

Continuing Education for Pharmacists

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New Drugs of 2003 for Treatment of Cancer: Iressa and Velcade

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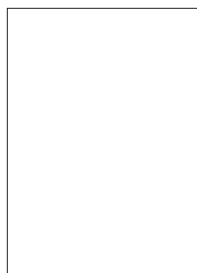
Goals. The goals of this lesson are to provide background information on non-small cell lung cancer and multiple myeloma, and review new drugs approved in 2003 to treat them.

Objectives. At the conclusion of this lesson, successful participants should be able to:

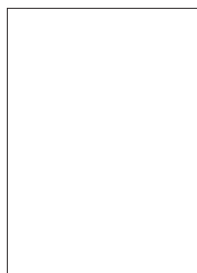
1. discuss the etiology and incidence of non-small cell lung cancer and multiple myeloma, and identify the primary independent risk factors;
2. exhibit knowledge of the pharmacologic classification and therapeutic considerations for the drugs discussed; and

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3. select from a list, the indications, mechanisms of action, adverse effects and toxicities, drug interactions, and benefits and limitations of the drugs presented.

Two cancer treatments were approved in 2003 under FDA's accelerated approval process that brings early access of promising new drugs. **Iressa** is a single-agent treatment for advanced non-small cell lung cancer, and **Velcade** is a new drug for multiple myeloma. The new drugs are shown in summary in Table 1.

Cancer

It is estimated that 1,334,100 new cases of cancer will be diagnosed in the U.S. during 2003. While cancer death rates decreased in both males and females in the 1990s, an

estimated 556,000 people will die from cancer in 2003. The death rate remains higher in males; however, incidence rates continue to increase in females, largely due to an increasing number of women smokers. African-American males had the largest decline in mortality, although diagnosis is generally made at a later stage which leads to poorer overall survival.

In spite of the continued decline in cancer death rates in the U.S., the total number of cancer deaths continues to rise slightly because of an expanded aging population. Worldwide, it is estimated that there are more than 22.4 million cancer survivors; approximately nine million live in the U.S. This is largely due to the medical advances in diagnosis and treatment of cancer achieved over the past several decades. New medical, social and political challenges come into play as researchers struggle with how to best reduce suffering and promote long-term quality of life.

Lung Cancer. Two major groups of lung cancer comprise more than 90 percent of all cases: small cell lung cancer and non-small cell lung cancer. Squamous cell, adenocarcinoma, and large cell

Table 1
New Cancer Chemotherapy Drugs of 2003

Trade/Generic Name (Sponsor/Manufacturer)	Dosage Form	Indication/ Dose	Date Approved
Iressa/gefitinib (AstraZeneca)	250mg tablet	lung cancer 250mg daily	5/03
Velcade/bortezomib (Millennium)	3.5mg/10mL injection	multiple myeloma 1.3mg/m ² twice a week for 2 weeks	5/03

carcinoma are grouped together in the more common category, non-small cell lung cancer. The means by which these tumors metastasize to other systems and their medical management differ from the characteristics of small cell lung cancer. Thus, it is imperative that the cell type be identified early so that optimal treatment can be initiated.

Small Cell Lung Cancer.

Small cell lung cancer comprises 20 to 25 percent of all lung cancers. This includes tumors of oat cells (shaped like oat kernels; very invasive), intermediate cells (spindle-shaped cells with multiple sides), and combined cells (small cells combined with other types of cancer). Oat cells and intermediate cells are frequently found together within the same tumor. This cancer is most often located in the bronchial submucosa (beneath the epithelium), and has a higher likelihood to have metastasized by the time of diagnosis. Small cell lung cancer is distinguished by its extremely rapid growth rate. Eighty percent of tumors are located within the central portions of the lung.

Non-small Cell Lung Cancer. *Squamous cell* (epidermoid) carcinoma is the most common form of lung cancer worldwide, accounting for over 30 percent of all tumors of the lung. This cancer usually begins in the large bronchi and often remains there without spreading for longer periods of time than other lung cancers. In the U.S., *adenocarcinoma* is increasing and has surpassed squamous cell carcinoma in the number of reported cases, accounting for 35 percent of all lung cancers. These tumors are often located along the periphery of the lung and within the submucosal lining of the bronchi. *Large cell carcinoma* describes tumors of the lung that do not fit into other categories of epidermoid, adenocarcinoma or small cell tumors. Large cell carcinoma includes about 15 percent of all lung cancer cases. It is usually located in the small bronchi.

Other Lung Cancers. Other cancers of the lung include carcinoid tumor and bronchioalveolar carcinoma, a subtype of adenocarcinoma. Carcinoids (slow-growing tumors) originate in the glands near the bronchi. Bronchioalveolar carcinoma develops around scars on the outer edges of the lungs.

Lung Cancer Facts. Lung cancer accounts for 28 percent of all cancer-related deaths in the U.S. Unfortunately, most lung cancers are not diagnosed until it is too late to receive effective treatment. At present, nearly 90 percent of all lung cancer deaths are attributed to smoking. Since the majority of women in the U.S. who smoke did not start until later in life than the average male smoker, mortality from lung cancer in females is not expected to peak until 2013.

Exposure to radon over time is thought to be the second leading cause of lung cancer in the U.S. Radon is an invisible, odorless and tasteless radioactive gas found naturally in substantial amounts in soil, rocks and building materials.

Numerous other environmental chemicals and pollutants have also been identified as playing a role in lung cancer. These include arsenic, chloromethyl ethers, chromium, and hydrocarbons in coal, petroleum products, benzene, paraffin and tar. Lung cancer is common in persons who work in the asbestos industry and also smoke. Lung cancer is also more common in persons who have certain pulmonary diseases such as tuberculosis. Moreover, a person who had lung cancer once is more apt to develop a second tumor in the lung than a person who has never had this cancer.

Multiple Myeloma. Approximately 45,000 people in the U.S. have multiple myeloma, with an estimated 14,600 new cases identified each year. Multiple myeloma affects plasma cells, a type of white blood cell. Plasma cells and other white blood cells develop in the bone marrow and are part of the body's immune system. Some migrate out of the bone marrow to mature in

other parts of the body. Plasma cells develop from these migrant cells. They produce antibodies, which are proteins that form in response to invasion by foreign substances.

As cancer invades plasma cells, the body produces these cells in large numbers – all abnormal and identical – called myeloma cells. Circulating myeloma cells collect in the bone marrow and in the outer layers of bones where they may concentrate in only one bone to form a single tumor (plasmacytoma) or in numerous bones to cause widespread tumors (multiple myeloma).

Cancer is classified by the type of cell or site in the body in which the neoplasm originates. While plasmacytoma and multiple myeloma are detected in the bones, they actually originate within the immune system. This is important because they differ from bone cancer, which originates within cells that form the hard tissue of bone, and the diagnosis and treatment differ.

Since multiple myeloma is characterized by an abnormally large number of identical plasma cells that produce large quantities of antibodies, the cells and antibodies can incite serious medical problems. The large number of myeloma cells damage and weaken bones to cause pain and fractures. Bone damage releases calcium into the blood leading to hypercalcemia. Hypercalcemia can cause loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness and confusion. Myeloma cells prevent the bone marrow from forming normal plasma cells and other white blood cells that are important for normal immune functioning. Patients may, therefore, be unable to fight infection and disease. The cancer cells also may prevent formation of new erythrocytes, resulting in anemia. Multiple myeloma patients may experience kidney disorders because of the large quantity of circulating antibody protein and calcium that the kidney must accommodate.

In the earliest stage of multiple myeloma, there may be no symp-

toms. When symptoms occur, bone pain, often in the back or ribs, may be among the first. Patients also may experience broken bones, weakness, fatigue, weight loss or repeated infections. In advanced disease, symptoms may include nausea, vomiting, constipation, urinary problems, and weakness or numbness in the legs. It is not uncommon for persons with multiple myeloma who are still symptom free to not receive treatment because the risks from chemotherapy may outweigh the benefits. These patients are watched closely; when symptoms appear, treatment is begun. Multiple myeloma is highly treatable but rarely curable. One treatment protocol includes melphalan (Alkeran) and prednisone. Thalidomide in combination with dexamethasone is also useful.

Iressa (Gefitinib)

The mechanism of action of gefitinib remains incompletely characterized. The drug inhibits intracellular phosphorylation of tyrosine kinases associated with transmembrane cell surface receptors. These enzymes include those affiliated with the epidermal growth factor receptor (EGFR). This is expressed on the surface of many normal and cancer cells. Iressa is the first in a new drug class of antitumor agents that target the EGFR, at one time viewed as a very promising mechanism for treatment of a variety of tumors. No clinical studies have been conducted to date that correlate EGFR receptor expression and therapeutic response to gefitinib. There may be additional mechanisms.

Iressa's approval was based on the outcome of a study of 216 patients with non-small cell lung cancer. This included 142 patients with tumors that were resistant or unresponsive to two earlier treatment protocols. The outcome was that 10 percent of these patients experienced tumor shrinkage of at least 50 percent that persisted one month or longer. The median

duration of response for the group was seven months. FDA's Oncologic Drugs Advisory Committee indicated that when there are no available treatment options, a third-line treatment with a 10 percent response rate was sufficient to predict modest clinical benefit in non-small cell lung cancer. The Committee recommended that Iressa be approved. Subsets of patients experienced greater response rates, about 17 percent for women and patients with adenocarcinoma. Men and smokers, on the other hand, had lower response rates, about 5 percent.

Further studies are planned to measure the drug's clinical benefit. One investigation will evaluate gefitinib in patients with lung cancer resistant to two previous chemotherapy regimens with focus on assessing whether the drug prolongs survival compared to maximized supportive care alone. A second trial will compare gefitinib to treatment with docetaxel (Taxotere) in patients whose lung cancer has been shown to be resistant to one previous chemotherapy regimen. A third investigation will assess whether gefitinib will modulate cancer symptoms in lung cancer patients resistant to all available chemotherapy.

Adverse Effects. The most common adverse effects reported with Iressa in clinical trials included nausea, vomiting, diarrhea, acne, dry skin and rash. As with all cancer chemotherapeutics, the drug may cause fetal harm when given to pregnant women.

A safety concern has emerged from Japan. Clinicians described potentially fatal interstitial lung disease in patients treated with Iressa. After careful review of information from all sources involving approximately 23,000 patients, the incidence of interstitial lung disease was determined to be approximately 2 percent in the Japanese experience, versus approximately 0.3 percent of patients in the U.S. Approximately one-third of affected patients in the U.S. died

Table 2
Patient Information for Iressa

- Read the patient information leaflet provided by the manufacturer before you start taking this medicine, and each time you get your prescription filled.
- Notify your doctor immediately if you notice severe or persistent diarrhea, nausea, loss of appetite, vomiting, shortness of breath or cough, irritation of your eyes, or any other new symptom.
- This medicine can be taken with or without food.
- Tell your doctor about all other prescription, nonprescription (OTC) and herbal or natural medicines you are taking.
- Women: Avoid becoming pregnant while taking this medicine.

from this toxicity. FDA determined that this rare, although serious, toxicity did not outweigh its therapeutic benefit, and the drug should remain on the market.

Drug Interactions. Gefitinib is metabolized extensively, predominantly by CYP3A4. Inducers of CYP3A4 (e.g., rifampin, phenytoin) stimulate gefitinib metabolism, thus decreasing its plasma concentrations. Patients receiving a potent CYP3A4 inducer should receive gefitinib at a dose increased to 500mg daily in the absence of severe adverse drug reactions. Potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) decrease gefitinib metabolism and increase its plasma concentrations. This increase may be clinically significant since adverse experiences correlate with dose and extent of exposure, so caution is needed when administering CYP3A4 inhibitors with Iressa. Drugs that induce sustained elevation in gastric pH values (e.g., H₂-receptor antagonists, sodium bicarbonate) may reduce plasma concentrations of gefitinib. Finally, bleeding events have been noted in patients taking warfarin while on Iressa therapy. Patients taking the drugs concurrently should be monitored closely.

Table 3
Patient Information
for Velcade

- Read the patient information leaflet provided by the manufacturer before you start taking this medicine, and each time you get your prescription filled.
- Be careful when driving or operating machinery while taking this medicine since it may make you tired, dizzy, or feel faint; or cause blurred or double vision.
- Notify your doctor immediately if you notice the symptoms listed above, or develop a sensation of numbness, pain or a burning feeling in your hands or feet.
- Drink lots of fluids and electrolytes to help prevent dehydration.
- Do not begin taking other drugs while receiving treatment with this medicine without talking with your doctor first.
- Women: Avoid becoming pregnant while taking this medicine.

Indications and Uses. Iressa is supplied as tablets containing 250mg of gefitinib. The recommended daily dose is 250mg with or without food. Higher doses do not enhance the response and may cause increased toxicity.

Persons with poorly controlled diarrhea or adverse drug reactions involving the skin may be managed by allowing a brief drug holiday of up to 14 days followed by reinstatement of the 250mg daily dose. Persons with acute onset or worsening of pulmonary symptoms (cough, fever, difficult breathing) or interstitial lung disease should be taken off gefitinib therapy and prompt investigation of symptoms undertaken with appropriate treatment initiated. Patients with onset of new ocular symptoms including eye pain should be evaluated and managed appropriately, including Iressa therapy interruption. After symptoms have resolved, the drug may be reinstated at the 250mg daily dose. Information for patients is listed in Table 2.

Velcade (Bortezomib)

Bortezomib inhibits the chymotrypsin-like activity of the 26S proteasome. Bortezomib is the first in a new class of cancer chemotherapeutic agents known as proteasome inhibitors.

The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway is an important system involved in degradation of many cellular regulatory proteins. Ubiquitin is a 76-amino acid residue that, when conjugated to proteins, marks them for degradation by the ubiquitin-proteasome pathway. (The presence of ubiquitinated proteins is often one of the hallmarks of pathologic conditions including cancer.) Inhibition of this pathway adversely affects signaling cascades within the tumor cells which can lead to their death. Velcade has been shown *in vitro* to be cytotoxic by causing a delay in tumor growth in a variety of cancer cell types. This drug action includes toxicity to cells that comprise multiple myeloma.

The drug's safety and efficacy were determined from a study of 202 patients who had received at least two prior types of drug therapy. Patients demonstrated progression of disease with their most recent therapy. Twenty-eight percent of 188 patients evaluated showed a positive response to bortezomib with a median duration of response of one year. A second investigation in 54 patients with relapsed multiple myeloma revealed similar responses.

At this point there are no controlled trials that demonstrate bortezomib has clinical benefit such as improvement in survival. Additional studies are underway, including a comparison of bortezomib to standard therapy of multiple myeloma.

Adverse Effects. The most commonly reported adverse events noted in clinical trials included nausea, vomiting, diarrhea, constipation, headache, decreased appe-

tite, fever, fatigue, peripheral neuropathy, and decreased platelets and red blood cells. Orthostatic hypotension was reported in 12 percent of patients.

Drug Interactions. No formal drug interaction studies have been conducted with Velcade to date. No clinically-significant reactions with other drugs have been reported. Bortezomib is metabolized by cytochrome P450 enzymes so drugs that enhance or inhibit them may be expected to interact with bortezomib. Patients taking Velcade and these drugs should be monitored for either increased toxicity or decreased efficacy.

Indications and Uses. Velcade is indicated for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. Effectiveness of bortezomib is based on response rates, not controlled trials demonstrating a clinical benefit.

Dosage and Administration. Velcade is supplied in vials containing 3.5mg of bortezomib. Unopened vials may be stored at controlled room temperature (77° F). The recommended dose is 1.3mg/m²/dose given as a bolus injection IV twice weekly for two weeks followed by a 10-day rest period. At least 72 hours should elapse between consecutive doses. Information for patients is presented in Table 3.