COLORECTAL CANCER

Cancers of the colon and rectum (colorectal cancers) are the fourth most commonly diagnosed cancers and rank second among cancer deaths in the U.S. About 150,000 new cases of these cancers occur annually. Over a lifetime, colorectal cancer affects about one in 18 people, resulting in 56,000 deaths in the U.S. each year.

Just recently, oxaliplatin, in injection form (Eloxatin®, Sanofi-Synthelabo) was approved by the Food and Drug Administration (FDA) for use in combination with infusions of 5-fluorouracil (5-FU) and leucovorin (LV). The combination is used for the treatment of patients with metastatic carcinoma of the colon or rectum when symptoms have recurred or worsened during initial therapy or within six months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan (Camptosar®, Pharmacia).

Oxaliplatin belongs to a new class of platinum agents. It contains a platinum atom complex with oxalate and diaminocyclohexane (DACH). The bulky DACH is thought to contribute greater cytotoxicity than that contributed by cisplatin (Platinol®, Bristol-Myers Squibb) and carboplatin (Paraplatin®, Bristol-Myers Squibb). The exact mechanism of action of oxaliplatin is not known. Oxaliplatin undergoes nonenzymatic conversion in physiological solutions to active derivatives via displacement of the active oxalate ligand. Oxaliplatin forms reactive platinum complexes that are believed to inhibit synthesis of deoxyribonucleic acid (DNA) by forming inter-strand and intra-strand cross-linking of DNA molecules. These cross-links inhibit DNA replication and transcription.

Oxaliplatin is not generally cross-resistant to cisplatin or carboplatin, possibly because of the DACH group and resistance to DNA mismatch repair. Preclinical studies have shown that oxaliplatin is synergistic with FU and SN-38, the active metabolite of irinotecan. Oxaliplatin is a radiation-sensitizing agent and is cell cycle–phase-nonspecific.

In the pivotal clinical trial, oxaliplatin for injection in combination with infusions of 5-FU/LV demonstrated a statistically significant (P < .05) response rate compared with infusions of 5-FU/LV alone. The response rate was defined as a 30% or greater reduction in overall tumor size, maintained for four weeks or more. The effects of the combination on survival are not yet known. Oxaliplatin is not intended for patients with newly diagnosed colorectal cancer.

Oxaliplatin for injection should not be administered to patients with a history of known allergy to oxaliplatin or to other platinum compounds. Women of childbearing age should be advised not to become pregnant while undergoing treatment with oxaliplatin. As with other platinum compounds, hypersensitivity and anaphylactic or anaphylactoid reactions have been reported. Oxaliplatin is associated with potentially fatal pulmonary toxicity and two distinct types of primarily peripheral sensory neuropathies: an acute, reversible type of early onset and a persistent type (lasting longer than 14 days). An acute syndrome of pharyngolaryngeal dysesthesias, observed in 1% to 2% of patients, was characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm. Both 5-FU and oxaliplatin are associated with gastrointestinal and hematological adverse events.

The most frequently reported adverse events with oxaliplatin in combination with infusional 5-FU/LV were acute peripheral neuropathy in 56%, persistent neuropathy in 48%, fatigue in 68%, diarrhea in 67%, nausea in 65%, and vomiting in 40%. Changes in hematological parameters were also seen, for example, anemia in 81%, leukopenia in 76%, neutropenia in 73%, and thrombocytopenia in 64%. The diarrhea and myelosuppression normally associated with 5-FU/LV were accentuated by oxaliplatin. Most of the neurotoxic events were reversible. Neutropenia was the major hematological toxicity.

Oxaliplatin for injection is intended for use by physicians who have experience in administering anticancer agents. The labeling for oxaliplatin includes a “black box” warning detailing this use and highlighting anaphylactic-like reactions associated with the product. This drug can have a toxic effect on nerve endings and may cause either an acute or a cumulative pattern of side effects. The result can be a feeling of numbness or tingling, which generally improves after the treatment is completed.

An injection is scheduled every two weeks as follows: Day one. Oxaliplatin 85 mg/m2 IV infusion and leucovorin 200 mg/m2 IV are administered over two hours at the same time in separate bags, followed by a 5-FU 400-mg/m2 IV bolus given over two to four minutes, followed by a 5-FU 600 mg/m2 IV given as a 22-hour continuous infusion.

Day two. A leucovorin 200-mg/m2 IV infusion is administered over two hours, followed by a 5-FU 400-mg/m2 IV bolus given over two to four minutes, followed by a 5-FU 600 mg/m2 IV given as a 22-hour continuous infusion.

Premedication with antiemetics, including 5-hydroxytryptamine (5-HT3) blockers, with or without dexamethasone, is recommended.

METASTATIC BREAST CANCER

Fulvestrant (Faslodex®, AstraZeneca) was approved by the FDA for the treatment of hormone receptor–positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant is an estrogen receptor (ER) antagonist without known agonist activity.

Fulvestrant binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. Many breast cancers contain estrogen receptors, and the growth of these tumors can be stimulated by estrogen. Fulvestrant down-regulates and degrades the estrogen receptor protein and the receptor in human breast cancer cells.

In a clinical study of postmenopausal women with primary...
breast cancer treated with single doses of fulvestrant 15 to 22 days before surgery, increasing the dose demonstrated evidence of increasing down-regulation of estrogen receptors. This result was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the estrogen receptor pathway were also associated with a decrease in the Ki67 labeling index, a marker of cell proliferation.

Intramuscular fulvestrant was compared with the standard therapy for metastatic breast cancer—oral anastrozole (Arimidex®, AstraZeneca), an aromatase inhibitor—in two randomized, controlled clinical trials (a North American double-blind study and a European open-label study) in postmenopausal women with locally advanced or metastatic breast cancer. In all patients, the cancer had progressed after previous therapy with an antiestrogen or progesterin for breast cancer in the adjuvant or advanced disease setting. A total of 851 patients were enrolled, with 428 randomly assigned to receive fulvestrant 250 mg monthly by intramuscular injection and 423 patients randomly assigned to receive anastrozole 1 mg daily. Response rates of 17% and 20% were reported in the fulvestrant treatment arms in the North American and European trials, respectively. These rates were similar to the response rates of 17% and 15% reported in the anastrozole treatment arms. There were no significant differences (P > .05) in time to progression or survival between the two arms in either trial.

The safety profile of fulvestrant was similar to that of anastrozole. Fulvestrant appears to be as effective as anastrozole. The most commonly reported adverse events were of mild to moderate severity, including nausea, vomiting, constipation, diarrhea and abdominal pain, headache, back pain, vasodilation (hot flashes), and pharyngitis. Mild reactions at the injection site were reported in 7% of patients (in 1% and 5% of treatments) who had been given fulvestrant. Mild reactions at the injection site were reported in 7% of patients (in 1% and 5% of treatments) who had been given fulvestrant injections of 5 ml and 2 x 2.5 ml, respectively.

Fulvestrant should not be used in patients with bleeding diatheses or thrombocytopenia or in patients who are taking anticoagulants. Other adverse events that were reported as drug-related and that were observed infrequently (<1%) included thromboembolic phenomena, myalgia, vertigo, and leukopenia.

Women of childbearing age should be advised not to become pregnant while receiving fulvestrant therapy. No studies of fulvestrant in pregnant women have been conducted. If fulvestrant is used during pregnancy or if a woman becomes pregnant while receiving fulvestrant, she should be apprised of the potential hazard to the fetus and the potential risk of the loss of the pregnancy.

The recommended daily dose of fulvestrant is 250 mg at one-month intervals, slowly administered into the buttock either as a single 5-ml injection or as two concurrent 2.5-ml injections.

**ADVANCED PROSTATE CANCER**

Leuprolide acetate as an injectable suspension (Eligard® 22.5 mg, Atrix Laboratories) is a new proprietary product for the palliative treatment of advanced prostate cancer. An innovative drug-delivery system, Atrigel® (Atrix Laboratories), is used to administer leuprolide acetate over a three-month period. The formulation joins a previously approved leuprolide, a 7.5-mg sustained-release product that is administered once a month.

The American Cancer Society estimates that approximately 189,000 new cases of prostate cancer will be diagnosed in the U.S. in 2002 and approximately 30,200 men will die of the disease. According to the National Cancer Institute, most patients with advanced prostate cancer receive luteinizing hormone–releasing hormone (LHRH) therapy during the course of treatment. For men with advanced prostate cancer, the standard treatment regimen often includes starting with one month of LHRH therapy, then switching to a longer-release product if there is a therapeutic response.

Leuprolide acetate is a synthetic nonapeptide analogue of naturally occurring gonadotropin-releasing hormone (GnRH or LHRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. This effect is reversible upon discontinuation of drug therapy. The analogue possesses greater potency than the natural hormone does.

The administration of 22.5 mg of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in men and estrone and estradiol in premenopausal women). Although patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks, continuous administration of leuprolide acetate results in decreased LH and FSH levels. In men, testosterone is reduced to below the castrate threshold (50 ng/dl). These decreases occur within two to four weeks after the initiation of treatment. Long-term studies have shown that continuation of therapy with leuprolide acetate maintains testosterone concentrations below the castrate level for up to seven years and suppresses tumor growth in patients with hormone-responsive prostate cancer.

The adverse effects noted during clinical trials with leuprolide after 6 months included mild, transient burning or stinging; mild bony pain in 3.5% of study injections; mild erythema; mild bruising; and mild pruritus. No patient discontinued treatment as a result of adverse events.

The liquid leuprolide products are injected subcutaneously with a small-gauge needle, forming a solid implant in the body. The implant slowly releases leuprolide acetate as the implant is bioabsorbed. The new formulation is administered subcutaneously every three months.

Leuprolide acetate for injection, 22.5 mg, is prefilled and is supplied in two separate sterile syringes whose contents are mixed prior to administration. The two syringes are joined, and the single-dose product is mixed until it is homogenous; it is then injected. One of the two syringes contains the biodegradable, non-gelatin polymeric delivery system.

**REFERENCES**