

Improving Patient Adherence

with Oral Chemotherapy

by Steve D'Amato, RPh, BCOP

IN BRIEF

Non-adherence can have profound clinical consequences in the treatment of chronic diseases—especially cancer. Medication non-adherence in patients with cancer is a growing concern today due to the increasing availability of new oral agents. Many factors contribute to patient non-adherence to treatment regimens. Understanding the potential barriers and factors that affect patient adherence will help providers develop strategies to promote patient adherence to oral treatment regimens. Optimal patient outcomes require adherence, education, communication, ongoing monitoring, and follow-up.

The use of orally administered antineoplastic agents continues to rise and is likely to increase in the coming years with the development and approval of new oral formulations to fight cancer. As research identifies new “targets,” the subsequent development of new agents to affect those targets (Table 1) is changing the approach to treating various malignancies. Patients diagnosed with cancer today have five-year survival rates, and these rates continue to increase over time. In some cases, cancer is becoming a chronic disease, where traditional chemotherapy is combined with newer therapies over prolonged periods of time. At the same time, oral agents introduce challenges for providers and patients.

Benefits and Risks of Oral Chemotherapy

Oral antineoplastic agents offer patients many potential advantages. For example, a patient who is on oral chemo-

therapy may be able to return to work sooner than one who is receiving more “traditional” cancer treatment. Oral agents are also more convenient for most cancer patients. They do not require IV access, thereby avoiding complications with infusion, clotting, and infections. Self-administration also means fewer trips to the hospital or practice. Finally, there is some evidence that these oral agents may have less severe adverse effects compared with intravenous therapies.¹

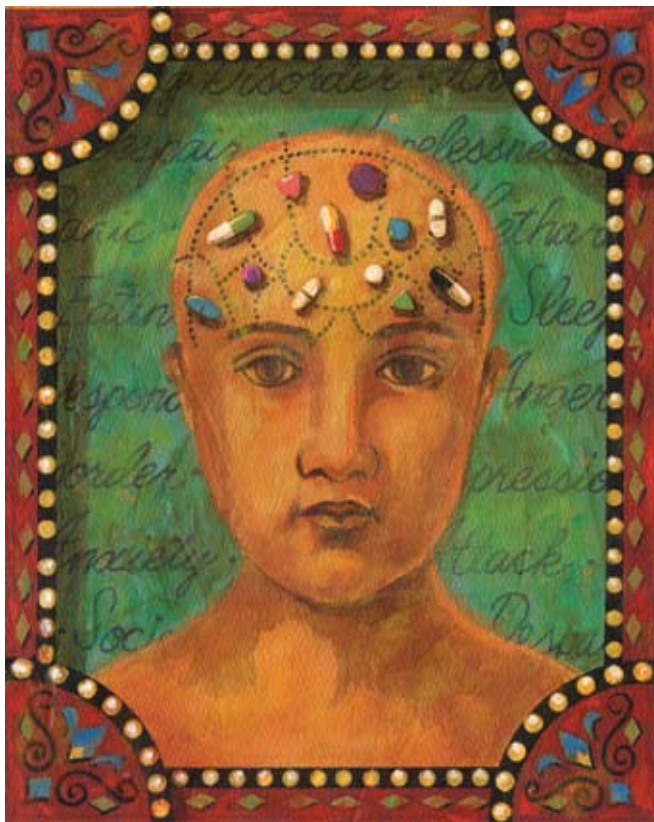
While patients prefer the convenience of oral medications, the self-administration of oral chemotherapeutic agents presents its own challenges. For example, self-administration may increase the risk of medication errors and possibly compromise the effectiveness of the anti-cancer therapy. Some oral agents may have drug/drug interactions. To prevent unwanted toxicity and therapeutic misadventures, providers and patients need to understand the mechanisms of action and potential drug/drug interactions associated with these newer agents. Clinicians can then take the necessary steps to prevent problems and maximize the efficacy of oral chemotherapeutic agents.¹ Other potential problems associated with oral chemotherapy may include:

- Patient non-adherence
- Nausea and vomiting
- Lack of patient education
- Toxicity profiles of newer agents
- Dysphagia (difficulty in swallowing)
- Odynophagia (painful swallowing)
- Cost.

Many of these potential problems need to be identified and discussed with the patient *prior* to starting any

Table 1. Newer Oral Antineoplastic Agents

| Agent | Indication |
|--------------------------|--|
| Capecitabine (Xeloda®) | Breast and colon cancer |
| Dasatinib (Sprycel®) | Chronic myeloid leukemia/acute lymphocytic leukemia |
| Erlotinib (Tarceva®) | Non-small cell lung cancer and pancreatic cancer |
| Gefitinib (Iressa®) | Non-small cell lung cancer |
| Imatinib (Gleevec®) | Chronic myeloid leukemia/gastro-intestinal stromal tumor |
| Lapatinib (Tykerb®) | Breast cancer |
| Lenalidomide (Revlimid®) | Multiple myeloma/myelodysplastic syndrome |
| Nilotinib (Tasigna®) | Chronic myeloid leukemia |
| Sorafenib (Nexavar®) | Renal cell carcinoma/hepatocellular carcinoma |
| Sunitinib (Sutent®) | Renal cell carcinoma/gastro-intestinal stromal tumor |
| Thalidomide (Thalomid®) | Multiple myeloma |
| Vorinostat (Zolinza®) | Cutaneous T-cell lymphoma |



oral chemotherapeutic regimen. Drug interactions are of particular importance. An excellent article on this topic was published in the *American Journal of Health-System Pharmacy*.²

The increasing use of complementary and alternative medicine—along with nutritional supplements and herbal products—further complicates medication management for many patients taking oral chemotherapeutic agents.

Another area where there is a paucity of data concerns the safe handling of these oral agents. For example, oral chemotherapeutic agents could lead to inadvertent exposure of family members to hazardous substances and environmental contamination. The safe practice standards that have been applied to intravenous chemotherapy must also be applied to oral chemotherapy.³

A Matter of Semantics

Adherence and compliance are terms that are used to describe the extent to which patients take medications as prescribed. Compliance is defined as the consistency and accuracy with which a patient follows the regimen prescribed by a physician or other health professional. This term has largely been replaced by the term adherence as the term compliance implies a patient has a subordinate relationship to the provider. Additionally, the World Health Organization (WHO) also determined that the term “compliance” is too closely associated with blame. Therefore, most providers use the term adherence to define the extent to which a patient’s behavior (e.g. taking medications, following a diet)

Adherence is Critical

In the past, almost all chemotherapy was delivered intravenously. Assuming a patient received all scheduled cycles of chemotherapy within the defined treatment period, providers could monitor and be assured of adherence with intravenous therapy. Today the treatment landscape has changed. When patients receive self-administered oral antineoplastic medications as part of their treatment regimen, they may not receive the same intensive teaching and monitoring as patients receiving intravenous therapy only. Thus, patients may not receive the same amount of education and monitoring as patients receiving intravenous therapy.⁴

Oral chemotherapy is effective *only if* patients adhere to their administration schedule. But it can be challenging for providers to monitor true adherence because the patient is not taking the drug at the hospital or practice. Clinicians are further limited by the lack of a gold-standard measurement for assessing patient adherence.

With relatively few studies on patient adherence to oral chemotherapy, however, it is difficult to measure the prevalence of this problem. In developed countries, adherence rates average around 50 percent in patients with chronic illnesses. For oncology, published studies reflect a highly variable adherence rate:⁵

- 17 to 27 percent for hematologic malignancies
- 53 to 98 percent for breast cancer
- 97 percent for ovarian cancer.

In one study of 2,378 breast cancer patients who started adjuvant tamoxifen therapy between 1990 and 1996, adherence during the first year of treatment was 87 percent, but declined to only 50 percent after 4 years.⁵ These findings showed that nearly one fourth of tamoxifen-treated patients

corresponds with agreed upon recommendations.

Related terms include “concordance” and “persistence rate.” Concordance is defined as the agreement in the types of data that occur in natural pairs. In healthcare, this term reflects the agreement between a patient and provider that involves the patient in decision making. Persistence rate refers to the number or percentage of patients still receiving therapy at the end of a defined period of time.^{1,2}

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were put at risk for suboptimal clinical response due to poor adherence. Other studies have shown similar results.^{5,6,7}

As cancer is generally perceived as a life-threatening and serious disease, one would expect a higher rate of adherence, and yet some patients do adjust their doses without informing their healthcare provider. For example, some cancer patients may exhibit over-adherence to self-administered medication, increasing the dose because of perceived ineffectiveness or because they believe more is better. Often unrecognized by clinicians, this practice can lead to a substantial increase in toxicity. Conversely, a cancer patient may decrease the dose because of actual or perceived toxicity. Patients taking very expensive oral agents may also reduce their dose to delay the need to refill the costly drug.

Barriers and Predictors to Non-adherence

Adherence to treatment depends on many co-existing factors. Major predictors of poor adherence to oral medications have been well characterized⁸ (see Table 2). Common barriers to adherence are often under the patient's control. Reasons cited by patients for not taking medications include forgetfulness, decision to omit doses, lack of information, emotional factors, and other priorities. Healthcare systems can create barriers to adherence by limiting access to care, using restricted formularies, and having high costs for drugs, co-payments, or both. Complex administration schedules, prohibitive cost, adverse effects, and poor access to medications all affect adherence rates.

Another barrier: patients may have a limited understanding of the rationale for therapy. Patient education is extremely important so that the individual understands the purpose of the intervention along with the expected results and potential side effects that may be encountered. Providers must recognize and respect the patient's cultural and religious beliefs and be aware of language deficits and poor literacy. Poor communication with the healthcare team and patient dissatisfaction with care also contribute to poor adherence.

Other factors that can play a role in non-adherence include:⁹

- Failure to fill an initial prescription
- Failure to refill a prescription appropriately
- Omitting doses
- Unsanctioned therapeutic holidays
- Taking too many doses, also known as over-adherence
- Prematurely discontinuing medication
- Taking a dose with prohibited foods, liquids, or other medications.

In the end, patient adherence to a long-term intervention depends on the patient's view of the benefits, risks, and cost of the intervention.

Improving Adherence to Oral Chemotherapy

Adherence is a complex and multifaceted issue that can alter the outcomes of therapy.^{5,10} Over-adherence and non-adherence are dangerous and can lead the practitioner to change the dose or prescribe a different agent because of apparent non-responsiveness or unexpected adverse effects. They can also result in unnecessary diagnostic testing, changes in dose or therapeutic regimen, and hospitalizations. These outcomes all bring about increased costs to the healthcare system. Table 3 provides a brief list

Table 2. Factors Associated with Non-adherence to Oral Medications

- Presence of cognitive impairment
- Presence of psychological problems, especially depression
- Treatment of asymptomatic disease
- Inadequate follow-up or discharge planning
- Adverse effects of medication
- Patient's lack of belief in the benefits of treatment
- Patient's lack of insight into the illness
- Missed appointments
- Poor provider-patient relationship
- Presence of barriers to medications or care
- Complexity of treatment
- Cost of medication, co-payment, or both

Table 3. Potential Consequences of Non-adherence with Oral Medications

- Increase in physician visits
- Increased hospitalization rates
- Longer hospital stays
- Decreased patient satisfaction
- Poor patient-provider relationships
- Compromised disease outcomes, such as decreased time to relapse and decreased survival

of potential consequences related to non-adherence to oral chemotherapy.

Since numerous factors contribute to patient medication adherence, it is unlikely that one single approach will be optimally effective. Instead, providers should use a multidisciplinary approach to promote medication adherence in their cancer patients. For example, collaboration among pharmacists, pharmacy technicians, oncology nurses, behavioral specialists, and physicians has been shown to improve patient adherence to oral chemotherapy.^{5,11} Complex treatment regimens can adversely affect patient adherence. Pharmacists, in particular, can play a key role by working with prescribers on ways to simplify treatment regimens and reviewing patient medication profiles to identify potential drug interactions.

Educating cancer care providers about the issues and barriers to adherence is imperative. Educated providers can then communicate this important information to their cancer patients. Involving cancer patients in all aspects of the decision-making process has been shown to increase patient motivation and adherence. Providers can ensure that patients feel like they are part of the cancer care team by:

- Reassuring patients that oral anti-cancer therapies are very effective cancer treatments
- Educating patients that responses can take time to evolve
- Assuring patients that the healthcare team is there to support them
- Conducting regular, follow-up calls
- Providing frequent reassurance that patients can always call someone for clarification or advice

Case Study

A 50-year-old woman with metastatic breast cancer is prescribed capecitabine 1250 mg/m² by her medical oncologist. The physician instructs her to take four 500 mg tablets in the morning and four 500 mg tablets in the evening for 14 days, take 7 days off, return to the clinic in 3 weeks for a follow-up appointment, and to call if she has any problems.

Three weeks later the patient returns to the clinic with painful erythema and swelling of the hands along with diarrhea which caused her to miss several days of work. She also complained of nausea. She said she began taking antacids with her medication to help the nausea but it did not improve. She stated that she stopped taking her capecitabine with four days left to go because she felt so miserable. When asked why she did not call the clinic, the patient stated "I did not want to bother anyone and I thought everyone gets sick with chemotherapy."

This not uncommon illustration could have been prevented by education and early contact.

Education. Patient and family education is probably the most important factor in achieving a successful outcome. The benefits (value of the treatment) and

the expected side effects of the medication should be explained in detail to the patient prior to initiation of treatment. Written, drug specific information should also be provided to the patient. A careful patient history and list of current medications is required to identify any potential adherence issues and possible drug interactions (e.g. phenytoin, warfarin, aluminum containing antacids). In this case, the patient started taking antacids with capecitabine. This contributed to the toxicity she encountered as antacids increase plasma levels of capecitabine.

Early contact. Capecitabine requires close monitoring during initiation of therapy, and providers should maintain repeated contact with the patient during the first cycle of treatment. This contact serves to establish trust and a connection with the patient to assess patient understanding of the treatment regimen and to identify any patient issues. A clinic contact should be provided to the patient, and the patient should be encouraged to call for any issue. In addition, a follow-up appointment in 7 days, instead of 3 weeks should be scheduled to assess the patient during the first week of therapy and to reinforce patient education and provide support. In this case, nausea could have been identified earlier, the appropriate intervention initiated, thus preventing the unwanted toxicity seen here (diarrhea, hand and foot syndrome).

- Taking reports of adverse events seriously and attempting to minimize their severity.

Equally important is for providers to actively listen to their cancer patients. This practice helps providers understand the patient's wishes and develop a customized approach to a specific treatment regimen as necessary. Regularly scheduled meetings to evaluate patient responses to therapy may also help identify issues with adherence and the resulting effect on outcomes.

Comprehensive patient and family education has been shown to enhance adherence to oral chemotherapy. This education should address the dose, frequency, timing of dosing, what to do if a dose is omitted, side effects and symptom management, and what to do if an adverse effect is encountered. Written aids and explanations of the importance of adherence, along with the possible ramifications of non-adherence should be fully discussed. Providers should not overload patients with detailed drug information if they are receiving information about their diagnosis, prognosis, or proposed treatment options. Scheduling a different time to discuss specific drug therapy may be required. Other aids such as pillboxes, calendars, diaries, alarms, and other tools may also be helpful.

Follow-up is critical to optimal patient adherence. Providers should monitor adherence and persistence on a regular basis. Refills on prescriptions should be restricted as appropriate. Patients who have missed or cancelled appointments should be contacted. These patients are often the ones who need the most help to improve their adherence to a treatment regimen. Efforts should be made to schedule follow-up visits that are convenient and efficient for the patient.

In the end, establishing trust and communication, providing support and education, instituting effective treatment plans, and providing effective follow-up with

patients all contribute to improved patient adherence rates and (hopefully) improved outcomes.^{8,12} 📄

Steve D'Amato, RPh, BCOP, is a clinical pharmacy specialist with the Maine Center for Cancer Medicine and Blood Disorders in Scarborough, Maine.

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