

## REVIEW ARTICLE

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# Oral administration of antineoplastic agents: the challenges for healthcare professionals

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## Summary

Recent progress in cancer treatment has increased the use of oral antineoplastic agents. It is now estimated that at least 25% of the existing antineoplastic agents are planned to be used as oral agents and this mode of administration is likely to increase in the coming years. The use of oral antineoplastic agents affects many aspects of cancer treatment, and despite advantages, it also poses challenges to health care professionals and patients, many of which refer to the adherence and safety. Low patient adherence demonstrates the need for better management and monitoring of patients on oral antineoplastic agents. Patient education is essen-

tial to maintain adherence to oral antineoplastic therapy, promoting a better understanding of the patient treatment regimen, treatment goals and potential side-effects, patient safety and implementation of self-care measurement. This article discusses the above-mentioned challenges, as well as the possibilities of patient and family education to improve adherence, outcomes of treatment and quality of life, and offers recommendations for practice and further research.

**Key words:** adherence to treatment, oral antineoplastic agents, patient education

## Introduction

Recent progress in the treatment of cancer has accelerated an increasing use of oral antineoplastic agents [1]. From less than 5% a decade ago, the number of oral cancer agents in use has increased to approximately 17% by 2007, and it is now estimated that at least 25% of the existing antineoplastic agents are planned to be used as oral agents [2-4]. Many new therapies are available only in oral form [5], and this mode of administration is likely to increase in the coming years [6].

The new agents in development are heterogeneous. Some are cytotoxic, but with the development of new drug targets the majority of oral drugs to be approved in the future will constitute targeted therapies or biologic therapies [2,3,7].

The number of oral antineoplastic agents approved by the United States Food and Drug Ad-

ministration (FDA) has grown substantially over the past 10 years [8]. More than 30 new oral antineoplastic agents had been approved since 1998, when capecitabine was approved [9]. Capecitabine, cyclophosphamide, methotrexate, temozolomide, melphalan and targeted drugs such as imatinib, lapatinib, sorafenib, sunitinib, gefitinib and erlotinib are examples out of a long list of oral antineoplastic agents [5,8,10-12].

The use of oral antineoplastic agents affects many aspects of cancer treatment, and creates significant safety and adherence issues, shifting some traditional roles and responsibilities of doctors, nurses and pharmacists to patients and caregivers [3]. This new treatment paradigm shifts delivery of intravenous (IV) chemotherapy from a controlled and monitored process by physicians and oncology nurses in hospitals and outpatient

clinics, to patients' homes where the complexity of knowing dosing and side effects becomes a responsibility of the patient, their family and caregivers [1].

The development of oral agents has changed the paradigm of patients' education also. This has resulted in new challenges for oncology professionals to ensure that patients receive education regarding oral agents in a comprehensive, consistent and practical manner [2].

Compared to IV chemotherapy, oral antineoplastic agents provide many advantages to the patients, including greater flexibility and convenience, less time away from work and family, no need for, sometimes painful, IV access, and greater sense of independence because the agents can be self-administered [7,13-15]. Taken together, the use of oral antineoplastic agents has the potential to enhance a better quality of life in comparison to parenteral chemotherapy [4,9,14]. Although IV therapy has advantages, it has also some disadvantages like risks of extravasations, venous sclerosis, infection and injection site reaction. In addition, patients with poor venous access may require insertion of a venous access device, which carries the risk of intraoperative or postoperative complications such as pneumothorax. Long-term use of venous access devices might be associated with infection, bleeding, and venous thrombosis [5,14].

On the other hand, oral antineoplastic therapy is not free from toxicities either. It has side effects some of which exceed the prevalence and severity of those observed with IV chemotherapy. Also, some newer oral antineoplastic agents may cause unusual side effects or those that are not easily recognized. Patients should be aware that oral chemotherapy is not less effective than IV chemotherapy because this misconception still exists [7,16,17].

According to the results of several studies, most cancer patients prefer to be on oral antineoplastic therapy compared to IV therapy [18-21]. For example, a randomized, crossover study comparing patients' preference for oral capecitabine and IV 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer had shown that the majority of patients prefer oral to IV therapy [18]. Liu et al. found similar results. In their study of 103 patients, 89% reported a preference for oral chemotherapy over infusion therapy, pointing as a major reason that oral chemotherapy did not require IV access or additional visits to the clinic/hospital for treatment [20]. Catania

et al. showed that patients taking oral chemotherapy felt less ill and were able to face their illness easier in comparison with traditional IV chemotherapy [21]. Therefore, oral administration of antineoplastic agents offers advantages, which could promote better quality of life of cancer patients and their families [7].

Despite advantages, oral antineoplastic agents also pose challenges to health care providers and patients, many of which refer to the adherence and safety [7,9,10]. This article discusses these challenges, as well as the possibilities of patient and family education to improve adherence, outcomes of the treatment and quality of life and offers recommendations for practice and further research.

### **Patient's adherence and persistence**

The International Society for Pharmacoeconomics and Outcome Research (ISPOR) Medication Compliance and Persistence Working Group recently defined adherence as synonymous with compliance, which is "the degree on extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency" [22]. It may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [22]. Although the terms "adherence" and "compliance" are used alternately, "adherence" is generally preferred to "compliance" because "compliance" suggests that the patient is a passive follower of the doctor's orders, and "adherence" implies that the treatment plan is based on a therapeutic alliance between the patient and the healthcare provider [23,24]. Optimal adherence is achieved "if no doses are missed, no extra doses are taken, and no doses are taken in the wrong quantity or at the wrong time" [25]. Medication persistence may be defined as "the duration of time of initiation to discontinuation of therapy" [22]. Optimal persistence occurs when a patient takes a medication as long as it is prescribed. Currently, there is no consensus regarding a definition for "adequate adherence", with investigators using ranges of between 80 and 95%, although there are limited data to support this standpoint [25]. In general, a patient is considered to be adherent if he takes 80% of a prescribed medication [1,23-25].

Healthcare professionals often presume that their patients are taking medications as prescribed and believe patients are adherent to the treatment. Lack of adherence to drug regimens

has been reported as a major problem in virtually all medical specialties, patient populations, and healthcare settings [8,14,26]. Consequently, if patients do not take their medications in the way their doctors prescribed (right dose in right time) they will not be able to benefit from them [25]. When oral chemotherapy is considered, in many cases the degree of patient adherence is related directly to the degree of treatment success, so poor adherence represents a significant clinical problem [6,26-28].

It has been estimated that approximately 50% of the patients with chronic illness do not take oral medications as prescribed (i.e., the right dose, at the right time, on the right day, in the right way) [13,24,29]. In a quantitative review of all published empirical studies about patients' adherence to medical treatment from 1948 to 1998 Di Mateo found that the average non-adherence rate was 24.8% and that adherence was highest in HIV disease, arthritis, gastrointestinal disorders and cancer [30]. Medication-taking behavior of patients with cancer is presumed to be particularly the adherent one, since cancer is a life threatening disease. However, literature data report that adherence rates on oral antineoplastic agents range from 16 to 100% depending on the drug and method of measurement [25,31,32]. Decker and others observed that as many as 23% of the patients did not take their oral chemotherapy as it had been prescribed either because of side effects or because they had merely forgotten to take the medication [33]. Spolestra et al. examined an intervention to improve adherence and management of symptoms for patients prescribed oral chemotherapy regimens and found that 42% of 119 patients were nonadherent, with missed doses increasing with regimen complexity [6]. In 2012 Wood reviewed the literature regarding adherence to oral chemotherapy and concluded that clinical trials involving oral agents, such as adjuvant tamoxifen, present much different data regarding adherence, which has been reported to range from 72 to 96% [8]. This can be explained by the fact that patients participating in clinical trials are usually very motivated and closely monitored; therefore their high adherence rate may not be indicative of the general cancer patient population [8].

Adherence to prescribed antineoplastic therapy is more than taking medicine on time - non-adherence generally can have multiple consequences such as ineffective treatment, drug resistance, disease progression and consequently decreased

survival and side effects caused by toxicities. Non-adherence also may be associated with increased resource use and higher healthcare costs due to increased number of clinical visits and frequent and longer hospitalization [1,25]. Low patient adherence, even when patients are taking life-saving therapy, demonstrates the need for better management and monitoring of patients on oral antineoplastic agents [8].

#### *Factors influencing adherence and persistence*

A number of different factors have been shown to influence patients' adherence and persistence. In 2003 the World Health Organization (WHO) classified these factors into 5 categories: social and economic factors, healthcare team/system-related factors, disease-related factors, therapy-related factors, and patient-related factors [34]. This classification was used by Verbrugghe et al. [4] for a recent systematic review about factors influencing medication adherence and persistence to oral anticancer drugs. This review of 25 studies showed that age, like older or younger, and therapy-related side effects are predominant factors associated with medication adherence and persistence to oral antineoplastic therapy. Being inadequately informed about side effects before therapy is commenced was found to be a factor associated with increased patient's non-persistence and vice versa. Understanding the clinical relevance of oral antineoplastic therapy is helpful for 90% of the patients to adhere to their therapy [4]. Younger women with breast cancer are more affectively distressed and tend to cope with stress in a less adaptive way. Older patients are often more influenced by polypharmacy for comorbidities, physical, psychosocial issues and memory problems [4]. On the other hand, in 2013, Spolestra et al. found that symptom severity, depressive score, gender and age were not associated with adherence, whereas site of cancer was, as the drug and drug regimen depended on types of cancer. In this study factors such as complexity of the medication regimen, patient confusion and adverse effects consequently lead to nonadherence [6]. Schneider et al. also noted multiple factors affecting adherence to treatment: patient and condition-related factors such as cognitive impairment, comorbidities, gender, psychopathology and other medications; therapy-related factors such as adverse events, length of treatment, patterns of dosing, polypharmacy, route of administration, complex regimens, safety and handling, problems with refills and side effects; socioeconomic-related factors such as atti-

**Table 1.** Factors influencing patient’s adherence and persistence

<i>Patient-related and condition-related factors</i>	<i>Therapy-related factors</i>	<i>Socioeconomic-related factors</i>	<i>Clinician-related factors</i>
Cognitive impairment	Side-effect of disease or treatment	Attitude toward treatment	Relationship and communication with healthcare providers
Comorbidities	Disease type and stage	Cost of treatment	Provision of information
Gender	Length of treatment	Financial support	After-care management
Psychopathology	Patterns of dosing	Distance to treatment center	Proper follow-up and surveillance
Other medications	Route of drug administration	Social rank of illness	Belief in the treatment
Beliefs about treatment	Polypharmacy and drug interactions	Social support environment	Use of guidelines
Outcome expectation	Complexity of dosing regimen	Supervision of treatment	
Depression	Safety and handling		
Health literacy	Prescription refills		

Source: Given [1], Schneider [15]

tude toward treatment, travel distances to obtain treatment, financial cost and social support. Clinician-related factors included relationship with healthcare providers, provision of information, proper follow-up and surveillance [15]. Given et al. in their recent review pointed out similar issues, adding outcome expectations, health literacy, disease type and stage, and extra costs [1]. All these factors influencing patients’ adherence and persistence to oral antineoplastic agents are summarized in Table 1. In broader terms, these above-mentioned factors fall into the 3 main categories: patient-related factors, healthcare provider-related factors and health system/team building-related factors [24]. Patients-specific factors, treatment-related factors and healthcare provider-related factors are categories defined by other authors [8,23,25].

*Monitoring patient adherence and persistence*

Monitoring patient adherence and persistence is challenging because adherence is an individual patient behavior [24]. Existing methods for assessment include subjective methods, such as self-reporting, counting tablets and microelectronic monitoring system (MEMS), and objective methods such as the measurement of metabolites of the medication in body fluids [4]. Self-reporting has traditionally been used to measure patients’ adherence to oral therapies, but unfortunately, this method is not reliable due to poor patient recall or patient reluctance to admit noncompliance [8,35,36]. Also, since patients might be aware that

adherence or persistence is being studied (“Hawthorne effect”), this must be taken into account [4,25]. To improve patient recall, self-reporting of adherence can include patients recording methods at home, such as a calendar and patient diary which can then be reviewed during clinical visits [8]. The packaging of oral medication can also be useful for patient monitoring. Daily blister packs can be used and pill counts can be done at each visit to check adherence to treatment regimens. However, this method does not guarantee compliance, particularly if the patients are aware that the empty blisters will be counted [25,36]. A more effective, but more costly, way to monitor patient adherence to treatment is via the MEMS in which a tablet bottle electronically records the time and date at which the cap is removed [8,35]. A recent literature review showed that in several studies, higher rates of adherence were reported when oral antineoplastic treatment was monitored by MEMS, but this system does not guarantee that the patient actually takes the medication, since the act of opening a pill bottle is counted [8]. A newer integrated approach for supporting self-management of symptoms and monitoring adherence to oral agents called Automated Voice Response (AVR) system is flexible and low-cost [6]. Serum and urine drug or metabolite levels are more objective measures of adherence and persistence, but can also be unreliable and are available only for certain drugs [25]. The above-mentioned methods are shown in Table 2. Currently, a combination of these methods is used to assess adher-



**Table 2.** Methods for assesment patient's adherence and persistance

<i>Subjective methods</i>
Self-reporting (calendar, patient dairy, self-reporting questionnaire, self-report in patient interviews)
Packaging of oral medication (counting tablets, daily blister packs)
MEMS (Microelectronic Monitoring System)
AVR (Automated Voice Response) System
<i>Objective method</i>
Measurement of metabolites of the medication in body fluids

ence behavior [24, 37]. A combination of MEMS and self-reported questionnaires is found to be most accurate in measuring patient's adherence [4].

### Patient education

There is no single standard intervention to overcome barriers to patient's adherence [23]. Because these barriers are complex and varied, interventions to improve adherence must be multifactorial [24]. They may include improvement of clinician-patient relationships, educational strategies such as one-to-one counseling, written information with verbal explanation, involvement of the patient in the discussion of treatment goals, tailoring the treatment to the patient's lifestyle, use of reminders, encouragement of family support, monitoring of adherence, and provision of the feedback to the patient [14]. However, the literature places the primary emphasis on patient education by healthcare professionals [5,23,25]. Patient education is essential to maintain adherence to oral antineoplastic therapy promoting a better understanding of the patient treatment regimen, treatment goals and potential side effects, patient safety and implementation of self-care measurement [8,26]. Quality of patient education will directly affect compliance with the treatment regimen [5] and consequently improve the patient outcomes and quality of life. Patient education, therefore, becomes the cornerstone of successful oral chemotherapy [26].

Education is especially important at the beginning of treatment and should be tailored for individual patients according to their preferences. The time of the initial consultation with the oncologist may not be the optimal time to provide detailed teaching because patients are given a large amount of information and may be anxious, upset or frightened. Ideally, patients should

be scheduled for an education visit and that will improve the understanding of the given information [8,26].

Patient education is an ongoing process that occurs in the clinic or oncology office, at the patient's pharmacy, and over the telephone [26]. However, patients generally prefer direct interaction with the healthcare professionals [8], where the duration, frequency and quality of that interaction are associated with compliance. Consistent patient follow-ups to answer questions, obtain information and remind patients about treatment regimens are important component of patient education [8,25].

Studies have shown that up to 50% of what doctors tell their patients is forgotten almost immediately [8,25]. Therefore, verbal information should be supported by written instructions about oral antineoplastic agents individualized to the patient's regimen, dose, and medication administration dates as well as CD ROMs and websites [5,26]. Also, the involvement of a family member or caregiver may be very helpful in reinforcing educational information at home and motivating patients to adhere to treatment. This is particularly relevant both in the elderly population, when cognitive difficulties may affect treatment adherence and in children and adolescents, where the relationship between parental involvement and adherence is critical [8]. Some practices have considered group visits or educational sessions, which can save time, of course, only if patients express interest in that kind of teaching [5].

Ultimately, the important issue is to match patient needs and learning preferences with the resources available in the practice. It is important to review each item carefully such as dose, time(s) of administration, how to take the drug, what to do if doses are missed, how to contact members of the healthcare team, side effects management, and how to store and handle medication safely [5,38].

Education should be carried out by an appropriately trained healthcare professional to ensure that patients fully understand how and when to take their oral antineoplastic agents. It should be structured and supported by protocols and checklists. At the completion of the educational session, the patient should be asked to repeat the key points to confirm understanding of the education provided. Understanding should be checked before the patient is given his oral medication [39].

### Impact on quality of life and outcomes

Patient and family education are important

factors for successful outcome of the treatment in patients receiving oral chemotherapy, such as improvement in overall survival, life expectancy, safety and quality of life [5,15]. Quality of life is an important measure in the evaluation of health status and treatment efficacy. Health-related quality of life is a component of general life quality, which is mainly determined by the individual disease, and may also be affected by clinical interventions that incorporate education, early symptom identification, reminder and psychosocial support [15,40]. Djurdjevic and Nikolic showed that better understanding and knowledge might have great impact on quality of life and treatment outcomes because specifically educated patients are able to reduce unpleasant symptoms of disease and therapy, to prevent disabilities and to achieve the best possible quality of life [41,42]. Leung et al. in a longitudinal study regarding social support and health-related quality of life in women with breast cancer confirmed that certain aspects of social support such as provision of emotional, affectionate, and informational support were more influential on health-related quality of life than the provision of instrumental support [43].

Most patients perceive their quality of life to be better with the use of oral therapies, and they also may derive significant emotional benefit by envisioning themselves as partners in the therapeutic process [5,15]. Furthermore, as oncologists pay more attention to patient preferences and quality of life issues in clinical care, treatment options that enhance flexibility for patients are likely to be used more often [27]. Also, quality of life issues are paramount in palliative care oncology and it could be anticipated that oral formulations will become the primary route of chemotherapy administration in this setting [32].

### **Recommendations for practice and further research**

As oral antineoplastic therapy becomes more prevalent, the number of patients and caregivers who need to be educated will also increase [5]. It means that the primary roles of oncology health-care professionals and institutions are to facilitate patient education, communication, symptom management and proactive follow-up. These roles do not end when the patient leaves the clinics [14]. All patients receiving oral antineoplastic agents need to know when, who, and how to call for healthcare support during and after clinic hours. Symptoms can quickly escalate at home, resulting in exacerbation of minor side effects into serious

acute conditions that require hospitalization [36].

The large number of oral antineoplastic agents in the pharmaceutical pipeline prompts consideration of how the practice of oncology could change in the future [3]. Development and implementation of different patient education programs as well as oral chemotherapy administration safety standards are of great importance for clinical practice. Even in 2007 Moore [5] suggested that developing validated tools for oral chemotherapy compliance and research-proven educational methods for patients receiving oral chemotherapy and their families would be worthwhile research endeavors. Identification of certain health professionals to be responsible for the oral therapy educational programs and development of patient educational materials (e.g. brochures, newsletters) additionally may improve patient adherence, outcomes and quality of life.

A University of California (UC), Davis Comprehensive Cancer Center pilot program designed to better manage cancer patients taking oral chemotherapy drugs has demonstrated that one-to-one counseling, education, and monitoring can improve adherence to therapy. This program started in September 2013 and early indications suggest it is working. In one assessment of 44 patients enrolled in the pilot program, 92% adhered to their drug regimen. Today, 80 patients at UC Davis Comprehensive Cancer Center are enrolled in the program. Beginning this fall, the Cancer Center will employ a full time pharmacist dedicated to the program, offering the services to all UC Davis cancer patients [44].

The Multinational Association of Supportive Care in Cancer (MASCC) Education Study Group also identified that education is essential to ensure that oral agents are being taken correctly. This group developed and evaluated a teaching tool for patients receiving oral agents for cancer treatment to meet the need for a complete and dependable approach to education for worldwide use. The tool was created by a panel of experts, reviewed by an oncology pharmacist, and then evaluated in 15 countries. It helps clinicians to identify barriers and facilitators to adherence and also provides suggestions for patient educations throughout structure format to ensure that assessment, symptom management, and strategies for adherence are addressed. This valuable instrument is available in eleven other languages and has been incorporated in research projects. The MASCC Teaching Tool for Patients Receiving Oral Agents for Cancer (MOATT) and MOATT User

Guides are available free of charge on the MASCC website ([www.mascc.org](http://www.mascc.org)). MOATT has the potential to become an international patient education resource; however, further research is needed to determine the reliability of the translated versions of the tool and identify the tool's impact on patients' outcomes. Additional research is also needed to assess the utility of the teaching tool in additional countries, and in particular, developing countries. [2,14,45-47].

There is also a clear need for guidance about what is considered safe delivery of oral chemotherapy because multiple factors can compromise patient safety and contribute to medication errors, contamination, and inadvertent exposure to other individuals [37,48]. In response to this need, the ASCO/ONS chemotherapy administration safety standards including oral agents have been established in 2013. These standards represent a set of expectations and a framework for individual healthcare providers as well as practices and institutions in relation to oral chemotherapy. The challenge is an implementation of the standards, especially how they can be used to guide practice and facilitate improvement [37,49].

An International pharmacy panel also provides recommendations for safe handling of oral chemotherapeutic agents in clinical practice, which can be adapted by institutions, and practices for development of standardized procedures specific to their needs regarding the safe handling of oral chemotherapeutic agents [48]. Ensuring oral chemotherapy safety requires improvements in the way these drugs are ordered, dispensed, administered, and monitored [50].

To date, there have been a limited number of studies focusing on adherence issues related to oral antineoplastic agents, and further research in this area is needed [37]. Additional research is needed to determine the best practice in patient education, monitoring, and safety management [1,23], and furthermore to identify the correlation

between patient education and quality of life.

Oral chemotherapy is an area where quality improvement projects using experience-based design methods may be especially well suited. Experience-based design is an approach to improving health care and redesigning service delivery by bringing patients and providers together and using their experiences of care to guide quality improvement [37].

## Conclusion

The era of oral antineoplastic agents has arrived and posed a big challenge both for healthcare professionals and patients for years to come. With this paradigm shift come changes in how patients must be managed in order to ensure adherence to treatments that are self-administered over potentially long periods of time. The best way to effectively address the individual needs of patients and families and ensure compliance is through well-planned patient and family education. Efforts spent on patient and family education and active side effect management during oral antineoplastic therapy can help patients to remain on their therapeutic regimens and achieve positive clinical outcomes while minimizing distress from side effects and dose modifications. Empowering patients with knowledge may help increase patients self-care behaviors and quality of life as well as decrease anxiety and symptom severity. Healthcare professionals should be prepared to meet the challenges of oral administration of antineoplastic agents. Adequate safety and support systems must evolve as quickly as development of oral antineoplastic agents themselves.

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