

5-2011

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Assessment and Measurement of Adherence to Oral Antineoplastic Agents

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Acknowledgements: Michigan Nurse Corp Fellowship

KEY WORDS: Cancer, Oral Antineoplastic, Adherence, Measurement

Abstract

OBJECTIVES: The increase in oral anticancer medications with complex regimens creates a need to assure patients are taking therapeutic dosages as prescribed. This article reviews the assessment and measurement of adherence to oral antineoplastic agents.

DATA SOURCE: Research and journal articles from CINAHL and Pub Med.

CONCLUSION: Assessing and measuring adherence to oral antineoplastic should include three dimensions: the percentage of medications taken, the duration, and the timing of taking the medication.

IMPLICATIONS FOR PRACTICE: Clinicians need to conduct ongoing assessment and measurement of adherence to oral antineoplastic agents. This includes eliciting patient report of adherence, pill counts, drug diaries, and pharmacy or medical record audits.

Introduction

Despite efforts of providers, pharmaceutical manufacturers, and healthcare providers to encourage adherence, irregular and incomplete oral therapeutic drug dosing is common and may be particularly troublesome among cancer patients prescribed oral antineoplastic agents.^{1,2} Consequently, clinicians need to conduct ongoing assessment and measurement to assure that a prescribed oral antineoplastic agent is taken appropriately.³ In this paper, the assessment and measurement of adherence to oral antineoplastic agents for cancer treatment are discussed.

Therapeutic Oral Antineoplastic Agent Dosing

A large body of literature has reported that adherence to standard chemotherapy doses and schedules can have a positive effect on treatment outcomes. This literature and the theories that characterized the relation of the doses of chemotherapy to efficacy are summarized in the AMGEN® Relative Dose Intensity newsletter endorsed by the Oncology Nursing Society.⁴ To summarize, this includes higher doses reduces the likelihood of survival of chemotherapy-resistant clones; that decreasing the interval between chemotherapy cycles can result in greater treatment efficacy; that a percentage of cells may be killed with each dose; and that tumor cells grow between cycles of chemotherapy, yet cell growth is the greatest when tumor cell burden is the smallest. These theories can then be used to explain the impact of non-adherence (dose delays or reductions) for oral antineoplastic agents. The importance of maintaining a therapeutic drug level in the curative cancer treatment setting is discussed at the beginning of this article to provide clinicians with an awareness of the need to improve the delivery of oral antineoplastic agents by minimizing dose reductions and dose delays.

The Complexity of Oral Antineoplastic Agents

Some oral antineoplastic agents have simple regimens, while others are extremely complex. Drug manufacturers attempt to simplify the regimen by developing dosing schedules that are simple. However, the nature of oral antineoplastic agents does not lend itself towards simple regimens. An example of a simple regimen is continuous daily doses as long as the medication is prescribed. An example of a complex regimen is twice daily doses 30 minutes after a meal and 12 hours apart, administered in 21-day

treatment cycle of 2 weeks of the treatment followed by 1 week rest period. Other examples are provided in Table 1. Further complicating the complexity is when 2 antineoplastic agents are prescribed simultaneously and administered on an alternating schedule. Additionally, medications the patient may be taking for other conditions can interfere with the oral agent regimen.

Obtaining the oral agent is a complicated procedure for the patient, family member, or caregiver, and can lead to problems with adherence. First, the prescription for the oral antineoplastic agent must be obtained from the oncologist. Second, the prescription must be filled, and some scripts are sent by the oncologist to a specialty pharmacy while some patients fill prescriptions themselves. To further complicate the filling of the prescription, some oncologists' orders are partial scripts and in some instances, prescriptions are partially filled by the pharmacy. Partial prescriptions are written or filled when modifications to the regimen are expected, as there is a desire to not waste expensive medications that may not be used. Third, is the delivery of the pills. Some pills are picked up by the patient at the pharmacy, some are delivered directly to the home while others are mailed, which can create problems with early or late arrival of the pills. Another important component of filling the prescription is when patients actually receive the prescription as compared to when they should initiate their dosing. The timing of the receipt of the pills can be a problem, as some prescriptions are filled a week or two prior to initiation of the dosing, which can create confusion for the patient, family or caregiver, with regard to when the patient should start the medication; upon receipt of the pills from the pharmacy or on a specified date in the regimen cycle. Finally, another important component is how the pills are packaged. This can include a bulk quantity in a pill bottle or pre-packaged blister pack containers, which are labeled for daily use. A seldom examined step in this procedure is, once a patient has the pills, how clearly do they understand the dosing regimen procedures (duration, timing, with or without foods or liquids). Further, to fully appreciate the complexity of patient adherence to oral therapeutic agents, changes made by oncologists during the course of treatment can be made during the beginning or middle of a filled prescription. If and how those changes affect pills to be taken from the already prescribed and received pill order are not taken into account, the patient may become confused and not take the correct dosage.

Unfortunately, little information is available on filling of prescriptions for oral therapeutic agents, an important component of care. These potential threats to adherence have not been systematically addressed and need to be included in future research on adherence to oral antineoplastic agents.

The Importance of Defining Adherence Prior to Assessment and Measurement

Precise definition of adherence prior to assessment and measurement is imperative.⁵ Lack of a clear-cut description of the meaning of adherence when assessing and measuring the concept may create confusion and miscommunication in clinical practice. Chapter 2 identifies the International Society for Pharmacoeconomics and Outcome Research (ISPOR) definition of adherence to medications for this article. ISPOR defines adherence along two dimensions: first as “the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency”; and, second as the persistence which they define as “the duration of time from the initiation of the medication to discontinuation of therapy”.⁶ Some measures of adherence are simple, while others are detailed and complex. A simple, commonly used measurement of adherence is a percent of the prescribed dose taken (where the numerator is what was taken ordered and the denominator is what was prescribed).⁷ An example of a more complex operational definition of adherence includes the prescribed number of doses taken as determined by pill count as confirmed by the a Medication Event Monitoring System (MEMS [electronic pill boxes that alarm and measure cap openings]) within 2-hours of prescribed time of the dosing interval and with the correct number of doses on each time of day and day of treatment.⁸

The main point in regard to defining adherence is that clinicians need to clearly understand which dimensions of adherence they are assessing and measuring when caring for patients on oral antineoplastic agents. In most instances, this should include three components. First, the percentage of medications taken must be defined (to include number of doses and doses by day of treatment). Second, the duration (i.e., number of days, weeks, months, or years) of taking the medication (persistence) is needed. Finally, with some types of medications, the timing of taking the medication is of importance (a defined dosing interval, i.e. at a specific time of day so that under and overdosing can be evaluated), as well as taking the

oral antineoplastic agent lying down or with or without food. Next, the assessment and measurement of oral antineoplastic agents is reviewed.

Methods of Assessment and Measurements of Adherence Commonly Used and their Limitations

Despite the importance of adherence to clinical care and therapeutic outcomes, little rigorous research has been completed to measure adherence to complex dosing because they require direct observation and long-term assessment. Because of the time and cost involved in measuring adherence, often only one method of assessment is used. Furthermore, the degree to which adherence can be legitimately assured from measures such as self-report are questionable.⁹ To conduct evaluation of adherence to oral chemotherapeutic agents a number of difficulties must be overcome. First, to properly assess adherence, the prescription regimen including dose, timing, and duration must be identified, and any ongoing adjustments or modification to the dose, timing, and duration. Next, a clear definition of what adherence entails must be identified (i.e., percentage of adherence based on number of pills and days to be taken [80%, 90%, 100%]) and the numerator and denominator to calculate this percentage clarified. If timing of the dosage is required, the window of time that must elapse before a patient is considered to be nonadherent [i.e., 1-hour; or 30-minutes]) must be identified. Strict attention must be paid to underdosing and overdosing, so that missed doses of medication and additional doses of medication are assessed. Finally, the assessment and measurement of the patterns of nonadherence must be sensitive enough to capture both the frequent, as well as erratic, occurrences of nonadherence. However, the majority of adherence measures are indirect and include some form of self-report and cannot truly capture if the medication was actually taken. Furthermore, even if all of these complexities are assessed and measured in a research setting, translation into a clinical setting may be time consuming and therefore impractical.

Previous studies have shown that adherence measures have limitations, prompting questions about how best to measure drug-taking behavior.^{10,11} Although drug levels are a direct measure of drug exposure, they provide only a snapshot of behavior and are affected by factors other than adherence. While, indirect measures cannot truly capture if the medication was actually taken. Each of these available measures and their limitations will be reviewed.

Direct Methods of Measuring Adherence

Physiological biomarkers to measure adherence. Serum or urine drug metabolite levels are more objective measures of adherence, but do not describe the timing of doses and can still be manipulated by patients (medication dosing can be resumed or extra doses can be taken before an office visit to avoid appearing nonadherent).¹² Additionally, because of pharmacokinetic variability in drug absorption, distribution, metabolism, and excretion, ranges that are consistent with adherence may be wide.¹² Furthermore, accurate measurement of serum or urine drug metabolites is only available for certain drugs (e.g., prednisone and 6-mercaptopurine [6-mp]).¹² However, in some diseases, intermediate markers of drug use may be useful. For example, plasma viral load in patient with the human immunodeficiency virus (HIV) can act as a surrogate for adherence to antiviral therapy.¹³ However, most of the oral drugs used to treat cancer do not at this time have intermediate markers of adherence that can be easily measured in a clinical setting. This is something that might be developed in the future to ensure therapeutic dosing and effectiveness.

Indirect Methods of Measuring Adherence

Pill counts. Pill count is also commonly used to measure medication adherence in research, but it is too time-consuming and computationally complex for most clinical purposes. Several studies emphasized the shortcomings of pill counts in overestimating adherence, often due to “medication dumping”.¹⁴ Pill counts, requiring patients to return unused pills at each visit so that the number of missed doses can be calculated, have also been shown to overestimate the number of pills actually taken.^{15,16} Patients may throw away missed doses to avoid being viewed as nonadherent. Nonetheless, pill counts are often used as an adjunct to self-report. However, most clinicians do not have the time to perform the pill count, making this an impractical method of assessing adherence day-to-day. Technology has been developed to facilitate pill count measurement. This includes blister packs or a MEMS pill boxes that contain a microchip and reports each time the container is opened. The iPill application, where a patient can touch the screen and record when (date and time) the pill is taken, might make pill counts somewhat easier in the future.

Pharmacy and administrative records. Although pharmacy and administrative records are a convenient source of adherence information they are time consuming to evaluate and only report if the prescription was filled, not if the medication was actually taken.¹⁷ Analysis of prescription refills can be calculated as the proportion of days within a given time period during which a patient has filled prescriptions (i.e., “days covered”).¹² Using pharmacy records may falsely demonstrate adherence, as it is possible that some patients may miss and/or double up on pills and still refill prescription on time, and there is no information provided regarding the timing of doses. Furthermore, some prescription refill studies fail to separate nonadherence from lack of persistence because they simply estimate the proportion of days a patient had pills available, not distinguishing between those who are taking the medication incorrectly and those who stop the medication entirely.¹⁸ Nevertheless, the strength of studying refill rates is that it provides an objective measure of adherence available in a large population over a long period of time. Using pharmacy or insurance records also avoids the Hawthorne effect (i.e., when a patient is being monitored for taking their medication they are adherent, but when the observation stops the patient is no longer adherent), as well as patient manipulation for social desirability because subjects would generally not be aware that their refill rate was reviewed.¹² Another issue related to the use of pharmacy records to measure adherence is that pharmacies deliver or mail oral therapeutic agents to the home prior to when the medication is to be taken and do not identify on the prescription when the patient is suppose to start the medication, which may be confusing.

Medical record review and healthcare provider reports. The medical record is also a source of prescriptions ordered, modifications to the regimen, and adherence.¹⁹⁻²⁷ However, medical records are known to be incomplete or inaccurate.²⁸ When electronic medical records are fully implemented, this may become a more reliable source of information. Healthcare provider interviews are also known to be inaccurate, due to problems with recall of specific patient care events or the provider not being aware of patient adherence as the patient wants to please the provider and does not report nonadherence.²⁸ Patients also often report appropriate adherence to medications so as not to appear socially undesirable to their physician. Regardless of the format of the record review or provider reports, what is still not known is if

the patient actually took the pill. In most instances, record review and provider reports measures were used in conjunction with other assessment techniques to supplement data.

Self- or caregiver report of adherence. Patient self-report has been used extensively to assess medication-taking. This method tends to overestimate adherence as the questions asked are not specific enough to get at all dimensions of adherence (i.e., time taken, took with grapefruit juice, laid down for 30 minutes, etc.).^{29,30} Self-report, in which patients are asked to recall how accurately they followed their prescribed regimen, have been repeatedly shown to suffer response bias, with patients usually over-reporting rates of adherence because of desire to please providers.³¹ Patient-completed diaries may provide flawed information regarding adherence for the same reason, although they may be less susceptible to recall bias because the patient is asked to record each dose as it is taken.¹² Furthermore, cognitive impairment due to aging, disease process, or side effects of the medications can influence memory and ability to remember if the medication was taken properly. Finally, when caregiver reports of medication adherence are used, overestimation often occurs.²⁸

Relative dose intensity. A novel method of assessing adherence by examining the therapeutic level of the dose of the oral antineoplastic agent is identified in the AMGEN® newsletter⁴ discussed earlier. This includes two methods of analysis. Delivered dose intensity (mg/m²/unit time) is total dose delivered over total time to complete the chemotherapy. Relative dose intensity is the ratio (percentage) of delivered dose intensity to standard (referenced) dose intensity, often expressed as a percentage.⁴ These calculations are depicted in Figure 1.

Electronic medication monitoring system. A novel approach for the measurement of adherence is the MEMS®.^{32,33} The MEMS® consists of an “intelligent” cap that electronically records every time the cap of the pill bottle is removed. MEMS data provides a computerized record of each date and time the bottle is opened. The MEMS® provides an objective measure of pill bottle opening, but it is not effective when pill storage devices are used or for liquid medications, and only records the bottle opening and not the ingestion of the medication. Even with the more objective measures, data may still be influenced by the Hawthorne effect and patient desire to appear optimally adherent. Furthermore, the

MEMS® technique is quite expensive and therefore is used primarily in clinical research and is not feasible in many other settings. The MEMS® is also not able to evaluate if pills were taken at the appropriate time of day as prescribed, only that the cap was opened.

A new electronic medication monitoring system in development and testing for both the research and clinical setting is the Maya® from MedMinder.³⁴ The tool is plugged into an electrical outlet and uses an internal wireless modem to communicate with a central server, so the patient has no need for a computer, wireless router or any form of internet access. The electronic pillbox prompts the patient to take the pill(s) with a visual or auditory alert. If a pill cup is not removed at the scheduled day and time, a compartment in the pillbox starts to flash; and if the pill cup is not removed after a period of time, other alerts, such as beeps, phone calls, emails or text messages can be initiated. The electronic message can be sent to a family member or caregiver to assist with medication adherence. A summary statement of pillbox use can be sent to the clinician to evaluate adherence. The pillbox uses a web interface so a patient can program the cups in the pillbox or call, fax, or mail a company provider to program the regimen. The pillbox can also be refilled in a blister pack, for ease in managing a complex regimen, such as oral therapeutic agents. The pillbox is currently being tested in two control trials (NCT01105104 and NCT01188135) promoting medication adherence for patients with heart and kidney disease.

iPhone® and i Pill®. There is a new application for the iPhone® called i Pill® for tracking medication management.³⁵ i Pill® acts as a virtual pillbox, allowing a person to easily see what medications have been taken and what medications are left to be taken. A picture of what a pill looks like can be inserted into the medication regimen schedule and the patient taps the picture of the pill when it is taken to record ingestion. i Pill can set up a schedule with intervals and alarms as a reminder when to ingest the pill, and can provide a complete record of all medications taken, time taken, and missed doses. Studies need to be conducted examining the efficacy of cell phone pill reminder alarms and adherence, as none were found. Although the i Pill® application is not expensive, a prohibiting factor may be the cost of the iPhone and its associated monthly fee.

Tools used in Research to Measure Adherence

There are a few research tools to measure medication-taking behavior of adherence in the research setting. These tools do not measure specifics of taking pills, but instead focus on attitudes or behaviors associated with medication adherence. The two commonly used tools are the Morisky³⁶ and the Brief Medication Questionnaire (BMQ).³⁷ The Morisky medication adherence scale, developed in 1986, is composed of 4 yes/no questions about past medication use patterns and is thus quick and simple to use during drug history interviews.³⁶ The BMQ is a self-report tool for screening adherence and barriers to adherence that includes 5 items asking patients how they took each medication in the past week, 2 items that ask about drug effects and bothersome features, and 2 items that ask about potential difficulties remembering.³⁷ Research studies on adherence, and particularly the studies examined for this review, used modified versions of the questions in one of these two tools to interview patients about adherence.^{24,25,38} One study used a single question from the Hot Flashes and Nights Sweats Questionnaire for adherence, “In the past week have you taken your Tamoxifen every day?”³⁹ In addition to there being few research tools to measure medication adherence, the ones that do exist do not appear to obtain the range of information (dosage, timing, duration) necessary to examine adherence to oral antineoplastic agents.

Summary. After analyzing 50 years of adherence research, DiMatteo²⁸ found that research studies employing certain objective measures of adherence (such as pill counts and physical measures) registered somewhat better average adherence than studies using subjective measures such as self-report. Evaluation of adherence to oral antineoplastic agents requires the use of 2 or more methods including the dosage, timing, and duration. The only way to build a library of reliable and valid methods of measurement of oral therapeutic agent adherence for research is to use the multi-method approach.⁴⁰ However, translating these methods to the clinical setting is a challenge. A review of the literature on adherence to oral antineoplastic agents provides some direction for clinicians.

An Integrative Review of Literature on Measurement of Adherence to Antineoplastic

There is a wide range, diversity, and variable pattern of medications patients use at home, making adherence particularly challenging. Pharmionics is an emerging field concerned with quantitative assessment of what patients do with prescription drugs.⁴¹ Recent research in the field of Pharmionics has revealed three major findings.^{41,42} The first is the recognition of the need to analyze adherence and persistence separately. Second is an understanding that adherence influences persistence, in part through the impact of patient perceptions of therapeutic outcome, and in part through the impact of beneficial and/or adverse effects. The third is the discovery that intervals between dosages are often ‘the’ most important factor in determining the clinical and economic consequences of nonadherence from a prescribed dosing regimen. This is particularly true in the case of oral antineoplastic agents. The dosing and timing regimens are often complex, with cycles of days-on and days-off often referred to as absences, rest periods, or drug free days and most chronic disease do not have that type of disrupted routine. Furthermore, the side effects, potential adverse events due to toxicity, and polypharmacy can disrupt administration making adherence difficult. Moreover, many of these medications must be taken over extended periods of time, often for years, making persistence a challenge.

Research literature on assessment and measurement of oral antineoplastic agents. Relatively few published studies have focused on adherence to oral antineoplastic for cancer treatment. In part this occurs because the vast majority has been delivered intravenously.⁴³ A search strategy to identify studies that examined adherence to oral antineoplastic among oncology patients was conducted. A CINAHL and Pub Med search for English-language articles published between 1975 and 2010 was performed, linking the subject search headings “compliance”, “adherence”, with “chemotherapy”, “oral therapy”, and “antineoplastic agents.” Reviews were restricted to those with adherence as a primary outcome. Manual searching of the reference lists within relevant articles identified additional studies. This review identified 3 systematic reviews, 30 adult studies and 13 pediatric studies (Table 2.). This review included assessment and measurement of adherence to both “hormonal” and “non-hormonal” agents. This was done to incorporate lessons learned from all available previous studies on oral agents in oncology

patients. Three systematic reviews^{12,43,44} examining oral antineoplastic in oncology patients. Overall, these reviews verified that adherence to oral antineoplastic agents is variable, not easily predicted, with adherence rates of 20% to 100% reported. Furthermore, no “gold” standard definition, and in some instances no definition, of adherence made comparison of results between studies difficult.

The adult adherence literature includes 12 hormonal studies and 18 non-hormonal studies and the 13 pediatric studies included more non-hormonal drugs (Table 2.). A majority of the hormonal studies conducted examined Tamoxifen adherence using pharmacy records.^{21,22,45-49} Although, the lessons learned from these studies support the importance of including prescription refill information and methods of calculating the number of days covered by filled prescriptions in future studies of one of the many multivariate measures. Two Tamoxifen studies also conducted phone interviews regarding adherence, asking patients if they continued taking their medication,^{21,39} while another taped interviews⁵⁰ questioning reasons why pills were not taken. The two most common reasons for nonadherence were side effects from the medication and that there was nothing to be gained by taking the medication. These studies provided important lessons for future studies of oral agent adherence, regarding use of self-report as a measure and eliciting patient input to better understand reasons for nonadherence.

Drug trials testing effectiveness of the oral route use multivariate measures of adherence. This includes MEMS, pill counts, self-report or diaries, medical record review, and pharmacy record review.^{7,51-54} Several ‘tightly’ controlled drug trials noted over adherence or overdosing when medications were not stopped or resumed at the proper time. Overall, minimal attention has been paid to the potential hazards related to overdosing. This is also an important lesson learned when assessing and measuring adherence, to include questioning regarding the timing of taking the medication.

Self-report (to include drug diaries) was by far the most commonly used measure of adherence, with 24 studies using this method.^{7,20,21,23-25,38,39,50,51,55-59} Although the MEMS is touted as a “gold standard” measurement in medication compliance, only 6 of the adult studies^{8,48,52,53,60} and one pediatric study⁶¹ used this method of measurement. MEMS is not considered to be a practical tool in the clinical setting due to its excessive cost. Pill counts^{7,56} and medical record clinical note audits occurred,^{19-23,25,62} yet were not

very common, probably due to the labor intensive nature of conducting these measures. Direct serum or urine^{55,57} measures were rare in adults, yet very common in pediatric oncology.^{26,63-72} However, these measures can only occur in the clinical setting when feasible and cost effective.

Summary. Collectively, this provides a state of the science on assessment and measurement of adherence to oral antineoplastics. To date, assessment and measurement of adherence has included self-report, use of MEMS, pill counts, record review, and in some instances, biologic measures. Based on these studies, use of multiple assessment and measures of adherence is recommended, as no measure alone can confirm adherence. However, minimal information is available on the cost of or time it takes a clinician to implement these assessment and measurement techniques in a “real” clinical setting. An understanding of the factors contributing to adherence provides some direction to clinicians when caring for patients on oral antineoplastic agents.

Patient Characteristics Contributing to Adherence and Implications for Practice

There are many factors that can influence adherence. These factors are important to take into consideration when assessment and measuring if a pill was taken. Correlations between adherence and sociodemographic factors, while somewhat statistically significant, are generally quite modest in magnitude ($r < 0.15$ in all cases),²⁸ yet must be examined when conducting adherence research. Psychological factors of depression,^{73,74} anxiety,^{75,76} and self-efficacy seem to contribute to adherence.^{20,21,24,25,50,58} Although type of disease is known to influence adherence in certain circumstances,⁷⁷⁻⁸⁰ there is a paucity of information on cancer stage and its effects on adherence, and these data need to be included in future adherence research. In cancer patients, the gravity of the disease may produce adherence in some patients. Conversely, a sense of fatalism may prevail in other patients leading to non-adherence. Studies of cancer and non-cancer diseases indicate that patients decrease adherence as symptoms and side effects occur.^{73,81-85} Few studies to date have linked symptom severity with non-adherence⁸⁶ and further study is needed. Adherence is inversely related to medication regimen complexity⁸⁷ Incorporating a medication calendar into each study is imperative. Cognitive impairment due to the disease or its associated treatment, or age⁸⁸ is also known to influence adherence and should be

measured. Comorbidities and associated polypharmacy can lead to adverse clinical outcomes, and it may be difficult to assess and measure the difference between outcomes related to polypharmacy and symptoms or adverse events related to the oral agent.⁸⁹⁻⁹¹ Finally, adherence correlates with patients' beliefs in the severity of the disease to be prevented or treated,⁹²⁻⁹⁴ and there are some tools (i.e., BMQ) that examine expectations about medications that can be incorporated into daily practice. Although many of these factors may have modest influence on adherence, it is imperative to assess each element to better understand where clinicians could influence adherence.

Drug-to-drug Interactions, Symptoms, Adverse Events and Adherence to Oral Antineoplastic Agents

Sorting out the difference between drug-to-drug interactions (a change in the way a drug acts in the body when taken with certain other drugs), symptoms (an indication a person has a condition or disease) caused by side effects of the disease, and adverse events (an unexpected medical problem that happens during treatment with a drug) is truly a challenge. Assessing and measuring the difference between these three elements is a daunting task. For example, complexity of disaggregating the affects from oral agents alone, compared with their interactions with other drugs and how, together, they may produce adverse events may lead patients to discontinue or alter dosages of all medications. Sorting out the difference between these three problems has implications for assessment and measurement of adherence. Evaluation of symptoms and monitoring adverse events needs to be based on the known effects of the specific oral therapeutic taken by a patient, and is needed in both the research and clinical setting. Furthermore, to effectively evaluate drug-to-drug interactions, a review of medications should include 'all' prescription and over-the-counter medications taken. An example of a summary for known effects of oral therapeutic agents is shown in Chapter 3. Use of assessment measurement tools that are sensitive enough to detect changes in a patient's condition to identify differences in drug-to-drug interactions, symptoms, or adverse events would be necessary when conducting research.

Conclusions

Providing efficacy and tolerability are not compromised, oral antineoplastic agents can be attractive to patients because of the associated benefits in convenience, avoidance of visits to the clinic, and reduced impact on daily activities.¹ Daily or more frequent dosing provides numerous opportunities to modify the dose and effectively manage side effects, also making oral antineoplastic agents more attractive. However, adherence to oral antineoplastics is a major obstacle to successful oncology treatment, while over adherence can lead to potentially life-threatening toxicity. The challenge is to assure that the oral therapeutic is taken as prescribed. With the increase in the number of oral anticancer agents available during recent years, a simple and cost efficient mechanism to assess and measure adherence in the clinical setting needs to be developed.

Implications for Research

Assessment and measurement of adherence to oral antineoplastics in research should include a multivariate, multimethod approach. Multivariate assessment and measurement of adherence in the oncology population should also include a range of known risk factors for nonadherence. This includes socio-demographics, psychological self-efficacy type of disease and stage, medication regimen complexity, cognitive impairment, comorbidities and associated polypharmacy, and the patient's belief in the severity of the disease to be prevented or treated. Multiple tools exist that can measure these factors. The multimethod approach to assessment and measurement of adherence could include self-report, use of a medication reminder system (i.e., MEMS or calendars), pill counts, record review, and when possible, biologic measures. New pill reminder systems like the i Pill® application on the iPhone® and the Maya MedMinder® need to be tested in the research setting to determine if improved adherence rates occur.

Implications for Nursing Practice

Although some interactions may be only 5 minutes, addressing oral therapeutic adherence can become second nature as clinicians work seamlessly from one patient to the next.⁹⁵ As shown in detail in Chapter 5, promoting and assuring adherence begins with educating the patient, family, or caregiver when the medication is prescribed. Clinicians can introduce medication reminders that may help the patient

adhere to the oral therapeutic(s), such as pill-boxes, alarms, or calendars. Patient-generated documentation in a diary or medication log may also help avoid the need to question patients during office visits, which may lead them to become defensive if they feel blamed for not adhering to the oral therapeutic.⁹⁶ Then, at a minimum, clinicians need to assess for risk factors that may influence adherence, and then ask patients if they are taking their oral therapeutic agents as directed, what they expect or are experiencing from the oral therapeutic agents, and whether they are having any problems with adherence to include all dimensions, prescribed timing, dosage, frequency, and persistence.^{2,97} The line of questioning should come across as nonthreatening and nonjudgmental, with the goal of understanding the patient's issues.⁹⁵ Consider asking open-ended questions such as these:

- What are you taking this oral therapeutic agent for?
- What dose are you taking?
- What time of day are you taking your pill?
- How many days/months have you taken your pill?
- What causes you to miss your oral therapeutic agent?
- What helps you remember to take your oral therapeutic agent?
- What motivates you to stay on this oral therapeutic agent?
- What side effects or symptoms can you live with, and which ones would make you consider stopping your oral therapeutic agent?

Clinicians can play a key role in improving oral antineoplastic agent adherence by conducting ongoing assessment and measurement. The key is to communicate with the patient, focusing on solutions to promote oral therapeutic agent adherence, despite the limited time that clinicians have to address the issue.

Figure 1. Delivered Dose Intensity and Relative Dose Intensity

$$\text{Delivered Dose Intensity} = \frac{\text{Total Dose Delivered}}{\text{Total Time to Complete Therapy}}$$

$$\text{Relative Dose Intensity \%} = \frac{\text{Delivered Dose Intensity}}{\text{Standard Dose Intensity}} \times 100$$

Standard dose = 100% of prescribed dose

Total delivered dose = percentage of what patient actually took

Standard duration of treatment = number of weeks dose prescribed to be taken

Actual duration of treatment = number of weeks dosage was actually taken by patient

TABLE 1.
Examples of Oral Antineoplastic Agent Drug Regimens

Regimen type	Drug	Commonly ordered dosages and rest periods
Simple regimen	Erlotinib (Tarceva)	Daily dosing (100–150 mg daily)
	Sorafenib (Nexavar)	BID dosing (400 mg BID)
Moderately difficult regimen	Sunitinib (Sutent)	50 mg capsule once/day for 4 weeks (28 days) and 2 weeks of rest, may be taken with or without food
Complex regimen	Capecitabine (Xeloda)	Starting dose 1250mg per meter squared taken BID 30 minutes after a meal 12 hours apart; administered in 21-day treatment cycle treatment (2 weeks followed by 1 week of rest)
	Lapatinib (Tykerb)	Taken with Xeloda with different dosing; 1,250 mg (5 tablets) taken once a day at the same time each day, 1 hour before or 1 hour after a meal, for 21 continuous days (repeat therapy in 21-day cycles) then a rest period of 7 days
	Temozolomide (Temodar)	150–200 mg/m ² daily for 5 consecutive days, followed by 23 days of rest for first cycle, with an escalation to 200 mg/m ² for cycles 2 through 6

Abbreviation: BID, twice daily administration of medication.

Drug manufacturer name, city/state location: Tarceva, OSI Pharmaceuticals, Melville, NY; Nexavar, Bayer/Onyx, Emeryville, CA; Sutent, Pfizer, New York, NY; Xeloda, Genetech, San Francisco, CA; Tykerb, GlaxoSmithKline, Middlesmith, UK; Temodar, Schering Corporation, Kenilworth, NJ.

TABLE 2. Studies of Adherence to Oral Therapeutics					
Study	N	Cancer	Oral therapy	Adherence definition	Adherence Measures
Smith et al, 1979 ⁶⁴	52	Leukemia, non-Hodgkin lymphoma	Prednisone	100% compliance with taking medication as prescribed	Urinary metabolites
Lansky et al, 1983 ⁶⁵	31	ALL	Prednisone	100% compliance with taking	Urinary metabolites medication as prescribed
Tabbi et al, 1986 ⁶⁶	46	Multiple types	Tamoxifen, prednisone, 6-MP, methotrexate, and procarbazine	Missing \leq 1 dose/month	Self-report and serum prednisone
Levine et al, 1987 ⁶⁷	108	Hematologic malignancy	Prednisone and allopurinol	Not defined	Serum metabolites, medical record review, self-report
Richardson et al, 1988 ⁶⁸	107	Hematologic malignancy	Cyclophosphamide and/or prednisone	90%–100% of pills taken	Self-report
Lebovitz et al, 1990 ⁶⁹	51	Breast cancer		90%–100% of pills taken	
Levanthal et al, 1991 ⁶⁵	11	Ovarian cancer	Atretamine	Not defined	MEMS
Lee et al, 1992 ⁷¹	21	Lymphoma	Chlorambucil, prednisone, or dexamethasone	Overall compliance or the number of bottle openings/number expected, daily discrepancies between bottle openings and prescribed daily number/treatment period	MEMS
Tamiroff et al, 1992 ⁶⁷	50	ALL and Hodgkin lymphoma	Prednisone or prophylactic penicillin	100% compliance with taking medication as prescribed	Serum dehydroepiandrosterone sulfate suppression (for prednisone) and urinary growth inhibition assay (for penicillin)
Festa et al, 1992 ⁶⁸					Self-report, pill count, MEMS
Walshouse et al, 1993 ⁶⁷	26	Breast cancer	Tamoxifen	<80% of prescribed dose	MEMS
Lee et al, 1993 ⁶⁴	12	Small cell lung cancer	Etoposide	Overall compliance, daily irregularity index and hourly irregularity index	
Lennard et al, 1995 ⁶⁸	327	ALL	6-MP	Not stated	Two metabolites in red blood cells

MacLeod et al., 2007 ²⁴	52	Colon cancer	Capecitabine	100% adherence and over adherence (taking of timed dose or daytime). Also assessed and monitored symptoms	Patient diaries, prospective medical record audit-drug schedule, cycles, starting dose, number of treatment modifications (delays or reductions), response to treatment, occurrence of adverse events, and need for physical consultation, including general practitioner Prescription refill records
Partridge et al., 2006 ²⁵	12,391	Breast cancer	Anastrozole	Proportion of days that patient had the medication available over the observation period (ie, days covered, <80% of days covered were defined as nonadherent	
Partridge et al., 2006 ²⁶	161	Breast cancer	Capecitabine	Extent to which patient's behavior coincides with medical advice at ≥80% Not stated	MEMS
Hawwa et al., 2009 ²⁷	19	ALL	Oral thiopurines		Self-report and drug metabolite concentrations
Mayer et al., 2009 ²⁸	18	Breast cancer	Gefitinib, capecitabine	Secondary endpoint: >80% was considered adherent	Self-report, diary and MEMS
Vinson et al., 2009 ²⁹	131	Multiple types	Hydroxyurea, imatinib, capecitabine, thalidomide, sunitinib, sorafenib	Not defined	Self-report
Decker et al., 2009 ³⁰ (Pilot study)	30	Breast, colon, & lung cancer	Xeloda, cyclophosphamide, tarceva, tykerb		
Given et al., 2010 ³¹	119	Breast, colon, lung, gastrointestinal, renal, gynecologic and other cancer	Xeloda, cyclophosphamide, tarceva, tykerb, gleevec, nevaser, sulint, temodar, and other	Anything <100% of prescribed pills taken Anything <78% of prescribed pills	Medical record review, prescription refills, self-report Medical record review, prescription refills, self-report

Abbreviations: ALL, acute lymphoblastic leukemia; 6-MP, 6-mercaptopurine; MEMS, microelectronic monitoring system.

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