit doctoraatsonderzoek tonen het belang aan van inzicht in de beleving van patiënten die orale antitumorale medicatie nemen om therapie(on)trouw en het al dan niet vroegtijdig beëindigen van de behandeling te begrijpen. Een complexe interventie gebaseerd op onze resultaten en op maat van patiënten, kan ontwikkeld worden om therapietrouw en zelfmanagement bij patiënten die orale antitumorale medicatie nemen te ondersteunen.

CURRICULUM VITAE

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Scientific staff member at the University Centre for Nursing and Midwifery, Department of Public Health, Ghent University, 2011 – 2014 (PhD candidate 2012-2015)

Psychologist GP practice (Independent secondary activity), 2013 – present

Researcher at Mensura Occupational Health Services, 2015 – present

INTERNATIONAL PEER-REVIEWED JOURNALS

Verbrugghe M, Beeckman D, Van Hecke A, Vanderwee K, Van Herck K, Clays E, Bocquaert I, Derycke H, Geurden B, Verhaeghe S. (2013). Malnutrition and associated factors in nursing home residents: a cross-sectional, Multi-centre study. *Clinical Nutrition*; **32**(3):438-443.

Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. (2013). Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. *Cancer Treatment Reviews*; **39**(6): 610-21.

Van Lancker A, Velghe A, Van Hecke A, **Verbrugghe M**, Van Den Noortgate N, Grypdonck M, Verhaeghe S, Bekkering G, Beeckman D. (2013). Prevalence of symptoms in older palliative cancer patients: a systematic review and meta-analysis. *Journal of Pain and Symptom Management*; **47**(1):90-104.

Verbrugghe M, Duprez V, Beeckman D, Grypdonck M, Quaghebeur M, Verschueren C, Verhaeghe S, Van Hecke A. (2015). Factors influencing adherence in cancer patients taking oral tyrosine kinase inhibitors: a qualitative study. Accepted for publication in *Cancer Nursing*.

Verbrugghe M, Verhaeghe S, Decoene E, Van Hecke A. (2015). Factors influencing the process of medication (non-)adherence and (non-)persistence in breast cancer patients with adjuvant antihormonal therapy: a qualitative study. Accepted for publication in *European Journal of Oncology Care*.

Verbrugghe M, Timmers L, Boons C, van den Bemt B, Hugtenburg J, Van Hecke A. (2015). Adherence to oral anticancer agents: healthcare providers' perceptions, beliefs and shared decision making in Belgium and the Netherlands. Submitted.

Timmers L, Boons C, **Verbrugghe M**, van den Bemt B, Van Hecke A, Hugtenburg J. (2015). Adherence to oral anticancer agents: healthcare providers' perceptions and usual care in Belgium and the Netherlands. Submitted.

ARTICLES IN NATIONAL JOURNALS

Han S, Van Belle S, Peeters M, Goffin F, **Verbrugghe M**, Vergote I. (2014). Evaluatie van een versnelde registratie door het College voor Oncologie van gestationele trofoblastziekten in België. *Tijdschrift voor geneeskunde*; **70**(16):895-901.

ORAL PRESENTATIONS

Verbrugghe M, Duprez V, Van Hecke A (2013). Therapietrouw bij patiënten met kanker die orale tyrosine kinase inhibitoren innemen: een kwalitatief onderzoek. Oncolunch: Orale kankerbehandelingen: de patiënt in regie?, 13 november, Gent. (C1)

Verbrugghe M, Duprez V, Quaghebeur M, Grypdonck M, Beeckman D, Verhaeghe S, Van Hecke A. (2013). Adherence in patients taking oral anticancer drugs: results of a qualitative study. ESPACOMP, 17th Annual Meeting, 15-16 November, Budapest, Hongarije. (C1)

Verbrugghe M, Duprez V, Beeckman D, Grypdonck M, Quaghebeur M, Verhaeghe S, Van Hecke A. (2014). Multidisciplinaire aanpak van therapietrouw in de oncologie: orale oncolytica als voorbeeld. (C1)

Verbrugghe M, Van Hecke A. (2014) Beïnvloedende factoren van therapietrouw en zelfmanagement bij orale TKIs: een kwalitatief onderzoek. Symposium therapietrouw in de oncologie, 13 oktober, Elewijtcenter Zemst. (C1)

Van Hecke A, Decoene E, **Verbrugghe M** (2015). Factors influencing medication adherence and persistence in breast cancer patients with adjuvant antihormonal therapy: a qualitative study. Care4 – International Scientific Nursing and Midwifery Congress, 4-6 February, Antwerp.

OTHER SCIENTIFIC OUTPUT

Verhaeghe S, Lauwaert K, Filion N, Caillet O, Gobert M†, Lagrange S, Van Lancker A, **Verbrugghe M**, Dardenne O, de la Ketule Y, Beeckman D, Van Hecke A, Goossens J, Darras E, Leys J. (2011). Agressiemanagement in de psychiatrie. Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu. (Misc)

Verbrugghe M, Verhaeghe S, Lauwaert K, Beeckman D, Van Hecke A. (2012). Determinants and associated factors influencing medication adherence and –persistence to oral anticancer drugs: a systematic review. Poster

presentation, 16th Annual Meeting European Society for Patient Adherence, Compliance and Persistence, October 25-27, Ghent, Belgium.

Daem M, **Verbrugghe M**, Schrauwen W, Leroux S, Decoene E, Verhaeghe S, Van Hecke A, Beeckman D, Grypdonck M. (2013). Psychosociale zorg voor patiënten met kanker: een gedeelde opdracht. Brussel: Vlaamse Liga tegen Kanker. (Misc)

Verbrugghe M, Duprez V, Beeckman D, Grypdonck M, Quaghebeur M, Verhaeghe S, Van Hecke A. (2014). Aanbevelingen voor de ondersteuning van therapietrouw en zelfmanagement bij patiënten die orale tyrosine kinase inhibitoren innemen. Brussel: Vlaamse Liga tegen Kanker. (Misc)

Timmers L, Boons CCLM, **Verbrugghe M**, van den Bemt B, Van Hecke A, Hugtenburg JG. (2014). Adherence to oral anticancer agents: a study among Dutch and Belgian healthcare providers. Poster presentation, 18th Annual Meeting European Society for Patient Adherence, Compliance and Persistence, November 20-22, Lausanne, Switzerland.

Honourable mention “Prijs Magda Dierendonck” 2014 – University Hospital Ghent.

Laureate qualitative research “Prijs Magda Dierendonck” 2015 – University Hospital Ghent.

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