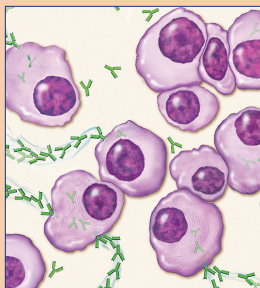


■ Online Exclusive Article

Carfilzomib: A Next-Generation Proteasome Inhibitor for Multiple Myeloma Treatment

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Although the incidence of multiple myeloma (MM) is increasing, the median overall survival and the number of agents in the pipeline for treating MM also are increasing. Response rates higher than 80% are not uncommon in the frontline setting when the novel agents thalidomide, lenalidomide, and bortezomib are used in combination. Response rates and survival also have improved in disease that has relapsed after treatment with conventional therapies. The focus of research has now shifted to improving survival and disease response in patients refractory to current treatment paradigms. New agents are targeting new pathways, as well as existing mechanisms known to be effective, but with different safety profiles. Carfilzomib is a potent, selective, irreversible inhibitor of the ubiquitin-proteasome pathway. The drug is a next-generation proteasome inhibitor found to be safe and effective for patients with relapsed and refractory MM, where treatment options are limited. As with any newly approved agent, one should recognize that drugs within the same class will be administered differently and often cause dissimilar treatment-related toxicities. Oncology nurses are crucial to the successful administration of chemotherapeutic agents such as carfilzomib, and an understanding of management techniques is paramount to quality patient care.

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Multiple myeloma (MM) is the second most common hematologic malignancy, with an estimated 22,350 new cases and 10,710 deaths in 2013 (Siegel, Naishadham, & Jemal, 2013). MM, a result of clonal plasma cell overproliferation, typically is characterized by the production of a monoclonal protein (immunoglobulin) leading to end-organ damage presenting as hypercalcemia, renal dysfunction, anemia, and skeletal destruction.

Prior to 2000, standard therapeutic options included conventional chemotherapeutic agents (e.g., melphalan, vincristine, doxorubicin) often in combination with steroids (prednisone and dexamethasone); median survival was 29.9 months (Kumar et al., 2008). High-dose chemotherapy conditioning followed by autologous stem cell transplantation continues to be a mainstay of therapy for eligible patients. However, four new drugs were approved for the treatment of MM since the early 2000s, including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, the proteasome inhibitor bortezomib, and the anthracycline liposomal doxorubicin. With the use of those novel

agents, the median survival for patients diagnosed since the early 2000s has improved to 44.8 months (Kumar et al., 2008). In an international, multicenter analysis of 286 patients refractory to bortezomib and either refractory to, relapsed from, intolerant of, or ineligible for an IMiD, overall survival and event-free survival from the time they were identified were nine and five months, respectively (Kumar et al., 2012). This patient population with an unmet need requires continued research and development of new agents.

Background

The activity of bortezomib has confirmed the proteasome as an important therapeutic target in MM. Proteasome inhibition leads to accumulation of ubiquitinated (the process by which a protein is tagged with ubiquitin for transport to the proteasome for degradation) proteins, inhibition of myeloma cell proliferation, and induction of apoptosis (Moreau et al., 2012). Carfilzomib (Kyprolis™) is a selective, irreversible proteasome inhibitor