



FACULTEIT GENEESKUNDE EN
GEZONDHEIDSWETENSCHAPPEN

Tailored approach of the older person with a haematological malignancy

Thesis submitted in fulfilment of the requirements for the degree
of PhD in Medical Sciences

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Cover photo: preventing the domino effect.

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Opgedragen aan mama

(1943 – 2001)

*Grow old along with me!
The best is yet to be,
The last of life, for which the first was made.*

Robert Browning

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LIST OF ABBREVIATIONS

aCGA:	Abbreviated comprehensive geriatric assessment
ADL:	Activities of daily living
ADR:	Adverse drug reaction
AE:	Adverse event
AML:	Acute myeloid leukemia
ASCT:	Autologous stem cell transplantation
AUC:	Area under curve
BMI:	Body mass index
CGA:	Comprehensive geriatric assessment
CI:	Confidence interval
CIRS-G:	Cumulative illness rating scale – geriatrics
CR:	Complete remission
CRASH:	Chemotherapy risk assessment score for high-age patients
DDI:	Drug-drug interaction
DLBCL:	Diffuse large B-cell lymphoma
ECOG:	Eastern cooperative oncology group
EFS:	Event free survival
E-IPI:	Elderly – international prognostic index
GDS:	Geriatric depression scale
GFI:	Groningen frailty index
GRP:	Geriatric risk profile
HGS:	Hand grip strength
IADL:	Instrumental activities of daily living
ICF:	International classification of functioning, disability and health
IPI:	International prognostic index
IPSS:	International prognostic scoring system
IPSS-R:	Revised international prognostic scoring system
kP:	KiloPascal
MDS:	Myelodysplastic syndrome(s)
MM:	Multiple myeloma
MMSE:	Mini mental status examination
MNA:	Mini nutritional assessment
MNA-SF:	Mini nutritional assessment – short form
NHL:	Non Hodgkin lymphoma
OS:	Overall survival
PFS:	Progression free survival
PS:	performance status
QoL:	Quality of life
R-CHOP:	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
ROC:	Receiver operating curve
SD:	Standard deviation
SE:	Standard error
VES-13:	Vulnerable elders survey

Chapter 1

INTRODUCTION AND MAIN RESEARCH QUESTIONS

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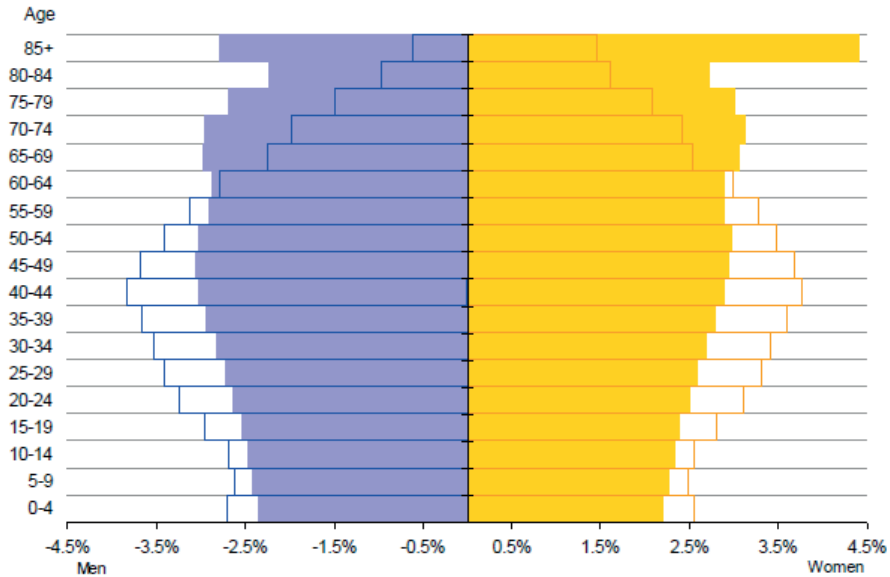
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1. INTRODUCTION

1.1 An ageing population

Population ageing is a global demographic trend and is expected to continue in future decades due to increasing life expectancy and consistently low levels of fertility over the past decades. Together with a growing number of ageing baby boomers, this trend will result in a changed population pyramid with a narrowing base and a larger top⁽¹⁾ (Fig. 1).



2010 (bordered): observed populations

2060 (solid colour): EUROPOP 2008 convergence scenario

Figure 1. Future-oriented version of the population pyramid (2010 and 2060)

Demography report 2010. European Commission; 2011.

In addition there is the progressive ageing of the older population itself. The proportion of "oldest-old" (those aged 80 and over) is growing faster than any other segment of the population and is projected to almost treble by 2060 (Fig. 2)⁽¹⁾.

Remarkable improvements in life expectancy over the past century also meant a shift in the leading causes of disease and death, with an emerging importance of chronic and degenerative diseases like cancer, heart disease, and diabetes⁽²⁾.

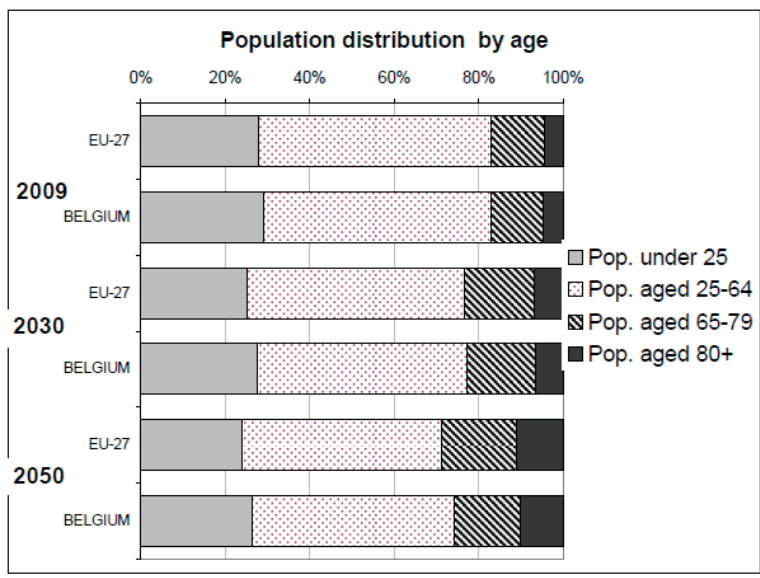


Figure 2. Demographic trends in Belgium and Europe
Demography report 2010. European Commission; 2011.

1.2 Ageing and cancer

Over a third of all cancers are diagnosed in individuals over the age of 75 ⁽³⁾. The association between ageing and cancer may be explained by two mechanisms: i) carcinogenesis occurs over time and ii) the molecular changes of ageing enhance the susceptibility of ageing cells to carcinogenesis ⁽⁴⁾. Following on global aging, one can expect the incidence of cancer to further increase in the coming decades ⁽²⁾.

A quarter of cancers in males aged 75 and over are prostate cancers while lung and bowel cancers contribute 17% and 15% respectively of cases in this age group. Breast (21%), bowel (15%), and lung (15%) cancers are the most common neoplasms in females aged 75 and over ⁽³⁾. Unlike the mortality of cardiovascular diseases, which is declining among persons of all ages, the mortality of cancer is rising for individuals above the age of 65 ⁽⁴⁾. In 2010, in Europe, cancer was the second most common cause of death at old age with over half of cancer deaths occurring in people aged 65 years and over (3;5). Therefore, in the last decade, geriatric oncology has become an evolving field of interest. Research, however, has mainly concentrated on solid tumours, while in older adults, haematological malignancies constitute a common cause of morbidity and mortality as well.

Figure 3 shows age-specific incidence rates (per 100.000) for lymphoid and myeloid malignancies, by age class ⁽⁶⁾. Incidence for both increases steadily with advancing age, reaching a maximum between 75 and 99 years. Approximately one fifth of haematological malignancies in older individuals constitute aggressive disease, like acute myeloid leukemia (AML), or high-grade lymphoma, that will shorten the patient's

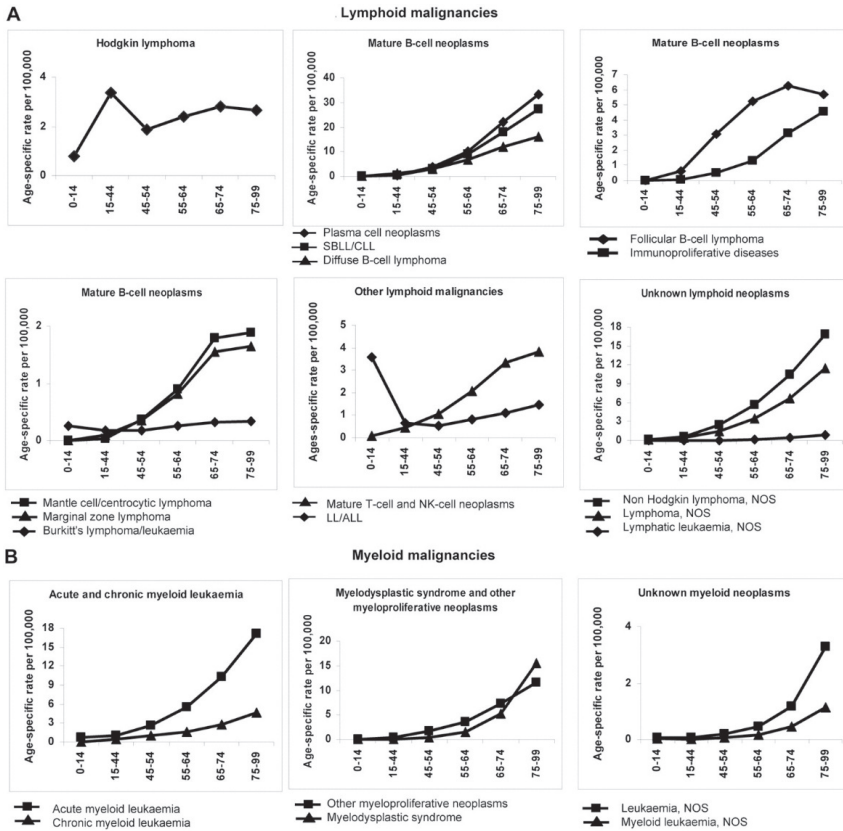


Figure 3. Age specific incidence rates for haematological malignancies (2000-2002)
Sant *et al.* Blood 2010; 116(19): 3724-34.

life and may cause severe discomfort ⁽⁷⁾. As yet, available evidence in older patients with haematological malignancies is derived primarily from studies in which, besides patients with solid tumours, a limited number of haematological patients were included. Research, purely focusing on older patients with haematological malignancies, is therefore much-needed.

- In view of the research project this introduction will further focus on
- haematological malignancies with higher incidence and unfavourable prognosis in older individuals,
 - the heterogeneity of ageing,
 - comprehensive geriatric assessment and screening, and
 - treatment principles in older patients with haematological malignancies

1.3 Haematological malignancies in older patients

Taking incidence rates and prognosis into account, and in close collaboration with the haematologists in our hospital, this research project will focus on 4 subtypes of haematological malignancies, i.e. acute myeloid leukemia, non Hodgkin lymphoma (NHL), myelodysplastic syndromes (MDS) and multiple myeloma (MM).

1.3.1 Acute myeloid leukemia

Acute myeloid leukemia is characterized by the malignant transformation of myeloid stem cells in the bone marrow, which are incapable of normal differentiation and maturation, resulting in “blast” cells. AML incidence is strongly related to age: age-specific incidence rates rise gradually from around the age of 40 with the highest rates in the 85+ age group (fig. 3). Compared with younger patients, AML in older patients emerges more often secondary to myelodysplasia or chemotherapy for a previous cancer or an auto-immune disease, and is more frequently associated with an unfavorable karyotype and expression of MDR1 (encoding for multidrug resistance) ⁽⁸⁾.

1.3.2 Non Hodgkin lymphoma

Non Hodgkin lymphoma is the most common malignant disease of the lymphatic system and is most frequently diagnosed among older people aged 65 to 74 with a median age of 66 years, while 9.4% of patients are 85 years or older ⁽⁹⁾. Non Hodgkin lymphoma is not a single disease, but rather a group of several closely related entities. The World Health Organization estimates that there are at least 61 types of NHL. Non Hodgkin lymphomas are broadly divided into two major groups: B-cell lymphomas, accounting for 85 percent of all NHLs, and T-cell lymphomas. NHLs may also be classified as indolent or aggressive. Diffuse large B-cell lymphoma (DLBCL) is accounting for more than 80% of aggressive lymphoma's and is the most frequent subtype of NHL in older people, with poorer prognosis than in younger patients. Other subtypes commonly associated with a poor prognosis, like the morphologically defined immunoblastic variant, the activated B-cell (ABC) subtype and the Epstein-Barr virus (EBV)-positive DLBCL, are all overrepresented in older patients ⁽¹⁰⁻¹²⁾.

1.3.3 Myelodysplastic syndrome(s)

Myelodysplastic syndrome is a disease of older people, with a median age at diagnosis of 70 years. The incidence of MDS in Europe is about 4 cases/100 000 inhabitants/year, reaching 40–50/100 000 in patients aged ≥ 70 years ⁽¹³⁾. MDS is characterized clinically and morphologically by ineffective hemopoiesis leading to bone marrow failure. Haematopoietic progenitors show a decreased capacity for differentiation and an increased tendency for apoptosis ⁽¹⁴⁾. Patients with MDS suffer from chronic cytopenias that may lead to recurrent transfusions, infections, and increased risk for bleeding. Incidence of secondary MDS, occurring after cytostatic treatment for cancer or prolonged immunosuppressive therapy, is increasing and is associated with a poor prognosis. Moreover, patients with MDS are at risk for progression to AML.

1.3.4 Multiple myeloma

Multiple myeloma is most frequently diagnosed among older people aged 65 to 74 with a median age of 69 years, while 9.3% of patients are 85 years or older (9). MM is characterized by a proliferation of malignant plasma cells producing monoclonal immunoglobulin (M protein) and invading and destroying adjacent bone tissue. The presentation of MM can range from asymptomatic to severely symptomatic. Manifestations include bone pain, bleeding, recurrent infections, renal failure, and pathologic fractures with spinal cord compression. The International Myeloma Working Group agreed on diagnostic criteria for symptomatic myeloma as well as asymptomatic or smouldering myeloma as shown in table 1⁽¹⁵⁾.

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
 - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
 - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
 - Renal insufficiency: creatinine clearance <40 mL per min[†] or serum creatinine >177 μ mol/L (>2 mg/dL)
 - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
 - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[‡]
 - Any one or more of the following biomarkers of malignancy:
 - Clonal bone marrow plasma cell percentage* $\geq 60\%$
 - Involved:uninvolved serum free light chain ratio \S ≥ 100
 - >1 focal lesions on MRI studies \P

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT = ¹⁸F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ -light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. [†]Measured or estimated by validated equations. [‡]If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. [§]These values are based on the serum FreeLite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥ 100 mg/L. [¶]Each focal lesion must be 5 mm or more in size.

Table 1. Diagnostic criteria for multiple myeloma and smouldering multiple myeloma
Raykumar et al. Lancet Oncol 2014; 15(12): e538-48.

1.4 The heterogeneity of ageing

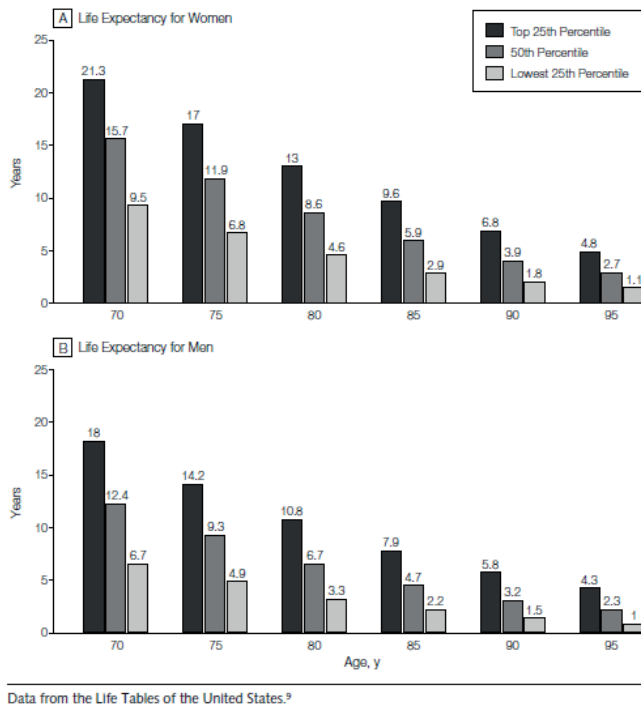
As people get older there is an increasing heterogeneity in health as well as in physical, mental and cognitive functioning.

1.4.1 Defining an older patient

To define “an older patient”, the concept of chronological age might seem easy and practical. There is, however, no generally accepted age cut-off defining an older patient, leading to substantial differences in lower age limits throughout studies. In most haematological cancer trials, the lower age limit to define older patients is arbitrarily chosen between 60 and 70 years of age⁽¹⁶⁻²⁵⁾. In a retrospective analysis of a population-based non Hodgkin lymphoma registry patients were considered old once complete remission (CR) and overall survival (OS) rates decreased⁽²⁶⁾. Definition of older age therefore differed according to histological type. Patients with indolent lymphomas were considered old as from the age of 70, while for patients with aggressive lymphoma older age was defined as 65 and over. Eventually, in some cancer studies, lower age thresholds are determined by treatment intensity. In a study on “older” transplant recipients, an age limit of 50 years has been adopted⁽²⁷⁾. Although a generally accepted age cut-off could resolve this variety in age limits, chronological age does still not take into account another important aspect of ageing, i.e. the heterogeneity of ageing.

1.4.2 Chronological age versus biological age

Ageing is a highly individualized and very heterogeneous process with a broad spectrum ranging from older persons who are *functionally independent* to those who are at high risk of *functional decline* and mortality and all the others in between. Chronological age does not reflect this variability, both between and within individuals⁽²⁸⁾. Biological age on the other hand is believed to reflect a person's remaining functional reserves and life expectancy. Figure 5 is a clear example of the difference between chronological and biological age. Instead of an average life expectancy, it represents the distribution of life expectancy, according to age and sex, thereby illustrating the substantial variability in life expectancy that exists at each age. Biological age, therefore, might help clinicians to predict whether a specific patient is expected to live longer or shorter than an average patient of the same age. For instance, patients with severe comorbidities like end-stage renal disease or stage IV chronic obstructive lung disease, and functionally dependent, bedridden patients, will have a life expectancy that is substantially lower than average for his/her age category. High-functioning older adults without comorbidities worth mentioning, on the other hand, might likely live substantially longer than their contemporaries. Unfortunately, for most patients, there is no simple way to assess biological age. The best tool available to date is a comprehensive geriatric assessment (CGA). As explained below, a CGA exploring all domains likely to undergo age-related changes, allows a more accurate estimation of the patient's active life expectancy and functional reserve than a standard clinical evaluation. (4:28).

Figure. Upper, Middle, and Lower Quartiles of Life Expectancy for Women and Men at Selected Ages**Figure 5.** From Walter et al. JAMA 2001; 285 (21): 2750-2756

As previously mentioned, ageing is a highly individualized and very heterogeneous process. As people get older, there is an accumulation of impairments in multiple physiological systems resulting in a decrease in physiological reserves and functional status and an increase in their vulnerability to adverse outcomes⁽²⁹⁾. The vulnerable subset of this ageing population has also been identified as “older adults with comorbidity” or “those who are disabled”. Although distinct clinical entities, the terms of comorbidity, disability and frailty are often used interchangeably⁽³⁰⁾. The distinction between these entities is one of the cornerstones of this thesis.

1.4.3 Comorbidity, disability and frailty

Comorbidity can be defined in several different ways. In the light of this thesis comorbidity refers to the simultaneous presence of multiple health conditions with an index condition, in this case, cancer and other unrelated conditions. The presence of comorbidity increases with age⁽³¹⁾. Therefore, in an ageing population, one can expect a growing percentage of patients with a diagnosis of cancer and other medically relevant conditions in addition. The presence of comorbidity might adversely affect outcome. Comorbidity has been associated with mortality, hospitalization and longer hospital stays, institutionalization, lower quality of life, loss of

physical functioning, depression, multiple drug use and higher health care utilization and costs⁽³²⁾. Its measure in research studies, especially in older individuals, has therefore become increasingly important. In theory, a simple count of chronic conditions can be used as a measure for comorbidity. However, the impact of comorbidity is related, not only to the number of chronic conditions, but also to their degree of severity. Several indices have been described to measure comorbidity. The Cumulative Illness Rating Scale-Geriatrics (CIRS-G) is one of the most frequently used, valid comorbidity instruments (appendix 1)⁽³³⁾. The CIRS-G score correlates with mortality, hospitalization rate and duration, hospital re-admission, medication usage, abnormal laboratory test results, and functional disability in geriatric populations. In older cancer patients, CIRS-G also correlates with progression-free survival⁽³⁴⁾. It takes into account total number as well as severity of comorbid conditions. Therefore, during this research project, comorbidity has been measured using CIRS-G. However, the impact of comorbidity is related, not only to the number of chronic conditions, but also to their degree of severity. Several indices have been described to measure comorbidity. The Charlson comorbidity index (CCI) and the CIRS-G are two of the most frequently used, valid comorbidity instruments. The CCI correlates with mortality risk, postoperative complications, length of hospital stay and discharge to a nursing home. In older cancer patients, CCI correlates with progression free survival (PFS). Its performance in predicting mortality and length of stay compares very well with the CIRS-G. The CIRS-G (appendix 1) score correlates with mortality, hospitalization rate and duration, hospital re-admission, medication usage, abnormal laboratory test results, and functional disability in geriatric populations. In older cancer patients, CIRS-G also correlates with PFS⁽³⁴⁾. In the CIRS-G every disease requires grading, thus taking into account not only the number but the severity of comorbid conditions as well and making it the most detailed. In addition, the rating manual is aimed at a geriatric population and therefore includes details on several geriatric problems⁽³⁵⁾. Therefore, during this research project, comorbidity has been measured using CIRS-G.

Disability, according to the International Classification of Functioning, Disability and Health (ICF), is defined as “an impairment, activity limitation or participation restriction that is the result of the interaction between contextual factors (personal and environmental) and health conditions”⁽³⁶⁾. Disability is mainly the resultant of diseases and physiologic alterations with ageing on one hand and social, economic, and behavioral factors as well as access to medical care on the other. In the narrow sense, disability is “the difficulty of coping with self-care tasks (Activities of Daily Living, ADL) and tasks of household management (Instrumental Activities of Daily Living, IADL)”⁽³²⁾. The likelihood of developing a disability rises steadily with age. In the Participation and Activity Limitation Survey in Canada in 2006, the disability rate tripled from 23 percent among individuals age 55 to 64 to 73 percent among individuals age 85 and older (Fig. 4)⁽³⁷⁾. Mobility and agility disabilities were the most common disabilities experienced by older people as shown in table 2⁽³⁷⁾. Most people with disabilities have more than one type of disability. Disability has been associated with mortality, hospitalization, length of hospital stay and institutionalization⁽³²⁾.

Frailty is characterized by an age-related increased vulnerability to stressors due to decreased physiological reserves and/or dysregulation in multiple physiologic systems. This results in difficulties to maintain homeostasis in response to “normal” perturbations that would not create such problems at younger age⁽³⁸⁾. The definitions of ageing and frailty share a basis of failure in homeodynamics, but with ageing this failure is global whereas in frailty loss of homeostasis is related to energy metabolism and neuromuscular changes. Frailty is a risk factor for adverse health outcomes, not just in terms of morbidity and mortality, but also with regard to disability, dependency, falls and institutionalization. Although the concept of frailty has gained considerable attention during the last decades, consensus is still lacking on its definition and the criteria that should be used for its recognition. Therefore estimates of prevalence differ widely. The most frequently used operational definition is the “phenotype of frailty” proposed by Fried et al. Frailty was assessed based on the identification of five criteria: (1) low handgrip strength; (2) self-reported fatigue; (3) unintentional weight loss; (4) reduction of physical activity; and (5) slow walking speed. Older persons are considered pre-frail or frail if they meet at least two, respectively three out of these five criteria (30). Based on these Fried criteria, in the English Longitudinal Study of Ageing, prevalence of frailty rose with increasing age, from 6.5% in those aged 60–69 years to 65% in those aged 90 or over⁽³⁹⁾. Pivo-

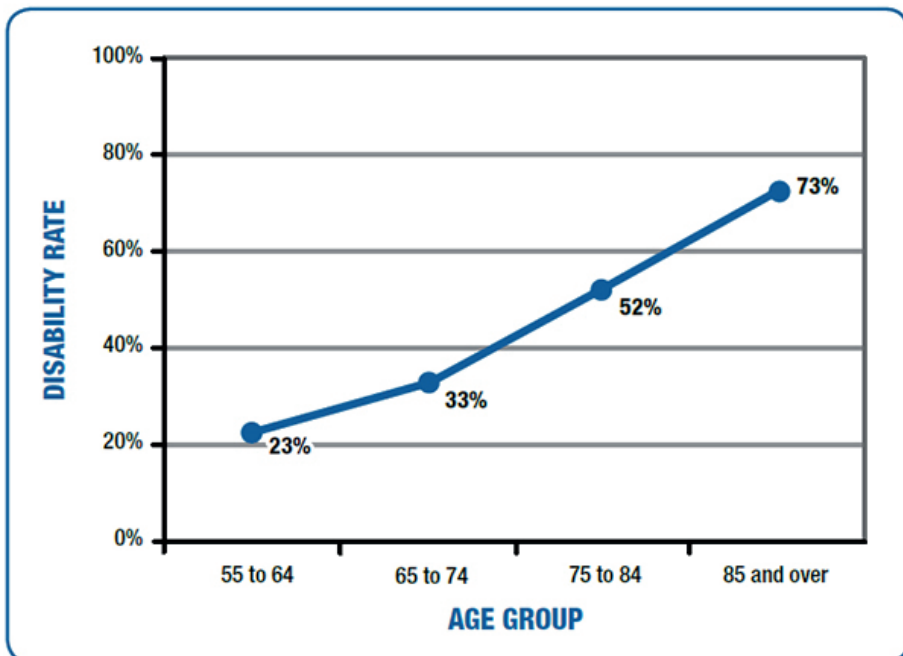


Figure 4. Disability rates, by age group (%)

Federal Disability Report: Seniors with Disabilities in Canada. Government of Canada 2015.

Type of disability	Age group			
	55 to 64	65 to 74	75 to 84	85 and over
Mobility	17	24	41	61
Agility	16	23	38	57
Pain	17	23	33	42
Hearing	6	12	21	44
Seeing	4	6	11	25
Memory	2	3	5	13
Communication	2	2	4	10
Learning	3	2	2	6
Emotional	3	2	2	2

Table 2. Frequency of type of disability by age group (%)

Federal Disability Report: Seniors with Disabilities in Canada. Government of Canada 2015.

tal to the clinical definition of frailty is the concept that no single altered system defines this state, but that multiple systems must be involved. Comorbid diseases may contribute to the development of frailty and disability might exacerbate frailty, but individual diseases are not sufficient for the identification of frail individuals, nor are any two diseases, or disability alone. In the presence of disease, other manifestations must also be present ⁽³⁰⁾. Frail patients also appear to have specific care needs, beyond care of underlying comorbidity and associated disability.

The loss of homeostatic reserve and the development of frailty can be manifested in the myriad of geriatric syndromes including falls, delirium, malnutrition, urinary incontinence, and deconditioning. However, frailty is a dynamic concept. The process of frailty can be changed or reversed with a possibility of transition from being frail to less frail or even non-frail if frailty is detected and treated at onset ⁽⁴⁰⁾. Therefore, one of the main challenges in geriatrics is the detection of frail individuals to determine, by a systematic evaluation or CGA, who might benefit by medical and rehabilitation efforts.

In accordance with the differences in life expectancy in figure 5, a CGA is assumed to distinguish between three groups of patients ^(41,42). In the literature distinct terms are used interchangeably to identify these three patient groups. Most articles follow the criteria as defined by Balducci, identifying fit (group 1), unfit (group 2) and frail (group 3) patients ⁽⁴²⁾. A frail patient is then considered a candidate only for palliative treatment, while the patients in between might benefit from some special (pharmacological) approach. Saarelainen identified robust, prefrail and frail individuals while Deschler divided his patients into a low, intermediate and high risk group ^(43,44). Each one of these classifications fails to recognize the concept of frail-

ty and the goals of a geriatric assessment. As previously mentioned, frailty is a dynamic concept with the possibility of transition. The goal of a CGA is to detect these frail patients, patients amenable for improvement due to geriatric interventions and follow-up, and thus the patients in between. In the light of this argumentation we've defined respectively fit, frail and unfit patients as follows:

- fit patients are functionally independent patients without medically relevant comorbidity
- unfit patients are identified by the presence of at least one of the following: multiple comorbidities, the presence of one or more geriatric syndromes, or dependence in ADL. Most patients aged ≥ 85 years are attributed to this group.
- frail patients represent the group in between with minor dependencies in IADL and/or one or two comorbidities in the absence of a geriatric syndrome or dependence in ADL.

1.5 Comprehensive geriatric assessment

A CGA is a multidisciplinary, in-depth evaluation to determine an older person's medical, psychological and functional abilities in order to develop a coordinated treatment plan with the aim to preserve or restore normal function and independence whenever possible^(45, 46). Given the reversibility of frailty, as stated above, a CGA is especially beneficial to frail individuals. Although no golden standard exists, there is a consensus that CGA should include functional, cognitive, emotional and psychosocial status as well as the aspects of nutrition, mobility, and polypharmacy, in addition to comorbidity assessment⁽⁴²⁾. Extensive evidence is available for the efficacy of a CGA, in a wide variety of settings and patient populations, with benefits related to functional status, mortality, cognition, length of hospital stay and rates of readmission and institutionalisation⁽⁴⁷⁻⁵¹⁾.

In the field of geriatric oncology, increasing evidence suggests that a geriatric assessment identifies previously unknown geriatric problems - thereby allowing targeted and tailored interventions-, adds prognostic information, might influence treatment decisions and might predict treatment toxicity and/or complications⁽⁵²⁻⁶⁰⁾. Quality of life (QoL) parameters, especially patient's self-reported physical symptoms and/or physical functioning, have repeatedly proven to correlate with survival⁽⁶¹⁻⁶³⁾.

There is evidence that, also in patients with haematological malignancies, a geriatric assessment can reveal additional health problems, even in apparently fit patients⁽⁶⁴⁾. Most often, these impairments were not noticed by the treating physician, although they might affect prognosis and treatment response. Several studies have shown that physical functioning (measured by means of ADL, IADL or objective measures like grip strength and short physical performance battery) is an independent prognostic predictor for survival^(27,61,65-69). In AML patients, both cognitive decline and QoL appeared statistically significant prognostic factors for survival^(61,63,65) while in older allogeneic haematopoietic cell transplantation recipients low mental

health was associated with inferior OS ⁽²⁷⁾. There is one small study in MDS/AML patients that looked at the effects of different treatments on QoL, a much more valid outcome parameter for older patients than just survival. At follow-up, up to 32% of patients showed new functional dependencies while cognitive changes became obvious in a quarter of all patients. Global QoL deteriorated in 1/3 of patients ⁽⁷⁰⁾. Evidence on other CGA domains in this patient group is almost non-existing ⁽⁷¹⁾.

Despite its assumed/proven benefits, an assessment is both time- and staff-consuming and might not be necessary for every older patient. Therefore cancer specialists are looking for a short screening tool that can distinguish between fit older cancer patients and more vulnerable (both unfit and frail) patients that should subsequently receive a full CGA ⁽⁷²⁾.

1.6 Screening

The challenge of identifying those patients who will most likely benefit from a CGA led to the incorporation of a two-step approach. In a first step, patients are screened for the presence of frailty, using a validated screening tool. Patients who screen negative are likely to be fit and should not be considered differently from younger patients. Patients who screen positive require a more in-depth evaluation, linked to appropriate geriatric interventions when indicated ^(73;74). Thus, screening tools should have the potential to separate fit older patients from frail and unfit patients ⁽⁷⁵⁾. They should be short and simple with a high sensitivity and negative predictive value (NPV), and, if in any way possible, a high specificity as well. Several frailty screening tools (Vulnerable Elders Survey (VES-13), G8, Groningen Frailty Index (GFI), Geriatric Risk Profile (GRP), abbreviated CGA (aCGA)) are available in geriatrics but only two, the aCGA and the G8, were designed specifically to detect frailty in older cancer patients ⁽⁷⁵⁾. None has thus far been validated in patients with a haematological malignancy.

Patients with a positive screen should not automatically be excluded from standard treatment. These patients should undergo a full CGA to detect potential deficits for which targeted interventions can be applied, e.g. dietary advice or parenteral nutrition in case of malnutrition. They might still be eligible for a standard approach after these geriatric interventions have solved those biological, clinical and/or social issues limiting the applicability of oncological guidelines ⁽⁷⁶⁾. If not eligible, treatment modifications and/or the introduction of new agents are currently under study for these patients and will likely constitute the future.

1.7 Treating older people with haematological malignancies

In the first paragraph, general treatment principles for older patients are discussed. Afterwards, this principles will be applied, as far as evidence is available, for the different subtypes of haematological malignancies discussed in this thesis.

1.7.1 General treatment principles

When cancer is diagnosed in an older patient, treatment decisions will often be complex. One of the main challenges of treating older patients with cancer is to assess whether the expected benefits of treatment are superior to the risks in a population with decreased life expectancy and decreased tolerance to stress⁽⁷⁷⁾. Age is an important adverse prognostic factor due to comorbid conditions, functional decline, cognitive deterioration, reduced treatment tolerance, poor nutritional status and potential drug-drug and drug-disease interactions^(78,79). At all ages, patients with a haematological malignancy will benefit from a significantly better overall survival if treatment results in a durable remission. To obtain this remission, in most cases, full-dose aggressive therapy is needed⁽⁸⁰⁾. Age itself should not preclude patients from full intensity treatment and intensive therapy with curative intent should be given to all patients who can tolerate such therapy^(41;42;81). Thus, older patients, considered fit through screening or CGA, should receive the same treatment as their younger counterparts. This was clearly illustrated in a group of patients with DLBCL. All patients underwent a CGA and were subdivided in fit and unfit patients. For all patients, treatment was chosen according to clinical judgement of the attending physician, who was blind to the results of the CGA. Patients considered fit by CGA could be safely treated with aggressive therapy and achieved an outcome similar to that of younger DLBCL patients, while in unfit patients full therapy could not improve outcome compared with palliative treatment⁽⁸²⁾. Thus, with a life expectancy below that of the cancer-related life expectancy, in unfit patients, symptom palliation and quality of life preservation are paramount.

The main problem however is the group of frail patients at increased risk for treatment complications. Both cancer and its treatment are significant stressors with the potential to challenge physiological reserves⁽⁸³⁾. A frail older person, in general, will no longer be a candidate for aggressive life-prolonging treatment. However, his life expectancy, although limited, is not necessarily short, as already illustrated in figure 5, and usually above that of the cancer-related life expectancy⁽⁷⁾. In addition to symptom management and quality of life preservation – pillars of treatment in unfit patients –, treatment in frail patients should focus on prolongation of active life expectancy (rather than survival), and prevention of adverse drugs reactions (ADRs)⁽⁷⁶⁾. However, a limited ability to identify frail patients and the systematic underrepresentation of older patients in clinical trials, makes it difficult to define specific treatment strategies in frail older patients^(84;85). The absence of studies guiding physicians in their choice of the right treatment dose and/or regimen exposes these patients to arbitrarily defined dose reductions and/or adaptations in treatment schedules, with possible far-reaching consequences⁽⁶⁸⁾. Therefore, current research should focus on means to describe more accurately the health status of an older individual and on the possibilities of an individualized management, tailored to differences in functional reserve, life expectancy, social and economic support and possible other factors⁽⁸⁴⁾. This is especially needed in haematology, where some novel treatments became available, with good prospects for these frail older patients⁽⁸⁰⁾.

One important point of attention should be made here. Especially in patients with

haematological malignancies, there is always the risk that a reduced performance status, depending only on advanced and symptomatic disease, might lead to a faulty diagnosis of frailty, with the consequence of undertreatment.

1.7.2 Acute myeloid leukemia

Treatment options vary from intensive chemotherapy of the same type offered to younger patients over non-intensive chemotherapy to supportive care alone. Despite the fact that intensive therapy is associated with hospitalization, a high risk of complications and a decrease in functional status, a full dose regimen is the only available option to achieve a long-term remission⁽⁸⁶⁾. It should therefore be considered, at the very least, in all fit older patients. In younger patients, intensive treatment and particularly the advances in supportive therapy, have steadily improved outcome over the last 30 years with currently a 45 -50% 5 year event free survival (EFS). Oppositely, in older patients treated with the same regimen, little improvement was seen over the years. Approximately 40-65% will achieve remission but 85% will relapse within 2 to 3 years, with a 5-year survival rate of about 15%⁽⁸⁷⁾. Apart from an unfavorable biology, older age itself is hereby an independent risk factor⁽⁸⁶⁾. Certain groups of patients who are not candidates for intensive chemotherapy can be treated non-intensively with chemotherapeutic drugs such as azacitidine, a hypomethylating agent, or low-dose cytarabine. Choice of treatment hereby is related to pretreatment disease characteristics rather than individual patient characteristics. At present, the question remains whether and how these regimens can be applied in both frail and unfit patients. Besides the group of patients in whom just a supportive treatment can be offered given an absolute lack of physiological reserves, there is also a group of patients in whom only a supportive treatment can be applied, not due to a lack of reserves, but as a result of non-existing therapeutic alternatives. The latter group can be given purely supportive care or they can be offered to participate in a therapeutic trial.

In the light of this unfavorable perspective, the impact on quality of life, of disease as well as therapy, becomes equally or even more relevant than survival, as already mentioned before. Although few studies have been carried out in older AML patients, QoL has been shown to be compromised at the time of diagnosis. Fatigue hereby is a prevalent condition with a negative impact on QoL^(16,63). In intensively treated patients, QoL decreased during hospitalization but rebounded after discharge. For those patients who survived beyond six months from diagnosis significant improvements were achieved in QoL, fatigue and physical function over time^(25,88). Overall, 97% of patients confirmed that QoL for them was more important than length of life. Compared to intensive chemotherapy, supportive care and cytoreduction with hydroxyurea do not provide a significantly better perspective in terms of improving quality of life⁽⁸⁹⁾. For novel treatments like azacitidine no studies could be found regarding their impact on QoL.

1.7.3 Non Hodgkin lymphoma

Treatment is usually tailored according to the individual risk profile based on the International Prognostic Index (IPI). The IPI is a clinical tool used to predict outcome

for patients with aggressive NHL. Based on the number of negative prognostic factors present at the time of diagnosis (age > 60 years, stage III/IV disease, elevated lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance status (ECOG PS) \geq 2, more than one extranodal site of disease), 4 outcome groups were identified with a 5-year OS ranging from 26% to 73%⁽⁹⁰⁾. The Elderly-International Prognostic Model (E-IPM), using an age cut-off of 70 years instead of 60 years, has been recently proposed to refine the risk profile in older patients, but still needs validation⁽⁹¹⁾.

R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab) is currently considered one of the most effective first-line treatments for B-cell NHL⁽⁸⁵⁾, and is the treatment of choice in young patients as well as in fit older patients, with 5-year OS rates of about 60% in the older age group⁽⁹²⁾. In patients over 80 years of age, reduced doses of CHOP with a conventional dose of rituximab (R-mini-CHOP) appear feasible with potential long-term cure expectation⁽⁹³⁾. In frail patients studies are ongoing as to the best form of treatment, including regimen modifications^(73;94), the use of a pre-phase treatment with vincristine and corticosteroids⁽⁹⁵⁾, and dose modification based on age⁽⁹³⁾ or CGA results. Monfardini et al. used the results of the CGA to select unfit older patients in order to treat them with a less toxic combination of vinorelbine and prednisone⁽⁹⁶⁾. Main problem was the lack of referral. Therefore, patient accrual was low and no firm conclusions could be made on treatment effect. Visani et al. evaluated the use of non-pegylated liposomal doxorubicin instead of conventional doxorubicin for the treatment of NHL in unfit patients, with promising results but study sample was, once again, small with inclusion of 20 patients over an 11 month period⁽⁹⁴⁾. In the study by Spina et al., DLBCL patients were classified as fit, frail, or unfit based on ADL, IADL, and the presence or absence of comorbidities. Drug regimen was adapted according to comorbidity, while doses were reduced, dependent on ADL- and IADL-scores. Fit patients received full dose treatment while frail and unfit patients received 75% and 50% respectively, of the usual doses. All 3 groups had similar complete remission (CR) rates. There was no statistical significant difference between groups in the occurrence of severe or life-threatening (grade 3 and 4) toxicities. Survival rates were better in fit patients⁽⁹⁷⁾. Oliveiri et al. divided patients into fit, frail and unfit patients, based on age, ADL, comorbidities, and the presence or absence of geriatric syndromes. In frail patients doxorubicin was replaced by pegylated liposomal doxorubicin, while unfit patients received a 50% dose reduction (mini-CHOP), without rituximab. No differences were found in the rates of complete remission or grade 3 and 4 toxicities. Not unexpectedly, OS and EFS were, again, better in fit patients⁽⁹⁸⁾. These studies show that the results of a CGA can be used as a parameter to modify doses and regimens of chemoimmunotherapy in older patients with DLBCL with encouraging results regarding treatment-related mortality, toxicity and outcome.

In current practice, frail and unfit patients, no longer candidate for intensive therapy and not willing to participate in ongoing trials, can be offered rituximab monotherapy. If a patient responds and his condition improves, bendamustine or vinblastine can be added.^(12;99)

1.7.4 Myelodysplastic syndrome

Available treatment options range from potentially curative, intensive treatment with standard induction chemotherapy and consolidation including stem cell transplantation, over non-intensive chemotherapy to best supportive care alone. (100). To assist in decision making regarding treatment, several prognostic systems have been developed and validated in patients with MDS. Among these the International Prognostic Scoring System (IPSS) is the simplest and most commonly used. The IPSS is based upon the cytogenetic abnormalities, the percentage of blasts in the marrow and the number of lineages affected in the cytopenia and then stratified into four prognostic groups: low, intermediate-1, intermediate-2 and high risk. New insights in prognostic variables have led to the development of the Revised IPSS (IPSS-R) (table 3), with 5 instead of 4 major prognostic categories thereby allowing a better prognostication for survival and evolution to AML ⁽¹⁰¹⁾. This might enable earlier recognition of patients at high risk of progression to aggressive disease and might consequently optimize treatment timing. Median overall survival (OS) times, according to risk group, are 8.8, 5.3, 3.0, 1.6 and 0.8 years for patients with very low risk, low risk, intermediate risk, high risk, and very high risk IPSS-R scores.

Prognostic variable	0	0,5	1	1,5	2	3	4
Medullary blasts (%)	≤2	-	>2-<5	-	5-10	>10	-
Cytogenetics	very good	-	good	-	intermediate	poor	very poor
Hemoglobin	≥10	-	8-<10	<8	-	-	-
Platelets	≥100	50-<100	<50	-	-	-	-
Absolute neutrophil count	≥0.8	<0.8	-	-	-	-	-

Table 3. Revised International Prognostic Scoring System (IPSS-R)

Greenberg et al. *Blood* 2012; 120(12): 2454-65.

To date, the only curative treatment is allogeneic stem cell transplantation. Recent studies in reduced-intensity-conditioning HSCT patients have shown that performance status as well as comorbidities are major prognostic parameters, whereas age is not ⁽¹⁰²⁻¹⁰⁵⁾. However, only a minority of patients in excellent health are eligible for this therapy ⁽⁴¹⁾. Therefore, in the group of high-risk patients, azacitidine should be considered. With azacitidine, although not curative, OS was significantly increased when compared to conventional care regimens. Moreover, median time to AML transformation was longer and rates of complete and partial remission and any haematologic improvement were significantly higher. Subgroup analysis in patients ≥ 80 years of age suggest that azacitidine is effective even in older patients displaying a compromised performance status. Transfusion independence, improvement of quality of life as well as relief of symptoms can be achieved with this

treatment option. It's use is recommended in fit as well as in frail patients and might even benefit a minor portion of unfit patients. For the majority of unfit patients however, merely best supportive care, including transfusions, and palliation remain suitable options.

1.7.5 Multiple myeloma

Although 5-year relative survival for patients younger than 65 improved in recent years, in older people little improvement was seen with 5-year overall survival rates of 22.7% in patients 75 years and over ⁽¹⁰⁶⁾. Treatment should be initiated in all patients with symptomatic MM. For fit patients, induction followed by high-dose therapy with autologous stem cell transplantation (ASCT) is the standard treatment. No randomized trials on the efficacy of ASCT in older patients are currently available. Although some cohort studies have found a lower progression free survival (PFS) and OS for older patients, most studies found no difference between younger and older patients. However, to date no formal criteria exist as to which older adults are eligible for ASCT ⁽¹⁰⁷⁾.

In older patients in a non-transplant setting oral combinations of melphalan and prednisone plus novel agents (thalidomide, bortezomib) are considered standard of care. In patients with clinical neuropathy, precluding the use of thalidomide or bortezomib, a combination of bendamustine plus prednisone can be used ⁽¹⁰⁸⁾. A recent analysis showed that, along with the development of newer therapies, a significant improvement was seen in OS, especially in the older age group, reflecting the increased use of these novel agents also in older patients ⁽¹⁰⁹⁾. Unfortunately, these standard schedules induce a high rate of grade 3-4 non-haematological adverse events (AE). In a recent study 869 newly diagnosed multiple myeloma patients were divided into three categories (fit, frail, and unfit) based on age, functional status (ADL and IADL) and comorbidity. All patients participated in one of three multicenter prospective trials and treatment regimens did widely differ. Nevertheless, the 3-year OS was higher in fit patients compared to frail and unfit patients, while the risk of grade ≥ 3 non-haematological AE and the risk of drug discontinuation were lower. ⁽¹¹⁰⁾. Due to a complete lack of further studies, no changes in dose and/or schedule are approved according to age or performance status to date ⁽¹¹⁰⁾. Treatment choices for frail and unfit patients therefore are still left at the discretion of the treating physician.

Summarizing, it may be said that more research is needed on the incorporation of CGA results into an individualized treatment plan and on how this treatment plan should look like for real life, frail older patients. Therefore every patient should at least be invited to participate in a clinical trial. Although limited in number, the above-mentioned studies make it clear that older patients can be enrolled in clinical studies. However, the period for inclusion needs to be longer and it might take more persuasiveness to convince patients and, particularly, family members.

2. GENERAL STUDY PROTOCOL

2.1 Participants

Between July 2011 and October 2013 all patients, 70 years or older, with a new diagnosis of AML, intermediate or high grade MDS, MM or high grade NHL, referred to the haematology department of a university hospital, were asked to participate in the current study. Patients were recruited proactively: daily review of the list of patients, newly admitted to the hospital, daily review of the agenda for the outpatient clinic and close contacts with haematologists, head nurses and nurse specialists. The possibility that a potential candidate was not addressed, therefore seems unlikely. Overall 71 patients were included and 14 patients refused to participate. The four main reasons for refusal were 1) candidate himself fails to see the added value or considers it an extra burden, 2) family does not want the candidate to be overburdened, 3) candidate is suspicious towards signing an informed consent, and 4) one candidate considered himself not old enough for a "geriatric" evaluation. Fifty patients had at least one reassessment and 33 patients had 2 or more. Fourteen patients died before a first reassessment could take place (20%). At 6 months follow-up 17 (24%) patients had died, while at the end of the study, 3 years after first inclusion, 46 (65%) patients had died. Five patients dropped out and 2 patients were lost to follow-up. All participants provided written consent. The study was approved by the local Ethics Committee.

2.2 Composition of the CGA

2.2.1 Activities of daily living

ADL was assessed using the Katz index of activities of daily living (Katz ADL) ⁽¹¹¹⁾. The Katz ADL is designed specifically to assess a patient's ability to perform ADL activities independently. The index ranks adequacy of performance in six domains: bathing, dressing, toileting, transferring, continence, and feeding. If no supervision, direction, or personal assistance is required, then 1 point is given to that functional activity. If the client requires supervision, direction, personal assistance, or total care, then a 0 is assigned to that functional activity. A score of 6 indicates ADL independence.

2.2.2 Instrumental activities of daily living

IADL was assessed using the Lawton scale (appendix 2). The Lawton IADL scale, based on self-reporting, is validated in older people to assess independent living skills, at a given moment as well as over a certain period of time (112). There are 8 domains of function measured: ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Each item is rated dichotomously (0=less able, 1=more able) according to the highest level of functioning in that category. Women were scored on all 8 areas of function; for men, the areas of food preparation, housekeeping and laundering were excluded. A summary score ranges from 0 to 8 for women, and 0 through 5 for men. A score of 8 for women and 5 for men indicates IADL independence.

2.2.3 Performance status

Performance status was assessed using the ECOG-PS ⁽¹¹³⁾. The ECOG-PS describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. It is also a way to track changes in a patient's level of functioning as a result of treatment. The ECOG-PS defines 5 levels of functioning:

- 0: fully active, able to carry on all pre-disease performance without restriction
- 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2: ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
- 3: capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
- 4: completely disabled; cannot carry on any selfcare; totally confined to bed or chair
- 5: dead

2.2.4 Nutrition

The Mini Nutritional Assessment – short form (MNA-SF) is a simple, well-validated screening tool for malnutrition in older persons and is recommended for early detection of risk for malnutrition ⁽¹¹⁴⁾. The MNA-SF incorporates three cut-off points for nutritional status, thus allowing the identification of those who are normally nourished (12 – 14), at risk for malnutrition (8 - 11), or malnourished (\leq 7).

2.2.5 Mood

Mood was assessed using the 4-item geriatric depression scale (GDS-4) ⁽¹¹⁵⁾. The GDS-4 is easy and quick to perform with a high sensitivity and specificity. GDS-4 is of limited clinical value in monitoring the severity of the depressive episode but more useful in excluding depression. Each question has a yes/no answer, with the scoring dependent on the answer given. A cut-off of \geq 2 indicates depression.

2.2.6 Cognition

Cognition was assessed using the mini mental state examination (MMSE), one of the most widely used measures of cognitive function. It provides an objective, relatively brief, and inexpensive preliminary evaluation of cognitive status. The MMSE has a maximum score of 30 points, with different domains assessed: orientation to time and place, registration of 3 words, attention and calculation, recall of 3 words, language, and visual construction. A score of $<$ 24 was considered abnormal ⁽¹¹⁶⁾.

2.2.7 Falls

Falls history is one of the strongest predictors of future falling with a relative risk found to be 3.0 compared to non-fallers ⁽¹¹⁷⁾. Therefore, falls history was assessed using the question "have you fallen in the last year" or, in case of reassessment, "have you fallen since the previous evaluation".

2.2.8 Comorbidity

Comorbidity was assessed using the CIRS-G (appendix 1) (33). It classes comorbidities by organ system affected (14 organ systems), and rates them according to their severity from 0 to 4 (grade 1: mild problem, grade 2: problem of moderate severity requiring active therapy, grade 3: severe or constant disability, grade 4: extremely severe or urgent clinical problem), hereby taking into account total number as well as severity of comorbid conditions. Within each category, if two diseases are present, the disease with the highest severity is counted. We summarized as the number of grade 1-2 and grade 3-4 diseases.

2.2.9 Quality of life

Quality of life was assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) (118). The FACT-G has 27 questions, each of which is answered using a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). Questions measure the patients' health state over the last 7 days in four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being.

2.3 Methods

Main aim of this observational, monocentric study was to explore the added value of a CGA in older patients with haematological malignancies. Patients willing to participate were included after providing a written informed consent. All patients were assessed before start of therapy, 2 to 4 months later depending on the treatment schedule, and once again 6 months after inclusion. During assessment all questionnaires stated above were completed. In addition some questions were asked concerning social framework and sensory impairment. Our final reference CGA consisted of a set of six questionnaires: ADL, IADL, GDS-4, MMSE, MNA-SF and any falls in the previous year.

3. AIM OF THIS RESEARCH AND CHAPTER OVERVIEW

A significant increase has been seen in the number of older patients with cancer due to population ageing. One of the main challenges of treating older patients with cancer is to assess whether the expected benefits of treatment are superior to the risks in a population with decreased life expectancy and decreased tolerance to stress. In recent years research has mainly focused on solid tumours. The overall aim of this research was to explore whether in patients with haematologic malignancies a geriatric approach and the use of a comprehensive geriatric assessment might prove worthwhile in the selection of patients with a geriatric profile, in the detection of geriatric syndromes and in the prediction of patient outcomes.

In geriatric oncology, evidence suggests that a geriatric assessment identifies previously unknown geriatric problems in an individual. In haematology on the other hand, literature on the use of a CGA is scarce. In Chapter 2, the results of a geriatric assessment in older patients with a haematological malignancy are presented with focus on malnutrition and medication management in patients with polypharmacy. Furthermore their importance for this group of patients will be discussed.

This thesis will not only focus on the detection of geriatric syndromes, but also on a correct selection of patients with a geriatric profile, as the administration of a CGA is time- and staff-consuming. Therefore a two-step approach is proposed with the use of a screening tool to identify those patients that subsequently would benefit most from a CGA. Two different screening tools were evaluated. In Chapter 3 the performance of the G8 questionnaire as a screening tool for frailty in older patients with aggressive haematological malignancies is tested. Additional information is provided on the composition of a CGA, and more specifically on the relation between CGA and comorbidity. In Chapter 4, hand grip strength (HGS) is studied as a screening tool to detect frailty. Frailty is, among other things, characterized by a loss of skeletal muscle mass and strength (sarcopenia). Hand grip dynamometry is a valid and reliable tool to represent total body muscle strength. In addition, the prognostic value of HGS in patients with haematological malignancies is tested.

Finally, in Chapter 5, a summary is given of the main findings of the thesis, together with general concluding remarks.

An overview of the different studies, and the main research questions are described in table 4.

Table 4. Main research questions

Paper	Focus	Main research questions
Paper 1 (Chapter 2)	Nutritional assessment using the MNA-SF, in older patients with high-grade haematological malignancies	How is the baseline nutritional status ? What is the prevalence of malnutrition and risk for malnutrition? Which MNA-SF items are most frequently involved? Can BMI be used as a marker for nutritional problems ? Is nutritional screening by MNA-SF useful?
Paper 2 (Chapter 2)	Polypharmacy and functional autonomy in medication management	How does IADL independence evolve after start of therapy? Is there a change in independent medication management after start of therapy? Is there a correlation between independent medication management and polypharmacy? Is there a correlation between independent medication management and drug regimen complexity? Which medication regimen characteristics contribute to regimen complexity?
Paper 3 (Chapter 3)	G8 as a screening tool for CGA	What is the prevalence of an impaired score for the various CGA questionnaires? Can the G8 be validated as a screening tool to identify patients who would benefit from a CGA before start of therapy? What is the optimal cut-off point for likelihood of abnormal CGA?
Paper 4 (Chapter 4)	Hand grip strength as a screening tool for CGA	How is the muscle function at diagnosis? Can HGS be validated as a screening tool to identify patients who would benefit from a CGA before start of therapy? What are the optimal cut-of points for likelihood of abnormal CGA for both men and women? Is there an association between HGS and concurrent abnormal G8? Is there an association between HGS and subsequent adverse events during therapy? Is there an association between HGS and subsequent 6-month mortality?

MNA-SF = mini nutritional assessment – short form, BMI = body mass index.

IADL = instrumental activities of daily living, CGA = comprehensive geriatric assessment,

HGS = hand grip strength

Scoring Sheet

CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)

Miller, Paradis, and Reynolds 1991

PATIENT _____ AGE _____

RATER _____ DATE _____

Instructions: Please refer to the CIRS-G Manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use the reverse side for more writing space).

RATING STRATEGY

- 0 - No Problem
- 1 - Current mild problem or past significant problem
- 2 - Moderate disability or morbidity/requires "first line" therapy
- 3 - Severe/constant significant disability/"uncontrollable" chronic problems
- 4 - Extremely Severe/immediate treatment required/end organ failure/severe impairment in function

	SCORE
<u>HEART</u>	_____
<u>VASCULAR</u>	_____
<u>HEMATOPOIETIC</u>	_____
<u>RESPIRATORY</u>	_____
<u>EYES, EARS, NOSE AND THROAT AND LARYNX</u>	_____
<u>UPPER GI</u>	_____
<u>LOWER GI</u>	_____
<u>LIVER</u>	_____
<u>RENAL</u>	_____
<u>GENITOURINARY</u>	_____
<u>MUSCULOSKELETAL/INTEGUMENT</u>	_____
<u>NEUROLOGICAL</u>	_____
<u>ENDOCRINE/METABOLIC AND BREAST</u>	_____
<u>PSYCHIATRIC ILLNESS</u>	_____
<hr/>	
TOTAL NUMBER CATEGORIES ENDORSED.....	_____
TOTAL SCORE.....	_____
Severity Index: (total score/total number of categories endorsed).....	_____
Number of categories at level 3 severity.....	_____
Number of categories at level 4 severity.....	_____

Appendix 1. CIRS-G scoring sheet.

Miller et al. Psychiatry Research 1992; 41(3): 237-48

LAWTON - BRODY INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)			
Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).			
A. Ability to Use Telephone		E. Laundry	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
2. Dials a few well-known numbers	1	2. Launders small items-rinses stockings, etc.	1
3. Answers telephone but does not dial	1	3. All laundry must be done by others	0
4. Does not use telephone at all	0		
B. Shopping		F. Mode of Transportation	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		G. Responsibility for Own Medications	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		H. Ability to Handle Finances	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		Score	
		Total score	
A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.			

Appendix 2. Lawton IADL scale.

Lawton et al. Gerontologist 1969; 9(3): 179-186

REFERENCE LIST

- (1) Demography report 2010. European Commission; 2011.
- (2) Global Health and Ageing. [2014 [updated 19-6-2014]; Available from: http://www.nia.nih.gov/sites/default/files/global_health_and_aging.pdf.
- (3) Cancer Research UK. [2015 [updated 5-8-2015]; Available from: <http://www.cancerresearchuk.org/health-professional>.
- (4) Balducci L, Extermann M. Cancer and aging. An evolving panorama. *Hematol Oncol Clin North Am* 2000 Feb;14(1):1-16.
- (5) Causes of death in the EU28 in 2010
Circulatory diseases main cause of death for men and women aged 65 years and over. [Eurostat; 2013 [updated 1-12-2014]; Available from: <http://ec.europa.eu/eurostat/en/web/products-press-releases/-/3-28112013-AP>.
- (6) Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010 Nov 11;116(19):3724-34.
- (7) Balducci L, Stanta G. Cancer in the frail patient. A coming epidemic. *Hematol Oncol Clin North Am* 2000 Feb;14(1):235-50, xi.
- (8) Pollyea DA, Kohrt HE, Medeiros BC. Acute myeloid leukaemia in the elderly: a review. *British Journal of Haematology* 2011;152(5):524-42.
- (9) SEER 2008 - 2012. 2015. 27-5-2015. Ref Type: Internet Communication
- (10) Morrison VA, Hamlin P, Soubeyran P, Stauder R, Wadhwa P, Aapro M, et al. Diffuse large B-cell lymphoma in the elderly: impact of prognosis, comorbidities, geriatric assessment, and supportive care on clinical practice. An International Society of Geriatric Oncology (SIOG) expert position paper. *J Geriatr Oncol* 2015 Mar;6(2):141-52.
- (11) Oyama T, Yamamoto K, Asano N, Oshiro A, Suzuki R, Kagami Y, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. *Clin Cancer Res* 2007 Sep 1;13(17):5124-32.
- (12) Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. *Blood* 2010 Dec 9;116(24):5103-10.
- (13) Neukirchen J, Schoonen WM, Strupp C, Gattermann N, Aul C, Haas R, et al. Incidence and prevalence of myelodysplastic syndromes: data from the Dusseldorf MDS-registry. *Leuk Res* 2011 Dec;35(12):1591-6.
- (14) Ria R, Moschetta M, Reale A, Mangialardi G, Castrovilli A, Vacca A, et al. Managing myelodysplastic symptoms in elderly patients. *Clin Interv Aging* 2009;4:413-23.
- (15) Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma.(1474-5488 (Electronic)).
- (16) Alibhai SM, Leach M, Kermalli H, Gupta V, Kowgier ME, Tomlinson GA, et al. The impact of acute myeloid leukemia and its treatment on quality of life and functional status in older adults. *Crit Rev Oncol Hematol* 2007 Oct;64(1):19-30.
- (17) Bauduer F, Scribans C, Dubernet E, Capdupuy C. Evaluation of the nutritional status of patients over 60-year admitted in a hematology department using the mininutritional assessment (MNA). A single centre study of 120 cases. *J Nutr Health Aging* 2003;7(3):179-82.
- (18) Etienne A, Esterni B, Charbonnier A, Mozziconacci MJ, Arnoulet C, Coso D, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007 Apr 1;109(7):1376-83.
- (19) Giles FJ, Borthakur G, Ravandi F, Faderl S, Verstovsek S, Thomas D, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* 2007 Feb;136(4):624-7.
- (20) Kantarjian H, Ravandi F, O'Brien S, Cortes J, Faderl S, Garcia-Manero G, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood* 2010 Nov 25;116(22):4422-9.

- (21) Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia. *New England Journal of Medicine* 2009 Sep 24;361(13):1235-48.
- (22) Lee KW, Kim DY, Yun T, Kim DW, Kim TY, Yoon SS, et al. Doxorubicin-based chemotherapy for diffuse large B-cell lymphoma in elderly patients. *Cancer* 2003;98(12):2651-6.
- (23) Merli F, Luminari S, Rossi G, Mammi C, Marcheselli L, Tucci A, et al. Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. *Leuk Lymphoma* 2012 Apr;53(4):581-8.
- (24) Oran B, Weisdorf DG. Survival for older patients with AML: a population based study. *Haematologica* 2012 Jul 6.
- (25) Sekeres MA, Stone RM, Zahrieh D, Neuberg D, Morrison V, De Angelo DJ, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. *Leukemia* 2004 Feb 5;18(4):809-16.
- (26) Maartense E, Kluin-Nelemans HC, le CS, Kluin PM, Snijder S, Noordijk EM. Different age limits for elderly patients with indolent and aggressive non-hodgkin lymphoma and the role of relative survival with increasing age. *Cancer* 2000 Dec 15;89(12):2667-76.
- (27) Muffy LS, Kocherginsky M, Stock W, Chu Q, Bishop MR, Godley LA, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic celltransplantation recipients. *Haematologica* 2014 May 9.
- (28) Repetto L, Comandini D. Cancer in the elderly: assessing patients for fitness. *Crit Rev Oncol Hematol* 2000 Sep;35(3):155-60.
- (29) Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunanathan S, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007 Jul;62(7):731-7.
- (30) Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004 Mar;59(3):255-63.
- (31) Starfield B. Threads and Yarns: Weaving the Tapestry of Comorbidity. *The Annals of Family Medicine* 2006 Mar 1;4(2):101-3.
- (32) Abizanda P, Romero L, Sanchez-Jurado PM, Martinez-Reig M, Alfonso-Silguero SA, Rodriguez-Manas L. Age, frailty, disability, institutionalization, multimorbidity or comorbidity, which are the main targets in older adults? *J Nutr Health Aging* 2014;18(6):622-7.
- (33) Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, et al. Rating chronic medical illness burden in geropsychiatric practice and research: Application of the Cumulative Illness Rating Scale. *Psychiatry Research* 1992 Mar;41(3):237-48.
- (34) Extermann M. Measuring comorbidity in older cancer patients. *European Journal of Cancer* 2000 Mar;36(4):453-71.
- (35) Miller M, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). 1991. Ref Type: Generic
- (36) International Classification of Functioning, Disability and Health (ICF). [WHO; 2015 [updated 30-9-2015]; Available from: <http://www.who.int/classifications/icf/en/>.
- (37) Federal Disability Report: Seniors with Disabilities in Canada. [Government of Canada; 2013 [updated 4-9-2015]; Available from: http://www.esdc.gc.ca/eng/disability/arc/federal_report2011/index.shtml.
- (38) Fedarko NS. The biology of aging and frailty. *Clin Geriatr Med* 2011 Feb;27(1):27-37.
- (39) Gale CR, Cooper C, Aihie Sayer A. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age and Ageing* 2014 Oct 12.
- (40) Gobbens RJ, Luijckx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. *Nurs Outlook* 2010 Mar;58(2):76-86.
- (41) Stauder R. The challenge of individualised risk assessment and therapy planning in elderly high-risk myelodysplastic syndromes (MDS) patients. *Ann Hematol* 2012 Sep;91(9):1333-43.
- (42) Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;5(3):224-37.

- (43) Deschler B, Ihorst G, Platzbecker U, Germing U, Marz E, de FM, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. *Haematologica* 2013 Feb;98(2):208-16.
- (44) Saarelainen LK, Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, et al. Potentially inappropriate medication use in older people with cancer: Prevalence and correlates. *Journal of Geriatric Oncology*(0).
- (45) Rubenstein LZ. An overview of CGA: rationale, history, program models, basic components. In: Rubenstein LZ, Wieland GD, Bernabei R, editors. New York, NY: Springer; 1995.
- (46) Lipschitz S. Comprehensive geriatric assessment. *Continuing Medical Education* 2007;25(9):418-20.
- (47) Stuck AE, Siu AL, Wieland GD, Rubenstein LZ, Adams J. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *The Lancet* 1993 Oct 23;342(8878):1032-6.
- (48) Baztan JJ, Suarez-Garcia FM, Lopez-Arrieta J, Rodriguez-Manas L, Rodriguez-Artalejo F. Effectiveness of acute geriatric units on functional decline, living at home, and case fatality among older patients admitted to hospital for acute medical disorders: meta-analysis. *BMJ* 2009;338:b50.
- (49) Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. *SO: Cochrane Database of Systematic Reviews* 2011;(7).
- (50) Caplan GA, Williams AJ, Daly B, Abraham K. A Randomized, Controlled Trial of Comprehensive Geriatric Assessment and Multidisciplinary Intervention After Discharge of Elderly from the Emergency Department GÖThe DEED II Study. *J Am Geriatr Soc* 2004;52(9):1417-23.
- (51) Nikolaus T, Specht-Leible N, Bach M, Oster P, Schlierf G. A randomized trial of comprehensive geriatric assessment and home intervention in the care of hospitalized patients. *Age Ageing* 1999 Oct;28(6):543-50.
- (52) Aaldriks AA, Maartense E, le Cessie S, Giltay EJ, Verlaan HACM, van der Geest LGM, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Critical Reviews in Oncology/Hematology* 2011;79(2):205-12.
- (53) Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. *J Clin Oncol* 2011 Sep 20;29(27):3636-42.
- (54) Chaibi P, Magne N, Breton S, Chebib A, Watson S, Duron JJ, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. *Crit Rev Oncol Hematol* 2011 Sep;79(3):302-7.
- (55) Hurría A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *Journal of Clinical Oncology* 2011 Sep 1;29(25):3457-65.
- (56) Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen HO, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Critical Reviews in Oncology/Hematology* 2010 Dec;76(3):208-17.
- (57) Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Annals of Oncology* 2013 May 1;24(5):1306-12.
- (58) Marengo D, Marinello R, Berruti A, Gaspari F, Stasi MF, Rosato R, et al. Multidimensional geriatric assessment in treatment decision in elderly cancer patients: 6-year experience in an outpatient geriatric oncology service. *Critical Reviews in Oncology/Hematology* 2008 Nov;68(2):157-64.
- (59) Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002 Jan 15;20(2):494-502.
- (60) Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C, et al. Predictors of Early Death Risk in Older Patients Treated With First-Line Chemotherapy for Cancer. *J Clin Oncol* 2012 Apr 16.
- (61) Deschler B, Ihorst G, Platzbecker U, Germing U, M+nrz E, de Figuerido M, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. *Haematologica* 2013 Feb 1;98(2):208-16.

- (62) Maione P, Perrone F, Gallo C, Manzione L, Piantedosi F, Barbera S, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. *J Clin Oncol* 2005 Oct 1;23(28):6865-72.
- (63) Oliva EN, Nobile F, Alimena G, Ronco F, Specchia G, Impera S, et al. Quality of life in elderly patients with acute myeloid leukemia: patients may be more accurate than physicians. *Haematologica* 2011 May 1;96(5):696-702.
- (64) Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Ellis LR, et al. The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. *J Am Geriatr Soc* 2011 Oct;59(10):1837-46.
- (65) Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 2013 May 23;121(21):4287-94.
- (66) Wedding U, Rohrig B, Klippstein A, Fricke HJ, Sayer HG, Hoffken K. Impairment in functional status and survival in patients with acute myeloid leukaemia. *J Cancer Res Clin Oncol* 2006 Oct;132(10):665-71.
- (67) Winkelmann N, Petersen I, Kiehnkopf M, Fricke HJ, Hochhaus A, Wedding U. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. *J Cancer Res Clin Oncol* 2011 Apr;137(4):733-8.
- (68) Nabhan C, Smith SM, Helenowski I, Ramsdale E, Parsons B, Karmali R, et al. Analysis of very elderly (≥80-åyears) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *British Journal of Haematology* 2012;156(2):196-204.
- (69) Tucci A, Martelli M, Rigacci L, Riccomagno P, Cabras MG, Salvi F, et al. Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL). *Leukemia & Lymphoma* 2014 Aug 11;56(4):921-6.
- (70) Deschler B, Ihorst G, Lubbert M. Effects of different treatments on geriatric assessment and quality of life parameters in elderly MDS/AML patients. *Haematologica* 95[s2], 189. 2010. Ref Type: Abstract
- (71) Extermann M, Wedding U. Comorbidity and geriatric assessment for older patients with hematologic malignancies: A review of the evidence. *Journal of Geriatric Oncology* 2012 Jan;3(1):49-57.
- (72) Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. *Ann Hematol* 2014 Jun;93(6):1031-40.
- (73) Soubeyran P, Bellera C, Goyard J, Heitz D, Cure H, Rousselot H, et al. Validation of the G8 screening tool in geriatric oncology: The ONCODAGE project. *ASCO Meeting Abstracts* 2011 Jun 9;29(15_suppl):9001.
- (74) Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *Journal of Geriatric Oncology* 2013 Jan;4(1):32-8.
- (75) Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *The Lancet Oncology* 2012 Oct;13(10):e437-e444.
- (76) Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. *Surgical Oncology* 2010 Sep;19(3):117-23.
- (77) Hurria, A., Wildes, T., Baumgartner, J., Browner, I., Burhenn, P., Cohen, H. J., deShazo, M., Dotan, E., Edil, B., Extermann, M., Bergman, M., Ganti, A., Gross, A., Holmes, H., Hubbard, J., Jagsi, R., Keating, N., Korc-Grodzicki, B., McKoy, J., Medeiros, Bruno C., Mrozek, E., O'Connor, T., Rugo, H., Rupper, R., Silliman, R., Stirewalt, D., Tew, William P., Walter, Louise C., and Weir, A. NCCN Clinical Practice Guidelines in Oncology - Senior Adult Oncology. [National Comprehensive Cancer Network; 2015 [updated 11-2-2015]; version 1.2015 [Available from: http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf.
- (78) Mato A, Feldman T, Richter J, Siegel DS, Goy A. Liquid tumors in the elderly. *Clin Geriatr Med* 2012 Feb;28(1):115-52.
- (79) Kristjansson SR, Wyller TB. Introduction. In: Schrijvers D, Aapro M, Zakotnik B, Audisio R, Van Halteren H, Hurria A, editors. *ESMO handbook of cancer in the senior patient*. first ed. Informa Healthcare; 2010. p. 1-7.

- (80) Noens L. Geriatrics and haematological malignancies: is comprehensive geriatric assessment a useful tool? *European Journal of Cancer* 2011 Sep;47, Supplement 3(0):S362-S363.
- (81) Fields PA, Linch DC. Treatment of the elderly patient with diffuse large B cell lymphoma. *British Journal of Haematology* 2012;157(2):159-70.
- (82) Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer* 2009;115(19):4547-53.
- (83) Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Annals of Oncology* 2014 Nov 17.
- (84) Balducci L. The geriatric cancer patient: equal benefit from equal treatment. *Cancer Control* 2001 Mar;8(2 Suppl):1-25.
- (85) Bellera C, Praud D, Petit-Moneger A, McKelvie-Sebileau P, Soubeyran P, Mathoulin-Pelissier S. Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: a systematic review. *Cancer Treat Rev* 2013 Nov;39(7):812-7.
- (86) Krug U, Buchner T, Berdel WE, Muller-Tidow C. The treatment of elderly patients with acute myeloid leukemia. *Dtsch Arztebl Int* 2011 Dec;108(51-52):863-70.
- (87) Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol* 2011 Feb 10;29(5):487-94.
- (88) Alibhai SM, Breunis H, Timilshina N, Brignardello-Petersen R, Tomlinson G, Mohamedali H, et al. Quality of life and physical function in adults treated with intensive chemotherapy for acute myeloid leukemia improve over time independent of age. *J Geriatr Oncol* 2015 May 2.
- (89) Ossenkoppele G, L'Aménil B. How I treat the older patient with acute myeloid leukemia. *Blood* 2014 Dec 16;125(5):767-74.
- (90) Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007 Mar 1;109(5):1857-61.
- (91) Advani RH, Chen H, Habermann TM, Morrison VA, Weller EA, Fisher RI, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). *Br J Haematol* 2010 Oct;151(2):143-51.
- (92) Lindenmeyer LP, Hegele V, Caregnato JP, Wust D, Grazziotin L, Stoll P. Follow-up of patients receiving rituximab for diffuse large B cell lymphoma: an overview of systematic reviews. *Ann Hematol* 2013 Nov;92(11):1451-9.
- (93) Peyrade F, Jardin F, Thiebtemont C, Thyss A, Emile JF, Castaigne S, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet Oncology* 2011 May;12(5):460-8.
- (94) Visani G, Ferrara F, Alesiani F, Ronconi S, Catarini M, D'adamo F, et al. R-COMP 21 for frail elderly patients with aggressive B-cell non-Hodgkin lymphoma: a pilot study. *Leuk Lymphoma* 2008 Jun;49(6):1081-6.
- (95) Bachy E, Salles G. Treatment approach to newly diagnosed diffuse large B-cell lymphoma. *Semin Hematol* 2015 Apr;52(2):107-18.
- (96) Monfardini S, Aversa SM, Zoli V, Salvagno L, Bianco A, Bordonaro R, et al. Vinorelbine and prednisone in frail elderly patients with intermediate-high grade non-Hodgkin's lymphomas. *Ann Oncol* 2005 Aug;16(8):1352-8.
- (97) Spina M, Balzarotti M, Uziel L, Ferreri AJ, Fratino L, Magagnoli M, et al. Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. *Oncologist* 2012;17(6):838-46.
- (98) Olivieri A, Gini G, Bocci C, Montanari M, Trappolini S, Olivieri J, et al. Tailored therapy in an unselected population of 91 elderly patients with DLBCL prospectively evaluated using a simplified CGA. *Oncologist* 2012;17(5):663-72.
- (99) Horn J, Kleber M, Hieke S, Schmitt-Graff A, Wasch R, Engelhardt M. Treatment option of bendamustine in combination with rituximab in elderly and frail patients with aggressive B-non-Hodgkin lymphoma: rational, efficacy, and tolerance. *Ann Hematol* 2012 Oct;91(10):1579-86.
- (100) Estephan F, Tiu RV. Current and novel therapeutic approaches in myelodysplastic syndromes. *J Community Support Oncol* 2014 Jul;12(7):236-49.

- (101) Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sol+® F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. *Blood* 2012 Jun 27;120(12):2454-65.
- (102) Deschler B, Binek K, Ihorst G, Marks R, W+ñsch R, Bertz H, et al. Prognostic Factor and Quality of Life Analysis in 160 Patients Aged 60 Years with Hematologic Neoplasias Treated with Allogeneic Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation* 2010 Jul;16(7):967-75.
- (103) McClune BL, Weisdorf DJ, Pedersen TL, Tunes da Silva G, Tallman MS, Sierra J, et al. Effect of Age on Outcome of Reduced-Intensity Hematopoietic Cell Transplantation for Older Patients With Acute Myeloid Leukemia in First Complete Remission or With Myelodysplastic Syndrome. *Journal of Clinical Oncology* 2010 Apr 10;28(11):1878-87.
- (104) Chevallier P, Szydlo RM, Blaise D, Tabrizi R, Michallet M, Uzunov M, et al. Reduced-Intensity Conditioning before Allogeneic Hematopoietic Stem Cell Transplantation in Patients Over 60 Years: A Report from the SFGM-TC. *Biology of Blood and Marrow Transplantation* 2012 Feb;18(2):289-94.
- (105) Bokhari SW, Watson L, Nagra S, Cook M, Byrne JL, Craddock C, et al. Role of HCT-comorbidity index, age and disease status at transplantation in predicting survival and non-relapse mortality in patients with myelodysplasia and leukemia undergoing reduced-intensity-conditioning hemopoietic progenitor cell transplantation. *Bone Marrow Transplant* 2012 Apr;47(4):528-34.
- (106) Pulte D, Gondos A, Brenner H. Improvement in Survival of Older Adults with Multiple Myeloma: Results of an Updated Period Analysis of SEER Data. *The Oncologist* 2011 Nov 1;16(11):1600-3.
- (107) Wildes TM, Rosko A, Tuchman SA. Multiple myeloma in the older adult: better prospects, more challenges. *J Clin Oncol* 2014 Aug 20;32(24):2531-40.
- (108) Moreau P, San MJ, Ludwig H, Schouten H, Mohty M, Dimopoulos M, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013 Oct;24 Suppl 6:vi133-vi137.
- (109) Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014 May;28(5):1122-8.
- (110) Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood* 2015 Mar 26;125(13):2068-74.
- (111) Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970;10(1):20-30.
- (112) Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86.
- (113) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982 Dec;5(6):649-55.
- (114) Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin Geriatr Med* 2002 Nov;18(4):737-57.
- (115) van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Br J Gen Pract* 1995 Apr;45(393):195-9.
- (116) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov;12(3):189-98.
- (117) Persad CC, Cook S, Giordani B. Assessing falls in the elderly: should we use simple screening tests or a comprehensive fall risk evaluation? *Eur J Phys Rehabil Med* 2010 Jun;46(2):249-59.
- (118) Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79.

Chapter 2

COMPREHENSIVE GERIATRIC ASSESSMENT

EVALUATION OF THE NUTRITIONAL STATUS IN OLDER PATIENTS WITH AGGRESSIVE HAEMATOLOGICAL MALIGNANCIES USING THE MNA-SF

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EVALUATION OF THE NUTRITIONAL STATUS IN OLDER PATIENTS WITH AGGRESSIVE HAEMATOLOGICAL MALIGNANCIES USING THE MNA-SF

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ABSTRACT

Background: Malnutrition is common both after the age of 70 and in many types of cancer, being responsible for poor quality of life, poor treatment response and a shorter survival time. Patients with haematological malignancies face specific challenges regarding nutrition because of intensive treatments they endure. Early detection of nutritional problems is important to allow interventions.

Objectives: to assess the nutritional status of a group of older patients with aggressive haematological malignancies before the onset of systemic therapy using the MNA-SF.

Setting: the haematology department of a university hospital

Participants: patients, ≥ 70 years, with newly diagnosed aggressive haematological malignancies

Methods: observational single centre study. Patients were screened for malnutrition before and two months after start of therapy using the Mini Nutritional Assessment Short Form (MNA-SF).

Results: Seventy patients were included. Mean age was 77.4 ± 4.7 years (range 70.0-91.0). At baseline, 20% (CI95 = 11-31%) were malnourished and 61% (CI95 = 49-73%) were at risk for malnutrition. Recent weight loss and declined food intake were the most recorded MNA-SF parameters. Mean Body Mass Index (BMI) was 26.3 ± 4.1 (range 19.8 - 41.1) and 41% (n=29) of patients had a BMI < 25 .

Conclusions: Using the MNA-SF, most of older patients with an aggressive haematological malignancy are at risk for malnutrition. Therefore, nutritional assessment with individualized dietary advice and follow-up during treatment should be recommended as an integrated part of the treatment plan.

INTRODUCTION

Malnutrition is frequent after 70 years of age due to inadequate dietary intake and particularly protein intake. Causes of poor nutritional status in older people are multi-factorial and include the physiological, psychological and social changes associated with aging which affect food intake and body weight⁽¹⁾. Nutritional screening aims to identify, in a simple and non-invasive way, those patients who may be at risk for malnutrition⁽²⁾.

Studies in community-dwelling older persons, using the Mini Nutritional Assessment (MNA), show that between 0 and 2% are malnourished and between 15% and 44% are at risk for malnutrition⁽³⁾. The prevalence of malnutrition amongst patients with cancer depends on the tumour type, location, stage and treatment. However, this prevalence has not been well established in the specific case of onco-haematological patients. Patients with haematological malignancies face specific challenges associated with eating and nutrition because of the intensive and aggressive treatments they endure^(4;5).

In this study we wanted to assess the nutritional status of a group of older patients with aggressive haematological malignancies using the MNA-SF.

MATERIALS AND METHODS

Patients

Between July 2011 and October 2013 all patients, 70 years or older, with a new diagnosis of Acute Myeloid Leukaemia (AML), intermediate or high grade Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM) or high grade Non Hodgkin Lymphoma (NHL), referred to the haematology department of a university hospital, were asked to participate in this observational monocentric study. All participants provided written consent. The study was approved by the local Ethics Committee.

Nutritional screening

Before the start of therapy all patients were screened for malnutrition by means of the MNA Short Form (MNA-SF). Nutritional screening was repeated two to four months later, depending on the treatment schedule. The MNA-SF is a simple, well-validated screening tool for malnutrition in older persons and is recommended for early detection of risk for malnutrition⁽³⁾. The MNA-SF incorporates three cut-off points for nutritional status, thus allowing the identification of those who are normally nourished (≥ 12), at risk for malnutrition⁽⁸⁻¹¹⁾, or malnourished (≤ 7).

Statistical methods

Descriptive analyses were performed to summarize patient and treatment characteristics. Continuous variables were expressed as mean \pm standard deviation (SD) (range). Countable variables were presented as absolute number (n) and percentage (%) of the study population. Additionally 95% confidence intervals (CI95) were computed. All analyses were performed in Medcalc® Version 12.7.0.0 (Medcalc Software bvba).

Table 1. Baseline characteristics of the patients

Characteristics	
Sex, n (%)	
Male	36 (51)
Female	34 (49)
Age (years), n (%)	
<75	22 (31)
75-80	28 (40)
>80	20 (29)
ECOG performance status, n (%)	
0-1	46 (66)
2-4	24 (34)
Diagnosis, n (%)	
AML	22 (31)
NHL	28 (40)
MDS	11 (16)
MM	9 (13)
Number of comorbidities, mean (range)	
Grade 1 – 2 [‡]	3 (0 – 8)
Grade 3 – 4 [‡]	2 (1 – 5)
Weight (kg), mean (range)	73.3 (50.0 – 117.0)
BMI, mean (range)	26.3 ± 4.1 (19.8 – 41.1)
> 3 medications, n (%)	46 (66)
Patients with MMSE < 24, n (%)	3 (4.8)
Patients dependent in IADL, n (%)	29 (41.4)

ECOG = Eastern Cooperative Oncology Group, AML = Acute Myeloid Leukaemia, NHL = Non-Hodgkin Lymphoma, MDS = Myelodysplastic Syndrome, MM = Multiple Myeloma, BMI = Body Mass Index
[‡] grade 1: mild problem, grade 2: problem of moderate severity requiring active therapy, grade 3: severe or constant disability, grade 4: extremely severe or urgent clinical problem
 MMSE = mini mental state examination
 IADL = instrumental activities of daily living

RESULTS

Seventy patients were included. Mean age was 77.4 ± 4.7 years (range 70.0-91.0). Baseline patient characteristics are summarized in table 1.

At baseline, 20% (CI95 = 11-31%) of the patients (n=14), assessed by MNA-SF, were malnourished and 61% (CI95 = 49-73%) of the patients (n=43) were at risk for malnutrition. Recent weight loss (63%, n=44) and declined food intake (49%, n=34) were the most recorded MNA-SF parameters. Mean BMI was 26.3 ± 4.1 (range 19.8 – 41.1) and 41% (n=29) of all patients had a BMI < 25.

DISCUSSION

Our first research question addressed the baseline nutritional status of a group of older patients with aggressive haematological malignancies. Older people who are already malnourished at home may additionally be at a disadvantage in the presence of cancer. Using the MNA-SF, we found a high percentage of individuals at risk for malnutrition in this group of older onco-haematological patients. Only few studies have been conducted on the prevalence of malnutrition or risk for malnutrition in older patients with haematological diseases^(6; 7). Bauduer et al. randomly tested 120 patients, treated for miscellaneous blood disorders, the day of their admission to either the out- or inpatient clinic, by means of the MNA. They found a prevalence of malnutrition of 13%. Our results with 20% of malnourished patients are in concordance with the findings of the aforementioned study. In contrast, about 50% of their patients were free of nutritional problems compared to 19% in our patient group. However, Bauduer et al. included patients with non-malignant haematological problems and indolent malignancies. We included only patients with an aggressive haematological malignancy. Moreover, mean age in our study population was higher (74.6 years vs. 77.4 years)⁽⁶⁾.

Malnutrition in older patients with cancer is associated with negative outcomes including increased morbidity, poor quality of life, poor response to and tolerance of chemotherapy, a shorter survival time and increased healthcare costs⁽²⁾. In our study, recent weight loss and diminished food intake were the most prevalent MNA-SF items indicating (risk for) malnutrition. In general, in patients with cancer, baseline weight loss is associated with poorer survival, reduced likelihood of complete response to treatment and poorer quality of life⁽⁸⁾. Tubiana et al. have shown that weight loss greater than 10% of body weight in the previous six months was associated with a shorter survival in patients with Hodgkin's Disease⁽⁹⁾. In a large study of 3047 patients enrolled in 12 chemotherapy protocols of the Eastern Cooperative Oncology Group, median survival was significantly shorter for the patients with weight loss. Among haematological malignancies, this observation was true for NHL (favourable as well as non-favourable) but not for AML cases. In these AML

cases survival was very short in all patients regardless of weight loss. In these patients other factors were more important than weight loss in determining survival. In patients with unfavourable NHL the median survival was approximately twice as long in those with no weight loss as in those with weight loss. Moreover, in this study was shown that even small amounts of weight loss (less than 5 percent of body weight) may significantly worsen prognosis. Patients with weight loss respond poorly to chemotherapy and experience increased toxicity. In addition, reduced functional capacity and performance status contribute to a lower quality of life⁽¹⁰⁾. In addition, qualitative research among haematological patients indicated that issues surrounding food and eating are considered to be of great significance both for patients and for their caregivers. The significance of food is not seen purely in relation to its nutritional value, but as an important quality of life issue⁽⁵⁾.

Once patients are identified through screening to be at moderate or high risk, a comprehensive nutritional assessment follows. A nutritional assessment incorporates anthropometric measurements, laboratory tests, medical history, clinical indicators, current and planned medications, a detailed dietary history and a functional assessment including physical activity⁽¹¹⁾. An in-depth nutritional evaluation is time-consuming and requires a skilled dietician, preferably with an expertise in oncology. Therefore nutritional assessment might be difficult to implement in many settings. However, 81% of our patients already scored positive on MNA-SF at the time of diagnosis. Therefore systematic screening in older patients with an aggressive haematological malignancy, using the MNA-SF, does not seem to provide an added value since nutritional assessment would be necessary in a large majority of the patients. Consequently, in this group of patients, nutritional assessment should be considered as a first step approach. Gómez-Candela et al. recommend nutritional assessment instead of nutritional screening as a first step approach for those onco-haematological diagnoses where anti-neoplastic therapy is associated with a moderate to high nutritional risk⁽⁴⁾. As we selected patients facing an aggressive anticancer therapy, our findings are in line with these recommendations.

In our study, recent weight loss and declined food intake were the most prevalent MNA-SF items indicating (risk for) malnutrition. In routine clinical practice BMI is still often used as a measure for malnutrition. Only 41% of our patients had a BMI < 25. A low BMI indicates chronic malnutrition, whereas unintentional weight loss indicates a more acute deterioration of nutritional status as can be expected in patients with an aggressive malignancy⁽¹²⁾. In high grade malignancies, nutritional screening based on BMI will result in a delay in the start of nutritional support and thereby endanger patient's outcome.

To our knowledge, this is the first report on the baseline nutritional status in a group of older patients with a diagnosis of an aggressive haematological malignancy. Based on the MNA-SF, nutritional risk appears high in older patients, apart from anti-neoplastic therapy. Therefore, nutritional assessment with individualized dietary advice and follow-up during treatment is preferable. In order to overcome a lack of attention from hospital staff, nutritional assessment performed by a dietician, pre-

ferably with experience in the field of haematology, needs to become an integrated part of the treatment plan of a patient.

Our study had several limitations. First, there might have been a referral bias. Only 41% (n=29) of our patients was dependent in Instrumental Activities of Daily Living (IADL) and only 4% (n=3) of them had an abnormal Mini Mental State Examination (MMSE) score (< 24) at baseline. This is considerably less than what can be found in the literature⁽¹³⁾. As a tertiary centre, a significant number of patients are referred from other hospitals. Referring physicians may have considered older patients with physical, cognitive or emotional problems no longer candidates for aggressive therapy. On the other hand, the risk of being malnourished would be even higher when these patients were included. Second, the sample size was relatively small due to the patients' fragile condition, possible referral bias and the reluctance to participate in a clinical study. The latter improved once geriatric evaluation was introduced as "standard of care" for all haematological patients above the age of 70. Third, one can argue that some items of the MNA short form scale can be altered by the haematological disease more than by malnutrition, since the MNA-SF has not been validated to detect malnutrition in haematological patients. Lastly, at this moment, we have no information on the impact of nutritional assessment as a first step approach on the outcome of our patients or their quality of life. This will be the subject of a future study.

In summary, these results demonstrate that most of the older patients with a haematological malignancy facing aggressive therapy are malnourished or at risk for malnutrition. Therefore, we recommend nutritional assessment by a dietician with individualized dietary advice and follow-up during treatment to become an integrated part of the treatment plan in this group of older patients.

REFERENCE LIST

- (1) Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009;(2):CD003288.
- (2) Santaripa L, Contaldo F, Pasanisi F. Nutritional screening and early treatment of malnutrition in cancer patients. *J Cachexia Sarcopenia Muscle* 2011 Mar;2(1):27-35.
- (3) Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin Geriatr Med* 2002 Nov;18(4):737-57.
- (4) Gomez-Candela C, Canales Albendea MA, Palma MS, de Paz AR, Diaz GJ, Rodriguez-Duran D, et al. Nutritional intervention in oncohematological patient. *Nutr Hosp* 2012 May;27(3):669-80.
- (5) McGrath P. Reflections on Nutritional Issues Associated with Cancer Therapy. *Cancer Practice* 2002 Mar 1;10(2):94-101.
- (6) Bauduer F, Scribans C, Dubernet E, Capdupuy C. Evaluation of the nutritional status of patients over 60-year admitted in a hematology department using the mininutritional assessment (MNA). A single centre study of 120 cases. *J Nutr Health Aging* 2003;7(3):179-82.
- (7) Horsley P, Bauer J, Gallagher B. Poor nutritional status prior to peripheral blood stem cell transplantation is associated with increased length of hospital stay. *Bone Marrow Transplant* 2005 Jun;35(11):1113-6.
- (8) Baldwin C, Spiro A, Ahern R, Emery PW. Oral Nutritional Interventions in Malnourished Patients With Cancer: A Systematic Review and Meta-Analysis. *Journal of the National Cancer Institute* 2012 Mar 7;104(5):371-85.
- (9) Tubiana M, Attie E, Flamant R, Gerard-Marchant R, Hayat M. Prognostic factors in 454 cases of Hodgkin's disease. *Cancer Res* 1971 Nov;31(11):1801-10.
- (10) Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* 1980 Oct;69(4):491-7.
- (11) Kumar NB. Assessment of Malnutrition and Nutritional Therapy Approaches in Cancer Patients. *Nutritional Management of Cancer Treatment Effects*. Springer Berlin Heidelberg; 2012. p. 7-41.
- (12) Neelemaat F, Meijers J, Kruizenga H, van Ballegooijen H, van Bokhorst-de van der Schueren M. Comparison of five malnutrition screening tools in one hospital inpatient sample. *Journal of Clinical Nursing* 2011 Aug 1;20(15-16):2144-52.
- (13) Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007 May 10;25(14):1824-31.

LOSS OF FUNCTIONAL AUTONOMY IN MEDICATION MANAGEMENT AFTER START OF THERAPY IN OLDER PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Purpose: Guidelines on older cancer patients recommend a comprehensive geriatric assessment, preferably including an item on medication management since cancer treatment further increases risks of polypharmacy. So far, little attention is given to non-adherence due to functional changes. We aimed to assess autonomy in drug self-administration after start-up of therapy in older patients with haematological malignancies. In case of inadequate compliance, we tried to identify the causes.

Methods: Longitudinal single centre cohort study in patients ≥ 70 years. Patients underwent a geriatric evaluation before and two months after start of therapy. Medication was registered both times.

Results: Sixty-two patients, median age 77 years, were included. At baseline 49 patients (79%) took their long-term medication independently. Independent medication management was significantly higher in patients taking <5 medications (93.7% vs. 63.3%, $p < 0.005$). After start of therapy, polypharmacy rates increased from 48.3% to 98.3% ($n=61$) while 55.6% of the initially independent patients became dependent for medication management. The median increase in the number of medications was significantly higher in dependent patients (6 vs. 4.5, $p < 0.05$). Multiple daily doses (80%, $n=50$), varying doses (59.7%, $n=37$) and medication splitting (45.3%, $n=27$) further contributed to regimen complexity. Unlike results at baseline, no correlations were found between autonomy in medication management and medication regimen two months after therapy start-up.

Conclusion: Haematological patients have to face a wide turnover of chemo drugs to treat malignancies. A considerable number of them require assistance in drug administration during time: attention has to be paid to patient compliance, and improving it, highlighting the challenges of an ambulatory setting.

INTRODUCTION

The incidence rates of haematological malignancies increase steadily with age. Treating older patients suffering from aggressive haematological malignancies is becoming a challenging task for all caregivers involved, since the heterogeneity of the aging process is characterised by marked variability in the rate of functional loss, both between and within individuals^(1,2). However, chronological age does not reflect

these individual differences and therefore is not a good predictor of remaining functional reserves or life expectancy. Guidelines on older cancer patients, such as those from the National Comprehensive Cancer Network (NCCN) or the International Society of Geriatric Oncology (SIOG), recommend the use of a Comprehensive Geriatric Assessment (CGA) as a multidimensional, interdisciplinary diagnostic process focusing on determining a frail older person's physical, psychological and functional capabilities⁽³⁻⁵⁾. Although no gold standard exists, there is consensus that the CGA should include functional, cognitive, emotional and psychosocial status as well as the aspects of nutrition, mobility and polypharmacy, in addition to comorbidity assessment⁽⁶⁾.

Polypharmacy schedules involving five or more drugs, with increased drug regimen complexity and risk of adverse drug reactions (ADRs), drug-drug interactions (DDI), inappropriate self-medication and poor drug adherence are an area of concern, especially in older patients. In the older cancer cohort, chemotherapy and supportive drugs to prevent side-effects or treat symptoms additionally increase the risks and complications of polypharmacy. Guidelines recommend reviewing the number and the type of medications in all patients and, in case of more than three medications, looking for duplications, interactions, and non-adherence⁽⁶⁾. Studies on the optimization of geriatric pharmacotherapy focus most commonly on pharmacological outcomes and prognosis, ADRs and potentially inappropriate medication. However, little attention has so far been paid to (unintentional) non-adherence due to functional problems or changes, despite the well-known fact that older patients experience a gradual decline in their cognitive and functional abilities which are required for medication management.

Although a CGA, as a multidimensional diagnostic process, generally includes an evaluation of functional, cognitive, emotional and psychosocial status as well as the aspects of nutrition, mobility and polypharmacy, the assessment tools included may differ widely. Nevertheless, most CGAs currently used in studies do not include an item on medication management, except for one item in the Lawton Instrumental Activities of Daily Living Scale (IADL)⁽⁷⁾. Apart from "taking medication as prescribed", seven more independent living skills are assessed. For each of these skills one can identify the overall social and autonomous patient function at time 0 and whether an improvement or deterioration follows upon it.

In our study population, based on IADL assessment during treatment, we aimed to assess autonomy in medication management after the start of therapy in older patients with a haematological malignancy. Additionally, in cases of deterioration, we aimed to search for predetermining factors.

MATERIALS AND METHODS

Patients

This was a longitudinal single centre cohort study. All patients aged 70 years or older with a new diagnosis of Acute Myeloid Leukaemia (AML), intermediate or high

grade Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM) or high grade Non Hodgkin Lymphoma (NHL) who were referred to the haematology department of a tertiary hospital between June 2011 and January 2013, were asked to participate in the current study. All participants provided written consent. The study was approved by the local Ethics Committee.

Geriatric evaluation

Before chemotherapy administration all patients underwent Comprehensive Geriatric Assessment (CGA) by a member of the geriatric team. Since no gold standard exists, our CGA consisted of a set of six questionnaires, i.e. Activities of Daily Living (ADL) (8), Instrumental Activities of Daily Living (IADL) (7), 4-item Geriatric Depression Scale (GDS-4) (9), Mini Mental State Examination (MMSE) (10), Mini Nutritional Assessment – Short Form (MNA-SF)(11), and any falls in the previous year. Comorbidity was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). In addition, patients were asked some questions on social and financial items. This geriatric evaluation was repeated two to four months later, depending on the treatment schedule.

The Lawton IADL Scale, based on self-reporting, is validated in older people to assess independent living skills, at a given moment as well as over a certain period of time. There are 8 domains of function measured: ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Each item is rated dichotomously (0=less able, 1=more able) according to the highest level of functioning in that category. Specifically for medication intake patients score 1 point only when they are able to manage their medication completely independently. If someone else is preparing the medication in advance, a patient is scoring 0 points, even if he/she is taking his/her pills autonomously throughout the day.

Medication review

Habitual medication was registered on entrance in the study and two months later. Medication lists, as written down in the letter to the treating general practitioner, were reviewed shortly after the start of therapy. Polypharmacy was defined as \geq 5 medications. In the initial design of the study (and thus before the results of IADL were available) eye-drops, mouth rinses and topical creams were not taken into consideration as these products were unlikely to produce a systemic effect. Neither did we count "as needed" medication as it was not known whether or not the patient was taking this medication.

Statistical methods

Descriptive analyses were performed to describe patients' characteristics and geriatric evaluation results. Continuous variables were expressed as median and range. Countable variables were presented as absolute number (n) and percentage (%) of the

study population. To assess differences between categories, the Pearson chi-square test was used. Univariate logistic regression analysis was used to identify medication regimen characteristics associated with (in)dependent medication management. All analyses were performed in Medcalc® Version 12.7.0.0 (Medcalc Software bvba).

RESULTS

Sixty two patients were included in the study. Baseline characteristics are presented in table 1. Median age was 77 years (range 70-91). The results of the geriatric evaluation as well as changes in IADL over time are presented in table 2. At baseline 49 patients (79%) took their chronic medication without any assistance. Independent medication management was significantly higher in the group of patients taking less than 5 medications (93.8% vs. 63.3%, $p < 0.005$). Two months after the start of therapy 8 patients died and 6 were lost to follow-up. Of the formerly independent patients, 55.6% (20 of the remaining 36) needed assistance for their medication.

Table 1. Baseline characteristics of the patients (N=62)

Sex, n (%)	
Male	30 (48.4)
Female	32 (51.6)
Age (years), n (%)	
<75	19 (30.6)
75-80	26 (41.9)
>80	17 (27.4)
Diagnosis, n (%)	
Acute Myeloid Leukaemia	16 (25.8)
High Grade Lymphoma	24 (38.7)
Myelodysplastic Syndrome	12 (19.4)
Multiple Myeloma	7 (11.3)
Number of comorbidities, median (range)	
Grade 1 - 2 [£]	4 (0 - 9)
Grade 3 - 4 ^{§,£}	1 (0 - 4)

[§] current haematological diagnosis not included

[£] grade 1: mild problem, grade 2: problem of moderate severity requiring active therapy, grade 3: severe or constant disability, grade 4: extremely severe or urgent clinical problem

Table 2. Results of the geriatric evaluation (N=62)

Living status, n (%)	
Alone	24 (38.7)
Living with spouse	33 (53.2)
Living with family member (other than spouse)	4 (6.5)
Long term care facility	1 (1.6)
"Do you expect financial problems because of your disease?", n (%)	
Yes	4 (6.5)
No	58 (93.5)
Patients with MMSE ^f < 24, n (%)	3 (4.8)
Number of patients (N=46) with decline from baseline in individual IADL-items, n (%)	
Ability to use telephone	1 (2.2)
Shopping	13 (43.3)
Food preparation	9 (33.3)
Housekeeping	12 (33.3)
Laundry	13 (46.4)
Mode of transportation	12 (41.4)
Responsibility for own medications	20 (55.6)
Ability to handle finances	2 (4.4)

^f Mini Mental State Examination

Polypharmacy was being administered in 48.4% of patients (n =30) at the time of diagnosis and increased to 98.3% (n=61) during follow-up. Likewise, the intake increased from a median of 4 (0-10) medications to a median of 9 (4-16) medications and 11 (4-22) pills a day. In patients dependent for medication management at baseline, the median increase in the number of medications was significantly higher than in their independent counterparts (6 vs. 4.5, $p<0.05$). The medication regimen characteristics are presented in table 3. Unlike results at baseline, no correlations were found between autonomy in medication management and medication regimen characteristics two months after the start of therapy.

Table 3. Medication and medication regimen characteristics (N=62)

Patients with at least 1 demanding dosage form, n (%)	25 (40.3)
Tablet splitting, n (%)	27 (43.5)
≥ 1 drug with multiple doses per day, n (%)	50 (80.6)
≥ 1 drug with different dosages depending on time of week, n (%)	37 (59.7)
≥ 12 drug administrations per day, n (%)	28 (45.1)
≥ 3 drugs with different dosing intervals, n (%)	18 (29.0)
N° of drug prescriptions, n (%) :	
Cardiovascular agents	151 (28.6)
Supportive agents	152 (28.8)

DISCUSSION

According to the guidelines, every older patient with cancer should undergo a geriatric assessment^(4,5). In our study population, the assessment was repeated two months after the start of therapy and compared with baseline evaluation. Two main aims of our study were to assess autonomy in medication management after the start of therapy and, in cases of deterioration, to search for predetermining factors. At baseline 21% of patients needed assistance with medication intake, which is comparable to what we found in the literature^(12,13). Independent medication management was significantly higher in the group of patients taking less than 5 medications ($p < 0.005$). Two months after the start of therapy, rates of polypharmacy, and hence drug regimen complexity, increased from 48% to 98% and from a median of 4 to a median of 9 prescription drugs, while more than a half of the remaining and initially independent patients became dependent for medication intake. Moreover, in patients dependent for medication management at baseline, the median increase in the number of medications was significantly higher ($p < 0.05$).

Drug regimen complexity has generally been defined as the number of medications and daily administrations of distinct drugs⁽¹⁴⁻¹⁶⁾. This definition does not take into account other regimen characteristics that might contribute to drug regimen complexity: tablet splitting^(13,16-18), the route of drug administration^(17,19,20), different doses throughout the day or week^(17,19,20), drugs with multiple doses per day⁽¹⁵⁾ or with different dosing intervals^(14,20), all of which were present in a considerable percentage of medication lists. Drug regimen complexity is related to patient non-adherence but also to medication errors, adverse drug events and therapeutic failure^(14,20).

With regard to the second aim, in contrast with the results at baseline, we could no longer find a correlation between polypharmacy and autonomy in medication ma-

nagement neither could we find a correlation between regimen complexity and (in) dependence in medication intake.

The most plausible explanation for this lack of statistical significance is the relatively small sample size. Furthermore the binary coding of IADL-items does not allow one to differentiate between degrees of dependence: patients already dependent for medication, albeit just needing pills to be prepared once a week by a caregiver using a dose administration aid, will keep the same score even if, after two months, the patient has moved to a nursing home where his medication is brought to him at set times.

As the IADL-item on “responsibility for own medications” purely addresses the practical aspects of medication management and provides no information as to the cause of the incapacity, plausible explanations other than regimen complexity were considered. General weakness, as a result of their illness and treatment, might be one. This is, however, doubtful if we look at other IADL-domains like housekeeping and food preparation, both physically demanding, where the percentage of patients with a decline proves less prominent. Cognitive decline is also unlikely as MMSE-scores remained stable over time and were, except for 3 patients, within normal range. We therefore believe that the loss of autonomy for medication management is largely related to regimen complexity.

For patients living together medication management is often taken over by the spouse. Spouses, in most cases, are of the same age as their partner and the same evaluation might apply to the spouse as well. However, patients without a spouse might be left on their own. Clinicians often fail to predict correctly a patient’s cognitive and/or functional capacity to manage medication ⁽²¹⁾ while patients might not report potential problems unless they’re specifically asked, for example in the course of a geriatric evaluation. No studies are available addressing the issue of self-medication becoming unsafe and when to switch the medication management to an informal or formal caregiver ⁽²¹⁾.

The findings of this study might make health care professionals in charge of older patients with haematological malignancies more aware of the impact of polypharmacy, frequent regimen changes and drug regimen complexity during treatment, and draw their attention to some unmet needs. Multidisciplinary teams including pharmacists and well-trained nurses or nurse specialists are already involved in medication reconciliation and patient education in order to improve medication adherence ^(21,22). However, in older patients with cancer, at least during treatment, increased emphasis should be placed on direct observation of medication handling for both, patient and spouse, preferentially using a patient’s own medication ^(23,24). In an era where health care systems are asked to establish quality indicators with an emphasis on appropriate medication use, our present findings call for development of a specific “self-administration of medications program” for older ambulatory cancer patients based on information, education and medication preparation under nursing supervision.

Our study had several limitations. First, the study was a single-centre study with a small sample size. Second, we did not take into account eye-drops, mouthwash and topical creams, or prescriptions for “as needed” medication. Although non-oral medications are probably less related to adverse drug reactions, they certainly contribute to the complexity of medication regimens. Inclusion of these medications would additionally have emphasized the magnitude of the problem. Third, we have no information as to the cause of the incapacity, but whatever the reason might be, the need for an individual appraisal of medication management remains. Finally, the appropriateness and quality of prescribing was not assessed.

In conclusion, haematological patients are subject to extensive changes in their medication regimen at the start of therapy. A considerable number of these patients show loss of independence for medication management. Future research, based on a larger study population, and future care pathways should focus on detection and remediation, taking particularly into account the challenges of an ambulatory setting.

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REFERENCE LIST

- (1) Kristjansson SR, Wyller TB. Introduction. In: Schrijvers D, Aapro M, Zakotnik B, Audisio R, Van Halteren H, Hurria A, editors. ESMO handbook of cancer in the senior patient. first ed. Informa Healthcare; 2010. p. 1-7.
- (2) Noens L. Geriatrics and haematological malignancies: is comprehensive geriatric assessment a useful tool? *Eur J Cancer* 2011 September;47, Suppl 3:S362-3.
- (3) Rubenstein LZ. An overview of CGA: rationale, history, program models, basic components. In: Rubenstein LZ, Wieland GD, Bernabei R, editors. New York, NY: Springer; 1995.
- (4) Extermann M, Aapro M, Bernabei R, *et al.* Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol* 2005 September;55(3):241-52.
- (5) Hurria A, Wildes T, Baumgartner J, *et al.* NCCN Clinical Practice Guidelines in Oncology - Senior Adult Oncology. [version 1.2015]. 2015. National Comprehensive Cancer Network. 11-2-2015. Online Source.
- (6) Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;5(3):224-37.
- (7) Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86.
- (8) Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970;10(1):20-30.
- (9) van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Br J Gen Pract* 1995 April;45(393):195-9.
- (10) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 November;12(3):189-98.
- (11) Kaiser MJ, Bauer JM, Ramsch C, *et al.* Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging* 2009 November;13(9):782-8.
- (12) Edelberg HK, Shallenberger E, Hausdorff JM, Wei JY. One-year follow-up of medication management capacity in highly functioning older adults. *J Gerontol A Biol Sci Med Sci* 2000 October;55(10):M550-3.
- (13) Mehuys E, Dupond L, Petrovic M, *et al.* Medication management among home-dwelling older patients with chronic diseases: Possible roles for community pharmacists. *The Journal of Nutrition, Health & Aging* 2012 August;16(8):721-6.
- (14) Witticke D, Seidling HM, Lohmann K, Send AF, Haefeli WE. Opportunities to reduce medication regimen complexity: a retrospective analysis of patients discharged from a university hospital in Germany. *Drug Saf* 2013 January;36(1):31-41.
- (15) Lee M, Kemp JA, Canning A, Egan C, Tataronis G, Farraye FA. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. *Arch Intern Med* 1999 October 25;159(19):2312-6.
- (16) Pollack M, Chastek B, Williams S, Moran J. Impact of treatment complexity on adherence and glycemic control: an analysis of oral antidiabetic agents. *Journal of clinical outcome management* 2010;17:257-65.
- (17) Lam PW, Lum CM, Leung MF. Drug non-adherence and associated risk factors among Chinese geriatric patients in Hong Kong. *Hong Kong Med J* 2007 August;13(4):284-92.
- (18) Barber N, Parsons J, Clifford S, Darracott R, Horne R. Patients' problems with new medication for chronic conditions. *Qual Saf Health Care* 2004 June;13(3):172-5.
- (19) Libby AM, Fish DN, Hosokawa PW, *et al.* Patient-level medication regimen complexity across populations with chronic disease. *Clin Ther* 2013 April;35(4):385-98.
- (20) de Vries ST, Keers JC, Visser R, *et al.* Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. *Journal of Psychosomatic Research* 2014 February;76(2):134-8.

- (21) Topinkova E, Baeyens JP, Michel JP, Lang PO. Evidence-based strategies for the optimization of pharmacotherapy in older people. *Drugs Aging* 2012 June 1;29(6):477-94.
- (22) Weingart SN, Cleary A, Seger A, *et al*. Medication reconciliation in ambulatory oncology. *Jt Comm J Qual Patient Saf* 2007 December;33(12):750-7.
- (23) Lam P, Elliott RA, George J. Impact of a self-administration of medications programme on elderly inpatients' competence to manage medications: a pilot study. *J Clin Pharm Ther* 2011 February;36(1):80-6.
- (24) Tran T, Elliott RA, Taylor SE, Woodward MC. A Self-Administration of Medications Program to Identify and Address Potential Barriers to Adherence in Elderly Patients (January). *Ann Pharmacother* 2011 January 12;45(2):201-6.

Chapter 3

G8 SCREENING TOOL

VALIDATION OF THE G8 SCREENING TOOL IN OLDER PATIENTS WITH AGGRESSIVE HAEMATOLOGICAL MALIGNANCIES

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VALIDATION OF THE G8 SCREENING TOOL IN OLDER PATIENTS WITH AGGRESSIVE HAEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Background: Incidence rates of haematological malignancies increase with age. In these older cancer patients, important information may be missed without a Comprehensive Geriatric Assessment (CGA). A validated screening instrument is needed to identify those patients for whom a CGA would be beneficial. The G8 has recently been validated as a screening tool for older cancer patients in need of a CGA.

Objectives: To test the performance of the G8 screening tool in older patients with aggressive haematological malignancies to identify those who would benefit from a CGA.

Methods: Cross-sectional study of patients ≥ 70 years with a recently diagnosed haematological malignancy. G8, CGA (including six questionnaires) and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) were completed in each patient. The CGA was considered abnormal when at least one questionnaire showed an impaired score.

Results: Fifty patients with median age of 76 years were included; 88% (N=44) had an abnormal CGA. ROC curve analyses revealed a G8 score ≤ 14 obtained a sensitivity of 89% (95% CI 75-96) and a specificity of 100% (95% CI 54-100), suggesting an optimal cut-off point. AUC \pm SE was 0.949 ± 0.030 . Inclusion of comorbidity in the CGA did not change the performance of the G8 (0.943 ± 0.034 ; $P = 0.895$).

Conclusion: The G8 can be used as a valid screening tool in older patients with aggressive haematological malignancies to identify those patients who would benefit from a CGA. Comorbidity should be assessed routinely and independently of the G8.

INTRODUCTION

Incidence rates of haematological malignancies increase steadily with age. Haematological malignancies have some unique features such as frequent bone marrow involvement, rapid response to chemotherapy which might lead to remarkable functional improvement and, even in advanced stages, treatments offering good chances of long-term remission or cure⁽¹⁾. However, treating older patients with aggressive haematological malignancies is a challenging task for all those involved, since the heterogeneity of the aging process is characterised by marked variability in the rate of functional deterioration, both between and within individuals^(2,3). The clinical implications include different tolerance to cancer and cancer treatment complications. Therefore, individualised management, tailored to differences in functional capacity, life expectancy, and social and economic support, is needed.

Over the years, extensive and robust evidence demonstrates that a Comprehensive Geriatric Assessment (CGA) improves outcomes (e.g. slower disability progression, a reduced fall risk, a lower rate of unplanned hospitalisation and nursing home admission) in older patients affected by multiple interdependent medical and social problems in different clinical settings ⁽⁴⁾. A CGA is a multidimensional, interdisciplinary diagnostic process focused on determining a frail older person's physical, psychological and functional capabilities in order to develop a co-ordinated and integrated plan for treatment and long-term follow-up ⁽⁵⁾. Evidence exists that important information may be missed if a CGA-based approach is not applied in older patients with cancer ⁽⁴⁾.

Since a CGA might be very time-consuming, the current challenge in oncology is to identify those unfit patients for whom the CGA would be most beneficial, justifying the use of a screening instrument ⁽⁶⁾.

The G8 tool has recently been validated as a screening tool in patients older than 70 with cancer. Patients who screen abnormal with the G8 tool would benefit from a CGA, followed by a geriatric intervention when indicated ⁽⁷⁾.

The aim of this study was to test the performance of the G8 as a screening tool in older patients with aggressive haematological malignancies to identify who would benefit from a CGA.

MATERIALS AND METHODS

Patients

This was a cross-sectional study. All patients aged 70 years or older with a new diagnosis of Acute Myeloid Leukaemia (AML), intermediate or high grade Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM) or high grade Non Hodgkin Lymphoma (NHL) who were referred to the haematology department of a tertiary hospital between June 2011 and January 2013, were asked to participate in the current study. All participants provided written consent. The study was approved by the local Ethical Committee.

G8 and CGA

The G8 screening tool (table 1) includes 8 items that yield a total patient score ranging from 0 (heavily impaired) to 17 (no impairment). A cut-off score of 14 was used to detect frailty in older cancer patients ⁽⁶⁾.

Since no golden standard exists, our CGA consisted of a set of six questionnaires, Activities of Daily Living (ADL) ⁽⁸⁾, Instrumental Activities of Daily Living (IADL) ⁽⁹⁾, 4-item Geriatric Depression Scale (GDS-4) ⁽¹⁰⁾, Mini Mental State Examination (MMSE) ⁽¹¹⁾, Mini Nutritional Assessment – Short Form (MNA-SF) ⁽¹²⁾, and any falls in the previ-

ous year. A CGA was considered abnormal when a patient received an impaired score on at least one questionnaire. In addition to these questionnaires, comorbidity was evaluated using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) ⁽¹³⁾.

In each patient, the G8, the CGA and the CIRS-G were completed by a member of the geriatric team before therapy was started.

Statistical methods

Descriptive analyses were performed to describe patient and treatment characteristics and geriatric assessment results. Quantitative continuous variables were described using mean and standard deviation (SD) for normal data or median and range otherwise. Countable variables were presented as absolute number (N) and percentage (%) of the study population.

The performance of the G8 screening tool was evaluated using Receiver Operating Curve (ROC) analyses and the area under the ROC curve (AUC) \pm standard error (SE). Sensitivity and specificity, with 95% confidence intervals (95% CI), were calculated at the G8 cut-off score \leq 14. AUCs from obtained ROC curves were statistically compared by using a two-sided z-test.

A sample of six patients for each CGA outcome (normal/abnormal) will be required to detect a difference of 0.409 between the AUC under the null hypothesis of 0.500 and an AUC under the alternative hypothesis of 0.909, assuming a power of 80% and a significance level of 5%. This number was based on the result of Pottel et al., who observed an AUC under the alternative hypothesis of 0.909 ⁽¹⁴⁾.

All analyses were performed in MedCalc® Version 12.7.0.0 (MedCalc Software Ltd).

Table 1. G8 screening questionnaire (total score 0–17).

	Score
Has food intake declined over the past 3 months owing to loss of appetite, digestive problems, chewing or swallowing difficulties?	
Severe decrease	0
Moderate decrease	1
No decrease	2
Weight loss during the past 3 months	
> 3 kg	0
Patient does not know	1
1 – 3 kg	2
No weight loss	3
Mobility	
Bed or chair bound	0
Able to get out of bed/chair but does not go out	1
Goes out	2
Neuropsychological problems	
Severe dementia or depression	0
Mild dementia or depression	1
No psychological disorders	2
BMI (kg/m²)	
< 18.5	0
18.5 - < 21.0	1
21.0 - < 23.0	2
≥ 23.0	3
Takes more than three medications per day	
Yes	0
No	1

In comparison with other people of the same age, how does the patient consider his or her health status to be?	
Not as good	0
Does not know	0,5
As good	1
Better	2
Age (years)	
> 85	0
80-85	1
< 80	2

RESULTS

Patient and treatment characteristics and geriatric assessment results

Fifty patients were included in the study. Baseline characteristics are summarised in table 2. Median age was 76 years (range 70-87). Sixty-four percent of patients (N=32) had at least one grade 3-4 comorbidity, most often cardiovascular disorders (22%) or renal insufficiency (20%).

Table 2. Baseline characteristics of the patients (N=50)

Sex, n (%)	
Male	25 (50)
Female	25 (50)
Age (years), n (%)	
<75	17 (34)
75-80	20 (40)
>80	13 (26)
Diagnosis, n (%)	
Acute Myeloid Leukaemia	17 (34)
Non Hodgkin Lymphoma	19 (38)
Myelodysplastic Syndrome	9 (18)
Multiple Myeloma	5 (10)
Weight (kg), mean (range)	71.7 (50 – 104)
Body Mass Index, mean (range)	26 (19.84 – 41.14)
Number of comorbidities, mean (range)	
Grade 1 - 2 [‡]	3 (0 – 8)
Grade 3 - 4 [‡]	2 (1 – 5)
> 3 medications, n (%)	33 (66)

[‡] grade 1: mild problem, grade 2: problem of moderate severity requiring active therapy, grade 3: severe or constant disability, grade 4: extremely severe or urgent clinical problem

Complete CGA results were available for 45 subjects (90%); MMSE was not performed in 5 patients due to their poor health at the time of inclusion. Nutritional problems were frequent with 66% (N=33) being at risk of malnutrition (MNA-SF score 8-11) and 16% (N=8) having malnutrition (MNA-SF score \leq 7). The proportion of subjects with an impaired score on each questionnaire is summarised in table 3. In total, 88% (N=44) of patients had an abnormal CGA.

Table 3. Questionnaires included in the comprehensive geriatric assessment (CGA) and proportion of subjects with an impaired questionnaire

Questionnaire	Domain	Score range	Impaired score if	Number of patients with an impaired score (%)
ADL	Autonomy	0-6	≤ 5	12 (24)
IADL	Autonomy	0-5 ♂ 0-8 ♀	≤ 4 ♂ ≤ 7 ♀	19 (38)
MMSE	Cognitive functions	0-30	≤ 23	2 (4.4)
GDS-4	Mood	0-4	≥ 2	15 (30)
MNA SF	Nutritional status	0-14	≤ 11	41 (82)
CIRS-G	Comorbidity	14 organ systems included	At least 1 comorbidity grade 3/4	32 (64)
History of falls in the previous year		0-1	1	16 (32)

ADL: Activities of Daily Living;

IADL: Instrumental Activities of Daily Living;

MMSE: Mini Mental State Examination;

GDS-4: 4 item Geriatric Depression Scale;

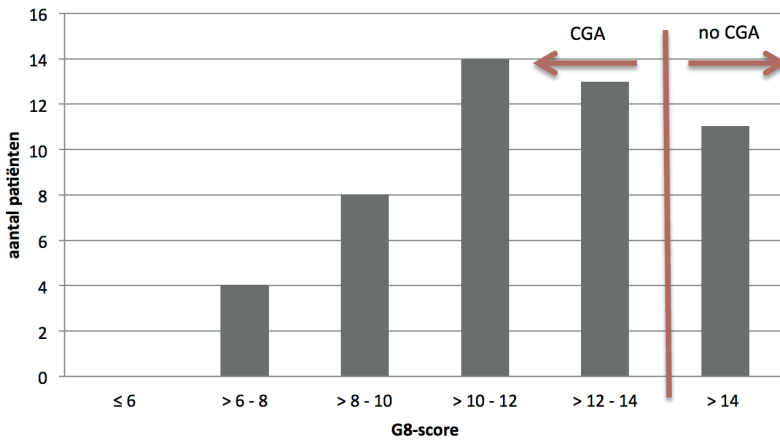
MNA-SF: Mini Nutritional Assessment Short Form;

CIRS-G: Cumulative Illness Rating Scale for Geriatrics

Performance of the G8 tool

Median score on the G8 screening tool was 12 (range 6.5-17) (fig.1); 76% (N=38) of patients scored ≤ 14 on the G8, indicating frailty (6).

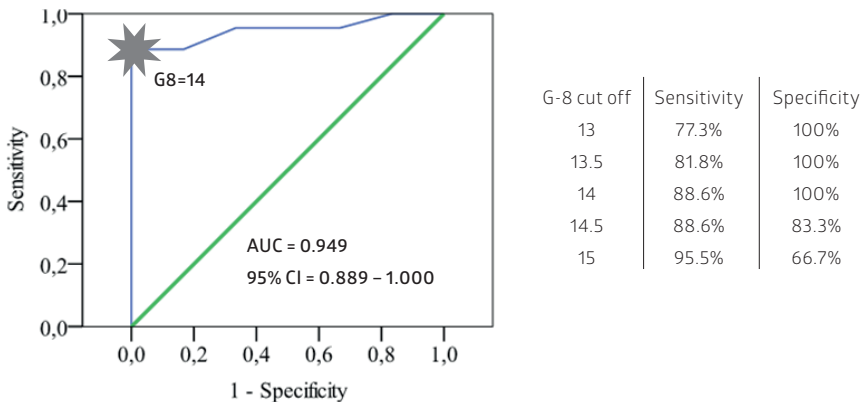
Figure 1. Results of the G8



In the analyses of the association between the G8 screening tool and the reference CGA, the ROC curve revealed a G8 score ≤ 14 as the optimal cut-off point, obtaining a sensitivity of 89% (95% CI 75-96) and a specificity of 100% (95% CI 54-100). The AUC \pm SE was 0.949 ± 0.030 (fig. 2).

The inclusion of comorbidity in the CGA did not significantly change the performance of the G8 tool (0.943 ± 0.034 ; $P = 0.895$); nor did the G8 performance change when ADL or IADL were excluded from the CGA.

Figure 2. ROC-curve analysis: performance of the G8 screening tool.



DISCUSSION

The G8 has recently been developed as a screening tool to identify patients in need of further CGA and appropriate care. It has been validated in older patients with cancer in a large prospective multicentre study⁽⁶⁾. Patients with various types of cancer were eligible for inclusion. Thirty percent of these patients were treated for Non-Hodgkin's Lymphoma but no other haematological diagnoses were included. Since then, the G8 has been assessed in further studies, all of them including predominantly patients with solid tumours⁽¹⁴⁻¹⁶⁾.

To the best of our knowledge, our study is the first to validate the G8 as a screening tool in a population of older patients with only haematological malignancies. The G8 enables the appropriate selection of frail patients in need of a CGA. Additional information gathered by the CGA will inform individualised treatment plans for these frail patients. This is especially true in haematology, as more novel and promising approaches based on targeted therapies will become available in the next few years^(3,17).

At the cut-off score proposed in the literature ($G8 \leq 14$), we obtained a sensitivity of 88.6% and a specificity of 100%, which is a similar sensitivity but a higher specificity than reported in previous studies validating the G8 screening tool in older cancer patients⁽¹⁸⁻²²⁾.

Consistent with the findings of Bellera et al.⁽⁶⁾, sensitivity and specificity estimates were comparable regardless of whether ADL, IADL, or both ADL and IADL were included in our CGA. We believe however that both ADL and IADL should be assessed as they address different stages of dependence and can imply a difference in life expectancy. Impairments in ADL involve limited life expectancy and near-to-exhausted functional reserve. For these patients, symptom palliation and quality-of-life preservation are essential⁽²³⁾, whereas patients with limitations only in IADL might benefit most from an individualised therapeutic approach.

The performance of the G8 tool did not change significantly when we included comorbidity in our CGA. In older cancer patients, comorbidity is an independent predictor of mortality and of survival⁽¹⁸⁻²²⁾. Comorbidity overlaps with, but is distinct from, frailty. Both comorbidity and frailty are independent risk factors for disability. Therefore we would discourage the inclusion of comorbidity in a CGA. Patients with a normal score on the G8 screening tool will be excluded from further assessment and incomplete or no information will be available about their comorbidity. Therefore, considering its predictive value, comorbidity should be assessed routinely, preferably by means of a comorbidity scale, and independently of the G8 result.

Screening of older patients with cancer by means of the G8 is only a first step. Older patients scoring >14 should be considered "fit" and therefore receive the same treatment as younger patients. However, older cancer patients with a score ≤ 14 should

not automatically be excluded from standard treatment. For these unfit patients, in a second step, a CGA might uncover those physical, psychological and/or functional impairments, limiting standard treatment options. Tailored interventions, based on CGA results, might allow at least part of these unfit patients to benefit from standard treatment anyway ⁽²⁴⁾.

With regard to prognosis in older patients with haematological malignancies, a few studies have demonstrated an impact of functionality on survival. However most studies on CGA and prognosis have focused either exclusively on solid tumours or on a general sample with a minority of haematological malignancies ⁽¹⁾. So far no conclusions can be made regarding other CGA domains in terms of prognosis, nor in terms of quality of life.

Our study had several limitations. First, there might have been a referral bias. Only 38% of our patients were dependent in IADL and only 4% had an abnormal MMSE score (< 24) at baseline. These are considerably lower percentages than those found in literature ⁽²⁵⁾. As a tertiary centre, our hospital receives a significant number of patient referrals from other hospitals. Referring physicians may have considered older patients with physical, cognitive or emotional problems ill-suited candidates for aggressive therapy. Second, patients with haematological malignancies differ in several ways from patients with solid tumours. Due to a lack of studies in haematology patients, we compared our results to those from studies of patients with solid tumours. Some differences in results can possibly be explained by differences between these patient populations. Finally, this was a cross-sectional study with the G8 and the CGA assessed on a single occasion.

In conclusion, our results show that the G8 tool can be used as a valid screening tool in older patients with aggressive haematological malignancies to identify frail patients who would benefit from a CGA. Comorbidity, however, should be assessed routinely, independently of the results of the G8.

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REFERENCE LIST

- (1) Extermann M, Wedding U. Comorbidity and geriatric assessment for older patients with hematologic malignancies: A review of the evidence. *Journal of Geriatric Oncology* 2012 Jan;3(1):49-57.
- (2) Kristjansson SR, Wyller TB. Introduction. In: Schrijvers D, Aapro M, Zakotnik B, Audisio R, Van Halteren H, Hurria A, editors. *ESMO handbook of cancer in the senior patient*. first ed. Informa Healthcare; 2010. p. 1-7.
- (3) Noens L. Geriatrics and haematological malignancies: is comprehensive geriatric assessment a useful tool? *European Journal of Cancer* 2011 Sep;47, Supplement 3(0):S362-S363.
- (4) Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol* 2005 Sep;55(3):241-52.
- (5) Rubenstein LZ. An overview of CGA: rationale, history, program models, basic components. In: Rubenstein LZ, Wieland GD, Bernabei R, editors. *New York, NY: Springer; 1995*.
- (6) Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012 Jan 16;23:2166-72.
- (7) Soubeyran P, Bellera C, Goyard J, Heitz D, Cure H, Rousselot H, et al. Validation of the G8 screening tool in geriatric oncology: The ONCODAGE project. *ASCO Meeting Abstracts* 2011 Jun 9;29(15_suppl):9001.
- (8) Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970;10(1):20-30.
- (9) Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86.
- (10) van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Br J Gen Pract* 1995 Apr;45(393):195-9.
- (11) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov;12(3):189-98.
- (12) Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging* 2009 Nov;13(9):782-8.
- (13) Miller M, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). 1991. Ref Type: Generic
- (14) Pottel L, Boterberg T, Pottel H, Goethals L, Van Den Noortgate N, Duprez Fd, et al. Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo)therapy. *Journal of Geriatric Oncology* 2012 Jan;3(1):24-32.
- (15) Baitar A, Van Fraeyenhove F, Vandebroek A, De Drooghe E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *Journal of Geriatric Oncology* 2013 Jan;4(1):32-8.
- (16) Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Annals of Oncology* 2013 May 1;24(5):1306-12.
- (17) Klepin HD, Balducci L. Acute myelogenous leukemia in older adults. *Oncologist* 2009 Mar;14(3):222-32.
- (18) Etienne A, Esterni B, Charbonnier A, Mozziconacci MJ, Arnoulet C, Coso D, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007 Apr 1;109(7):1376-83.
- (19) Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004 Mar;59(3):255-63.

- (20) Giles FJ, Borthakur G, Ravandi F, Faderl S, Verstovsek S, Thomas D, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* 2007 Feb;136(4):624-7.
- (21) Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. *Am J Surg* 2012 Aug;204(2):139-43.
- (22) Wedding U, Rohrig B, Klippstein A, Pientka L, Hoffken K. Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. *J Cancer Res Clin Oncol* 2007 Dec;133(12):945-50.
- (23) Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;5(3):224-37.
- (24) Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. *Surgical Oncology* 2010 Sep;19(3):117-23.
- (25) Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007 May 10;25(14):1824-31.

Chapter 4

HAND GRIP STRENGTH

HAND GRIP STRENGTH AS A SCREENING TOOL FOR FRAILTY IN OLDER PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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HAND GRIP STRENGTH AS A SCREENING TOOL FOR FRAILITY IN OLDER PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Objectives: Frailty is a geriatric syndrome characterized by decreased physiological reserves and an age-related vulnerability to stressors with higher risk of adverse health outcomes. Comprehensive Geriatric Assessment (CGA) might detect frailty but is time-consuming, implying the need for initial frailty screening. Most frailty screening tools do not include functional measures. Hand grip strength (HGS) is a reliable surrogate for overall muscle strength and predicts functional decline, morbidity and mortality. No studies are available in cancer patients on HGS as screening tool for frailty. We aimed to assess whether HGS can be used as a screening tool to predict an abnormal CGA and therefore frailty.

Methods: Single centre cohort study in 59 patients aged 70 years or more with a haematological malignancy. HGS was measured using a vigorimeter. A patient was considered frail if any of the CGA-elements was impaired.

Results: Mean HGS before start of therapy in women was 37.0 ± 14.3 kPa and in men 66.1 ± 13.1 kPa. An abnormal CGA was present in 52 subjects (88%). HGS was associated with concurrent abnormal CGA ($p = 0.058$ in women, $p = 0.009$ in men). AUC was 0.800 (SE = 0.130) in women and 0.847 (SE = 0.118) in men. Optimal HGS cut-off points for likelihood of abnormal CGA were ≤ 52 kPa in women and ≤ 80 kPa in men.

Discussion: In older patients with haematological malignancies, impairment in muscle function is present at diagnosis. HGS seems a promising screening tool to identify patients with abnormal CGA.

INTRODUCTION

Frailty is a geriatric syndrome characterized by decreased physiological reserves and an age-related vulnerability to stressors resulting in a limited capacity to maintain homeostasis, thus increasing vulnerability to adverse health outcomes⁽¹⁾. One tool to detect frailty in older patients is the Comprehensive Geriatric Assessment (CGA). CGA is a multidimensional, interdisciplinary diagnostic process to evaluate an older person's physical, psychological and functional capabilities and predict remaining life expectancy and functional age⁽²⁾. CGA commonly includes an evaluation of functionality, nutrition, emotional and cognitive function, polypharmacy, socio-economic issues and quality of life. In patients with cancer, the identification

of frailty might be relevant to detect potentially remediable medical problems with implications for prognosis, treatment and rehabilitation ⁽³⁾. However, one of the shortcomings of CGA is its time-consuming aspect. Therefore a two-step approach has been proposed with the use of a screening tool to detect possible frail patients that should subsequently undergo a CGA. Several screening tools exist but only five were specifically designed for older patients with cancer ⁽⁴⁾. One of them, the G8 questionnaire, was recently validated in a subgroup of older patients with haematological malignancies ⁽⁵⁾.

Most screening tools currently used in patients with cancer are questionnaires. Only two studies applied the Fried frailty criteria for screening purposes ⁽⁴⁾. The Fried criteria comprise hand grip strength (HGS) as one of two performance-based measures for physical function. HGS is a valid and reliable measure of muscle strength and correlates well with total body muscle strength. In patients without cancer, low muscle strength is a clinical marker of poor mobility and an independent predictor of adverse health outcomes ^(6,7). In advanced cancer patients, lower HGS was associated with lower BMI, lower albumin, lower quality of life and poorer performance status ⁽⁸⁾. Consequently, HGS might be a suitable marker for frailty. So far, no studies are available in patients with cancer on the use of HGS as a single item screening tool for frailty.

The primary aim of this study was to evaluate HGS as a screening tool for frailty in older patients with recently diagnosed haematological malignancy before start of therapy. Secondary aims were to explore the association between HGS before start of therapy and 1) concurrent abnormal G8, 2) subsequent occurrence of adverse events during therapy, 3) subsequent 6-month mortality.

MATERIALS AND METHODS

Patients

This was a single centre cohort study. All patients aged 70 years or more with a new diagnosis of Acute Myeloid Leukaemia (AML), intermediate or high grade Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM) or high grade Non Hodgkin Lymphoma (NHL), who were referred to the haematology department of a tertiary hospital, were asked to participate in the current study. All participants provided written consent. The study was approved by the local Ethical Committee (B670201110554).

Hand grip strength

HGS was measured before start of therapy, using a Martin vigorimeter. It consists of a rubber bulb connected by a tube to a manometer. The large bulb was selected for all subjects. Measures are expressed in kiloPascals (kP). Patients were sitting in a chair, shoulder adducted and neutrally rotated, elbow flexed at 90°, forearm in

neutral position, and wrist in slight extension (0° to 30°). Three consecutive HGS measurements of the dominant hand were taken with a brief pause between each measurement. The highest score was retained.

Comprehensive Geriatric Assessment

CGA was completed by a member of the geriatric team before start of therapy. Since no golden standard exists, our CGA included Activities of Daily Living (ADL)⁽⁹⁾, Instrumental Activities of Daily Living (IADL)⁽¹⁰⁾, 4-item Geriatric Depression Scale (GDS-4)⁽¹¹⁾, Mini Mental State Examination (MMSE)⁽¹²⁾, Mini Nutritional Assessment – Short Form (MNA-SF)⁽¹³⁾, and any falls in the previous year. A patient was considered frail if at least one of the individual CGA-elements was impaired.

Secondary outcomes

A G8 score was obtained by a member of the geriatric team before the start of therapy. Scores ≤ 14 were considered abnormal⁽⁵⁾.

Adverse events (AE) included any unplanned admission, treatment delay, dose reduction or disease progression. Only the first AE was taken into account. Data on mortality within the first six months were gathered from medical records.

Statistical analysis

Descriptive analyses were performed to describe patients' characteristics. Normally distributed continuous variables were expressed as mean \pm standard deviation (SD). Countable variables were presented as absolute number (N) and percentage (%) of the study population. Independent samples T-tests were used to detect differences in HGS between groups. Age-adjusted logistic regression analyses further explored the association between HGS and abnormal CGA, abnormal G8 score, occurrence of adverse events, and 6-month mortality.

The performance of HGS as screening tool for concurrent abnormal CGA was also evaluated using Receiver Operating Curve (ROC) analyses and the area under the ROC curve (AUC) with standard error (SE). Sensitivity and specificity were calculated at the cut-off point with the highest value of the Youden's index.

All analyses were performed using SPSS software, version 21.0.0.1. Statistical significance was indicated by a P value < 0.05 ; all P values were two-tailed.

RESULTS

Between June 2011 and January 2013, 71 patients were included in the study. Of these, 59 had complete data on HGS and CGA before start of therapy. Mean age was 77.3 ± 4.8 years. Mean HGS before start of therapy in women was 37.0 ± 14.3 kPa,

in men 66.1 ± 13.1 kPa. Further baseline characteristics are summarized in table 1. Adverse events were registered for 35 patients (59%). Within the first six months, 17 patients died (29%).

Differences in HGS between subjects with normal / abnormal CGA, normal / abnormal G8, none / at least one adverse event, 6-months survival / mortality according to gender are described in table 2. Furthermore, results from logistic regression analyses adjusted for age are presented in table 2.

Figure 1 shows the ROC curves of HGS as screening tool for concurrent abnormal CGA in women and men. Criterion for HGS associated with the Youden's index in women is ≤ 52 kPa (88% sensitivity and 67% specificity) and in men it is ≤ 80 kPa (93% sensitivity and 75% specificity).

Table 1. Characteristics of the study population before start of therapy (N = 59).

Characteristic	N (%)
Gender, female	28 (48)
Age, 80 years or more	21 (36)
Diagnosis	
Acute Myeloid Leukaemia	17 (27.9)
Non Hodgkin Lymphoma	24 (39.3)
Myelodysplastic Syndrome	11 (18.0)
Multiple Myeloma	9 (14.8)
IADL dependency	22 (37)
MMSE < 24	4 (7)
CGA, ≥ 1 impairment	52 (88)
CGA, ≥ 2 impairments	34 (58)
G8 ≤ 14	46 (78)

IADL = instrumental activities of daily living, MMSE = mini-mental state examination, CGA = comprehensive geriatric assessment

Table 2. Association between hand grip strength and abnormal comprehensive geriatric assessment, abnormal G8, occurrence of adverse event(s), and survival status according to gender (N = 59).

HGS (kPa)	Normal CGA mean ± SD	Abnormal CGA mean ± SD	P ^a	OR ^b	95% CI ^b	P ^b
Women	51.7 ± 13.1	35.2 ± 13.6	0.058	0.89	0.77 - 1.02	0.099
Men	81.5 ± 12.8	63.9 ± 11.7	0.009	0.85	0.72 - 1.00	0.044
HGS (kPa)	Normal G8 mean ± SD	Abnormal G8 mean ± SD	P ^a	OR ^b	95% CI ^b	P ^b
Women	48.7 ± 14.4	33.8 ± 12.8	0.021	0.91	0.82 - 1.00	0.051
Men	72.4 ± 14.8	64.3 ± 12.3	0.152	0.96	0.89 - 1.03	0.269
HGS (kPa)	0 adverse event mean ± SD	≥ 1 adverse event mean ± SD	P ^a	OR ^b	95% CI ^b	P ^b
Women	42.3 ± 9.1	34.9 ± 15.6	0.136	0.96	0.90 - 1.02	0.206
Men	63.6 ± 11.2	68.8 ± 14.8	0.28	1.04	0.98 - 1.11	0.173
HGS (kPa)	Alive mean ± SD	Death mean ± SD	P ^a	OR ^b	95% CI ^b	P ^b
Women	38.6 ± 14.9	29.6 ± 8.4	0.207	0.95	0.88 - 1.03	0.204
Men	67.0 ± 12.7	64.8 ± 14.2	0.65	1.00	0.94 - 1.06	0.961

HGS = hand grip strength, SD = standard deviation, CGA = comprehensive geriatric assessment, OR = odds ratio, CI = confidence interval

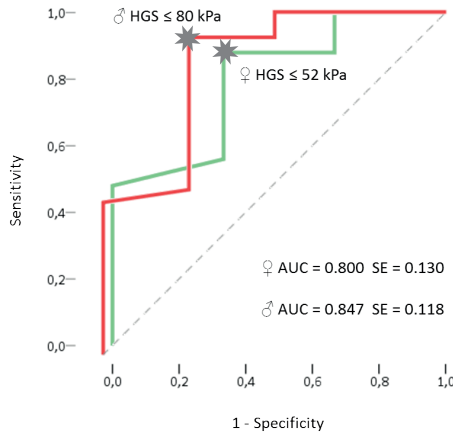
^aIndependent-samples T test

^bAge-adjusted logistic regression analysis

DISCUSSION

The primary aim of our study was to evaluate HGS as a screening tool for frailty in older patients with haematological malignancies. HGS was significantly higher in patients with a normal CGA compared to those with an abnormal CGA. Optimal cut-off points for likelihood of an abnormal CGA were ≤ 52 kPa in women and ≤ 80 kPa in men, respectively. Furthermore, HGS was significantly associated with abnormal G8 in women, but not in men.

Figure 1. Receiving operating curves of hand grip strength as screening tool for concurrent abnormal comprehensive geriatric assessment according to gender.



HGS = hand grip strength, AUC = area under the curve, SE = standard error

HGS in patients with recently diagnosed haematological malignancy

Desrosiers *et al.* developed normative data for the Martin vigorimeter, according to age and gender ⁽¹⁴⁾. Compared to these normative data, mean GS in our study population was less than expected for both men and women, in each age category. Christensen identified 194 studies reporting measures of muscle function, including muscle strength, in adult cancer patients. Studies reporting on muscle strength, in their entirety, indicate that cancer patients have significant impairments in muscle strength regardless of disease stage ⁽¹⁵⁾. Except for the study of Burney *et al.*, including ten patients with leukaemia or lymphoma, all included patients were diagnosed with a solid tumour ⁽¹⁶⁾. Our findings demonstrate that, also in patients with a haematological malignancy, a loss of upper extremity strength is present, even before the start of treatment. As in patients with solid tumours, the aetiology of haematological cancer-related muscle dysfunction might comprise comorbidities, malnutrition and/or weight loss with the resultant loss of muscle mass, physical inactivity and systemic inflammation due to pro-inflammatory cytokines ⁽¹⁵⁾.

HGS and subsequent health-related outcomes

We could not detect any significant associations between HGS and subsequent adverse events or 6-month mortality. Epidemiological studies in the general population found HGS to be predictive for increased risk of functional limitations and disability, and all-cause mortality ^(7,17-19). In patients, HGS was strongly predictive of postoperative complications, length of stay, loss of functional status and short term survival ⁽¹⁹⁾. Studies on the predictive value of HGS in cancer patients are limited. Two studies comprising patients with various cancers found HGS to be significant-

ly associated with survival^(8,20). Another three studies found lower HGS to be predictive of postoperative complications⁽²¹⁻²³⁾ and mortality within 6 months after the operation⁽²²⁾. In patients with haematological malignancies, only one study could be identified. Similar to our results, no relation could be found between physical function, including HGS, and short-term mortality (60 days) or ICU admission⁽²⁴⁾. This absence of correlation in oncohaematological patients might be related with some of the features of haematological malignancies: the existence of treatments offering good chances of cure or long-term remission, even in advanced stages, and often a rapid response to chemotherapy with subsequent marked improvement in functionality⁽²⁵⁾.

Our study had several limitations. First, it was a single centre study with small sample size. Some of the non-significant associations we found might be due to lack of power. Second, there might have been a referral bias. Only 37% of our patients were dependent in IADL and only 7% had an abnormal MMSE score (< 24) at baseline. These are considerably lower percentages than those found in the literature⁽²⁶⁾. As a tertiary centre, our hospital receives a significant number of patient referrals from other hospitals. Referring physicians may have considered older patients with physical, cognitive or emotional problems ill-suited candidates for aggressive therapy. Third, in several centres a Jamar dynamometer is used to measure HGS instead of a Martin vigorimeter. Although highly correlated, these results are not interchangeable, and therefore additional research is needed as to which cut points apply to the Jamar dynamometer.

To the best of our knowledge, this is the first study on the use of HGS as screening tool for frailty in patients with haematological malignancies. HGS is a simple performance test, feasible in a busy clinical practice, and potentially a quick and valid alternative for screening questionnaires. HGS and CGA data were collected from patients simultaneously which strengthens the consistency of our data. So far, no cross-sectional data are available comparing HGS with the results of a subsequent CGA. The use of a CGA, currently the gold standard to confirm frailty in older adults, as the reference frame can be considered an additional strength of our study.

In conclusion, this study suggests that HGS might be a promising screening tool in older patients with aggressive haematological malignancies to identify possibly frail patients who would present with abnormal CGA. This finding however requires validation in a larger multicentre prospective study.

REFERENCE LIST

- (1) Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunanathan S, et al. Frailty: an emerging research and clinical paradigm-issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007 Jul;62(7):731-7.
- (2) Rubenstein LZ. Joseph T. Freeman Award Lecture: Comprehensive Geriatric Assessment: From Miracle to Reality. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2004 May 1;59(5):M473-M477.
- (3) Ronning B, Wyller TB, Jordhoy MS, Nesbakken A, Bakka A, Seljeflot I, et al. Frailty indicators and functional status in older patients after colorectal cancer surgery. *J Geriatr Oncol* 2014 Jan;5(1):26-32.
- (4) Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Annals of Oncology* 2015;26:288-300.
- (5) Velghe A, Petrovic M, De BS, Demuyck R, Noens L. Validation of the G8 screening tool in older patients with aggressive haematological malignancies. *Eur J Oncol Nurs* 2014 Dec;18(6):645-8.
- (6) Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010 Jul;39(4):412-23.
- (7) De Buyser SL, Petrovic M, Taes YE, Toye KR, Kaufman JM, Goemaere S. Physical function measurements predict mortality in ambulatory older men. *Eur J Clin Invest* 2013 Apr;43(4):379-86.
- (8) Kilgour RD, Viganò A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer* 2013 Dec;21(12):3261-70.
- (9) Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970;10(1):20-30.
- (10) Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86.
- (11) van Marwijk HW, Wallace P, de Bock GH, Hermans J, Kaptein AA, Mulder JD. Evaluation of the feasibility, reliability and diagnostic value of shortened versions of the geriatric depression scale. *Br J Gen Pract* 1995 Apr;45(393):195-9.
- (12) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov;12(3):189-98.
- (13) Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging* 2009 Nov;13(9):782-8.
- (14) Desrosiers J, Bravo G, Hebert R, Dutil E. Normative data for grip strength of elderly men and women. *Am J Occup Ther* 1995 Jul;49(7):637-44.
- (15) Christensen JF, Jones LW, Andersen JL, Dagaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Annals of Oncology* 2014 May 1;25(5):947-58.
- (16) Burney BO, Hayes TG, Smiechowska J, Cardwell G, Papusha V, Bhargava P, et al. Low testosterone levels and increased inflammatory markers in patients with cancer and relationship with cachexia. *J Clin Endocrinol Metab* 2012 May;97(5):E700-E709.
- (17) De Buyser S, Petrovic M, Taes Y, Vetrano D, Onder G. A multicomponent approach to identify predictors of hospital outcomes in older in-patients: a multicentre, observational study. *PLoS ONE* 2015;9(12): e115413.
- (18) Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ* 2010;341:c4467.
- (19) Norman K, Stobaus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr* 2011 Apr;30(2):135-42.
- (20) Kanesvaran R, Koo KN, Chen W, Poon D. An analysis of the prognostic value of handgrip strength and its incorporation into the comprehensive geriatric assessment (CGA) in elderly Asian patients with cancer. *ASCO Meeting Abstracts* 2011 Jun 9;29(15_suppl):9093.

- (21) Guo CB, Zhang W, Ma DQ, Zhang KH, Huang JQ. Hand grip strength: an indicator of nutritional state and the mix of postoperative complications in patients with oral and maxillofacial cancers. *Br J Oral Maxillofac Surg* 1996 Aug;34(4):325-7.
- (22) Chen CH, Ho C, Huang YZ, Hung TT. Hand-grip strength is a simple and effective outcome predictor in esophageal cancer following esophagectomy with reconstruction: a prospective study. *J Cardiothorac Surg* 2011;6:98.
- (23) Sato T, Aoyama T, Hayashi T, Segami K, Kawabe T, Fujikawa H, et al. Impact of preoperative hand grip strength on morbidity following gastric cancer surgery. *Gastric Cancer* 2015 Oct 14.
- (24) Timilshina N, Breunis H, Brandwein JM, Minden MD, Gupta V, O'Neill S, et al. Do quality of life or physical function at diagnosis predict short-term outcomes during intensive chemotherapy in AML? *Ann Oncol* 2014 Apr;25(4):883-8.
- (25) Extermann M, Wedding U. Comorbidity and geriatric assessment for older patients with hematologic malignancies: A review of the evidence. *Journal of Geriatric Oncology* 2012 Jan;3(1):49-57.
- (26) Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007 May 10;25(14):1824-31.

Chapter 5

GENERAL DISCUSSION

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1. MAIN FINDINGS

The aim of this doctoral thesis was to explore the added value of a comprehensive geriatric assessment (CGA) in the detection of frailty and/or additional geriatric syndromes in older patients with haematological malignancies. Furthermore, we examined whether the results of screening and CGA were predictive for adverse events or mortality.

In Chapter 1 we provide a general overview of the literature on haematological malignancies in older patients. In addition to disease characteristics and treatment principles, we focus on the features of frailty and CGA. As the process of frailty can be changed or reversed, one of the main challenges in geriatrics is the detection and in-depth evaluation of frail individuals, by means of a CGA, to determine who might benefit by medical and rehabilitation efforts. The lack of studies on the use of CGA, specifically in patients with haematological malignancies, was the starting point of this thesis.

In Chapter 2 (i.e. papers 1 and 2) we focus on the geriatric problems we most frequently encountered when administering a CGA, and their importance for this specific group of patients.

The administration of a CGA is both time and staff-consuming. Therefore, a two-step approach is proposed with the use of a screening tool as the first step to identify those patients that subsequently would benefit most from a CGA.

In Chapter 3 we therefore test the performance of the G8 questionnaire as a screening tool for frailty in this group of patients.

In Chapter 4 we aim to assess whether functional measures like hand grip strength can be used as a screening tool, instead of questionnaires.

In Chapter 5 the major findings of each paper are recapitulated in the boxes. In the discussion we focus on implications and recommendations for current clinical practice while future perspectives for practice and research will complete this chapter.

1.1 Chapter 2

Analysis of the first results showed that 88% of patients had an impaired score for at least 1 CGA item. Further analysis of all results revealed some "red flags", i.e. a remarkably high number of patients with potential nutritional problems and a high rate of polypharmacy, indicating the necessity of further in-depth evaluation.

1.1.1 Chapter 2.1

The first paper addressed the baseline nutritional status of a group of older patients with haematological malignancies. In this observational monocentric study, 70 patients were screened for malnutrition by means of the MNA-SF, before the start of chemotherapy.

Using the MNA-SF, 81% of patients screened positive, with 61% considered at risk for malnutrition and 20% malnourished. On the second evaluation, two months later, 1 of the patients with a normal score had died while 9 more patients scored positive on MNA-SF, resulting in 95.7% (CI95 = 83-99%) of patients with (risk for) malnutrition.

However, only 41% of our patients had a BMI < 25. In routine clinical practice a low BMI is still often used as an indicator of malnutrition. Our study shows that using BMI, as an indicator for chronic malnutrition, might result in a delay of adequate nutritional support.

Most often patients scored positive on *recent weight loss* and *declined food intake*, both common side-effects of chemotherapy. Thus, during treatment, the percentage of patients with a positive screen can only rise. Given the high prevalence of malnourished patients or patients at risk, one can question whether screening for malnutrition, at least by means of the MNA-SF, is meaningful in patients with haematological malignancies, or whether nutritional assessment should be considered the first step approach. This assessment, incorporating also anthropometric measurements, comorbidity, and current and foreseen medication should be dedicated to a skilled dietician, preferably with an expertise in oncology.

This is, to our knowledge, the first report on the baseline nutritional status in a group of older patients with a diagnosis of an aggressive haematological malignancy.

The high number of patients with possible nutritional problems was mainly due to a high percentage of patients at risk and strikingly higher (61% vs. 37%) than what was found in the only available study in patients with (malignant and non-malignant) haematological disorders ⁽¹⁾. Moreover, about half of the patients from that study were free of nutritional problems in contrast to 19% in our study population. In comparison, in a review published in 2014, in a wide variety of patients with various types of cancer, the prevalence of nutritional problems, based on the MNA, ranged from 42% to 83% ⁽²⁾. Consequently, our results are in line with those in patients with solid tumours.

Since the MNA has not been validated to detect malnutrition in patients with cancer, one could argue that some items of the MNA scale could have been altered by the (haematological) disease, more than by malnutrition. Despite this lack of validation, at least 3 studies recently found a significant negative relationship between nutritional status assessed by MNA, and treatment complications or mortality ⁽³⁻⁵⁾. The Chemotherapy Risk Assessment Score for High-age patients (CRASH) score,

developed by Extermann et al., allows stratifying patients into 4 risk categories for severe chemotherapy toxicity. The instrument is valid across a wide range of chemotherapies. Low MNA, amongst other patient and cancer characteristics, was correlated with a higher risk of grade 3/4 non-haematological toxicity⁽⁴⁾. In a group of 202 patients with various cancers and an indication for chemotherapy, inferior MNA scores increased the probability of not completing chemotherapy, and also, showed an increased mortality risk after the start of chemotherapy⁽³⁾. There is only one study in patients with advanced lung cancer comparing MNA with weight loss⁽⁵⁾. The incidence of malnourished patients or patients at risk was higher with the MNA. MNA correlated with the number of metastatic sites and also with 9 of 14 laboratory values indicating adverse prognosis, malnutrition and inflammation-cachexia. Moreover, it was superior to weight loss history in the prediction of response to first-line treatment, time to progression and overall survival. Furthermore MNA refined short-term survival estimates, dividing patients in 3 categories (adequately nourished, risk of malnutrition, malnourished) with distinct median and 1 year survival.

Although it remains unclear whether a lower MNA score is an expression of (more progressive) disease, a true proof of malnutrition, or a combination of both, it is clearly shown that a low MNA score should raise concern about a patient. Moreover, if a low MNA score truly reveals (a risk of) malnutrition, MNA stratifies a group of patients with intermediate risk in which early anticachectic strategies and/or nutritional interventions might be more effective due to the timely demonstration of nutritional deterioration⁽⁵⁾. For the moment however, the number of studies on nutritional interventions is small and the data are heterogeneous, requiring further research⁽⁶⁾.

Implications for clinical practice:

Many older patients with a haematological malignancy facing aggressive therapy are malnourished or at risk for malnutrition, according to the MNA-SF. Therefore, as to the aspect of nutrition, our findings support baseline nutritional assessment by a dietician with dietary advice and follow-up during treatment to become an integrated part of the treatment plan for every individual patient. As to the aspect of prognosis however, it might be worthwhile to keep using the MNA, as it can yield additional information on the risk of treatment complications and/or median and overall survival.

1.1.2 Chapter 2.2

In the second paper of this chapter we examined the loss of autonomy in medication management after start of therapy and elaborated on predetermining factors. In this longitudinal monocentric cohort study 62 patients underwent a geriatric evaluation before and two months after start of therapy. Medication was registered both times.

Due to the initiation of chemotherapy and supportive drugs, patients with a haematological malignancy are confronted with extensive changes in medicinal treatment. In a single center cohort study we recorded alterations in medication regimen and concurrent changes in autonomy in medication management, based on IADL.

Polypharmacy increased from 48.3% of patients at baseline to 98.3% after start of therapy. At baseline, 79% of patients took their long-term medication independently. Being independent for medication management is significantly associated with the absence of polypharmacy. More than half of the formerly independent patients needed assistance for their medication after start of therapy.

IADL provides no information with regard to the cause of the incapacity. After careful consideration of all CGA data, drug regimen complexity seemed the most plausible explanation: apart from an increase in the number of medications, multiple daily doses, varying doses, and medication splitting further contributed to regimen complexity.

So far, little attention is paid to (unintentional) non-adherence due to functional problems or changes, despite the fact that older patients experience a gradual decline in their cognitive and functional abilities required for medication management.

The merit of this study lies in the fact that our findings might make health care professionals more aware of the huge impact of polypharmacy, frequent drug regimen changes, and regimen complexity during cancer treatment, especially in older patients. Moreover, the finding of this paper might draw attention of health care professionals to some unmet needs in current care pathways.

Besides problems with medication management related to polypharmacy, this chapter highlights another aspect in the care of older people receiving intensive treatment. This study clearly shows that patients, during chemotherapy, might develop new geriatric syndromes. This finding stresses the need for some kind of repetitive CGA evaluation. A CGA is both a diagnostic and therapeutic tool and should per definition include long-term follow-up. However, in an era where research mainly focuses on how to minimize the initial "comprehensive" geriatric assessment, recommendations on how and when to re-evaluate older patients with cancer still need to be formulated.

During the course of our study, patients had 1 or 2 follow-up visits, depending on treatment modalities. Except for patients with undeniably poor overall condition,

a second and eventually a third CGA was performed. However, due to the low number of surviving patients, we could not make any firm conclusions on the evolution of CGA items, except for autonomy in medication management (see above). Regarding cognition, we did not record apparent changes in MMSE overtime, keeping in mind however the low number of survivors and a rather short follow-up period to detect changes in mental functioning. Other items like ADL or quality of life did worsen for some and improved for others, without apparent correlation.

Apart from our study, three more articles could be found reporting on the results of consecutive CGA evaluations. In one study in community-dwelling older patients there was a continued yield of problems identified and recommendations made when CGA was repeated annually for 3 years⁽⁷⁾. There is one study in patients with breast cancer with a median age of 79 years. Each patient underwent a CGA at baseline and every 3 months, structured follow-up from the nurse practitioner, dietitian, social worker and/or pharmacist according to risk assignment, and specific interventions if necessary. CGA initially detected 6 problems and on average 3 new problems during a follow-up period of 6 months. A significant number of these problems interfered with cancer treatment. The study concerned a patient group with a rather simple oncological treatment. The authors therefore concluded that one can expect an even greater benefit from a comprehensive follow-up in patients with more complex oncological treatment⁽⁸⁾. In the third study, in head and neck cancer patients undergoing curative radio(chemo)therapy, patients were assessed before and 4 weeks after start of treatment⁽⁹⁾. During treatment, the incidence of vulnerability increased in most domains included within the CGA, with especially deterioration of nutritional, functional and emotional status.

In 2014, a study protocol was published for a multicentre randomized controlled trial in head and neck cancer patients⁽¹⁰⁾. Apart from a CGA at baseline, a standardized geriatric follow-up is planned for 1 to 6 months. This follow-up each time includes a brief assessment of nutrition, mood, pain, functional status, five comorbidities, self-perceived health status, and medication use as well as implementation of interventions. The primary aim of the EGeSOR¹ trial hereby is to demonstrate that multidimensional geriatric interventions based on an initial CGA might improve outcome. In addition, it might give direction to how (which domains) and when (visit frequency) older patients should be re-evaluated. Estimated study completion date is September 2018.

Implications for clinical practice:

In an era of hospital accreditation and the constant pressure to establish quality indicators regarding appropriate medication use, our findings depict a clearly defined target group for suitable intervention. Emphasis should be placed on the development of

1 EGeSOR: Impact de l'Evaluation approfondie et du suivi Gériatriques sur la Survie, l'état fonctionnel et nutritionnel des patients âgés atteints d'un cancer ORL : un essai randomisé contrôlé multicentrique

a multidisciplinary “self-administration of medications (SAM) program”, adapted for older ambulatory patients and based on information, education and medication preparation under supervision. Current literature on SAM has focused almost exclusively on inpatients. No suggestions could be found on SAM in an outpatient clinic. Based on what is known in the literature, assessment of medication management should be combined with (pharmacist-led) medication reconciliation. Moreover, it was shown that pharmacists who work in the context of a geriatric multidisciplinary team are more successful in reducing iatrogenic illness in older adults due to a global assessment: during medication review not only clinical but also functional parameters could be taken into account⁽¹¹⁾. Thus, in an ideal world, patients should have a CGA, followed by medication reconciliation, keeping in mind the results of the geriatric assessment. After discussion with the treating physician and the creation of a medication plan, patients should be informed. Finally, medication management should be assessed, using a validated instrument preferably based on the use of own medication.

Furthermore, pending the results of larger, multicentre trials, local geriatric and oncological teams should seek for the best possible way to incorporate the concept of CGA as a whole (assessment, recommendations and interventions), with some form of long term follow-up included.

1.2 Chapter 3

One of the main concerns of a geriatric assessment is the time and the staff needed to provide a comprehensive picture of a patient, including a report on the deficits that are detected and suggestions to improve overall functionality/health. Moreover, there is a group of obviously fit older patients for which a CGA might not be necessary. Therefore, the use of a two-step approach has been promoted with initial screening and subsequent CGA if indicated. A wide variety of screening tools are used in oncology, including G8. In the third paper we focused on the performance of the G8 screening tool in patients with a haematological malignancy. Fifty patients were included in this cross-sectional study. G8, CGA (consisting of six questionnaires) and CIRS-G were completed for each patient. CGA was considered abnormal when at least one questionnaire showed an impaired score.

We could validate the G8, at the cut-off score of $G8 \leq 14$, in a population of older patients with only haematological malignancies. We thereby obtained a sensitivity of 88.6% and a specificity of 100%.

Sensitivity and specificity estimates were comparable regardless of whether ADL, IADL, or both ADL and IADL were included in our CGA. However, as ADL and IADL address different stages of dependence, with an inherent difference in life expectancy, both should be assessed.

The performance of the G8 did not change significantly when we included comorbidity in our CGA. In older cancer patients, comorbidity is an

independent predictor of mortality. It overlaps with, but is distinct from, frailty. Therefore comorbidity should be assessed routinely, independent of the G8 result.

This study was, to the best of our knowledge, the first to validate the G8 as a screening tool in a population of older patients with only haematological malignancies.

Recently, 2 reviews highlighted most commonly used screening tools and their performance ^(12,13). Through studies, sensitivity was high (>80% in six of eight studies). Specificity on the other hand was rather moderate. In this review our analyses were not yet included (not published yet). With a comparable sensitivity and a higher specificity, our results support the use of G8 as a screening tool, also in patients with haematological malignancies.

G8 is to a great extent derived from the MNA. Therefore, in the process of validation, comparing G8 to a CGA comprising the MNA might raise the question whether we selected frail patients or just patients at risk for malnutrition.

No studies are yet published in which G8 is compared to a reference CGA containing another nutritional risk score than the MNA ⁽¹⁴⁻²⁰⁾. However, in the development of the G8, one has made sure that several domains were covered that are usually assessed by a geriatrician during the course of a CGA, with only 3 items directly related to nutrition ⁽²¹⁾. Furthermore, indirectly, we can presume from our results that G8 does indeed select a frail group of patients. First, when we, in our population, excluded the MNA from the CGA, 64% of patients (compared to 88%) remained frail, which is most likely an underestimation as no nutritional assessment is than incorporated in the CGA. Second, as we discussed already as a result of the first paper, a low MNA score, irrespective of the underlying mechanism, should raise concerns about a patient. The same therefore can be assumed for a lower G8 score. Third, the correlation we found between G8 score and hand grip strength (HGS), if confirmed in larger studies, might prove an additional argument. This argumentation is further supported by recent literature. In one study, older patients with a normal G8 had a low risk for functional decline in ADL and a less pronounced decline in IADL. Moreover, several studies have shown that abnormal G8 is associated with grade 3/4 chemotherapy toxicity and overall survival, although not in haematological malignancies ^(17,22,23).

Implications for clinical practice:

Based on our results, the G8 tool can from now on be used as a valid screening tool for frailty, also in older patients with haematological malignancies. In addition, and thus independently from the results of the G8, comorbidity should be assessed in every patient, also in the apparently fit.

1.3 Chapter 4

In this chapter we assessed the possibilities of HGS as a screening tool for frailty and its association with G8 and outcome respectively. In this single centre cohort study, HGS was measured in 59 patients, using a vigorimeter. As in Chapter 3, a patient was considered frail if any of the CGA-components was impaired.

Mean HGS before start of therapy was 37.0 ± 14.3 kPa in women, 66.1 ± 13.1 kPa in men. Compared to normative data, mean HGS in our population was below expected for both men and women, in each age category. Furthermore, HGS was significantly associated with abnormal G8 and was significantly higher in patients with a normal CGA compared to those with an abnormal CGA.

Optimal cut-off points for likelihood of an abnormal CGA were ≤ 52 kPa in women (88% sensitivity and 67% specificity) and ≤ 80 kPa in men (93% sensitivity and 75% specificity), respectively.

Adverse events were registered for 35 patients (59%). Within the first six months, 17 patients died (29%). We could not detect any significant associations between HGS and subsequent adverse events or 6-month mortality.

Our results suggest that HGS might identify possibly frail patients who would benefit from a CGA and thus, potentially, a quick and valid alternative for screening questionnaires. Our findings however require validation in a larger multicentre prospective study.

This study, to the best of our knowledge, proved to be the first attempt on the use of HGS as a single item screening tool for frailty in patients with haematological malignancies.

Keeping in mind the results presented in Chapters 3 and 4, logical question emerges on which one of two options, G8 or HGS, should be preferred as a screening tool. The answer however is far less obvious.

G8 has been developed specifically as a screening tool for frailty in older patients with cancer. G8 has proven, in different populations and different tumour types, to detect 87% of frail patients overall. However, as for all screening tools, specificity and negative predictive value are considered poor⁽¹³⁾.

Like G8, most screening tools used in the decision process whether or not to refer an older patient (any older patient) for further geriatric evaluation, are questionnaire- rather than performance-based. Questionnaires, if self-administered, are

cost and timesaving. However, and especially important in older people, they assume sufficient literacy, visual acuity and (residual) cognitive skills or the presence of a caregiver. Moreover, there is the risk of misinterpretation of what is being asked, and of a patient overestimating his (physical) capabilities. Also, the patients' desire to give socially acceptable answers should be taken into account. Moreover, questionnaires might lack sensitivity for detecting small changes.

A performance-based assessment requires to perform a task on-site rather than to select an answer from a list and might therefore be a more valid indicator of patients' abilities. Also, sensitivity to clinical change is often better. More specific in the light of this thesis, measuring HGS requires minimal equipment and time, places low demand on performing staff and is well-tolerated, even by wheelchair- and bed-bound patients ⁽²⁴⁾.

Research on HGS and its association with frailty has developed exponentially after the introduction of the frailty phenotype, introduced by Fried et al. According to the Fried criteria patients were considered frail in the presence of 3 or more of the following characteristics: unintentional weight loss of ≥ 10 pounds or $\geq 5\%$ of BW in the previous year, HGS in the lowest quintile, self-reported exhaustion, slowness in walking speed, and low physical activity level. HGS, as a single item or as part of the Fried criteria, has been associated with mortality, disease-specific morbidity and disability in various populations, ranging from healthy seniors living in the community to patients with chronic diseases including cancer, and geriatric inpatients ⁽²⁴⁻²⁸⁾. For most of these studies, the prognostic value of HGS as a frailty marker was determined in relation to firm clinical endpoints rather than the results of a comprehensive geriatric assessment.

In patients with cancer only 2 studies could be identified using the Fried criteria and none using HGS as a frailty screening tool in reference to a CGA ^(12,29,30). To the best of our knowledge, our study proved to be a first attempt to determine limits of strength below which every patient should be assessed by means of a CGA for the presence or absence of frailty. These findings however require validation in a larger multicenter prospective study. In accordance with the primary aim of a screening tool, i.e. to identify all patients at risk for functional decline, we obtained a high sensitivity. Specificity on the other hand is, as with most screening tools, rather low with at least 1 out of 4 patients unnecessarily undergoing a CGA.

Based on the current scarce literature, direct comparison between both G8 and HGS as screening tools for frailty is not possible. Our own analyses found no significant difference in AUC between G8 and HGS, potentially due to a lack of power. We did find a correlation between G8 and HGS for women. Although median HGS was higher also in the group of patients with $G8 > 14$, no significant correlation could be found for men. Partly due to the limited number of patients included in the sample, we are neither able to say whether both tools identify the same patients as being frail, nor to mention whether one tool is more prognostic than the other.

A third option, in addition to the use of G8 and HGS respectively, might be the combined use of G8 and HGS, thereby encompassing subjective as well as objective measures, i.e. questions as well as performance. Based on our limited data, combining G8 and HGS did not provide an added value. In the literature discussion is still going on as to whether cognition and mood should be considered additional dimensions of frailty or just comorbid conditions, catalyzing the transition from frailty to overt disability ⁽³¹⁾.

To a lesser extent, there is also the debate on the social dimension of frailty. A recent article favoured a broader approach towards frailty. Ávila-Funes and colleagues determined that adding cognitive impairment to the Fried criteria improved its' predictive value ⁽³²⁾. De Vries et al. listed 8 frailty (risk) factors, i.e. nutritional status, physical activity, mobility, energy, strength, cognition, mood and social support, considered to be of great importance to the concept of frailty ⁽³³⁾. HGS clearly comprises just 1 frailty factor and thus 1 frailty domain. G8 on the other hand covers nutritional status, mobility, cognition and mood, i.e. 4 frailty factors and 2 frailty domains. Theoretically, combining both covers 1 additional frailty factor and might therefore better reflect the interaction between health domains and the multidimensionality of the frailty concept, and thus better fit with the holistic approach typical for a geriatrician.

Finally, but equally important, one should take into account that the selection of a screening tool might vary, depending on the situation and the subpopulation of frail older people under study. This might be especially true for intervention studies.

Implications for clinical practice:

HGS is a simple performance test, feasible in a busy clinical practice, and potentially a quick and valid alternative for screening questionnaires. Our results regarding HGS however are preliminary and require validation in a larger multicentre prospective study. Therefore, implications for clinical practice are limited for the moment. Haematology departments in possession of a Martin vigorimeter might consider determining HGS in addition to their usual work out. This will allow to gain insight in baseline HGS and its association with CGA, its evolution during and after treatment and its correlation with clinical outcomes, by analogy with current trends in cardiology ^(24,31).

Through the writing of this thesis, data on quality of life were not discussed. Nevertheless it was stipulated in the study protocol that for all patients quality of life should be assessed using the FACT-G. However, after six months, full data were available only for 29 patients. Main reasons for not completing the questionnaire were 1) the extensiveness of the questionnaire and 2) the confronting nature of some of the questions. Over 6 months, total FACT-G score improved from 73 to 80 ($p = 0.007$). Functional well-being improved from 13 to 16 ($p = 0.019$), as did physical well-being (from 23 to 26; $p = 0.004$). Quality of life improved more in patients with normal MNA-SF score at baseline than in malnourished patients or patients at risk. Social well-being and emotional well-being appeared to remain stable over time. However, these findings are preliminary and must be interpreted with caution. Further research is clearly needed.

2. LIMITATIONS OF THE THESIS

First, one main limitation of this thesis is the fact that the presented data are mainly explorative. In preparation of this study, on 19 January 2011, a rough search through PubMed was performed on existing literature concerning the use of a CGA in patients with a haematological malignancy. Combining the MESH terms “geriatric assessment” and “Hematologic Neoplasms”, “Lymphoma, Non-Hodgkin”, “Myelodysplastic Syndromes”, “Multiple Myeloma”, and “Leukemia, Myeloid, Acute” respectively, resulted in a total of 20 hits. These included 7 reviews, 1 author reply and 2 posters without article publication. In comparison, the combination of “geriatric assessment” and “breast neoplasms” identified 121 articles. These figures just illustrate that, the moment our research started, no directive information was available on the target population, the format of the CGA, the feasibility of performing a CGA, the integration of CGA results in daily practice, or its correlation with clinical outcomes. Evidence still had to be built. This thesis therefore should be considered a first exploration of the terrain. For the sake of completeness, we repeated the search almost 5 years later, on 1 December 2015. This resulted in 27 additional publications (compared to almost 50 on breast neoplasms) of which at least 12 were reviews. Current research hereby seems to focus on AML and NHL. Overall, we can argue that interest in this group is growing although there is still a big gap. Hereby we have to bear in mind that, although incidence of haematological malignancies is rising with age, the absolute number of new cases per year is still limited. Inclusion of a sufficient number of patients therefore can take several years and therefore also the publication of new results. Moreover, in recent years, some major studies were published on a mixed population of patients with solid tumours as well as patients with haematological malignancies. These studies also provide – perhaps more global, but certainly relevant and renewing - insights in the approach of an older population with haematological malignancies.

Second, there might have been a referral bias. Only a minority of our patients was found to have functional or cognitive impairments. This is considerably less than what can be found in the literature ⁽³⁴⁾. As a tertiary centre, a significant number of patients are referred from other hospitals. Referring physicians may have considered older patients with physical, cognitive or emotional problems no longer candidates for aggressive therapy. Moreover, some patients and/or their caregivers were reluctant to participate in a clinical study.

Third, the sample size was relatively small due to the monocentric nature of the study, a possible referral bias, and the initial reluctance to participate. No sample size calculations were available at onset of the study. By referring to previous research, we were able to prove sufficient power for the study on the validation of the G8. For the other studies, no reference articles were available as such. For some outcome measures (mortality, adverse events, quality of life) post hoc power analysis could have been worthwhile. Overall, 71 patients were included consecutively, while 14 patients refused to participate. All analyses were performed in the same

(sub)group of patients. No corrections were made for possible alpha-inflation. Of the 71 patients included, 5 patients dropped out and 2 patients were lost to follow-up. In addition, almost one third of patients died within the first six months. Therefore, no firm conclusions could be drawn on outcome or other clinically meaningful endpoints like adverse events, the evolution of HGS or quality of life.

Fourth, since no golden CGA exists, we retained a set of six validated questionnaires, which are routinely used and often considered as components of a CGA. Choices have also been influenced by personal experience, feasibility, extensiveness, and the potential to compare with current literature. No single questionnaire results in a perfect assessment but, in the light of this thesis, for some instruments a critical appraisal is desirable. Lawton IADL is a commonly used index to measure functional status. Limitations of Lawton IADL can include the self-report or informant report method of administration rather than performance of a functional task, which makes it relatively quick and easy to administer, but which might lead either to over- or underestimation. Lawton IADL relies on a single item to assess functional ability within complex domains such as medication management. In addition, it may not be sensitive to small incremental changes in function. It also provides no information as to the cause of the incapacity⁽³⁵⁾. The MMSE is the most commonly administered cognitive screening test. Although sensitive for overt dementia, its utility decreases when patients with mild cognitive decline or psychiatric conditions are assessed. The MMSE may lack sensitivity to early signs of dementia. Moreover, repetitive testing in short time intervals with the same instrument may produce practice effects. For high-level IADLs such as medication management, MMSE has demonstrated inconsistent relationship with functional performance and lacks sensitivity in discriminating competent from incompetent individuals (35). We therefore cannot exclude that, despite normal MMSE score, for some patients MCI might have been the cause for a loss of autonomy in medication management. Finally, no clear definition exists as to what constitutes an abnormal CGA in relation to frailty. In accordance with previous research, we therefore considered the presence of at least one questionnaire with an impaired score as an abnormal CGA. In several studies a cut-off of 2 abnormal scores was used^(14,19,22,36,37). However the number of domains that were evaluated within the CGA differed. Moreover, in all of these studies, comorbidities were included in the reference CGA. Comorbidity overlaps with, but is distinct from, frailty. Comorbidity should be assessed routinely, independent of the results of screening or CGA. Specifically for the G8, when we considered using at least two abnormal scores, prevalence diminished from 88% to 60%, while specificity fell drastically (down to 50%) for a modest gain in sensitivity (97%).

Furthermore, as this study population is very specific, the obtained results might not be generalizable to other cancer populations.

3. STRENGTHS OF THE THESIS

The field of geriatric oncology is evolving. Recently, some major studies were published on the relevance of CGA in older cancer patients. Some of these studies also included a significant number of patients with haematological malignancies. This thesis however has been one of the few research projects dedicated solely to (older) patients with haematological malignancies. Although our findings on the G8 are consistent with those published by Soubeyran et al. who examined a mixed oncology population ⁽²⁰⁾, this distinction from patients with solid tumours is necessary if only because of the distinction in treatment goals. Treatment of a haematological malignancy, in contrast with solid tumours, intends at haematological toxicity. Other treatment goals imply other chemotherapeutics and therefore different interactions and side effects, e.g. malnutrition, can be expected.

Second, we have demonstrated that a standardized approach by means of a CGA seems useful and provides insight in some formerly unidentified problems. Although time-consuming, we were able to assess every patient before start of therapy, even in patients in whom initiation of therapy was urgent.

Third, we were the first to validate the G8 as a screening tool in a population of older patients with only haematological malignancies. Moreover, we made a first attempt to explore the possibilities of HGS as a single marker of frailty.

4. CLINICAL IMPLICATIONS

During the course of this project, a closer collaboration developed between the team members of the departments of haematology and geriatrics. Meanwhile, screening and assessment in hospitalized older patients with haematological malignancies became “standard of care” and is integrated in the way of working of the internal liaison team. This intensive collaboration has led also to cross-pollination of expertise in this specific population. Furthermore, attempts have been made to integrate our findings in daily routine (e.g. screening of cancer patients with G8 instead of Geriatric Risk Profile (GRP)) and to set up new research to tackle some of the encountered problems (e.g. the use of START/STOPP criteria in the light of polypharmacy).

5. FUTURE PERSPECTIVES

The number of older patients with a haematological malignancy will further increase in the next decades, due to aging of the population. Similarly, the number of frail patients will continue to grow.

Keeping in mind the time-investment needed to perform a CGA, future studies should focus on screening tools allowing an optimal selection of patients for further geriatric evaluation. Different tools with good sensitivity are already available. Now research should focus on the optimization of specificity and negative predictive value. Instead of developing new screening tools, combining existing tools in a flow diagram, might prove a valuable option.

Furthermore, the potential of HGS as a marker of increasing frailty during treatment should be further explored. Declining HGS below the proposed cut-points could be an indicator for renewed geriatric evaluation.

Growing evidence is available that geriatric parameters should be considered when planning cancer treatment. Studies nowadays are primarily focusing on treatment adaptations, with alterations in dose, frequency, or inclusion of less toxic agents. Geriatricians aim for a more holistic approach including geriatric interventions tailored to the results of the CGA. In the general geriatric population, these interventions, linked with follow-up, have proven their effectiveness in improving functional status and survival. A SIOG task force has been established to review available data on geriatric interventions in cancer patients. Ten articles and 5 abstracts have been identified, some of which suggest a positive impact on the patient's condition and outcome. Studies however are small, and very heterogeneous in patients as well as in interventions (case management type interventions, exercise-based interventions, nutritional interventions, interventions for prevention of delirium, chemotherapy toxicity, or post-operative pain, and quality of life interventions), and with different endpoints⁽⁶⁾. As yet no recommendations have been published. Meanwhile, geriatric interventions currently proven beneficial in the general population can be applied, keeping in mind some disease-specific limitations. In future research, a well-defined impairment in a CGA domain, an appropriate selection of patients, an appropriate intervention and a well-defined outcome measure seem crucial to achieve usable conclusions. Furthermore, one should focus on the incorporation of CGA results and interventions into an individualized treatment plan for frail older patients.

After all, optimizing the overall condition of a frail older patient with a haematological malignancy might indicate the difference between full therapy and downgrading of treatment or merely supportive care.

Briefly, haematologists are increasingly confronted with older patients, characterized by decreased physiological reserves and an increased vulnerability to adverse outcomes. Adequate screening tools allow a better selection of patients in need of further geriatric evaluation. CGA hereby does reveal additional health problems, also in patients with haematological malignancies. Particular attention should be paid to nutrition and polypharmacy. Elaboration of multidisciplinary care pathways and close collaboration between team members of the departments of haematology and geriatrics are of vital importance to tackle some currently unmet needs.

REFERENCE LIST

- (1) Bauduer F, Scribans C, Dubernet E, Capdupuy C. Evaluation of the nutritional status of patients over 60-year admitted in a hematology department using the mininutritional assessment (MNA). A single centre study of 120 cases. *J Nutr Health Aging* 2003;7(3):179-82.
- (2) Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014 Aug 20;32(24):2595-603.
- (3) Aaldriks AA, Maartense E, le Cessie S, Giltay EJ, Verlaan HACM, van der Geest LGM, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Critical Reviews in Oncology/Hematology* 2011;79(2):205-12.
- (4) Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 2012;118(13):3377-86.
- (5) Gioulbasanis I, Baracos VE, Giannousi Z, Xyrafas A, Martin L, Georgoulas V, et al. Baseline nutritional evaluation in metastatic lung cancer patients: Mini Nutritional Assessment versus weight loss history. *Annals of Oncology* 2010 Oct 11.
- (6) Cornélias F, Cornette P, Moor R, Alibhai S, Korc-Grodzicki B, McCorkle R, et al. Geriatric interventions in older cancer patients: International society of geriatric oncology (siog) recommendations. *Journal of Geriatric Oncology* 2014 Oct;5, Supplement 2:S60.
- (7) Alessi CA, Stuck AE, Aronow HU, Yuhas KE, Bula CJ, Madison R, et al. The process of care in preventive in-home comprehensive geriatric assessment. *J Am Geriatr Soc* 1997 Sep;45(9):1044-50.
- (8) Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. *Critical Reviews in Oncology/Hematology* 2004 Jan;49(1):69-75.
- (9) Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, et al. Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. *Eur J Cancer Care (Engl)* 2014 May;23(3):401-12.
- (10) Brugel L, Laurent M, Caillet P, Radenne A, Durand-Zaleski I, Martin M, et al. Impact of comprehensive geriatric assessment on survival, function, and nutritional status in elderly patients with head and neck cancer: protocol for a multicentre randomised controlled trial (EGeSOR). *BMC Cancer* 2014;14(1):427.
- (11) Onder G, van der Cammen TJM, Petrovic M, Somers A, Rajkumar C. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age and Ageing* 2013 May 1;42(3):284-91.
- (12) Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Annals of Oncology* 2014 Jun 16.
- (13) Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *The Lancet Oncology* 2012 Oct;13(10):e437-e444.
- (14) Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *Journal of Geriatric Oncology* 2013 Jan;4(1):32-8.
- (15) Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012 Jan 16;23:2166-72.
- (16) Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K, Scalliet P, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Annals of Oncology* 2013 May 1;24(5):1306-12.
- (17) Liuu E, Canou+»-Poirine F, Tournigand C, Laurent M, Chaubet M, Caillet P, et al. External validation of the G-8 geriatric screening tool to identify vulnerable elderly cancer patients: The ELCAPA-02 study. *Journal of Geriatric Oncology* 2012 Oct;3, Supplement 1:S45-S46.

- (18) Luce S, De Breucker S, Van Gossum A, Demols A, Mekinda Z, Ena G, et al. How to identify older patients with cancer who should benefit from comprehensive geriatric assessment? *Journal of Geriatric Oncology* 2012 Oct;3(4):351-8.
- (19) Pottel L, Boterberg T, Pottel H, Goethals L, Van Den Noortgate N, Duprez Fd, et al. Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo)therapy. *Journal of Geriatric Oncology* 2012 Jan;3(1):24-32.
- (20) Soubeyran P, Bellera C, Goyard J, Heitz D, Cure H, Rousselot H, et al. Validation of the G8 screening tool in geriatric oncology: The ONCODAGE project. *ASCO Meeting Abstracts* 2011 Jun 9;29(15_suppl):9001.
- (21) Soubeyran P, Bellera CA, Gregoire F, Blanc J, Ceccaldi J, Blanc-Bisson C, et al. Validation of a screening test for elderly patients in oncology. *ASCO Meeting Abstracts* 2008 Aug 18;26(15_suppl):20568.
- (22) Kenis C, Decoster L, Van Puyvelde K, De Gruyve J, Conings G, Milisen K, et al. Performance of Two Geriatric Screening Tools in Older Patients With Cancer. *Journal of Clinical Oncology* 2014 Jan 1;32(1):19-26.
- (23) Stokoe JM, Pearce J, Sinha R, Ring A. G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer. *Journal of Geriatric Oncology* 2012 Oct;3, Supplement 1:S81.
- (24) Chung CJ, Wu Chri, Jones Meag, Kato TS, Dam TT, Givens RC, et al. Reduced Handgrip Strength as a Marker of Frailty Predicts Clinical Outcomes in Patients With Heart Failure Undergoing Ventricular Assist Device Placement. *J Card Fail* 2014 May 22;20(5):310-5.
- (25) Chang YT, Wu HL, Guo HR, Cheng YY, Tseng CC, Wang MC, et al. Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases. *Nephrol Dial Transplant* 2011 Nov;26(11):3588-95.
- (26) Guo CB, Zhang W, Ma DQ, Zhang KH, Huang JQ. Hand grip strength: an indicator of nutritional state and the mix of postoperative complications in patients with oral and maxillofacial cancers. *Br J Oral Maxillofac Surg* 1996 Aug;34(4):325-7.
- (27) Kilgour RD, Vignano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer* 2013 Dec;21(12):3261-70.
- (28) Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc* 2003 May;51(5):636-41.
- (29) Biganzoli L, Boni L, Becheri D, Zafarana E, Biagioni C, Cappadona S, et al. Evaluation of the cardiovascular health study (CHS) instrument and the Vulnerable Elders Survey-13 (VES-13) in elderly cancer patients. Are we still missing the right screening tool? *Ann Oncol* 2013 Feb;24(2):494-500.
- (30) Molina-Garrido M, Guillén-Ponce C, Muñoz Sanchez M, Garcia-Cano J. A comparison of the fried criteria and the VES-13 questionnaire as screening instruments for frail elderly patients diagnosed with cancer. *European Geriatric Medicine* 2 (suppl 1), S34. 2011. Ref Type: Abstract
- (31) Gary R. Evaluation of frailty in older adults with cardiovascular disease: incorporating physical performance measures. *J Cardiovasc Nurs* 2012 Mar;27(2):120-31.
- (32) Avila-Funes JA, Amieva H, Barberger-Gateau P, Le GM, Raoux N, Ritchie K, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *J Am Geriatr Soc* 2009 Mar;57(3):453-61.
- (33) de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011 Jan;10(1):104-14.
- (34) Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007 May 10;25(14):1824-31.

- (35) Elliott RA, Marriott JL. Standardised assessment of patients' capacity to manage medications: a systematic review of published instruments. *BMC Geriatr* 2009;9:27.
- (36) Luciani A, Ascione G, Bertuzzi C, Marussi D, Codecá C, Di Maria G, et al. Detecting Disabilities in Older Patients With Cancer: Comparison Between Comprehensive Geriatric Assessment and Vulnerable Elders Survey-13. *Journal of Clinical Oncology* 2010 Apr 20;28(12):2046-50.
- (37) Mohile SG, Bylow K, Dale W, Dignam J, Martin K, Petrylak DP, et al. A pilot study of the vulnerable elders survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. *Cancer* 2007 Feb 15;109(4):802-10.

Samenvatting

Er is een belangrijke toename van de groep ouderen met kanker door de vergrijzing van de bevolking. Ouderen vormen echter een zeer heterogene groep met belangrijke verschillen in levensverwachting en functionaliteit tussen leeftijdsgenoten. Bijgevolg kunnen de behandelingsrichtlijnen, zoals deze worden gehanteerd bij jongere individuen, niet zomaar doorgetrokken worden naar de groep van ouderen. Het doel van deze doctoraatsthesis was dan ook om na te gaan of een geriatrische benadering en meer specifiek het gebruik van een CGA een meerwaarde kon betekenen in de selectie van patiënten met een geriatrisch profiel, in de detectie van geriatrische syndromen en in de keuze en de uitkomst van de ingestelde behandeling.

In deze thesis toonden we aan dat aan de hand van een CGA, ook in patiënten met een hematologische maligniteit, vooraf niet gekende problemen konden worden gedetecteerd. Een ruime meerderheid van de oudere patiënten vertoont bij screening een risico op ondervoeding of scoort ondervoed. Gezien de bewezen negatieve impact van ondervoeding op een oncologische behandeling zijn regelmatige opvolging en het introduceren van gerichte interventies in samenspraak met een diëtiste essentieel, ook al is op heden de doeltreffendheid van deze interventies nog onvoldoende bewezen.

Uit geriatrische evaluatie in deze thesis bleek ook duidelijk dat een behandeling met chemotherapie, en inherent hieraan het gebruik van supportieve medicatie, leidt tot polyfarmacie en frequente wijzigingen in het medicatieschema. Hierdoor is meer dan de helft van de patiënten niet langer in staat zelfstandig zijn medicatie klaar te zetten en in te nemen. Rekening houdend met het feit dat vele ouderen alleenstaand zijn of een partner hebben van dezelfde leeftijd dient in het behandelingstraject van deze patiënten op een gestructureerde manier, en bij herhaling, te worden gepeild naar de functionele autonomie van patiënten met betrekking tot medicatie.

Tijdens het onderzoek werd niet alleen gekeken naar de aanwezigheid van typisch geriatrische syndromen, maar werd ook gefocust op een correcte selectie van patiënten. Een CGA is immers zeer tijdrovend en niet voor iedere patiënt noodzakelijk.

Binnen de oncologie wordt gepleit voor een twee stappenbenadering waarbij patiënten eerst gescreend worden op de aanwezigheid van een geriatrisch profiel en pas in tweede tijd, indien de screening positief uitvalt, worden doorverwezen voor een CGA. Tijdens de studie werden twee screeningsinstrumenten beoordeeld op hun waarde. De G8 (met een afkapwaarde van ≤ 14) kon worden gevalideerd voor oudere patiënten met een hematologische maligniteit. In tegenstelling tot de G8, die is opgebouwd uit 8 vragen, is handgrijpkracht een performantiemaat waardoor men een meer objectieve weergave verkrijgt van de functionele mogelijkheden van een patiënt. In vergelijking met gezonde ouderen is de handgrijpkracht bij ouderen met hematologische maligniteiten lager, en dit al voor de start van de behandeling. Gebruik makend van een Martin vigorimeter werden, binnen de krijtlijnen van deze thesis, minimumwaarden voor handgrijpkracht berekend voor mannen en vrouwen. Alle patiënten met een lagere handgrijpkracht zouden moeten worden doorverwezen voor verdere geriatrische evaluatie.

Deze thesis vormt slechts een eerste aanzet in het onderzoek naar de multidisciplinaire aanpak van oudere patiënten met hematologische maligniteiten. Verder onderzoek moet zich richten, enerzijds op interventies die, voor de start van de behandeling, de functionaliteit van de kwetsbare patiënt kunnen optimaliseren, en anderzijds op nieuwe behandelingsmodaliteiten waarin de bevindingen van het geriatrisch bilan worden meegenomen. Integratie van de resultaten van beide onderzoekslijnen zou uiteindelijk moeten leiden tot een behandelingsplan op maat van de individuele patiënt.

Summary

A significant increase has been seen in the number of older patients with cancer due to population ageing. Ageing however is a highly individualized and very heterogeneous process with a broad spectrum ranging from older persons who are functionally independent to those who are at high risk of functional decline and mortality and all the others in between. Fit older patients should logically receive the same treatment as their younger counterparts. The main problem however is the group of frail patients at increased risk for treatment complications. The main aim of this doctoral thesis was to explore whether in older patients with haematological malignancies a geriatric approach, and in particular a comprehensive geriatric assessment (CGA), might be worthwhile in the selection of patients with a geriatric profile, in the detection of geriatric syndromes and in the prediction of patient outcomes.

In this thesis, we demonstrated that, also in patients with a haematological malignancy, a CGA can identify previously unknown geriatric problems in an individual. Through nutritional screening a large majority of patients was identified with potential nutritional problems. Given the negative impact of malnutrition on an anticancer treatment, regular follow-up and implementation of specific interventions, in collaboration with a dietician, are essential, even though efficacy of these interventions has not yet been adequately proven.

Moreover, geriatric evaluation in this thesis has clearly proven that chemotherapy, and inherent use of supportive medication, leads to polypharmacy and frequent changes in medication regimen. Because of this, more than half of the patients are no longer able to manage their medication independently. As most older patients are living alone or are taken care of by a partner of the same age, their current care pathway should include a structured and repeated evaluation of functional autonomy with regard to medication management.

This thesis did focus not only on the detection of geriatric syndromes, but also on a correct selection of patients with a geriatric profile, as the administration of a CGA is time and staff-consuming. Therefore a two-step approach is proposed with the

use of a screening tool to identify those patients that subsequently would benefit most from a CGA. During the conduct of our study we tested the performance of two different screening tools. G8 (with a cut-off of ≤ 14) could be validated for use in older patients with haematological malignancies. In contrast with G8, an 8-item questionnaire, hand grip strength is a performance-based measure and therefore a more objective reproduction of a patient's functional reserves. In contrast with healthy individuals, we found that hand grip strength was reduced in patients with haematological malignancies, even before onset of treatment. Using a Martin vigorimeter, we also determined minimum values for hand grip strength in men and women. Below these values, all patients should be referred for further geriatric evaluation.

This doctoral thesis should be considered a first onset in the development of a multidisciplinary approach in older patients with haematological malignancies. Further research should focus for one thing on interventions that, before start of treatment, can optimize the functional reserves of a frail patient, and for another thing on new treatment modalities incorporating the results of the CGA. Integration of the results of both lines of investigation should eventually lead to a treatment plan tailored to the individual patient.

Dankwoord

Op het einde van een doctoraat hoort een dankwoord. Dit dankwoord kwam tot stand in stukjes. Er kwamen stukjes bij in een plotse bui van inspiratie of wanneer ik op wolkjes liep omdat alles ging zoals ik het wou. Vaker nog kwamen er stukjes bij wanneer het wat moeilijker liep en een woord, een gebaar of een stevige knuffel van familie, vrienden of collega's mij telkens opnieuw deed beseffen door welke fijne mensen ik dag in dag uit omringd word.

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Geriatric wordt zelden beschouwd als "topklinische" of "topreferente" zorg. Geriatric haalt zelden de nationale pers, behalve door het tekort aan geriateren. Wat ik nochtans als "top" ervaren heb, is het feit dat de directie van het UZ Gent, door de toekenning van een KOF-mandaat aan dit onderzoek, een signaal heeft gegeven dat ook in een universitair centrum met een zeer gespecialiseerde visie, ruimte is voor onderzoek naar verbetering van de zorg voor oudere patiënten.

En met dit KOF-mandaat kwam Rein, mijn steun en toeverlaat. Rein, we hebben ruim twee jaar hetzelfde bureau gedeeld. We hebben veel gebabbeld. We hebben nog meer gewerkt. Alleen dankzij jouw onvermoeibare en onvoorwaardelijke inzet konden de gegevens verzameld worden waarop dit proefschrift is gebaseerd. Jouw minutieuze registratie van elk detail in het verhaal van de patiënt liet mij toe om steeds een antwoord te krijgen op nieuwe vragen die opdoken, ook nadat onze wegen zich scheidden. Lieve Rein, zonder jou stond ik hier niet.

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Curriculum Vitae

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Medical Degree, Ghent University, 1996
Internal Medicine, Ghent University, 2001
Geriatrics, Ghent University, 2002

Interuniversity postgraduate course in palliative care (2002 – 2003)
Postgraduate course: practically-oriented statistics, Ghent University (2002-2003)

TRAINING COURSES

European Academy for Medicine of Ageing
The End of the Disease Era – January 2009
How to provide Geriatric Care – June 2009
Detection and Assessment of Dementia – January 2010
Anti-ageing Medicine – June 2010

IAGG's intensive course on ageing (2012)

AWARDS

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SCIENTIFIC MEMBERSHIP

Member of the Belgian Society of Gerontology and Geriatrics
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Member of the European Union Geriatric Medicine Society

PUBLICATIONS, INTERNATIONAL, PEER REVIEWED

The role of ultrasonography in the assessment of renal function in the elderly.
N. Van Den Noortgate, [A. Velghe](#), M. Petrovic, C. Vandewiele, N. Lameire, D. Voet,
M. Afschrift.
J Nephrol. 2003;16(5): 658-62

Streptococcus milleri-sepsis with lung and brain abscesses.
[A. Velghe](#), N. Van Den Noortgate, W. Janssens, P. Smeets, D. Vogelaers.
Acta Clinica Belgica 2004; 59:369-372 .

Incremental prognostic value of combined perfusion and function assessment during myocardial gated SPECT in patients aged 75 years or older.
De Winter O, [Velghe A](#), Van de Veire N, De Bondt P, De Buyzere M, Van De Wiele C, De Backer G, Gillebert TC, Dierckx RA, De Sutter J.
J Nucl Cardiol. 2005;12(6):662-70.

Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E'/E').
J. De Sutter, J. De Backer, N. Van de Veire, [A. Velghe](#), M. De Buyzere, T. Gillebert.
Am J Cardiol 2005; 95: 1020-1023.

Echocardiographically estimated left ventricular end-diastolic and right ventricular systolic pressure in normotensive healthy individuals

N. Van de Veire, J. De Backer, A-K. Ascoop, B. Middernacht, [A. Velghe](#), J. De Sutter.
Int J Cardiovasc Imaging 2006; 22(5): 633-641.

Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk.

K. De Ruyck, M. Szaumkessel, I. De Rudder, A. Dehoorne, A. Vral, K. Claes, [A. Velghe](#), J. Van Meerbeeck, H.Thierens.
Mutat Res. 2007;631(2): 101-110

L'hôpital de jour gériatrique: quels objectifs, quelle organisation, quelle efficience? Une revue de la littérature.

J. Petermans, [A. Velghe](#), D. Gillain, X. Boman, N. Van Den Noortgate.
Ger psychol Neuropsychiatr Vieil 2011 ; 9(3) : 295-303.

The Belgian geriatric day hospitals as part of a care program for the geriatric patient: first results of the implementation at the national level.

[A. Velghe](#), L. Kohn, J. Petermans, D. Gillain, M. Petrovic, N. Van Den Noortgate.
Acta Clinica Belgica 2011; 66(3): 186-190

The process of decline in advanced activities of daily living: a qualitative explorative study in mild cognitive impairment.

P. De Vriendt, E. Gorus, E. Cornelis, [A. Velghe](#), M. Petrovic, T. Mets.
International Psychogeriatrics 2012; 24(6): 974-86

Validation of the G8 screening tool in older patients with aggressive haematological malignancies.

[A. Velghe](#), M. Petrovic, S. De Buyser, R. Demuynck, L. Noens.
Eur J Oncol Nurs 2014; 18(6): 645-8

Prevalence of symptoms in older palliative cancer patients: a systematic review and meta-analysis.

Van Lancker A., [Velghe A.](#), Van Hecke A., Verbrugghe M., Van Den Noortgate N., Grypdonck M., Verhaeghe S., Bekkering G., Beeckman D.
J Pain Symptom Manage 2014; 47(1): 90-104

Evaluation of the nutritional status in older patients with aggressive haematological malignancies using the MNA-SF.

[A. Velghe](#), L. Noens, R. Demuynck, S. De Buyser, M. Petrovic.
Eur Geriatr Med 2014; 5(4): 258-260

Hand grip strength as a screening tool for frailty in older patients with haematological malignancies.

[A. Velghe](#), S. De Buyser, L. Noens, R. Demuynck, M. Petrovic.
Acta Clin Belg 2016. Doi: 10.1080/17843286.2016.1162381

PUBLICATIONS, NATIONAL, PEER REVIEWED

Het Ewing-saroom bij volwassenen: verleden, heden en toekomst.

A. Velghe, I. Hoffman, S. Van Belle.

Tijdschrift voor Geneeskunde 2003; 59: 109-114

De nieuwe medicatie voor Alzheimerdementie: farmaco-economische benadering.

A. Velghe, W. Michielsens.

Tijdschrift voor geneeskunde 2004; 60: 1761-1765.

De behandeling van chronische pijn met opiaten bij een oudere populatie :
indicaties en aanbevelingen.

N. Van Den Noortgate, M. Petrovic, A. Velghe, W. Michielsens.

Tijdschrift voor Geneeskunde 2004; 61: 434-440.

Pijn en de bejaarde : basisprincipes van de behandeling.

A. Velghe, N. Van Den Noortgate, M. Petrovic, W. Michielsens.

Tijdschrift voor Geneeskunde 2004; 61: 428-433.

Is pijn bij de oudere echt een probleem?

M. Petrovic, N. Van Den Noortgate, A. Velghe, A. Mariman, W. Michielsens.

Tijdschrift voor Geneeskunde 2004; 61: 417-422.

Diabetes mellitus bij ouderen: richtlijnen voor het vroegtijdig opsporen van
geriatrische syndromen. N. Van Den Noortgate, W. Janssens, M. Petrovic,
A. Velghe, W. Michielsens.

Tijdschrift voor geneeskunde 2006; 62: 604-609

Verwikkelingen van diabetes mellitus bij ouderen: screening en behandelings-
strategieën.

M. Petrovic, N. Van Den Noortgate, W. Janssens, A. Velghe, W. Michielsens.

Tijdschrift voor Geneeskunde 2006; 62: 617-625.

Diabetes bij de hoogbejaarde: richtlijnen voor glycemiecontrole en behandeling.

W. Janssens, M. Petrovic, N. Van Den Noortgate, A. Velghe, W. Michielsens.

Tijdschrift voor Geneeskunde 2006; 62: 610-616

Slapeloosheid bij de oudere: farmacologische aanpak.

A. Velghe, M. Petrovic, A. Mariman, W. Michielsens.

Tijdschrift voor Geneeskunde 2007; 63(20): 969-973

Slapeloosheid bij de oudere: slaap-waakhygiëne en cognitieve gedragstherapie.

A. Mariman, M. Petrovic, A. Velghe, W. Michielsens.

Tijdschrift voor Geneeskunde 2007; 63(20): 965-968

Slaappatronen en de meest voorkomende slaapaandoeningen bij ouderen.
M. Petrovic, D. Pevernagie, [A. Velghe](#), A. Mariman, W. Michielsen.
Tijdschrift voor Geneeskunde 2007; 63(20): 974-978

Multiresistente micro-organismen in thuisvervangende instellingen.
[A. Velghe](#), D. Vogelaers.
Tijdschrift voor Geneeskunde 2007; 63(5): 169-173

Fragiele ouderen: verschillen ten opzichte van normale veroudering en maatregelen om de functie te behouden. G. Monsieur, N. Van Den Noortgate, [A. Velghe](#), M. Petrovic.
Tijdschrift voor Geneeskunde 2009; 65(17): 783-787

Een oudere patiënt met renale diabetes insipidus ten gevolge van lithiumintoxicatie.
K. Van Mulders, [A. Velghe](#), N. Van Den Noortgate, M. Petrovic.
Tijdschrift voor Geneeskunde 2010; 66(2): 85-89

Dertig jaren Percutane Endoscopische Gastrostomiesonde (PEG): ethische bedenkingen.
L. Vandenabeele, [A. Velghe](#).
Tijdschrift voor Geneeskunde 2011; 67(3): 126-128

Prevalence of symptoms in the elderly with incurable cancer: a systematic review.
A. Van Lancker, [A. Velghe](#), M. Verbrugghe, G. Bekkering, D. Beeckman.
JBI Database of Systematic Reviews and Implementation Reports 2012; 10 (28, suppl.): S118-S138

Chemotherapie voor colorectaal carcinoma bij oudere patiënten.
M. De Man, [A. Velghe](#), S. Laurent, K. Geboes.
Tijdschr. Voor Geneeskunde 2015; 71: 982-990.

Loss of functional autonomy in medication management after start of therapy in older patients with haematological malignancies.
[A. Velghe](#), L. Noens, S. De Buyser, R. Demuynck, M. Petrovic.
Eur J Oncol 2016; 21(1): 14-20.

PUBLICATIONS, NATIONAL

Evaluatie van de proefprojecten "geriatrie dagziekenhuizen". Partim exploratie van de barrières en stimuli voor het doorverwijzen naar de geriatrie dagziekenhuizen zoals gepercipieerd door de huisartsen.
N. Van Den Noortgate, J. Petermans, D. Giet, P. Denoël, C. Duchesnes, [A. Velghe et al.](#)
Brussel: Federale Overheidsdienst Volksgezondheid, veiligheid van de voedselketen en leefmilieu; Directoraat-Generaal Organisatie Gezondheidsvoorzieningen; 2008.

Evaluation des hôpitaux de jour gériatriques en Belgique. Partim exploration des barrières et des incitants en matière de référence aux hôpitaux de jour gériatriques tels qu'ils sont perçus par les médecins généralistes.

N. Van Den Noortgate, J. Petermans, D. Giet, P. Denoël, C. Duchesnes, A. Velghe *et al.* Bruxelles: Service publique fédéral – Santé publique, sécurité de la chaîne alimentaire et environnement. Direction Général Organisation des établissements de soins ; 2008.

BOOK CHAPTER

Velghe A. Baeyens JP. De patiënt met plasproblemen.

In: Olde Rikkert MGM, Flamaing J, Petrovic M, Schols JMGA, Hoefnagels WHL (eds) *Probleemgeoriënteerd denken in de geriatrie*; Tijdstroom uitgeverij Utrecht, 2008, p. 159-172

ABSTRACTS

Plaats van de "Clock Drawing Test" bij detectie van cognitieve dysfunctie bij gehospitaliseerde geriatrische patiënten.

C. Sached, M. Petrovic, N. Van Den Noortgate, A. Velghe, G. Van Maele, W. Michielsens. Proceedings van de 28ste wintermeeting van de Belgische vereniging voor Gerontologie en Geriatrie. Lannoo Campus 2006; p. 51-2

Quality of end of life policy.

R. Piers, N. Van Den Noortgate, W. Schrauwen, S. Maertens, A. Velghe, M. Petrovic *et al.*
J Nutr Health Aging 2008; p. 565

Systematic problem identification adds information to the admission reason in a geriatric day hospital.

A. Velghe, J. Petermans, D. Gillain, N. Van Den Noortgate.
J Nutr Health Aging 2008; p. 578

Screening for falls on the geriatric ward: are instruments performing better than nurses?

N. Van Den Noortgate, J. Dekoninck, A. Ligneel, A. Velghe, M. Petrovic.
J Nutr Health Aging 2009; p. S264

First steps towards validation of a symptom scale for palliative elderly.

M. De Roo, A-A. Uyttersprot, M. Petrovic, A. Velghe, R. Piers, N. Van Den Noortgate.
Palliat Med 2010; p. S201

Nurses' moral distress in the care of older persons at the end-of-life: the importance of care setting and involvement in end-of-life decisions.
R. Piers, M. Dewitte, E. Steeman, K. Clinquant, M. Petrovic, A. Velghe, N. Van Den Noortgate.
Tijdschrift voor Gerontologie en Geriatrie; 33e wintermeeting 2010.

Is screening for malnutrition useful in older patients with aggressive haematological malignancies?
A. Velghe, L. Noens, R. Demuynck, M. Petrovic.
Eur Ger Med 2013; p. S69

Validation of the G8 in older patients with a haematological malignancy.
A. Velghe, M. Petrovic, S. De Buyser, R. Demuynck, L. Noens.
Eur Ger Med 2013; p. S69

Optimization of pharmacotherapy and adherence in older patients with a haematological malignancy.
A. Velghe, M. Petrovic, R. Demuynck, L. Noens.
Haematological disorders in the Elderly, ESH International Conference, Abstract book. European School of Haematology 2013.

Nocturia and nocturnal polyuria in older patients.
M-A. Denys, V. Decalf, E. Bruneel, A. Velghe, M. Petrovic, K. Everaert.
Elautprijs, Samenvattingen 2016.

Evaluatie van de kwaliteit van voorschrijven bij oudere patiënten met onco-hematologische aandoeningen.
B. Vandervennet, A. Velghe, M. Petrovic.
Tijdschrift voor Gerontologie en Geriatrie 2016; p. 44

PARTICIPATION IN SCIENTIFIC PROJECTS

Hulpmiddelen in de thuiszorg voor de oudere met dementie: haalbaar en efficiënt?
(2005-2006)

De Vlaamse richtlijn voor de verpleegkundige continentiezorg in de woon- en zorgcentra (expert – 2008)

Evaluatie van de proefprojecten "Geriatrisch dagziekenhuis" (2007-2008)

Financing of the Geriatric Day Hospital (2007-2008)

Implementatie van een zorgmodel voor oudere patiënten met oncologische en hematologische aandoeningen in de acute zorgsetting (Aktie 24 van het kankerplan – 2012-2015)

