**A Changing Paradigm for Cancer Treatment: The Advent of New Oral Chemotherapy Agents**

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The development of numerous oral chemotherapy agents has led to a new paradigm in cancer treatment. Oral chemotherapy can be self-administered conveniently, so patients with cancer can receive their treatments in their homes instead of in a supervised and controlled healthcare environment. Cancer now is recognized as a treatable chronic disease, and new oral chemotherapy agents have been developed that offer targeted cancer treatment. Although the newer oral chemotherapy agents offer additional treatment options, they also pose challenges for patients and healthcare providers. Patient adherence and monitoring can be challenging, and reimbursement issues abound. Oncology nurses play a key role in assessing, educating, and monitoring patients receiving oral chemotherapy. In addition, they may be involved in assisting patients with obtaining reimbursement and, in some cases, may be instrumental in locating patient assistance programs. This article discusses patient care issues related to treatment with oral chemotherapy agents and provides a historical overview of their development and use.

**Key Words:** antineoplastic agents, pharmaceutical preparations

Oral agents also are effective and can control cancer and increase survival time and quality of life. Despite the demonstrated effectiveness of oral chemotherapy agents, misconceptions about them abound among patients as well as some healthcare providers. One perception is that oral chemotherapy represents an inferior treatment or even palliative care, because patients have difficulty comprending that a pill can be as “strong” as IV chemotherapy or that a single capsule of oral chemotherapy can be as effective as a multi-drug IV chemotherapy treatment. Therefore, patients must be educated about the efficacy and potency of oral chemotherapy agents. When patients misunderstand or underestimate these factors, they are at increased risk for poor compliance with self-administration.

Some newer agents actually have greater efficacy than the IV chemotherapies that historically have been used to treat a particular cancer. For example, the oral agent imatinib mesylate is superior to cytarabine chemotherapy and interferon as first-line therapy for patients with newly diagnosed chronic myeloid leukemia (CML) (O’Brien et al., 2003). Additional challenges occur as a result of viewing cancer as a chronic disease. Patients may need assistance staying engaged in the workforce and may need supportive care when they travel...
The use of oral chemotherapy agents to treat noncancerous conditions (e.g., methotrexate to treat rheumatoid arthritis) also has raised many issues for healthcare providers. Healthcare providers may be unclear as to who is responsible for teaching patients about these agents. In many settings, oncology nurses are assumed to be responsible for this patient teaching because they are the ones who teach patients about chemotherapy. Patient monitoring is yet another issue. Still compounding these issues is the potential for medication errors. Differences exist in dosing and schedules of administration when oral chemotherapy agents are used to treat cancer versus noncancerous conditions.

Finally, how patients pay for their oral chemotherapy treatments is a key component of the paradigm shift. Historically, Medicare only paid for treatments that skilled professionals administered in a medical facility. However, in 1993, Medicare expanded coverage to include oral chemotherapy agents that have an IV equivalent, such as cyclophosphamide or etoposide. In 1999, Medicare expanded coverage to include prodrugs, such as capcitabine and temozolomide, because these drugs are metabolized into an active agent that has an IV equivalent. However, Medicare does not cover many of the more recently approved agents. Given that 30% of seniors have no prescription drug coverage and that these agents cost between $1,900 and $2,500 per month, many patients are not able to afford to receive effective therapy (Bedell et al., 2002). Oncologists and nurses now need to consider not only whether a drug is efficacious and whether a patient will adhere to the treatment regimen, but also whether the patient will be able to afford the treatment (Thomas, Cahill, Mortenson, & Schoenfeld, 2000).

### Historical Overview

Although the emergence of oral chemotherapy agents is an exciting phenomenon, it is hardly new. Some of the first and most effective chemotherapy agents were oral formulations. In 1951, David Dalton, MD, began using chlorambucil to treat chronic lymphocytic leukemia (Rai, Dohner, Keating, & Montserrat, 2001). The introduction of oral melphalan, busulfan, cyclophosphamide, and methotrexate soon followed. These oral agents have a wide range of indications, including noncancerous uses. Over time, researchers have learned a great deal about these agents, including new indications for “old” agents. For instance, to treat ectopic pregnancy, oral methotrexate instead of intra-muscular methotrexate was given to women in two, divided, 60-mg/m² doses and the response rate to oral treatment was similar to the response rate when the drug was injected (Lipscomb, Meyer, Flynn, Peterson, & Ling, 2002). Another use of an “old” oral agent is the use of oral etoposide to treat children with recurrent intracranial ependymoma who are refractory to surgery, radiotherapy, and chemotherapy. In one study of 12 children, the oral etoposide was well tolerated, produced minimal toxicity, and had apparent activity (Chamberlain, 2001). Also, over time, researchers have learned more about the potential long-term effects and complications associated with some of these oral chemotherapy agents, such as the potential for inducing secondary malignancies.

The older generations of chemotherapy agents were classified according to activity within the cell cycle and were deemed either cell-cycle specific or nonspecific. The newer generations of agents also are classified by their actions, but these actions are novel and include immunomodulation and targeted therapies, such as protein kinase receptor inhibition and epidermal growth factor receptor inhibition. These newer agents offer innovative approaches and mechanisms of action in destroying cancer cells.

## Alkylating Agents

Alkylating agents interfere with cellular reproduction by causing breaks and cross-links in DNA strands. They are cell-cycle nonspecific; therefore, they are not as dependent on rapid cellular proliferation for efficacy. As a class of drugs, they are fairly myelosuppressive and require careful monitoring of complete blood counts to prevent complications associated with neutropenia, anemia, and thrombocytopenia. Many alkylating agents are metabolized by the liver via the microsomal P450 pathway. Consequently, caution must be used when alkylating agents are given with other drugs that have a similar metabolic pathway to prevent drug accumulation and toxicity.

Two of the oldest oral alkylating agents, developed in the early 1950s, are chlorambucil and busulfan. Chlorambucil is a very slow-acting agent, generally is administered in daily low doses, and is one of the least toxic of all the oral chemotherapy agents. The immunosuppressive properties of chlorambucil and its low toxicity profile make it a good drug for treating autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (Wilkes, Inghersen, & Barton-Burke, 2002).

A new off-label indication for chlorambucil is the treatment of uveitis, chronic inflammation of the eye that can lead to
blindness. Researchers at the University of Chicago followed 58 patients with uveitis who received chlorambucil at a dose of 10–30 mg a day for a mean of 16 weeks. Many of these patients were developing blindness despite ongoing immunosuppressive therapy. Four years following chlorambucil treatment, 77% of the patients maintained their improved sight and none developed secondary malignancies (Goldstein, Fontanilla, Kaul, Sahn, & Tessler, 2002).

Busulfan is approved to treat CML but is not frequently used because of the advent of newer, more effective agents. At standard doses, busulfan selectively destroys granulocytes and spares the remainder of the hematopoietic cell lines. Therefore, it is ideally suited to treat granulocyte-based diseases.

Melphalan is a derivative of nitrogen mustard. In the 1960s, it was a component of a chemotherapy combination used to treat multiple myeloma and response rates of 50%–60% were observed (Harousseau, 2002; Raje & Anderson, 2000). It also is used to treat ovarian cancer (Wilkes et al., 2002). It was one of the first agents used in adjuvant treatment of breast cancer. However, it lost popularity as adjuvant therapy when a high rate of nonlymphocytic leukemia, a secondary malignancy, occurred (Fisher et al., 1985). Melphalan continues to be widely used to treat multiple myeloma because it is a convenient treatment with minimal toxicity and is relatively inexpensive when compared to the newer treatment regimens for multiple myeloma (Harousseau).

Cyclophosphamide in IV formulation is indicated for a variety of hematologic malignancies and solid tumors. As an oral agent, it is well absorbed and tolerated. The most traditional use of oral cyclophosphamide is in what is referred to as the Bonadonna adjuvant breast cancer treatment regimen, which consists of oral cyclophosphamide, methotrexate, and fluorouracil (CMF) (Bonadonna et al., 1976). Oral cyclophosphamide was one of the first oral agents that presented many challenges to nurses. The toxicities associated with oral cyclophosphamide, namely nausea and vomiting and the potential for hemorrhagic cystitis, prompted compliance issues as well as the need for comprehensive patient education regarding symptom management.

Lomustine was approved in the early 1970s for the treatment of primary brain tumors (Burton & Prados, 2000). Lomustine is an alkylating agent but is in the nitrosourea subgroup and crosses the blood-brain barrier. It commonly has been used to treat colon cancer, gastric cancer, and malignant melanoma. Because it is supplied in three capsule strengths and a typical dose may contain two or three different strengths to achieve the prescribed amount, the dose must be computed and dispensed carefully and patients must double check their doses to avoid confusion that could result in under- or overdosing. One advantage of lomustine is that the total dose is taken at one time, as opposed to daily administration, so the potential for medication error is somewhat reduced. However, lomustine treatment is complicated by a fair amount of emetogenesis and delayed myelosuppression (Wilkes et al., 2002).

Altrétamine is a newer oral chemotherapy agent approved for recurrent or refractory ovarian cancer. Although the exact mechanism of action is unknown, it is considered an alkylating agent. It has a complex dosing regimen requiring three to four doses of the drug each day for two to three weeks. Nursing challenges associated with altrétamine administration include compliance with the frequent dosing schedule and monitoring for peripheral neuropathy (Fischer, Knobf, Durivage, & Beaulieu, 2003).

Three oral agents in this class of drugs are etoposide and topotecan. (At this writing, oral topotecan is in clinical trials.)

Etoposide is an older oral chemotherapy agent derived from the May apple plant and is active in an oral formulation. It is used to treat Hodgkin’s disease, small cell lung cancer, and ovarian cancer. The agent is well absorbed and can be taken with or without food. Patients who have Medicare without prescription drug coverage may find the IV formulation less costly than oral etoposide.

Oral topotecan has been undergoing clinical trials for several years. Researchers conducting phase II studies found the oral formulation of the drug to have superior efficacy when compared to IV topotecan in the treatment of small cell lung cancer (Von Pawel et al., 2001) and similar efficacy with less myelosuppression in the treatment of refractory ovarian cancer (Clark-Pearson et al., 2001). The availability and efficacy of the oral formulation of topotecan may give patients the ability to self-administer the drug for five consecutive days, rather than travel to a treatment facility for IV topotecan. Phase III trials of oral topotecan are under way.

Antimetabolites

Antimetabolites are cell-cycle specific, with their primary activity occurring during the S phase of the cell cycle. They inhibit DNA synthesis and repair, and they prevent cellular replication. They may block enzymes needed for DNA synthesis or mimic natural metabolites and become a nonfunctional part of the DNA strand, preventing replication (Wilkes et al., 2002).

Methotrexate initially was found to induce remissions in childhood leukemia and now is used to treat many different types of cancer. The oral formulation of methotrexate also has a long-standing history in treatment for a wide variety of immunologic disorders. In 1988, the U.S. Food and Drug Administration (FDA) approved methotrexate to treat psoriasis and rheumatoid arthritis (Jones & Paton, 2000). Patients may take low doses of oral methotrexate for years and need to be monitored for hepatic, renal, and bone marrow impairment. Patients who have been on long-term oral methotrexate therapy also may be more vulnerable to the side effects of chemotherapy if they are diagnosed with cancer and need chemotherapy treatment.

Hydroxyurea rapidly reduces the white blood cell or platelet counts in patients with CML, essential thrombocytosis, and acute myeloid leukemia in blast crisis. It is a potent radiation-therapy enhancer and has been used in combination with radiation to treat head and neck cancer. Hydroxyurea also is used to treat sickle cell anemia because it increases the production of fetal hemoglobin, which then leads to a decrease in red cell hemolysis, thus preventing a sickle cell crisis (Mayfield, 1999).

Plant Alkaloids

Topoisomerase II inhibitors, a subclass of plant alkaloids, are cell-cycle-specific agents active in the late S phase and G2 phase. These agents inhibit enzymes needed to coil and uncoil the DNA helix in the G2 phase. The two oral agents in this class of drugs are etoposide and topotecan. (At this writing, oral topotecan is in clinical trials.)

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Miscellaneous Agents

Procarbazine is a methylhydrazine derivative. Its mechanism of action is uncertain, but it appears to disrupt preformed DNA, RNA, and protein. It is an oral chemotherapy agent given in combination with other agents (e.g., along with nitrogen mustard, vincristine, and prednisone in the MOPP protocol to treat Hodgkin’s disease). Multiple capsules of the drug are taken, because dosage is based on body surface area.
and treatment duration is for one to two weeks, repeated monthly. The dosing schedule, along with moderate toxicities of the agent (potential for infection and gastrointestinal distress) present many challenges for patients taking this oral agent (Wilkes et al., 2002).

**Prodrugs**

Prodrugs are inert drugs that require cellular enzymatic activation to become active agents. The necessary enzyme often is more prevalent in malignant tissue than normal tissue, allowing for tissue selectivity and potentially less toxicity. Prodrugs generally are alkylation agents (e.g., temozolomide) or antimetabolites (e.g., capecitabine).

Temozolomide is FDA approved for the treatment of refractory anaplastic astrocytoma. It is a prodrug of dacarbazine. Because it crosses the blood-brain barrier, this drug is being evaluated in the treatment of melanoma and other solid tumor brain metastases. Temozolomide is well tolerated; however, dosing errors are an issue because patients may need to take different capsule strengths each day for five days.

Capecitabine, a prodrug of fluorouracil, is approved to treat metastatic breast and colorectal cancers. In patients with metastatic colorectal cancer, oral capecitabine has shown greater tumor response than IV fluorouracil plus leucovorin, although no significant difference in time to progression or overall survival has been found. The single drug oral regimen is better tolerated than the fluorouracil and leucovorin regimen (Hoff et al., 2001). Successful use of this agent depends on patient education and adherence with the administration schedule.

**Targeted Therapies**

The advent of genomics has led to an increased understanding of the intricate workings of the cell. Normal cells have signal pathways in which the cell communicates within itself and with the “outside world.” This communication signals when to enter the cell cycle, when to divide, and when to die. With cancer cells, these pathways and signals have gone haywire. Targeted therapies are aimed at the specific target in the cancer cell that is over expressed or out of balance so that the growth of the cancer cell can be stopped.

Imatinib is a Bcr-abl tyrosine kinase inhibitor. Bcr-abl tyrosine kinase is a protein that is over expressed in Philadelphia chromosome-positive CML, which, in that communication chain, is blocking the signal for the cell to die (apoptosis). Therefore, the administration of imatinib allows the cell to have normal communication for apoptosis or programmed cell death. Its efficacy in treating refractory solid tumors that also may have the Bcr-abl targets present is being studied (Fischer et al., 2003).

Gefitinib is also a tyrosine kinase inhibitor, but its target is an epidermal growth factor receptor (EGFR). EGFR stimulates cell growth and division. Blocking the EGFR protein is felt to decrease angiogenesis, cellular division, and metastases. It also may increase apoptosis. This agent has been approved to treat refractory non-small cell lung cancer and is being studied in clinical trials as a treatment for many refractory solid tumors, such as head and neck and colon cancers. Gefitinib is relatively easy to administer because it is given as a single agent, one 250-mg dose, once daily, for all patients unless they experience toxicity (AstraZeneca, 2003).

**Summary**

With all of the new oral chemotherapy agents available today and on the horizon, this is an exciting time for patients with cancer and for the nurses caring for them. Many of the older oral chemotherapy agents will continue to be used but in novel schedules, in combination with other agents, or for new indications. Numerous new targeted therapies or oral versions of older IV chemotherapy drugs are in development or clinical trials. Nurses need to become informed about the new oral chemotherapy agents, educate patients about these agents, develop compliance tools to assist patients, and advocate for reimbursement for all oral chemotherapy agents.

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**References**


Rapid Recap

A Changing Paradigm for Cancer Treatment: The Advent of New Oral Chemotherapy Agents

- Many new oral chemotherapy agents have been approved recently, and these agents account for at least 25% of all new drugs in the research pipeline.
- Oral agents present many challenges for nurses, including variability in absorption, patient compliance in taking the medication, patient self-assessment and management of side effects, and costs to the patient.
- The use of oral chemotherapy agents to treat noncancerous conditions, such as the use of methotrexate to treat rheumatoid arthritis, raises issues such as who is responsible for patient education and monitoring and who should advise patients about safe handling and safety issues. It also increases the potential for medication errors because doses used to treat cancer versus noncancerous conditions differ.
- Many older chemotherapy agents will continue to be used but in novel schedules, in combination with other agents, or for new indications.
- Nurses need to keep informed about the new oral chemotherapy agents, educate patients, develop compliance tools, and advocate for reimbursement to help ensure patient success with these agents.

For more information on this topic, visit the following Web sites.

Oralchemo.org
http://www.oralchemo.org

Chemo Care
http://www.chemocare.com

Association of Community Cancer Centers: The Future of Oral Chemotherapy Drugs

Links can be found at www.ons.org.