

Pharmaceutical-Approval Update: Oncology

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Bortezomib for Injection (Velcade™)

Manufacturer: Millennium Pharmaceuticals Corporation

Description: Bortezomib, the first of a new class of medications called proteasome inhibitors, was approved for patients with multiple myeloma, a cancer of the blood. The product, a modified dipeptidyl boronic acid, is provided as a mannitol boronic ester, which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.¹

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. This proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanism can lead to cell death.

In experiments, bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. In nonclinical tumor models, including multiple myeloma, bortezomib causes a delay in tumor growth *in vivo*.

Indication: Bortezomib for injection is indicated for the treatment of patients with multiple myeloma who have undergone at least two prior therapies and have demonstrated disease progression after the last therapeutic intervention.

Pharmacology: The safety and efficacy of bortezomib were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least two previous treatments and whose disease progressed after their most recent therapy. The median number of earlier therapies was six.

An intravenous (IV) bolus of bortezomib, 1.3 mg/m² per dose, was administered twice weekly for two weeks, followed by a 10-day rest period (in a 21-day treatment cycle) for a maximum of eight treatment cycles. Patients who responded to treatment with bortezomib were allowed to continue taking it in an extension study. No controlled trials have demonstrated a clinical benefit, such as an improvement in survival.

Warnings: Bortezomib should be administered under the supervision of a physician experienced in the use of anti-neoplastic therapy. Women of childbearing age should avoid becoming pregnant while taking bortezomib. No placental transfer studies have been conducted with the agent.

Precautions: Bortezomib therapy causes a peripheral neuropathy that is predominantly sensory, although cases of mixed sensorimotor neuropathy have also been reported. Patients



with pre-existing symptoms (e.g., numbness, pain, and a burning feeling in the feet or hands) or with signs of peripheral neuropathy may experience worsening of these manifestations during treatment.

Therapy can also lead to orthostatic and postural hypotension in approximately 12% of patients throughout the treatment period. Nausea, diarrhea, constipation, fatigue, headache, and vomiting have

been reported, with some patients needing antiemetic and antidiarrheal agents. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia occurred in 40% of patients while they were taking bortezomib. Patients with hepatic impairment should be closely monitored. Neutropenia occurred in 24% of patients.

Uniqueness of Drug: Bortezomib, acting through a novel mechanism, is a potent, specific inhibitor of the proteasome by binding to the core of mammalian cells and disrupting the pathway for tumor development and growth.

Conclusion: Phase II studies are in progress in patients with indolent lymphomas. Clinical studies are planned for the study of bortezomib for proteasome inhibition in solid tumors as a single agent or in combination with cytotoxic drugs. The drug is being considered as therapy for colon, pancreas, prostate, gastric, ovarian, and lung cancers.

Reference

1. Bortezomib (Velcade™) prescribing information, Millennium Corporation Inc. Available at: www.millennium.com/products/velcade/index.asp. Accessed July 22, 2003.

Gefitinib (Iressa™)

Manufacturer: AstraZeneca Pharmaceuticals, Inc.

Description: Gefitinib is a doublet, platinum-based chemotherapeutic agent and is the first in a new class of anti-cancer drugs known as epidermal growth factor receptor/tyrosine kinase (EGFR-TK) inhibitors. It is a signal transduction inhibitor.

On the surface of many types of cancer cells are structures known as epidermal growth factor receptors (EGFRs). The receptors allow epidermal growth factor (EGF), a particular protein present in the body, to attach to them. When attached to the receptor, EGF causes a chemical called tyrosine kinase (TK) to trigger cell growth and division. Gefitinib attaches itself to the EGF receptor inside the cell; this action blocks the activation of TK and switches off the signals from EGFR. It therefore has the potential to stop the cancer cells from growing and has different actions during both chemotherapy and hormonal therapy.

Previous trials have shown that when cancer cells have many EGF receptors, the cancer tends to develop quickly and to metastasize to other parts of the body. EGF receptors are found on many types of cancer cells, including those of the lung, breast, colon, rectum, and prostate gland. Theoretically,

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gefitinib might be effective in treating these cancers, but it has shown the most promise as therapy for non-small cell lung cancer (NSCLC).

Gefitinib has fulfilled the requirements for accelerated approval by the Food and Drug Administration (FDA). This form of approval is granted for life-threatening conditions when a new drug provides meaningful therapeutic benefit over available therapies or when no approved treatment exists, as in the case of this agent.

Indication: Gefitinib is indicated as monotherapy for patients with locally advanced or metastatic NSCLC after unsuccessful chemotherapy using platinum, for example, cisplatin (Platinol®, Bristol-Myers Squibb) or carboplatin (Paraplatin®, Bristol-Myers Squibb) plus docetaxel (Taxotere®, Aventis). As part of the accelerated approval of gefitinib, phase IV clinical studies are designed to satisfy FDA requirements for final approval.

Dosage: Gefitinib is administered alone as a 250-mg tablet once a day.

Pharmacology: A phase II clinical trial examined the efficacy and safety of two doses of gefitinib in 216 patients with NSCLC who previously received both platinum-based and docetaxel chemotherapies.¹ Of the 216 patients, 142 were included in the FDA's analysis of the drug. In the group receiving the recommended dose of 250 mg/day, 13.6% (95% confidence interval [CI]: range, 6.4–24.3) of the patients experienced tumor reduction by at least 50%. A higher dose (500 mg/day) did not produce a better response, and more side effects were observed.

The overall response rate for both doses combined in all 142 patients was 10.6% (95% CI: range, 6.0–16.8). The median duration of response was seven months (range, 4.4–18.6+ months).² The response rates appeared to be highly variable in subgroups of the treated population, according to their sex, smoking history, and histology (range, 4.6%–29.4%).¹

In the 142 evaluable patients with documented disease progression after platinum and docetaxel therapies or who had experienced unacceptable toxicity with these agents, gefitinib was considered as a third-line therapeutic agent.

The most common adverse drug events (ADEs) of gefitinib at 250 mg/day in clinical trials were diarrhea, rash, acne, dry skin, and nausea and vomiting. The 500-mg dose was associated with a greater incidence of most of these ADEs.

In two large trials of 2,130 patients with NSCLC, gefitinib 250 or 500 mg daily or a placebo, in combination with platinum-based chemotherapy regimens (using gemcitabine [Gemzar®, Eli Lilly] and cisplatin) or carboplatin and paclitaxel, did not produce a trend toward increased tumor response rates, time to progression, or overall survival.

Warnings: Interstitial lung disease (ILD) has been documented in patients receiving gefitinib at an overall incidence of about 1%, and approximately one third of these cases have been fatal. Reports have described the ADEs as interstitial pneumonia, pneumonitis, and alveolitis. ILD has occurred in patients who received prior radiation therapy (31%), previous chemotherapy (57%), and no previous therapy (12%).

In the event of acute onset or worsening of pulmonary symptoms (e.g., dyspnea, cough, or fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms

should begin. As with studies of reproduction in animals, harm to the fetus is a possibility when pregnant women use gefitinib, although no adequate or well-controlled studies have been performed with this agent in women during pregnancy.

Precautions: Hepatotoxicity is a potential effect. Because patients have experienced asymptomatic elevations in liver transaminases, periodic liver-function tests to determine transaminase, bilirubin, and alkaline phosphatase levels should be considered. Gefitinib should be discontinued if changes are severe.

In patients with hepatic impairment or dysfunction, the concentration of gefitinib may be increased. In patients with liver metastases and moderately to severely elevated biochemical liver abnormalities, the pharmacokinetic properties of gefitinib were similar to those in people without liver abnormalities. The influence of non-cancer-related hepatic impairment on the pharmacokinetics of gefitinib has not been evaluated.

Conclusion: Approximately 10% of patients receiving gefitinib who had not responded to conventional treatment achieved an objective response rate, and about 50% of treated patients experienced an improvement in objective signs.

The major benefit of gefitinib may be its ability to produce responses as a single agent in patients with refractory disease without major toxic side effects, and this agent appears to benefit patients with refractory NSCLC in whom conventional therapies have failed. The main benefits of this agent are its lack of bone marrow toxicity and its ease of administration.

For more information on gefitinib, see the Drug Forecast article on page 641.

Reference

1. Gefitinib (Iressa™) prescribing information, AstraZeneca Pharmaceuticals, LP, revised May 2, 2003. Available at: www.fda.gov/cder/approval.

Tositumomab and Iodine 131 Tositumomab (Bexxar®)

Manufacturer: Corixa Corporation/GlaxoSmithKline Oncology

Description: The Bexxar® therapeutic regimen represents a multistep treatment for non-Hodgkin's lymphoma (NHL), in which a mouse immunoglobulin G (IgG2a) lambda monoclonal antibody (tositumomab) is directed against the CD20 antigen, linked to a radioactive molecule, iodine I 131 (¹³¹I). ¹³¹I tositumomab is a radio-iodinated derivative of tositumomab that has been covalently linked to ¹³¹I. Tositumomab targets the CD20 protein, which occurs on the surface of normal and malignant B-lymphocytes.

Indication: Bexxar® is indicated for the treatment of CD20-positive, follicular NHL, with and without transformation, in patients whose disease has been refractory to rituximab (Rituxan™, Genentech, IDEC) and who have experienced relapse following chemotherapy.¹

Dosage: The product is administered in two discrete phases: a *dosimetric* step and a *therapeutic* step. The non-radioactive antibody, tositumomab, is used to improve the distribution of the subsequent radioactive antibody in the body and to increase its uptake in the tumor.

The dosimetric infusion contains the antibody and a trace

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amount of radioactive ^{131}I . This step allows the rate of clearance of radioactivity from the body to be determined by the use of gamma camera counts that are obtained at three time points.

The therapeutic step takes place seven to 14 days later. The patient returns for two infusions, again beginning with the non-radioactive antibody, followed by the calculated patient-specific radioactivity needed to deliver the targeted total body dose of radiation.

Both steps consist of a sequential infusion of 450 mg of tositumomab over 60 minutes, followed by the infusion of ^{131}I tositumomab over 20 minutes:

- In the dosimetric step, the ^{131}I tositumomab dose contains 35 mg of tositumomab and 5 millicuries (mCi) of ^{131}I .
- In the therapeutic step, the dose of ^{131}I tositumomab contains 35 mg of tositumomab and the dose of ^{131}I that is calculated to deliver 75 centigray (cGy) of total body irradiation.

For patients with mild, or grade 1 (per the National Cancer Institute's Common Toxicity Criteria), thrombocytopenia (a blood condition that may result in bruising and excessive bleeding), the therapeutic dose of ^{131}I tositumomab is reduced. For patients with thrombocytopenia, the dose of ^{131}I must be calculated to deliver 65 cGy of total body irradiation.

Pharmacology: The efficacy of Bexxar® was evaluated in a multicenter, single-arm study in patients with low-grade or transformed low-grade or follicular large cell lymphoma whose disease had not responded to, or had progressed after, rituximab therapy. The drug's clinical benefit was determined on the basis of evidence of durable responses without evidence of an effect on survival.

The overall response rate was 63%, with a median duration of response of 25 months. The complete response rate was 29%, but the median duration of complete response has not been reached.

These findings were supported by a demonstration of durable complete and partial objective responses in patients with low-grade or transformed low-grade or follicular large cell lymphoma in four additional, single-arm, multicenter studies. In these studies, the overall response rates ranged from 47%

to 64%, with median durations of responses ranging from 12 to 18 months.

Warnings (Boxed):

Hypersensitivity Reactions, Including Anaphylaxis: Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. If severe hypersensitivity reactions occur, infusions of Bexxar® should be discontinued and patients should receive medical attention.

Prolonged and Severe Cytopenias: Most patients who received Bexxar® experienced severe thrombocytopenia and neutropenia. This regimen should not be administered to patients with lymphoma marrow involvement that exceeds 25% or to those with impaired bone marrow reserve.

Special Requirements: Because the Bexxar® therapeutic regimen contains a radioactive component, it should be administered only by physicians and other health care professionals who have been qualified by training in the safe use and handling of therapeutic radionuclides. This therapy should be administered only by physicians who are becoming certified, or who have received certification, by Corixa Corporation in dose calculation and administration of the Bexxar® regimen.

Adverse Effects: The most common ADE in clinical trials was severe life-threatening cytopenia, including thrombocytopenia, neutropenia, and anemia. Myelodysplastic syndrome and leukemia were observed in some patients. Cancers of the breast, lung, bladder, head, and neck developed in a small number of patients.

Conclusion: Bexxar® comprises a dual-action therapy that combines the tumor-targeting ability of a cytotoxic monoclonal antibody and the therapeutic potential of radiation. The therapeutic regimen is the only treatment for NHL that is specifically administered according to clearance rates in individual patients. The risks associated with this therapy for NHL are high, and patients should be carefully monitored.

Reference

1. Tositumomab and ^{131}I tositumomab (Bexxar®) prescribing information, Corixa Corporation. Available at: www.corixa.com. Accessed July 24, 2003.