Cancer chemotherapy is widely regarded as a category of pharmacologic treatment with a narrow therapeutic index. Medication errors involving chemotherapy administration have the potential for harmful, even lethal, results. In recent years, considerable effort has been devoted to raising standards of care and minimizing the risk of medication error for patients receiving cancer chemotherapy at many institutions in the United States and elsewhere (Iizuka, Hosokawa, Hashimoto, Yamamoto, & Horinuchi, 2001; Kilbey & Summersgill, 2001; Perini, Topping, Brown, Roberts, & Robertson, 1997; Upton, 1997). Numerous articles have been published outlining suggestions for error prevention with antineoplastic agents (Attilio, 1997; Beckwith & Tyler, 2000a, 2000b; Cohen et al., 1996; Goldspiel, DeChristoforo, & Daniels, 2000; Ogletree, 2001). Recommendations often are based on the assumption that chemotherapy will be administered in the setting of a healthcare facility. Such published recommendations include improved staff education, laboratory value verification, restrictions on personnel involved in the process of treating patients with chemotherapy, and double and triple checks by healthcare professionals at various points in the process. Meanwhile, many patients with cancer are self-administering cancer chemotherapy regimens with a high potential for toxicity in the home, via the use of oral dosage forms (see Figure 1).

The amount and intensity of oral chemotherapy administered in the home likely will escalate in the foreseeable future. An estimated 20%–25% of the more than 300 new antineoplastic agents currently in development are oral products (Bowers, Silberman, & Mortenson, 2002; Thomas, Cahill, Mortenson, & Schoenfeldt, 2000). Some of these agents are new chemical entities, whereas others are drugs already available in IV form and under study as oral products. Recently, the U.S. Food and Drug Administration approved capecitabine, an oral fluorouracil derivative; temozolomide, an oral agent related to dacarbazine; and imatinib capsules, the first signal transduction inhibitor to become commercially available to treat cancer in the United States. These drugs are additions to an armamentarium that includes cyclophosphamide, methotrexate, etoposide, melphalan, and many more oral chemotherapeutic agents. See Figure 2 for a more complete list of chemotherapeutic agents commercially available or under study in the United States in oral dosage forms. Some of these drugs can be used for conditions other than cancer; for example, methotrexate often is administered orally to treat arthritis. This article pertains to chemotherapy agents such as direct cytotoxins that have a particularly narrow therapeutic window, while acknowledging that many agents not discussed also are given orally to treat cancer (e.g., corticosteroids, hormonal therapies).

Nurses who care for patients with cancer who self-administer oral chemotherapy medications can be of great service. Familiarity with the characteristics of various oral agents will provide a background to allow for effective education of patients so as to maximize benefit and minimize risk. Identification of specific barriers to safe and efficacious self-administration of chemotherapy and the development of strategies to overcome these barriers will provide an important measure of safety for patients in their homes.

What Are the Issues?

Although safety is the focus of this article, it is only one of many factors to be considered regarding oral chemotherapy. Efficacy, patient preference, quality of life, and economic issues all are considerations when determining the mode of treatment for a particular patient’s cancer. Oral chemotherapy offers several advantages to patients. The need for IV access with attendant care and risks may be obviated. Hospitalizations and

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### IV Chemotherapy in an Institutional Setting

1. Patient is assessed, and a regimen is selected.
2. Prescribing team checks height, weight, body surface area, dose, regimen, laboratory values, and appropriateness of supportive therapy.
3. Order is written and signed by a board-certified hematologist or oncologist as per institutional requirements.
4. Oncology RN checks all of the above.
5. Pharmacist checks all of the above.
6. Chemotherapy is prepared and delivered to the patient.
7. Oncology RN checks the order again and administers the medication.
8. Oncology RN ensures that supportive therapy is administered.
9. Patient is in the presence of healthcare professionals during and for a variable time period after administration.

### Oral Chemotherapy Administered in the Home

1. Patient is assessed, and a regimen is selected.
2. Prescribing team checks height, weight, body surface area, dose, regimen, laboratory values, and appropriateness of supportive therapy.
3. Prescription is written by a licensed physician or may be phoned in to a retail pharmacy by a physician or designee. Specialty board certification is not required.
4. An RN may or may not separately check the order.
5. Pharmacist checks during dispensing, but the pharmacist is not likely to have the necessary information to check all of the parameters listed above.
6. Chemotherapy prescription is filled and delivered or the patient picks it up.
8. Patient accepts responsibility for management of supportive therapy.
9. Patient is at a remote site and must establish threshold and mechanism for contacting healthcare providers.

### Step 1: Assessment

After diagnosis and staging, a treatment decision is made. Is this patient a good candidate for successful management of oral chemotherapy? The following steps will outline many factors that should be carefully considered and discussed with the patient during the initial assessment, prior to selecting the oral route for chemotherapy delivery. The assessment process is ongoing once oral chemotherapy treatment begins and continues through and beyond subsequent cycles.

### Step 2: Prescribing

The medication must be prescribed correctly and accurately. Institutional requirements may vary and generally are more strict than legal requirements for outpatient prescriptions. For example, the signature of an attending oncologist or hematologist may be required to activate an order for cancer chemotherapy to be administered to a hospital inpatient, but any licensed physician may legally write a prescription for oral chemotherapy to be filled at a community pharmacy. Application of the more conservative approach regardless of setting may offer a greater margin of safety for patients. The legibility and clarity of the prescription are of paramount importance. Encourage oral chemotherapy prescriptions that are printed in block letters, typed, or computer-generated rather than handwritten. Discourage telephone or fax transmission of prescriptions and the use of abbreviations. Present prescriptions to the pharmacy with adequate time for processing, including the possibility that the medication may need to be ordered from a wholesaler. Drugs that are seldom prescribed, very costly, or recently approved may not be immediately available in every patient’s pharmacy. Planning ahead will help to ensure that patients have the medication when treatment is scheduled to begin.

### Step 3: Procurement

Prescriptions must be filled accurately and in a timely fashion. A commercially available product may or may not exist that is suitable to provide a desired dose to patients. Inconsistencies between complex dosing recommendations and available dosage forms may present clinical dilemmas to prescribers (Ratain, 2002). If commercially available dosage forms cannot be used to provide the prescribed dose, perhaps extemporaneous compounding will be necessary. In general, manipulation of oral dosage forms in the home setting (i.e., crushing or breaking tablets, opening capsules) is not advisable because of the biohazardous nature of these products. Special equipment and time-consuming techniques may be required in the pharmacy to manipulate oral chemotherapy agents and obtain the desired dosage form, such as a liquid product. This may lead to a lengthy lag time between prescription drop-off and pick-up.

Many circumstances exist whereby patients may experience difficulties that interfere with timely procurement of medication.

### Frequently Prescribed Oral Chemotherapy Products

- Busulfan (Myleran\textsuperscript{®}, GlaxoSmithKline, Research Triangle Park, NC)
- Capecitabine (Xeloda\textsuperscript{®}, Roche, Nutley, NJ)
- Chlorambucil (Leukeran\textsuperscript{®}, GlaxoSmithKline)
- Cyclophosphamide (Cytoxan\textsuperscript{®}, Bristol-Myers Squibb, Princeton, NJ)
- Etoposide (VePesid\textsuperscript{®}, Bristol-Myers Squibb)
- Hydroxyurea (Hydrea\textsuperscript{®}, Bristol-Myers Squibb)
- Imatinib (Gleevec\textsuperscript{®}, Novartis, East Hanover, NJ)
- Lomustine (CeeNU\textsuperscript{®}, Bristol-Myers Squibb)
- Melphalan (Alkeran\textsuperscript{®}, GlaxoSmithKline)
- Mercaptopurine (Purinethol\textsuperscript{®}, GlaxoSmithKline)
- Methotrexate (various manufacturers)
- Procarbazine (Matulane\textsuperscript{®}, Sigma-Tau Pharmaceuticals, Gaithersburg, MD)
- Temozolomide (Temodar\textsuperscript{®}, Schering Corporation, Kenilworth, NJ)

### Selected Oral Drugs and Classes of Drugs Under Investigation for Cancer Treatment

- Fluorouracil derivatives
- Idarubicin
- Platinum derivatives
- Taxane derivatives
- Topotecan
- Vinorelbine

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**Figure 1. Steps and Safety Measures for IV Chemotherapy Administration Compared to Home Administration of Oral Chemotherapy\textsuperscript{a}**

\textsuperscript{a} This is a simplified example of how the two methods might typically compare; however, details will vary from case to case (e.g., prescribing requirements vary among states and institutions).

**Figure 2. Oral Chemotherapy Products**
Inclement weather, acute illness, and the need to take medications that interfere with safe driving all may hinder patients’ ability to obtain medication from a local pharmacy. Patients must have the resources to obtain the drug. Oral chemotherapy can cost thousands of dollars per cycle. Expected contributions from medical insurance, third-party programs, and projected out-of-pocket expenses should be assessed well in advance of medication pick-up. Carefully selected mail-order pharmacies may provide the necessary support and service for some patients in need of oral chemotherapy treatment.

Once patients have the medication in the home, they must be able to select the correct prescription container and open it for procurement to be complete. Many patients have multiple prescription vials and must select the correct medication when each dose is due. Patients must store the medication properly (e.g., heat-labile products such as etoposide capsules must be stored in a refrigerator). The potential toxicity of oral chemotherapy products is acknowledged and must be taken seriously. Every effort must be made to prevent accidental ingestion. For some patients, however, child-resistant safety prescription lids will be a barrier to medication administration and should be avoided. Remind patients to discuss this with their pharmacist if necessary. In addition, patients must protect children and pets by keeping medications out of their reach at all times.

**Step 4: Ingestion**

Patients must be reliable, thoroughly instructed regarding their prescribed regimen, and willing and able to comply for a successful self-administered chemotherapy treatment. Ensure that patients correctly understand how and when to take their medication. Explain food-drug interactions, dose and frequency, and potential adverse effects until patient understanding can be expressed verbally. Include herbal remedies and nutritional supplements for a thorough assessment of each patient’s regimen. Involve caregivers as appropriate. If laboratory results or other assessments are pending, specify exactly how and when patients will obtain clearance to begin the cycle of oral chemotherapy.

Patients must be able to swallow medications safely. Evaluate each patient’s risk for aspiration. Dry mouth, dysphagia, tremor, poor eyesight, and other physiologic conditions that impair ability to manipulate or swallow oral dosage forms must be assessed fully prior to initiating self-administration of oral chemotherapy. If patients cannot swallow the medication as provided, a reassessment is in order. Consider whether a more suitable dosage form is commercially available or can be compounded by the pharmacy. Address patient-specific factors, such as xerostomia or nausea, that may be overcome with treatment. If these obstacles prove to be insurmountable, patients may not be candidates for oral chemotherapy.

**Step 5: Dissolution**

Drugs must be in solution to be absorbed; therefore, dissolution in the appropriate section of the gastrointestinal (GI) tract is an important step toward bioavailability of an oral agent. Because pH is a major determinant of drug dissolution, variation in pH may contribute to the wide interpatient range in bioavailability. For example, etoposide, which is most stable at a pH of approximately 5, has an oral bioavailability of anywhere from 25%–75%, which is up to a threefold variation from patient to patient (Bristol-Myers Squibb, 1998). Attempts have been made to increase bioavailability by manipulating the pH of the GI tract (Joel et al., 1995), but this approach has not been widely accepted or applied.

The amount of time a drug spends in various portions of the GI tract affects dissolution. Drugs (e.g., metoclopramide) or physiologic conditions (e.g., severe diarrhea) that alter normal motility can indirectly affect drug dissolution by altering transit time through the GI tract. Are patients nauseated? If patients vomit, should the dose be repeated? Did emesis occur before or after dissolution? These questions can be answered only on an individual basis, depending on the nature of the regimen as well as patients’ status. In general, of course, the sooner patients vomit after ingesting a dose, the less will have been dissolved and absorbed. Antiemetics may be indicated as primary prophylaxis or added to the regimen if nausea or vomiting occurs. Vomitus, as well as urine and stool, after ingestion of chemotherapy should be treated as a biohazardous substance. The entire household should know the risks of exposure to biohazardous substances and how to safely handle patients’ bodily fluids and chemotherapy products.

**Step 6: Absorption**

Chemotherapy medication must be absorbed into the systemic circulation to exert its intended pharmacologic effect. To a large degree, absorption depends on the drug’s physical characteristics (e.g., size of the molecule, lipophilic tendency, presence or absence of electronic charges). Interaction with enzymes in the GI tract or liver may lead to activation or inactivation of the drug. For example, cytochrome p450 enzymes are active in the liver with up to a tenfold variation from patient to patient and in the GI tract with up to a sixfold variation (Demario & Ratain, 1998). Drug interactions may center around the cytochrome p450 enzyme system and could be manipulated to enhance oral bioavailability (e.g., ketoconazole [i.e., a CYP450 inhibitor] with etoposide [i.e., a CYP450 substrate]). However, inadvertent drug interactions could be harmful, resulting in unplanned toxic or subtherapeutic levels of drug (Kobayashi et al., 1996).

Some drugs are absorbed by simple concentration-gradient–dependent diffusion and others by active transport. Active transport mechanisms often are saturable. When a saturable mechanism is present, a large portion of a small dose will be absorbed, but the fraction absorbed declines as the dose increases. For example, methotrexate is almost completely absorbed at doses of less than 30 mg/m², yet only about 10% is absorbed when doses of 80 mg/m² or greater are given orally (Bleier, 1978). Etoposide is another drug with saturable absorption (Smyth, Pfeffer, Scalzo, & Comis, 1985).

Several patient-specific factors, such as pH of the GI tract, blood flow to the gut wall, and GI motility, can influence drug absorption. Medications (e.g., proton-pump inhibitors, histamine-2 antagonists, antacids) may increase the pH of the GI tract. Gut wall edema may compromise absorption and be present in patients with chronic renal failure or congestive heart failure. P-glycoprotein drug efflux pumps in the GI tract may inhibit drug absorption to varying degrees. In the future, research may lead to strategies to overcome this effect (Terwogt, Beijnen, Huinkink, Rosing, & Schellens, 1998).

The presence of food in the stomach may delay or decrease absorption. Manufacturers’ recommendations or readily available references regarding food-drug interactions should be followed as closely as possible.

In general, the lower oral bioavailability is, the greater interpatient variation will be regarding absorption from the GI tract (Hellriegel, Bjorjsson, & Hauck, 1996). As expected interpatient variation increases, the less predictable efficacy and toxicity will be. This understanding serves to underscore the need for close monitoring of any patient taking oral chemotherapy.

**Step 7: Monitoring**

The need for frequent assessment of efficacy and adverse effects is obvious for all patients being treated with oral chemotherapy. Patients, lay caregivers, and healthcare providers will perform monitoring. Patients
must agree to adhere to the appropriate schedule of appointments for office visits, blood draws for laboratory value assessments, and other monitoring requirements. Opportunities for professional assessment may be fewer and farther between than for patients who receive IV chemotherapy. Oncology nurses must assist patients in developing an appropriate threshold for establishing contact with the healthcare system. A reliable mode of transportation must be available at all times in the event that patients need to be seen by their healthcare providers.

**Strategies for Success**

Patient education is critical for successful oral chemotherapy treatment. Vital components of patient education include but may not be limited to dose, route, frequency, food-drug and drug-drug interactions, proper storage and handling of medication, expected adverse effects, serious adverse effects, and when to seek professional guidance regarding possible adverse effects. Patients must have a clear understanding of symptoms that can be self-managed as opposed to those that should prompt a phone call to healthcare providers or an immediate visit to a local healthcare facility. Personalized verbal counseling fortified with written information is recommended. After an educational session with an oncology nurse, patients should be asked to restate key points in their own words to demonstrate understanding. Pharmacists are expected to counsel patients as well, emphasizing important points regarding proper administration. Educational points listed in this article are in addition to routine counseling topics for patients receiving chemotherapy by any route (e.g., neutropenic, thrombocytopenic, body fluid precautions).

Various methods can be employed to enhance the safe use of oral chemotherapy. Some patients may benefit from medication calendars and planners, or timers can be set to remind patients of a scheduled dose. Witnessed ingestion by a healthcare professional may ensure proper dose and has been required during some investigational studies of oral chemotherapy. This precaution is probably not practical on a large scale and, in fact, would negate much of the advantage and convenience of oral self-administration.

Electronic surveillance devices have been built into prescription vials as a way to document compliance. An obvious limitation to this device is the fact that opening the vial does not necessarily mean the medication was taken at the time recorded and that time only. One study of this type of electronic tracking device reported a high rate of compliance (Lee, Nicholson, Souhami & Deshmukh, 1992); however, further study is needed.

Monitoring of drug levels after oral administration may be followed by dose adjustment in an attempt to individualize the dose and target a therapeutic level. One example of an oral chemotherapeutic regimen managed in this way is methotrexate (McLeod, 1997).

In 2000, the U.S. Food and Drug Administration approved Temodar® (temozolomide, Schering Corporation, Kenilworth, NJ), an oral chemotherapy agent that crosses the blood-brain barrier and is finding a place in the treatment of various malignancies of the central nervous system. Currently, temozolomide is indicated for the treatment of refractory anaplastic astrocytoma. Temozolomide is available in several capsule strengths, and dosage is based on body surface area. Dose adjustments are recommended according to patient tolerance. Patients may need to take several different capsule strengths in combination to achieve the proper dose, and this combination has the potential to change from cycle to cycle. Patients may become confused by the complexity of the treatment regimen, which may result in errors in self-administration. The product information for temozolomide requires pharmacists who dispense the drug to do so with individually prepared daily-dose packs. The capsule combination for each day’s dose should be individually packaged and labeled, so that patients only need to open one dose pack to obtain the proper dose to be ingested (Schering Corporation, 2001). This method seems to have considerable potential to reduce the risk of medication error with this product; however, actual dispensing practices do not always meet the requirements outlined in the product insert (Birner & Meyer, 2001). Healthcare professionals may wish to confer with their patients’ pharmacists to ensure that this drug is dispensed in daily-dose packs to facilitate compliance in individual cases.

**Summary**

Oral chemotherapy has distinct advantages and disadvantages in comparison to IV chemotherapy, and its use may expand in the future. Oncology nurses can be of great service to patients who require oral cancer chemotherapy administration. A basic knowledge of the characteristics and properties of oral chemotherapy agents, along with a thorough assessment of each patient’s ability to manage oral chemotherapy self-administration, is critical to successful treatment. Strategies to enhance success exist; arguably the most important strategy is meticulous patient education and close monitoring despite geographic distance between patients and healthcare providers.

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**References**


Rapid Recap

Safe Administration of Oral Chemotherapy

- Patients receiving oral or IV chemotherapy are at risk for toxicity because of the narrow therapeutic window inherent to many of these agents.
- Safety measures in place for hospitalized patients receiving IV chemotherapy may not be achieved for many patients who take oral chemotherapy at home.
- Oral chemotherapy safety and effectiveness are enhanced when patients are thoroughly assessed and monitored, medications are prescribed correctly, and patients are able to ingest and absorb their medications.
- Drug dissolution in and absorption from the gastrointestinal (GI) tract may be variable depending on GI pH, GI motility, comorbid conditions, drug interactions, and enzyme systems.
- Oncology nurses are in a key position to provide patient education, enhancing safety and promoting compliance in patients taking oral chemotherapy.