Pharmaceutical Approval Update: Oncology

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Cetuximab (Erbitux)

Manufacturer: ImClone Systems, Inc., Branchburg, NJ, and Bristol-Myers Squibb, Princeton, NJ

Indication: Cetuximab is indicated for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck that cannot be removed by surgery. Cetuximab is also approved as monotherapy for patients whose head and neck cancer has metastasized despite the use of standard chemotherapy.

Drug Class: This recombinant, human/mouse (murine) chimeric monoclonal antibody binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). It is composed of Fv regions of a murine anti-EGFR antibody with human immunoglobulin G_1 (IgG_1) heavy-chain and kappa light-chain constant regions. Its approximate molecular weight is 152 kilodaltons.

Uniqueness of Product: This is the first drug approved for head and neck cancer that has shown a survival benefit for patients.

Warnings:

Infusion Reactions. Severe infusion reactions have occurred after the administration of cetuximab in approximately 3% (17/633) of patients, although fatal outcomes have been rare (less than one subject in 1,000). Approximately 90% of these reactions were associated with the first infusion despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, and hoarseness), urticaria, and hypotension.

Caution must be exercised with every infusion, because some patients have experienced their first severe reaction during later infusions. If a severe infusion reaction occurs, cetuximab therapy must be interrupted immediately and permanently. Appropriate medical therapy, including epinephrine, corticosteroids, intravenous (IV) antihistamines, bronchodilators, and oxygen, should be on hand. Patients should be carefully observed until all signs and symptoms have completely resolved.

Cardiopulmonary Arrest. Cardiopulmonary arrest or sudden death has occurred in 2% (4/208) of head and neck cancer patients who received radiation therapy and cetuximab, although none of 212 patients treated with radiotherapy alone experienced this event. When combined with radiation, cetuximab should be used with caution in patients with known coronary artery disease, congestive heart failure, or cardiac arrhythmias.

Precautions:

Allergy. Severe allergic reactions, including difficulty breathing, rash, itching, low blood pressure, and heart attacks, have occurred in 3% of 1,485 patients receiving cetuximab. These reactions, caused by the infusion, have resulted in death on rare occasions.

Skin Reactions. An acne-like rash, drying of the skin, cracking, redness, and swelling have been observed. Sun exposure may worsen these effects. Patients should wear sunscreen and hats to limit sun exposure. A related nail disorder, most often observed in the large toes and thumbs, has also been reported.

Dosage and Administration: The initial loading dose of cetuximab, when combined with radiation, is 400 mg/m^2 as the first infusion, administered as a 120-minute IV infusion (maximum infusion rate, 5 ml/minute) one week before the initial course of radiation therapy. The recommended weekly maintenance dose is 250 mg/m^2, infused over 60 minutes weekly, for the duration of radiation therapy (six to seven weeks). Cetuximab is administered 1 hour prior to radiation therapy.

The recommended regimen for cetuximab as a single agent is 400 mg/m^2 initially, followed by 250 mg/m^2 weekly, until disease progression or unacceptable toxicity.

Commentary: Cetuximab is combined with radiation therapy for locally or regionally advanced head and neck cancer and as a single agent in recurrent or metastatic head and neck cancer when prior platinum-based chemotherapy has failed. This is an important goal, because cetuximab is the first agent approved for this purpose in more than 30 years. For patients with locally or regionally advanced disease, cetuximab plus radiation has demonstrated significant improvements in survival and locoregional control. Nearly 40,000 diagnoses of head and neck cancer were confirmed in the U.S. in 2005, and more than 11,000 Americans died as a result of this disease.

Sources: www.erbitux.com; www.biotechnologyhealthcare.com/daily/DailyDetail.cfm?chosen=809

Sunitinib Malate (Sutent)

Manufacturer: Pfizer, New York, NY

Indication: Sunitinib (SU-11248) is a newly targeted anticancer therapy for patients with gastrointestinal stromal tumors (GISTs), a rare stomach cancer, who are intolerant of treatment with imatinib mesylate (Gleevec, Novartis). The capsules are also indicated for the treatment of advanced kidney cancer.

Drug Class: Sunitinib malate is described chemically as butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-hydroxy-, (2S), compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-*3H*-indol-3-ylidine)methyl]-2,4-dimethyl-*1H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$. The molecular weight is 532.6 daltons.

Uniqueness of Drug: Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs). Some of these are implicated in tumor growth, pathological angiogenesis, and metastatic progression of cancer.

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Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT-3), colony-stimulating factor receptor type 1 (CSF-1R), and the glial cell line–derived neurotrophic factor receptor (RET). The primary metabolite exhibits potency similar to that of sunitinib in biochemical and cellular assays.

Sunitinib inhibits the phosphorylation of multiple RTKs (PDGFR-β, VEGFR-2, KIT) in tumor xenografts expressing RTK targets *in vivo* and blocks tumor growth in experimental models of cancer. Sunitinib has the ability to inhibit the growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFR-β–dependent and VEGFR-2–dependent tumor angiogenesis *in vivo*.

Warnings: Sunitinib was evaluated at doses of 0.3, 1.5, 3.0, and 5.0 mg/kg per day in pregnant rats and at doses of 0.5, 1, 5, and 20 mg/kg per day in pregnant rabbits to determine its effect on the embryos. At 5 mg/kg per day, significant increases in the incidence of embryo fatalities and structural abnormalities were observed in the rats; this is about 5.5 times the systemic exposure in patients receiving the recommended daily dose.

A significantly increased incidence of embryonic deaths was observed in the rabbits at a dose of 5 mg/kg per day, whereas developmental effects were observed at 1 mg/kg per day or more; this is about 0.3 times the area-under-the-curve (AUC) concentration in patients receiving the recommended daily dose of 50 mg/day.

Because angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib should be expected to result in an adverse effect on pregnancy; however, no adequate or well-controlled studies of sunitinib in pregnant women have been performed. If the drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus.

Precautions:

Left Ventricular Dysfunction. In the two studies of metastatic renal cell carcinoma studies, 25 patients (15%) exhibited decreases in left ventricular ejection fraction to below the lower limit of normal. If clinical manifestations of congestive heart failure are present, sunitinib should be discontinued. If patients have no clinical evidence of congestive heart failure but their ejection fraction is below 50% and more than 20% below the baseline measures, the sunitinib dose should be interrupted or reduced.

Hemorrhage. Sudden tumor-related hemorrhage has been observed after therapy with sunitinib. In the case of pulmonary tumors, severe and life-threatening hemoptysis and pulmonary hemorrhage have occurred.

Hypertension. All grades of hypertension were reported in 48 of 169 patients with renal cell carcinoma (28%), 31 of 202 GIST patients receiving sunitinib (15%), and 11 of 102 GIST patients taking placebo (11%).

Other Stressors. Physicians prescribing sunitinib are advised to monitor patients for adrenal insufficiency in those who experience stresses such as surgery, trauma, and severe infection.

Dosage and Administration: The recommended dose of sunitinib for GISTs and advanced renal cell carcinoma is one 50-mg oral dose, taken with or without food. Dose increases or reductions in 12.5-mg increments are recommended according to safety and tolerability in individuals.

Commentary: Sunitinib represents hope to patients with GISTs that are resistant to imatinib therapy because it can slow cancer growth and extend survival. This is the first time a molecularly targeted therapy has proved effective after another targeted therapy has failed.

Although GISTs are uncommon, the degree to which they are understood at a molecular level has made this disease a proving ground for new therapies that might be useful for other cancers. Sunitinib is generally well tolerated, with mild-to-moderate adverse effects such as fatigue, diarrhea, nausea, mouth sores, and skin discoloration. These events rarely interfered with the ability of patients to continue taking the drug.

Sources: www.pfizer.com; www.centerwatch.com/patient/drugs/dru893.html

Sorafenib Tosylate (Nexavar)

Manufacturer: Bayer Health Care, West Haven, CT, and Onyx, Emeryville, CA

Indication: Sorafenib tablets are indicated for the treatment of advanced renal cell carcinoma.

Drug Class: As a multikinase inhibitor that targets a number of serine/threonine and receptor tyrosine kinases, sorafenib has the chemical name 4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N^2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Uniqueness of Drug: Sorafenib possesses disruptive activity at intracellular CRAF, BRAF, and mutant BRAF receptors and at extracellular KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β receptors. Inhibition of these systems blocks the division and growth of tumor cells and potentiates cellular apoptosis. These kinases are involved in multiple systems of angiogenesis and intracellular signaling, and their disruption is thought to inhibit tumor growth.

Warnings: In pregnant rats and rabbits, sorafenib is teratogenic and induces embryo and fetal toxicity, including increased post-implantation loss, resorption, skeletal retardation, and retarded fetal weight. The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (about 500 mg/m^2 per day on the basis of body surface area). Adverse intrauterine development effects were seen at doses of 1.2 mg/m^2 per day or higher in rats and at doses of 3.6 mg/m^2 per day in rabbits (about 0.008 times the AUC level seen in cancer patients at the recommended human dose).

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, it is assumed that sorafenib causes fetal harm during pregnancy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

continued on page 213

continued from page 209

Precautions:

Skin Reactions. Hand and foot reactions and rashes represent the most common adverse events attributed to sorafenib.

Hypertension. In one study, treatment-emergent hypertension was reported in approximately 16.9% of sorafenib-treated patients and in 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurring early in the course of treatment, and was managed with standard antihypertensive therapy.

Hemorrhage. An increased risk of bleeding may occur following sorafenib administration.

Cardiac Events. In one study, the incidence of treatment-emergent cardiac ischemia and infarction events was higher in the sorafenib group of patients (2.9%) compared with the placebo group (0.4%).

Dosage and Administration: Each oral sorafenib tablet contains 200 mg of the drug. The recommended dosage is 400 mg (two tablets) twice daily. As necessary, the dose may be reduced to 400 mg once daily or once every other day to manage treatment-related toxicity.

Commentary: Sorafenib is a targeted drug that is specifically engineered to inhibit RAF kinase within cancer cells. RAF, in turn, is part of the RAS, a gene that drives cell division and is overexpressed in many cancers, including renal cell carcinoma.

The key advantage of sorafenib is its ability to double the progression-free survival in patients with advanced renal cell carcinoma. This is the first oral multikinase inhibitor that targets serine/threonine and receptor tyrosine kinases in the tumor cell and tumor vasculature. In two preclinical models, it targeted members of two classes of kinases involved in tumor cell proliferation and tumor angiogenesis—two important activities in cancer growth. This ability to block tumor growth may have led to prolonged progression-free survival. Sorafenib also delays the progression of cancer in most patients. Its manageable side-effect profile is a welcome advantage for patients and their oncologists.

Sources: www.centerwatch.com/patient/drugs/dru887.html; www.nexavar.com/wt/page/index ■