**NEW DRUGS**

**Gefitinib Approved for Lung Cancer**

The Food and Drug Administration (FDA) has announced the accelerated approval of gefitinib (Iressa™, AstraZeneca) tablets as a single-agent treatment for patients with advanced non-small cell lung cancer (NSCLC), the most common form of lung cancer in the U.S. Cancer of the lung and bronchus is the leading cause of cancer death in men and women in the U.S. NSCLC accounts for almost 80% of lung cancers.

The drug is intended for patients whose cancer has continued to progress despite chemotherapy with platinum and docetaxel (Taxotere®, Aventis), the two drugs that are currently the standard of care for this disease.

The drug was developed to block growth stimulatory signals in cancer cells. These signals are mediated, in part, by enzymes called tyrosine kinases. The drug blocks several of these tyrosine kinases, including one associated with epidermal growth factor receptor (EGFR).


**A Novel Therapy: Bortezomib for Multiple Myeloma**

Millennium Pharmaceuticals has announced the FDA’s approval of bortezomib (Velcade™) for patients with multiple myeloma who have received at least two prior courses of therapy and have demonstrated disease progression. Myeloma is the second most common cancer of the blood, responsible for approximately 1% of all cancers and 2% of all cancer deaths.

A proteasome inhibitor, bortezomib represents the only new and approved treatment option for multiple myeloma in more than a decade. It is a dipeptide boronic acid that has been found to enhance the sensitivity of cancer cells to chemotherapy agents and seems to overcome drug resistance. Proteasome inhibitors cause cancer cells to stop dividing and to eventually die. Researchers hope that disrupting the cancer cell proteasome can delay the disease and even bring about remissions.

Side effects of treatment were generally predictable and manageable.

(Source: Cancer Treat Rev 2003; 29[Suppl]:1; www.millennium.com.)

**First Treatment for Fabry Disease**

The FDA has granted accelerated approval for agalsidase beta (Fabrazyme®, Genzyme), the first treatment for patients with Fabry disease, a serious metabolic genetic disorder. Agalsidase beta is a version of the human form of the natural enzyme produced by recombinant DNA technology. Given intravenously, it replaces the missing enzyme and reduces certain lipid (fat) accumulations in many types of cells, including blood vessels in the kidneys and other organs. It is believed likely that this reduction of fat deposition can prevent the development of life-threatening organ damage. Biopsy specimens have shown significant clearance of lipid deposits in patients who received the drug.

Fabry disease affects approximately one in 40,000 men, but women can be seriously affected as well. The disease can eventually lead to organ failure. As a result, patients often must often cope with pain, disability, and a shortened life span.

In clinical studies, the main safety concern was infusion reactions, some of which were severe. Genzyme is continuing to assess the drug’s effects on the progression of kidney and heart disease and the incidence of strokes.

(Source: FDA News, April 25, 2003; www.fabrazyme.com.)

**Laronidase for Genetic Disease**

The FDA has approved laronidase (Aldurazyme®, BioMarin), the first treatment for certain forms of a rare genetic disease called mucopolysaccharidosis I (MPS I), which includes Hurler’s syndrome. This disease results from the absence or malfunctioning of an enzyme that breaks down molecules called glycosaminoglycans (GAG) in the cells. The buildup of GAG results in progressive cellular damage that affects appearance, physical abilities, organ function, and, in some cases, mental development.

In one study, treated patients showed improved lung and walking capacity in a six-minute walking test after 26 weeks.

The most serious adverse drug event was an anaphylactic (allergic) reaction approximately three hours after infusion. Safety concerns related to infusion reactions included flushing, fever, headache, and rash.

(Source: FDA, May 1, 2003; www.biomarinpharm.com.)

**NEW INDICATIONS**

**Infliximab Helpful for Sciatica**

Promising new data suggest that a single two-hour treatment with infliximab (Remicade®, Centocor), an anti–tumor necrosis factor alpha (TNF-α) monoclonal antibody therapy, may quickly relieve the painful symptoms of severe sciatica, enabling patients to forgo surgery and return to work within a month.

Sciatica may be caused by the effects of normal wear and tear to the body or by any sudden pressure on a disc that supports the vertebrae of the lower spine, resulting in a herniated disc. Symptoms can include weakness, numbness, or a burning or tingling sensation traveling down the leg that lasts more than six weeks.

Researchers at Oulu University Hospital in Helsinki, Finland, found that
infliximab rapidly relieved leg pain in patients with severe sciatica. One hour after the infusion, leg and back pain decreased by approximately 50%. At two weeks, 60% of patients in the infliximab group were pain-free, in contrast to only 16% of the historical controls. This benefit was sustained at three months.

At one month, each patient who received infliximab had returned to work; in the historical control group, 38% were still on sick leave. None of the infliximab patients underwent surgery during the three-month follow-up period, compared with 15% of the patients in the historical control group. No immediate or delayed adverse reactions resulting from the medication were noted.


**Imatinib Mesylate Approved for Pediatric Leukemia**

The FDA has approved imatinib mesylate (Gleevec™, Novartis) tablets for children with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase. This rare, life-threatening form of cancer accounts for approximately 2% of all leukemias in children. Originally indicated for adults, imatinib blocks the rapid growth of white blood cells and is intended for children whose disease has recurred after stem cell transplantation or whose condition is resistant to interferon alpha therapy.

The accelerated approval for pediatric use is based on extrapolation of results from treated adults with CML as well as from good responses in a small number of children. As a condition of approval, Novartis has agreed to conduct pediatric studies after approval to gain greater insight into the drug’s use in children.

The recommended dosage for children is 260 mg/m² per day. The drug can be given once daily, or the daily dose can be split in two (once in the morning and once in the evening).

For information on the need for appropriate drug labeling for children, see “Pediatric Drug Testing Update, United States,” on page 387 in this issue of P&T.

(Source: FDA News, May 20, 2003.)

**DRUG NEWS**

**Don’t Drop the Droperidol**

The recent “black-box” warning about life-threatening prolongation of the QT interval caused by droperidol (Inapsine®, Akorn/Taylor) use has probably come as a surprise to emergency-department physicians and their staffs who have been using the drug for years. In fact, it so alarmed researchers from Indiana University School of Medicine and the University of Virginia School of Medicine that they decided to investigate the basis for the warning.

Droperidol is widely used as a tranquilizer for agitated patients, as a presurgical medication before the administration of anesthesia, and as an emetic agent to prevent nausea after surgery. A black-box warning is the most serious type of warning for an FDA-approved drug.

After reviewing data from several sources, the investigators noted a short-lived and dose-dependent association between droperidol and QT prolongation but not between droperidol and torsades de pointes.

Although the FDA recommended the warning to advise caution and ongoing cardiac monitoring, the researchers are concerned that this warning might have the effect of halting the use of a “time-tested” therapy that is still often a safe and appropriate choice.


(Source: Crit Care Med 2003;31:1088–1093.)

**Toxicity Tests for Statins: Are They Needed?**

Is it really necessary to routinely measure alanine transaminase (ALT), aspartate transaminase (AST), and creatine kinase levels in patients who are taking statins? No, say researchers from Beth Israel Deaconess Medical Center. According to findings from their year-long study of 1,194 patients taking statins, abnormalities were rare.

An editorial appearing in the same issue as the reported study advises establishing baseline values of creatine kinase, ALT, and AST at the beginning of therapy and saving the monitoring for patients who really need it. The tests might safely be eliminated in patients who are taking low doses of statins, who are otherwise healthy, and who are not taking multiple medications. The editorial suggested that it might be prudent to teach patients the symptoms to watch for (e.g., unexpected muscular pain, weakness, flu-like syndrome, malaise, and dark-colored urine).


**Eptifibatide and Thrombocytopenia**

Prescribers should keep an eye on platelet counts in patients who are taking glycoprotein IIb-IIIa inhibitors. All three available GPIIb-IIIa inhibitors—abciximab (ReoPro®, Eli Lilly), eptifibatide (Integrilin®, Cor Therapeutics), and tirofiban (Aggrastat®, Merck)—have been associated with acute profound thrombocytopenia (an abnormally low platelet count). Occurrences are more common with abciximab and less often reported with eptifibatide. Although most cases are resolved without major complications, thrombocytopenia can lead to fatal intracranial hemorrhage.

Toronto researchers described two elderly patients whose platelet counts fell...
below 20 x 103/mm³ within four hours after administration of eptifibatide. Both patients recovered.

The investigators advise taking a complete blood count within two to four hours of the start of infusion of a GPIIb-IIIa inhibitor.

(Source: Pharmacotherapy 2003;23: 374–379.)

**A New Complication of Thalidomide Therapy**

Thalidomide (Thalomid®, Celgene), a drug that was blamed for birth defects years ago, is finding a new respectability as an experimental therapy for various malignancies, including multiple myeloma, gliomas, Kaposi’s sarcoma, and advanced breast cancer. The treatment, however, appears to be dogged by a complication: the more frequent occurrence of venous thromboembolism (VTE). A study of 70 men with advanced androgen-independent prostate cancer bears this out.

The men, aged 50 to 80, were given intravenous docetaxel (Taxotere®, Aventis) or docetaxel with thalidomide. None of the 23 who received docetaxel alone developed VTE, compared with nine of 47 (19%) who received the combination treatment.

The researchers could not determine why thalidomide might have a prothrombotic effect. The only measured factor that declined appreciably after the initiation of thalidomide/docetaxel therapy—which was not seen in the men taking docetaxel alone—was protein C.

Although the change was statistically significant, it wasn’t great enough to raise the risk of thrombosis; however, it was noted that thalidomide might cause endothelial damage. Agents used in combination with thalidomide that are toxic to the endothelium might be exposing the subendothelial tissue to the prothrombotic effect of the anti-angiogenic agent. The authors suggest that thalidomide and docetaxel, which has antiangiogenic effects in vitro, might have a synergistic harmful effect.

(Source: Pharmacotherapy 2003;23: 315–318.)

**Eye Inflammation from Bisphosphonates**

Drugs commonly prescribed to treat osteoporosis and cancer can cause serious ocular side effects, say scientists at the Oregon Health and Science University’s Casey Eye Institute. This research is expected to alert physicians to monitor patients for eye problems not previously associated with the drugs and may also help them identify problems earlier and thus prevent long-term sight damage. This finding might also prompt drug companies to update their product labeling.

Two medications in a class of drugs called bisphosphonates caused inflammation in several regions of the eye in some patients. Bisphosphonates are prescribed to increase bone density in patients with osteoporosis. Lung, breast, or prostate cancer that has spread to the bones can also cause a reduction in bone density. In cancer patients, bisphosphonates are often provided in conjunction with chemotherapy or other anti-cancer treatments.

Side effects included conjunctivitis, abnormal or blurred vision, eye pain, scleritis, and uveitis. The conjunctivitis eased as drug use continued, but other problems didn’t abate until the patients stopped taking the drugs altogether.


**Drug-Eluting Stents: New Hope for Clogged Arteries**

The FDA has approved the first drug-eluting stent for angioplasty procedures to open clogged coronary arteries. In most cases, a stent is left permanently in the artery to keep the vessel open after angioplasty. The new tiny stent slowly releases a drug that has been shown in clinical studies to significantly reduce the rate of re-blockage that occurs with existing stents.

Each year, 800,000 angioplasty procedures are performed in the U.S. to open the coronary arteries. In approximately 15% to 30% of patients, the artery becomes clogged again (restenosis) within a year, and it must be treated again with angioplasty or bypass surgery.

The Cypher Sirolimus-Eluting Coronary Stent (Cordis/Johnson & Johnson) is a tiny metal mesh tube that is covered with the drug sirolimus (Wyeth). The Cypher stent provides a mechanical scaffold to keep the vessel open while the drug is slowly released from the stent to prevent the buildup of new tissue that re-clogs the artery. In studies conducted by the firm, the stent reduced the rate of restenosis by about two thirds.

The types of adverse events seen with the drug-eluting stents were similar to those observed with the uncoated stents.

Patients who are allergic to sirolimus or to stainless steel should not receive a Cypher stent. Caution is urged for patients who have had recent cardiac surgery and for pregnant or nursing women. Patients receiving drug-eluting stents usually need to take certain kinds of antiplatelet drugs for several months after receiving the stent.

(Sources: FDA, April 24, 2003; Philadelphia Inquirer, April 25, 2003; www.cordis.com.)