

Proteasome Inhibition in Hematologic Malignancies: Clinical Update and Practical Applications

Guest Editor

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Throughout my career, I have collaborated with many colleagues who share a common goal of mapping and reversing the molecular mechanisms involved in the malignant transformation of plasma cells and resistance of myeloma cells to chemotherapy drugs. Over the years, I have had the privilege of participating in and witnessing the discovery of numerous promising molecular targets, which has led to the development of many unique antitumor drugs; however, the marketing of a compound that significantly impacts the lives of cancer patients is still rare.

One such compound that recently entered the market is bortezomib (PS-341, Velcade), a proteasome inhibitor with impressive antitumor activity in multiple myeloma and promising activity in other hematologic malignancies and solid tumors. Research regarding the antitumor benefits of proteasome inhibition, including reversal of de novo or acquired chemotherapy and radiation therapy resistance, led to the development and clinical use of bortezomib.

Bortezomib induces apoptosis and increases sensitivity or reverses resistance to standard chemotherapy agents in a wide variety of cancer cell lines, with relatively few toxic effects on normal cells. As a single agent or in combination with irinotecan (Camptosar), gemcitabine (Gemzar) with or without carboplatin (Paraplatin), liposomal doxorubicin (Doxil), or fluorouracil/leucovorin, bortezomib has demonstrated activity against multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, acute myelogenous leukemia, chronic lymphocytic leukemia, non-small-cell lung cancer, prostate cancer, and other human tumor xenografts.

The clinical development of bortezomib has been rapid and compelling, with promising results observed in patients with relapsed or refractory multiple myeloma. The results of a phase II trial evaluating bortezomib in 202

multiple myeloma patients with highly refractory disease showed a 27% overall response rate, including a 3.6% complete response rate, 6.2% near complete response rate, and 17.6% partial response rate. Based on the results of this and other phase II trials, the US Food and Drug Administration approved bortezomib as treatment of multiple myeloma in patients whose disease has progressed after they have received at least two prior conventional therapies.

The most common adverse effects reported with bortezomib in clinical trials included gastrointestinal events (ie, nausea, vomiting, diarrhea, constipation, anorexia), asthenia, thrombocytopenia, peripheral neuropathy, pyrexia, and anemia. Most toxicities were mild to moderate in severity. Bortezomib should be administered with caution in patients with preexisting fluid retention or baseline platelet counts of less than 70,000/ μ L. Patients with preexisting peripheral neuropathy, a history of neurotoxic drug use, or cardiovascular instability should be monitored closely during therapy.

This supplement, based on a symposium held at the 8th Annual "Making A Difference in Oncology" (MADONC) conference, summarizes the clinical development and applications of bortezomib. In the first article (see page 4), Laura Jung, Lisa Holle, and I summarize the preclinical, phase I, and phase II clinical trials of bortezomib, including predictors of response in patients with relapsed or refractory multiple myeloma and the effects of bortezomib on quality of life in responding patients. The second article (see page 14), by Rowena Schwartz and Terri Davidson, focuses on the pharmacology of bortezomib, including its mechanism of action, pharmacokinetics, pharmacodynamics, and toxicities. Recommendations for prescribing and monitoring bortezomib therapy are also provided.

Bortezomib is the first treatment in more than a decade to be approved for patients with multiple myeloma. It is the first in a new class of antitumor agents, the proteasome inhibitors, which hold promise as treatment for a variety of hematologic malignancies and solid tumors, including tumors resistant to cytotoxic drugs. In addition to their use as an antitumor agent, proteasome inhibitors have potential as treatment of several noncancer diseases, including neurodegenerative diseases, cystic fibrosis, and various immune or inflammatory responses, the pathogenesis of which include proteasomes. We eagerly await the results of current and planned studies assessing this compound in various tumor types and other diseases.

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