The past few years have been witness to exciting advances in the treatment of patients with cancer. Two trends in particular are of note: the use of chemotherapy that is less generally cytotoxic and more specifically targeted to cancer cells and the administration of oral medications to cure or control cancer.

This article focuses on oral chemotherapy agents that have been approved recently for use in the United States and includes a discussion about what makes them unique in their effects on cancer cells as opposed to healthy cells. Their effects may be a matter of preferential delivery to the anatomical site of the cancer, exploitation of molecular differences between cancer cells and healthy cells, or variation in enzymatic transformation of the drug that tends to spare healthy cells at the expense of cancer cells.

The earliest discoveries in cancer research featured chemotherapy agents. These drugs disrupted the cell cycle in various ways, leading to cell death. Because cancer cell growth is not as controlled as the growth of healthy cells, these therapies would, in theory, affect cancer cells to a greater degree than healthy cells. In reality, the effects on healthy cells were and often are quite toxic, particularly on cells with rapid growth rates. Thus, the typical adverse effect profile includes myelosuppression, alopecia, and mucositis. Recently, advancing knowledge regarding the genetic and molecular intricacies of human cells has allowed researchers to focus more specifically on the differences between healthy and malignant cells and to exploit these differences to target the latter.

How do researchers develop drugs, and what makes a suitable candidate for an oral agent? Substances may be derived from what makes a suitable candidate for an oral agent? Substances may be derived from natural products such as plants or created anew in the laboratory. Many thousands of molecular entities often are screened during the search for a single promising agent for further investigation. Although sophisticated techniques and instrumentation have improved efficiency greatly, the process still is an arduous and often lengthy one (Swinyard, 1990).

Development of drugs may be based on astute observations of the effects on humans of previously available chemicals. A classic example is the case of mechlorethamine. During World War I, the remarkable effects of chemical warfare in the form of nitrogen mustard gas on blood and bone marrow were observed (Krumbhaar & Krumbhaar, 1919). Eventually, mechlorethamine was approved and made commercially available. To this day, it is known as “nitrogen mustard” and is still used to treat certain malignancies. Whatever the basis of discovery, staggering amounts of data must be collected, from preclinical to human benefit and safety data, prior to submission to the U.S. Food and Drug Administration (FDA) for approval.

The advantages of oral drug delivery are numerous (Borner, Scheithauer, Twelves, Maroun, & Wilke, 2001; Liu, Franssen, Fitch, & Warner, 1997). Oral drugs may be derivations of previously available injected agents or developed as original concepts. During the oral drug development process, challenges that are specific to the route of administration must be overcome (Bardelmeijer, van Tellingen, Schellens, & Beijnen, 2000; Birner, 2003; Lipinski, 2002; Stenberg, Bergström, Luthman, & Artursson, 2002). Ideally, a drug is stable in a formulation that is suitable for oral use, is palatable, does not irritate the gastrointestinal tract, readily dissolves after ingestion, and is adequately and reliably absorbed into the systemic circulation.

Many drugs are, in fact, prodrugs. A prodrug is a pharmacologically inert compound that is converted to an active agent by metabolic transformation in vivo (Malet-Martino & Martino, 2002). A prodrug is developed with features that favor it over the pharmacologically active component. For example, an active cytotoxic agent may be manipulated to produce a compound that is relatively nontoxic and, therefore, easier to handle and produce. Prodrugs historically have improved the in vivo delivery of a drug when the active component faces obstacles such as poor oral absorption, insolubility, and instability. Double prodrugs, or “pro-prodrugs,” require two metabolic transformations before becoming chemically active.

The abundance of orally formulated chemotherapy agents reflects the expanding role of oral chemotherapy in the care of patients with cancer. Many oral chemotherapy agents have been used for a number of years, and several have been developed recently. Newer agents include the prodrugs capecitabine and temozolomide, the retinoid bebraxotene, the immunomodulatory agent thalidomide, the protein kinase inhibitor imatinib, and the epidermal growth factor receptor inhibitors gefitinib and erlotinib. Each agent has unique pharmacologic properties, dosing, and side-effect profiles. This article reviews these agents from a pharmacology perspective.

Key Words: antineoplastic agents, pharmacokinetics, prodrugs, retinoids

**Ann Birner, PharmD**

The abundance of orally formulated chemotherapy agents reflects the expanding role of oral chemotherapy in the care of patients with cancer. Many oral chemotherapy agents have been used for a number of years, and several have been developed recently. Newer agents include the prodrugs capecitabine and temozolomide, the retinoid bebraxotene, the immunomodulatory agent thalidomide, the protein kinase inhibitor imatinib, and the epidermal growth factor receptor inhibitors gefitinib and erlotinib. Each agent has unique pharmacologic properties, dosing, and side-effect profiles. This article reviews these agents from a pharmacology perspective.

Key Words: antineoplastic agents, pharmacokinetics, prodrugs, retinoids

---

Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.

Digital Object Identifier: 10.1188/03.CJON.S6.11-19
and may further enhance oral delivery of some medications (Bundgaard, 1989).

Following is a review of recent innovations in oral cancer chemotherapy, focusing on oral agents that have come to the forefront since the late 1990s.

Prodrugs

Capecitabine

Capecitabine is a fluoropyrimidine derivative, a prodrug of fluorouracil, that was first approved for use in the United States in 1998 under the brand name Xeloda® (Roche Laboratories, Inc., Nutley, NJ). As is true of other fluoropyrimidines, capecitabine is an antimetabolite chemotherapeutic agent. It inhibits cell division via interference with protein synthesis, DNA synthesis, and RNA processing. Capecitabine itself is relatively nontoxic in vitro, requiring several in vivo metabolic steps for conversion to the pharmacologically active entity. An enzyme required to complete one step of this process, thymidine phosphorylase, is expressed in many tissues throughout the body. In some human cancers, however, the enzyme is overexpressed, that is, present in higher concentrations than in healthy tissues. The result, as demonstrated in a pharmacokinetic study of capecitabine, is a degree of tumor selectivity with higher levels of active drug in cancer cells (Schuller et al., 2000). This unique property of capecitabine, along with adequate oral absorption, makes the drug an attractive option in the fluoropyrimidine class.

Indications: Capecitabine is approved by the FDA for first-line therapy for patients with metastatic colorectal carcinoma, when fluoropyrimidine therapy alone is the treatment of choice; in combination with docetaxel in patients with metastatic breast cancer who have failed prior anthracycline-containing regimen(s); and as monotherapy for patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing regimen, or resistant to paclitaxel when further anthracycline therapy is contraindicated (e.g., when the maximum cumulative dose of an anthracycline has been administered) (Roche Laboratories, Inc., 2001).

In patients with metastatic colorectal cancer, oral capecitabine showed greater activity than IV fluorouracil plus leucovorin in terms of the primary endpoint—objective measures of tumor response. No significant differences were observed in time to progression or overall survival. Capecitabine was well tolerated in comparison to fluorouracil and leucovorin (Hoff et al., 2001). Improvements in time to progression and survival were demonstrated in a comparison of capecitabine with docetaxel to single-agent docetaxel in patients with metastatic breast cancer that had recurred after anthracycline-based therapy (O’Shaughnessy et al., 2002).

Clinical trials are under way to determine the value of capecitabine in patients with prostate, renal cell, cervical, esophageal, stomach, pancreatic, and lung cancers. Investigational treatment strategies for capecitabine include concurrent radiation therapy and its administration in combination with gemcitabine, oxaliplatin, irinotecan, epirubicin, carboplatin, cisplatin, vinorelbine, paclitaxel, or gefitinib (National Cancer Institute, 2003).

Capecitabine has the potential to interact with numerous drugs metabolized by cytochrome P450 2C9.

Side effects: Important adverse effects of capecitabine include diarrhea that is potentially severe, nausea, vomiting, hand-and-foot syndrome, stomatitis, hyperbilirubinemia, paresthesia, dermatitis, and fatigue. Hematologically, as a single agent, the drug usually is well tolerated, but myelosuppression does occur in some patients with varying degrees of severity. Neutropenia and thrombocytopenia are relatively rare, but anemia is common. Capecitabine may cause harm to human fetuses; therefore, use during pregnancy should be avoided. Capecitabine use during lactation is not recommended, and the drug is not approved for use in pediatric patients (Roche Laboratories, Inc., 2001).

Patients requiring antiocoagulation with warfarin during capecitabine therapy must be managed with extreme caution. Capecitabine has been shown to increase warfarin levels significantly, most likely because of inhibition of warfarin metabolism by the cytochrome P450 2C9 enzyme. This interaction may occur within several months of initiation or dose adjustments, and close monitoring of the international normalization ratio with appropriate anticoagulant dose adjustments is necessary to avoid bleeding. A similar interaction has been reported between fluorouracil and warfarin (Copur et al., 2001; Kolesar, Johnson, Freeberg, Berlin, & Schiller, 1999; Roche Laboratories, Inc., 2001). Patients taking phenytoin, another drug metabolized by cytochrome P450 2C9, should have phenytoin levels closely monitored during capecitabine therapy. Capecitabine has the potential to interact with numerous other drugs metabolized by cytochrome P450 2C9. Several detailed reviews of cytochrome P450 interactions have been published (Flockhart, 2003; Lacy, Armstrong, Goldman, & Lance, 2002; Michalet, 1998).

Dosing: The recommended starting dose of capecitabine is 1,250 mg/m² administered twice daily for two weeks, followed by one week of rest, in three-week cycles. The dose should be rounded to accommodate available tablet sizes of 150 mg and 500 mg, and the drug should be administered morning and evening with a glass of water within 30 minutes after a meal. Although food somewhat decreases the rate and extent of absorption, this recommendation is based on methodology used during clinical trials. Theoretically, repeated administration of the usual dose on an empty stomach could lead to untoward effects because of increased absorption. The complex metabolic pathways followed by capecitabine include hepatic as well as nonhepatic steps. Although the manufacturer recommends caution when administering the drug to patients with underlying hepatic insufficiency, specific guidelines for dose reduction are not available. A portion of the parent compound itself is renally cleared, as are the majority of metabolites. An initial dose reduction to 75% is recommended for patients with moderate renal impairment, that is, creatinine clearance of 30–50 ml per minute as estimated by the method of Cockcroft and Gault (1976) (see Figure 1). The drug should not be administered to patients with estimated creatinine clearance of less than 30 ml per minute. Capecitabine is contraindicated in patients with known hypersensitivity to fluorouracil. Caution is advised with patients older than 80 because of an increased incidence of severe adverse effects, although initial dose reduction is not required. All patients must be monitored carefully for adverse effects; specific product information provides details regarding dose reductions based on such events. Once reduced, capecitabine doses should not be increased to previous levels (Roche Laboratories, Inc., 2001).

Temozolomide

Temozolomide presents another example of a prodrug that, when taken orally, is converted in vivo to the pharmacologically active component. In this case, after administration, temozolomide is hydrolyzed rapidly and extensively to 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC). Hy-
drosis is not enzyme-dependant and occurs reliably at physiologic pH. MTIC is cytotoxic and considered to be an alkylating agent that interferes with DNA synthesis and function (Schering Corporation, 2001). Interestingly, MTIC also is produced by the prodrug dacarbazine, available since 1975 for the treatment of metastatic malignant melanoma but only in IV form (Bayer Corporation, 1995). An important characteristic of MTIC is its ability to cross the blood-brain barrier, thus penetrating the central nervous system (CNS), whereas many cytotoxic agents cannot. Thus, temozolomide has generated particular interest as an orally available agent with the potential for efficacy in cancers with CNS involvement.

**Indications:** Temozolomide was approved for use in refractory anaplastic astrocytoma in 1999. It is marketed as Temodar® (Schering Corporation, Kenilworth, NJ). In an early, pivotal trial that enrolled 162 patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse, temozolomide was administered in an open-label fashion. In the absence of a control arm, the results were placed in a historical context, with a favorable comparison of temozolomide to procarbazine and carboptatin. The researchers’ interpretation of the data suggested that improved health-related quality of life (HRQOL) was associated with response to therapy with temozolomide (Yung et al., 1999).

As evidence accumulates, interest in using the drug alone or in combination with other antineoplastic drugs or with radiation therapy in patients with other types of cancer has escalated. Examples include lung cancer, malignant melanoma (particularly if metastatic to the brain), and primary CNS malignancies such as glioblastoma multiforme. Temozolomide has been combined with carbustine, irinotecan, cisplatin, docetaxel, and thalidomide in clinical trials (Bafaloukos et al., 2002; Hwu et al., 2002; Prados, 2001).

In a phase II trial of temozolomide as a single agent in 41 patients with recurrent or progressive brain metastases associated with a variety of tumor types, 41% achieved some degree of control, either stable disease or partial response (Abrey et al., 2001). HRQOL was measured in two studies of temozolomide in patients with recurrent glioblastoma multiforme, one examining temozolomide alone and the other featuring temozolomide versus procarbazine. Previously validated HRQOL instruments were used, and temozolomide was found to have HRQOL advantages over procarbazine (Osoba, Brada, Yung, & Prados, 2000). In the study of temozolomide versus procarbazine, favorable responses in terms of disease progression and survival were noted in patients enrolled on the temozolomide arm (Yung et al., 2000). The status of dacarbazine as the standard of care for malignant melanoma and the relationship between temozolomide and dacarbazine lend credence to the potential utility of temozolomide in metastatic melanoma. This theory was supported by the results of a phase III trial in which patients with advanced metastatic malignant melanoma were randomized to treatment with either temozolomide or dacarbazine. The patients did not have evidence of brain metastases. Temozolomide was well tolerated, and improvements in HRQOL were documented. Efficacy of temozolomide was at least equal to that of dacarbazine. Pharmacokinetic analysis showed that systemic exposure to MTIC, the active component of both drugs, was higher in the temozolomide group (Middleton et al., 2000).

**Side effects:** Adverse effects of temozolomide are typical of traditional cytotoxic chemotherapy. Myelosuppression often is dose limiting; specific guidelines regarding dose reductions based on neutrophil and platelet counts are available in the manufacturer’s package insert. Geriatric patients and women, who may clear the drug more slowly than men, are at greater risk for myelosuppression. Myelosuppression tends to occur late in the treatment cycle and generally is reversible within two weeks. The incidence of nausea and vomiting justifies the use of prophylactic antiemetic therapy. Patients taking temozolomide often experience fatigue as well as headache and other CNS effects, which may or may not be drug induced. The drug is contraindicated in patients with known hypersensitivity to dacarbazine and should be avoided during pregnancy and lactation (Schering Corporation, 2001). Temozolomide is not approved for pediatric use, although clinical trials evaluating its use in children are under way.

Temozolomide does not appear to be particularly susceptible to drug interactions. Valproic acid has been shown to decrease the clearance of temozolomide by about 5%, but whether this is of clinical significance is unknown. In comparison to patients with normal organ function, neither mild to moderate renal nor hepatic impairment adversely affected clearance of the drug. Because of lack of experience, caution is advised when administering temozolomide to patients with severe renal (creatinine clearance less than 36 ml per minute) or hepatic dysfunction (Schering Corporation, 2001).

**Dosage:** The usual starting dose of temozolomide is 150 mg/m² orally once daily for five consecutive days of each 28-day treatment cycle. Based on response and tolerance, the daily dose may be adjusted downward or escalated to 200 mg/m² during subsequent cycles. Treatment may continue as tolerated until disease progression. For patients with improved or stable disease, the optimum duration of therapy is not known. Treatment with temozolomide is not recommended for patients who are unable to tolerate the minimum recommended dose of 100 mg/m² per day for five days. Other doses and schedules may be administered within the context of clinical trials. Doses must be rounded to accommodate available capsule sizes because capsules must be swallowed whole (5 mg, 20 mg, 100 mg, and 250 mg capsules are available commercially). Temozolomide should be taken consistently with regard to food, and nausea may be minimized when it is taken on an empty stomach at bedtime. Coadministration of an antiemetic is beneficial to most patients. Pharmacists are instructed to dispense each day’s temozolomide dose in a separate labeled container to facilitate administration of the appropriate combination of capsule strengths required to achieve the prescribed dose (Schering Corporation, 1999). Fatal dosage errors associated with temozolomide self-administration have been reported (Holquist & Phillips, 2003).

---

**TABLE 1. COCKCROFT AND GAULT’S METHOD OF CREATININE CLEARANCE ESTIMATION**

Note. Based on information from Cockcroft & Gault, 1976; Lacy et al., 2002.

- For men:
  
  \[
  \text{estimated creatinine clearance} = \frac{(140 - \text{age in years}) \times \text{weight in kilograms}}{(72) \times \text{serum creatinine in mg/dl})}
  \]

- For women:
  
  \[
  \text{estimated creatinine clearance} = \frac{(0.85) \times (140 - \text{age in years}) \times \text{weight in kilograms}}{(72) \times \text{serum creatinine in mg/dl})}
  \]

Ideal or adjusted body weight may be considered for some patients who are over ideal body weight.

---

**FIGURE 1. COCKCROFT AND GAULT’S METHOD OF CREATININE CLEARANCE ESTIMATION**

- For women:
  
  \[
  \text{estimated creatinine clearance} = \frac{(0.85) \times (140 - \text{age in years}) \times \text{weight in kilograms}}{(72) \times \text{serum creatinine in mg/dl})}
  \]

Ideal or adjusted body weight may be considered for some patients who are over ideal body weight.
Immune-Modulating Agents

Bexarotene

A member of the class of drugs chemically related to vitamin A and known as retinoids, bexarotene (Targretin®, Ligand Pharmaceuticals Incorporated, San Diego, CA) selectively binds and activates retinoid X receptor subtypes RXRa, RXRb, and RXRg. Retinoids have biologic response modifying activities similar to those of interferon alpha, including promotion of differentiation as well as antiproliferative effects in vivo.

**Indications:** On December 29, 1999, the oral form of bexarotene was approved by the FDA for the treatment of cutaneous T cell lymphoma (CTCL, sometimes referred to as mycosis fungoides) in patients who are refractory to at least one prior systemic therapy. Because early-stage disease traditionally has been treated with topical remedies (including a topically applied bexarotene product), oral bexarotene’s primary role theoretically is limited to more advanced cases (Apisarnthanarax, Talpur, & Duvic, 2002; Ligand Pharmaceuticals Incorporated, 2001).

In practice, clinicians may choose to take advantage of bexarotene’s effect in early-stage disease. Although the exact mechanism of action of bexarotene against CTCL is yet to be elucidated fully, efficacy in both early- and late-stage disease has been demonstrated in two uncontrolled phase II/III clinical trials involving 152 patients with biopsy-proven CTCL. Although neither trial was sufficiently powered to compare dose levels, an apparent dose-related response was observed in the study of late-stage patients. A daily dose of 300 mg/m² was deemed optimal in terms of maximizing effect without undue toxicity (Duvic, Hymes, et al., 2001; Duvic, Martin, et al., 2001).

Future direction for the development of this drug likely will be in combination with other treatments for CTCL, such as interferon, denileukin diftitox (Ontak®, Ligand Pharmaceuticals), and phototherapy (Apisarnthanarax et al., 2002). The drug also has shown some preclinical activity against other tumor types. Clinical trials have been undertaken in patients with solid tumors such as breast cancer (Esteva et al., 2003), and the drug has been combined with IV chemotherapy in patients with non-small cell lung cancer (Khuri et al., 2001). Further study is needed to define application in these areas.

**Side effects:** Bexarotene undergoes metabolism by the hepatic enzyme cytochrome P450 3A4. Several metabolites have been identified, but their activity has not been determined. Gemfibrozil inhibits cytochrome P450, thus elevating the levels of bexarotene in vivo. Although not specifically studied, a similar interaction likely will occur with other known inhibitors of cytochrome P450 3A4, including, but not necessarily limited to, ketoconazole, erythromycin, itraconazole, and grapefruit juice. Caution is advised when bexarotene is administered to patients with hepatic dysfunction because clearance likely would be impaired and cause an elevated level of the drug. Specific guidelines for dose reduction are not available. Gender and age do not appear to significantly affect hepatic clearance or tolerance of the drug. Because bexarotene is highly protein bound, other highly bound drugs (such as aspirin or warfarin) might interact by displacement from plasma proteins. To date, no clinical evidence of this type of interaction has been documented. Although renal clearance of bexarotene because of the cytochrome P450 interaction (Apisarnthanarax et al., 2002). Other adverse effects of bexarotene include reversible suppression of thyrotropin secretion with resultant hypothyroidism, often requiring thyroid supplementation. Leukopenia, infection, headache, rash, dry skin, asthenia, edema, and generally mild gastrointestinal disturbances round out the list of the most common adverse effects. Abnormalities in liver function tests occur infrequently, but periodic monitoring is suggested, especially for patients on lipid-lowering agents. Pancreatitis, associated with extreme lipid abnormalities, has occurred rarely but may be severe and life-threatening. For this reason, patients at risk of pancreatitis generally should not receive bexarotene. This includes patients with uncontrolled diabetes, excessive alcohol consumption, biliary tract disease, or prior pancreatitis and those taking other medications that may elevate serum lipids or cause pancreatitis. A link between bexarotene therapy and cataract formation has been suggested. Although cause and effect have not been proven, patients with visual disturbances should be evaluated accordingly (Ligand Pharmaceuticals Incorporated, 2001).

Class effects of the retinoids include photosensitivity and teratogenicity. Patients should be advised to protect themselves from exposure to sunlight. This drug is absolutely contraindicated in pregnancy, and pregnancy must be ruled out prior to initiation of therapy. Two reliable forms of contraception are required for women of child-bearing potential for one month prior to, during, and one month after completion of bexarotene therapy. At least one form of contraception must be nonhormonal because bexarotene might induce enzymes, leading to increased clearance and lower levels of some hormones. This concern is based on the observation that women with breast cancer taking bexarotene and tamoxifen concomitantly had lower-than-expected plasma levels of tamoxifen. Male patients taking oral bexarotene should use condoms to avoid exposing female partners who are of child-bearing potential to the drug. For nursing mothers, risk versus benefit must be considered in the absence of evidence about what level of bexarotene, if any, is expressed in breast milk. The drug is not approved for use in pediatric patients (Ligand Pharmaceuticals Incorporated, 2001).

**Dosing:** For the treatment of CTCL, the recommended dose of bexarotene is 300 mg/m² per day as a single daily dose. The dose must be rounded to the closest available dose; the commercially available product is a 75 mg capsule. Capsules should be taken with

**Triglyceride and cholesterol elevations are seen in the great majority of patients taking bexarotene, to a degree that merits administration of lipid-lowering agents.**

meals. Foods, particularly those that contain fat, enhance absorption. The dose may be modified if adverse effects are noted or cautiously escalated to 400 mg/m² per day. Therapy is continued as long as benefit continues and tolerance is acceptable (Ligand Pharmaceuticals Incorporated, 2001).

**Thalidomide**

Thalidomide is a drug with immune-modulating and sedating properties. Wide-spread use after its initial development as a sedative and antiemetic for pregnant women experiencing morning sickness in the 1950s led to the revelation of its teratogenic properties, with tragic consequences, and the drug subsequently was removed from all markets.

**Indications:** In 1998, thalidomide was approved under the brand name Thalomid® (Celgene Corporation, Warren, NJ) for use in the United States for the treatment of erythema nodosum leprosum (ENL), commonly known as leprosy or Hansen’s disease. The drug is not FDA-approved in the United States for the treatment of any cancer. However, since the 1990s, interest in thalidomide’s immune-modulating and antiangiogenic properties has led to intense investigation of the drug’s value in the treatment of patients with cancer.

**Side effects:** Thalidomide very frequently causes sedation and dizziness. Patients must be warned about the potential interference with their ability to drive or operate machinery, as well as to use caution when combining thalidomide with other agents that cause drowsiness. Patients may become tolerant to or dependent on the sedative effects of the drug. Potentially irreversible peripheral neuropathy, rash, orthostatic hypotension, neutropenia, bradycardia, and constipation are other common adverse effects for which patients should be monitored. Viral load should be monitored in patients who are HIV seropositive because viral load was found to increase during early trials in this population. The incidence of adverse effects listed in the product information is derived from the populations for whom the drug is FDA-approved (i.e., patients with ENL) with further information regarding those who are HIV-positive. Although the profile of adverse effects is similar in patients with cancer, variations may occur. For detailed information about the effects in a particular patient population, refer to the results of applicable clinical trials.

For example, an unacceptably high rate of deep vein thromboses was observed in patients with multiple myeloma taking thalidomide in combination with dexamethasone during a clinical trial. The investigators found that prophylactic doses of warfarin did not suffice and amended the protocol to provide therapeutic anticoagulation to subsequent enrollees (Weber et al., 2003). A review of thromboembolic events reported during clinical trials and postmarketing surveillance of patients taking thalidomide has been published (Bennett et al., 2002).

**Molecularly Targeted Agents**

**Imatinib**

The approval of imatinib in May 2001 for use in the United States made the cover of *Time* magazine and received coverage from other media. Many heralded it as a breakthrough (Lemonick & Park, 2001). Although certainly not a panacea, the design rationale of this drug, specifically exploiting a molecular difference between cancer cells and healthy cells, demonstrates the cutting edge of cancer research. Imatinib, formerly known as STI571 and marketed as Gleevec® (Novartis Pharmaceuticals Corporation, East Hanover, NJ), represents a new class of agents used to treat cancer, known as protein kinase inhibitors. Protein kinases are enzymes that enable phosphorylation of certain amino acids, thus initiating signal transduction pathways that are crucial to cell growth, differentiation, and death (Savage & Antman, 2002). Protein kinases are over-expressed in some human cancers, so they make an appropriate target for anticancer drugs because the effect theoretically would target cancer cells over healthy cells. Numerous protein kinases exist in human cells and facilitate cellular communication via...
signal transduction. Their action may be prompted by activity at certain receptors and may be regulated by various oncogenes or proto-oncogenes. Discussion and nomenclature of drugs involved in signal transduction inhibition may be confusing because of interrelated factors in the cell regulation and proliferation processes.

**Indications:** Imatinib’s targets include the Philadelphia chromosome-associated BCR-ABL protein kinase, a genetic driving force for cell proliferation in many patients with chronic myelogenous leukemia (CML); platelet-derived growth factor, an apparent deregulator of cell growth in a variety of cancers; and c-kit, a proto-oncogene linked to some gastrointestinal stromal tumors (GISTs) (Savage & Antman, 2002). The drug is FDA-approved for use in patients with Philadelphia chromosome-positive CML that is newly diagnosed, in blast crisis, in accelerated phase, or in chronic phase after failing interferon alfa (Gary Appio, Novartis Pharmaceuticals Corporation, personal communication, April 21, 2003).

Since the approval, evidence has continued to accumulate in the medical literature that will help to further define the place of imatinib in the treatment of CML. A recently published clinical trial demonstrated the superiority of imatinib over interferon and cytarabine as first-line therapy in patients with newly diagnosed chronic-phase CML in terms of cytogenetic response rates, disease progression, and tolerability (O’Brien et al., 2003). As second-line therapy in patients with Philadelphia chromosome-positive CML after interferon alfa, dose escalation of imatinib was well tolerated and led to complete cytogenetic response in the majority of those treated (Cortes et al., 2003). Although neither of the trials demonstrated survival advantage, cytogenetic response may be considered a surrogate clinical end-point for overall outcome. To date, only allogeneic stem cell transplantation has been shown to be potentially curative, yet fewer than half of all patients diagnosed with CML are candidates for transplantation. Therefore, imatinib is an important addition to the armamentarium, considered by many to be the standard of care for CML patients not eligible for transplant and those without suitable donors. Treatment options such as imatinib as first-line therapy, imatinib combined with interferon or traditional chemotherapy to increase efficacy, or imatinib prior to transplantation may be considered for some patients (Peggs & Mackinnon, 2003; Savage & Antman, 2002).

Imatinib also is indicated for unresectable or metastatic malignant GISTs that are c-kit positive. A GIST is a rare tumor that has been unresponsive to chemotherapy and, therefore, is difficult to treat. After identification of the c-kit molecular target in many patients with GISTs, a rational basis for imatinib therapy was the basis for clinical trials in Europe and the United States. In each of the trials, the drug was shown to be well tolerated and efficacious (Demetri et al., 2002; Van Oosterom et al., 2001).

Because some acute leukemias are Philadelphia chromosome-positive and c-kit is expressed in numerous other human cancers, imatinib may have some promise for patients with these diagnoses. Additionally, imatinib’s ability to inhibit platelet-derived growth factor protein kinases, which may have a role in still more human cancers, fur-

---

**Epidermal growth factor receptors are promising targets for anticancer therapy because of a high level of expression in many human tumors.**

Epidermal growth factor receptors are promising targets for anticancer therapy because of a high level of expression in many human tumors.
2003). Imatinib was approved for use in pediatric patients with Philadelphia chromosome-positive CML in chronic phase on May 20, 2003 (U.S. FDA, 2003). A comprehensive guide to the management of patients with CML who are taking imatinib recently was published (Deininger, O’Brien, Ford, & Druker, 2003).

**Gefitinib**

A new class of agents in development for the treatment of patients with cancer is known for epidermal growth factor–tyrosine kinase inhibition. Epidermal growth factor receptors are promising targets for anticancer therapy because of a high level of expression in many human tumors. Activation of these receptors prompts signal transduction via tyrosine kinase-mediated pathways, thwarting apoptosis and leading to cellular proliferation, enhanced motility, survival, and angiogenesis (Baselga et al., 2002).

**Indications:** Iressa® (AstraZeneca Pharmaceuticals, LP, Wilmington, DE) is the trade name for gefitinib, identified during clinical trials as ZD1839. It is an epidermal growth factor receptor–tyrosine kinase inhibitor and received FDA approval on May 5, 2003, as monotherapy for treatment of advanced non-small cell lung carcinoma (NSCLC) for patients nonresponsive to both platinum-based and docetaxel chemotherapies (AstraZeneca Pharmaceuticals, LP, 2003; Natale & Zaretsy, 2002).

Two phase II, multicenter, randomized, double-blind clinical trials with a total of 425 patients were named IDEAL 1 and IDEAL 2, acronyms for Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2, respectively. In IDEAL 2, the trial considered to be pivotal, two or more prior regimens, including both a platinum and a docetaxel, were required. The supportive trial included patients with no more than two prior regimens, one of which was platinum based. The dose of gefitinib was either 250 or 500 mg daily by mouth for both trials, and the two primary endpoints were objective tumor response and clinically significant improvement in disease-related symptoms for a minimum of one month. Responses were observed in both trials at both dose levels, with the 250 mg dose being better tolerated than the 500 mg dose; both doses were comparably effective. Adverse effects most commonly documented included gastrointestinal disturbances and skin reactions, generally mild and noncumulative in nature. The potential for cytochrome P450 drug interactions has been identified but needs further evaluation. Drugs of particular concern include rifampin, metoprolol, itraconazole, and warfarin. Gefitinib should be administered with caution to patients with hepatic insufficiency, and liver function tests should be monitored periodically throughout treatment (AstraZeneca Pharmaceuticals, LP, 2003).

The approval process for gefitinib was anything but smooth. In contrast to support from the Oncologic Drugs Advisory Committee (the Center for Drug Evaluation and Research of the FDA) based on the IDEAL trials, the same data were criticized by other FDA staff on the basis that subjective measures of response such as symptom relief are difficult to interpret, particularly in the absence of a control group. Meanwhile, results of two large phase III trials featuring gefitinib with chemotherapy failed to demonstrate any added survival benefit, weakening the importance of tumor response results noted during the IDEAL trials (Twombley, 2002). Furthermore, reports of more serious adverse effects possibly related to gefitinib administration began to emerge from Japan, where the drug previously had been approved for use. Postmarketing reports there of interstitial pneumonitis in patients taking gefitinib, at times with fatal outcomes, prompted demands for additional warnings to be added to the product label. However, the small number of cases and the difficulty in sorting out disease-related and drug–related pulmonary effects have led some experts to question the claims of a cause-and-effect relationship between gefitinib and interstitial pneumonitis (Burton, 2002).

**Side effects:** In the patients who received gefitinib at a dose of 250 mg daily as monotherapy for treatment of NSCLC, the most common adverse drug reactions reported were diarrhea (sometimes associated with dehydration), rash, acne, dry skin, nausea, vomiting, and pruritus. These events generally occurred within the first month of therapy and usually were mild to moderate. Intestinal lung disease (ILD) has been observed in patients receiving gefitinib, and approximately one-third of the cases have been fatal. The incidence of ILD reported in various trials and postmarketing reports has varied, but clinicians and patients should be aware of the signs and symptoms and approach potential cases uncompromisingly. In the event of acute onset or worsening of pulmonary symptoms such as dyspnea, cough, or fever, gefitinib therapy should be interrupted. A prompt and thorough investigation of any such symptoms is mandatory. If ILD is diagnosed, gefitinib should be discontinued and the patient treated appropriately (AstraZeneca Pharmaceuticals, LP, 2003).

**Dosage:** The approved dose for the treatment of patients with locally advanced or metastatic NSCLC after not responding to platinum-based and docetaxel chemotherapies is one 250 mg tablet once a day. Higher doses do not result in better response and cause increased toxicity. Food does not appear to affect absorption, although alteration of gastric pH with high doses of ranitidine with sodium bicarbonate reduces bioavailability. The drug is not approved for use in pediatric patients. Use should be avoided during pregnancy and lactation.

Randomized, controlled clinical trials are planned to evaluate whether gefitinib treatment is associated with clinical benefit, such as improved survival or symptom improvement. Gefitinib remains an active focus of research, with potential application in the areas of lung, head and neck, prostate, breast, pancreatic, ovarian, and colorectal cancers (Baselga et al., 2002; Wakeling et al., 2002). Clearly, some patients have benefited from gefitinib, despite the lack of survival benefit. The key to success may be the ability to identify the small subset of patients who will respond and to single those individuals out for treatment with this agent (Natale & Zaretsy, 2002).

**Erlotinib**

Erlotinib (Tarceva™, investigated as OSI-774, Genentech Incorporated, South San Francisco, CA), like gefitinib, blocks the epidermal growth factor receptor pathway. Results of a phase I trial in patients with refractory, advanced solid tumors have been published. The primary objective of the trial was to determine the feasibility of protracted daily dosing. Principle toxicities were diarrhea and skin rash, and the incidence of side effects helped to establish the dose of 150 mg once daily for further study (Hidalgo et al., 2001). Erlotinib is under investigation both as monotherapy and in combination with standard chemotherapy in patients with NSCLC. Preliminary results in a study of heavily pretreated patients with NSCLC have demonstrated the activity of erlotinib. Encouraging results also were reported in patients with advanced, inoperable head and neck cancer. The manufacturer has expressed hope for FDA approval in mid-2004 (“Genentech Tarceva Trials ‘On Track,’ ” 2002; “News in Brief,” 2001).

**Summary**

Recent advances in the treatment of patients with cancer frequently have featured drugs administered orally. Prominent examples that have received FDA approval for
use in the United States in the past several years include capecitabine, imatinib, temozolomide, bexarotene, gefitinib, and thalidomide. Oral products on the horizon include the epidermal growth factor receptor erlotinib.

Author Contact: Ann Birner, PharmD, can be reached at Ann.M.Birner@hitchcock.org.

References
versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. Journal of Clinical Oncology, 18, 158–166.


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

Annual Review of Pharmacology and Toxicology http://pharmtox.annualreviews.org

Clinical Pharmacology Online www.cponline.gsm.com/

Links can be found at www.ons.org.

Rapid Recap
Pharmacology of Oral Chemotherapy Agents

- Ideal oral chemotherapy agents are palatable, do not irritate the gastrointestinal tract, readily dissolve after ingestion, and are adequately and reliably absorbed in the systemic circulation.
- A prodrug is a pharmacologically inactive compound that is converted to an active agent by metabolic transformation. Two examples of prodrugs are capecitabine and temozolomide.
- Imatinib, a protein kinase inhibitor, targets the Philadelphia chromosome-associated BCR-ABL protein kinase and is used to treat chronic myelogenous leukemia.
- Retinoids, such as bexarotene, have biologic response modifying activities similar to those of interferon alfa.
- Thalidomide is a drug with immune-modulating and sedating properties. The U.S. Food and Drug Administration has not approved its use for the treatment of cancer; however, the drug’s potential as a cancer treatment shows promise.
- A new class of agents in development for cancer treatment is epidermal growth factor receptor inhibitors, such as gefitinib and erlotinib.