Proteasome inhibitors have a 20-year history in cancer therapy. The first proteasome inhibitor, bortezomib, a breakthrough treatment for multiple myeloma, moved rapidly through development from the bench in 1994 to first FDA approval in 2003. Clinical Cancer Research has chronicled the development of proteasome inhibitors with publication of reports on bortezomib, carfilzomib, and the oral proteasome inhibitor ixazomib (MLN9708). Clin Cancer Res; 21(5); 939–41. ©2015 AACR. See related article by Teicher et al., Clin Cancer Res 1999;5(9) September 1999;2638–45

The incorporation of the first-in-class proteasome inhibitor, bortezomib, to the anti-myeloma armamentarium can be considered one of the major milestones in the treatment of patients with myeloma, greatly improving the response rates and overall survival in both first-line and relapsed/refractory settings.

The regulation of protein activities by proactive synthesis and degradation is vital to cellular metabolic integrity and proliferation. The proteasome, a large, multimeric protease complex, has a central role in cellular protein regulation through catabolism of a wide variety of proteins, resulting in the activation of certain pathways and the blocking of others (1). The proteasome degrades proteins that have been conjugated to multiple units of the polypeptide ubiquitin; this is the ubiquitin–proteasome pathway. In 1993, Alfred Goldberg, the discoverer of the proteasome, along with his colleagues founded the company MyoGenetics to develop proteasome inhibitors to treat muscle-wasting conditions. Julian Adams, a medicinal chemist, was recruited to head the company (Fig. 1). Because proteasome inhibitors were quite toxic, a new therapeutic focus was needed. The lead compound, MG-341, selectively inhibited the chymotryptic activity of the 20S proteasome. In 1994, the anticancer activity of the boronic acid dipeptide proteasome inhibitor MG-341 was examined in vitro and in vivo at the Dana-Farber Cancer Institute. Publication of the results was held up for several years, during which time MyoGenetics became ProScript and MG-341 became PS-341. PS-341 was a potent cytotoxic agent toward MCF-7 human breast carcinoma cells in culture, producing an IC50 of 0.05 μmol/L on 24-hour exposure. In the EMT-6 tumor cell survival assay, PS-341 was potently cytotoxic when administered to mice. PS-341 was also toxic to bone marrow CFU-GM from the same mice. PS-341 increased the tumor cell killing of radiotherapy, cyclophosphamide, and cisplatin in mice bearing the EMT-6 tumor. In the tumor-growth delay assay, PS-341 had antitumor activity against both primary and metastatic Lewis lung carcinoma. In combination regimens with 5-fluorouracil, cisplatin, paclitaxel, and doxorubicin, PS-341 produced additive tumor-growth delays against the subcutaneous tumor and was highly effective against disease metastatic to the lungs (2).

In 1995, PS-341, along with several analogues, was submitted to the NCI-60 cell line screen and was found to have potent, wide-ranging activity in solid and liquid tumor cell lines. A good correlation was established between proteasome inhibition and cell line response among tested compounds. PS-341 produced a unique pattern in the COMPARE analysis, suggesting that PS-341 had a novel mechanism of action. PS-341 had antitumor activity in several human solid tumor xenografts (3). In 1996, increased nuclear factor κB (NF-κB) activity was associated with increased tumor cell survival, adhesion of tumor to bone marrow, and IL6 secretion in the bone marrow milieu in multiple myeloma. The function of NF-κB is inhibited through binding to its inhibitor, IκB. Release of activated NF-κB follows proteasome-mediated degradation of IκB after phosphorylation and conjugation with ubiquitin. Myeloma cells have increased IκB phosphorylation and increased NF-κB activity compared with normal hematopoietic cells. PS-341 blocked nuclear translocation of NF-κB and demonstrated antitumor activity against chemoresistant and chemosensitive myeloma cells alone and in models of the bone marrow microenvironment in both in vitro and in vivo murine xenograft models of human myeloma. Moreover, the sensitivity of chemoresistant myeloma cells to chemotherapeutic agents was markedly increased when these agents were combined with PS-341 (4).

ProScript was acquired by Millennium Pharmaceuticals in 1999. Critical to enabling the development of PS-341 was the development of a suitable formulation that produced a stable composition that released the boronic acid compound in aqueous media (5). The formulation and preclinical safety testing of PS-341 in the formulation was carried out by the Developmental Therapeutics Program of the National Cancer Institute. Several phase I clinical trials were conducted with bortezomib with varied dosing schedules and patient groups. In 2002, a breakthrough
phase I clinical trial of bortezomib in patients with refractory hematologic malignancies was reported. Patients received bortezomib twice weekly for 4 weeks at escalating doses, followed by a 2-week rest period. Twenty-seven patients received 293 doses of bortezomib, including 24 complete cycles. Dose-limiting toxicities attributed to bortezomib included thrombocytopenia, hypotension, hypokalemia, fatigue, and malaise. In pharmacodynamic studies, bortezomib induced 208 proteasome inhibition in a time- and dose-dependent manner. Among 9 fully assessable patients with heavily pretreated plasma cell malignancy completing one cycle of therapy, there was one complete response and a reduction in paraprotein levels and/or marrow plasmacytosis in 8 other patients. In addition, one patient with mantle cell lymphoma and another with follicular lymphoma had shrinkage of nodal disease. Bortezomib showed activity against refractory multiple myeloma and possibly non–Hodgkin lymphoma in this study (6).

This phase I clinical trial, along with preclinical evidence of antitymoma activity, provided the rationale for a multicenter, open-label, nonrandomized phase II study of bortezomib for the treatment of relapsed, refractory myeloma. The phase II trial reported in 2003 enrolled 202 patients. Of 193 patients who could be evaluated, 92% had been treated with three or more of the major classes of agents for myeloma, and in 91%, the myeloma was refractory to the therapy received most recently. The overall rate of response to bortezomib was 35%, and those with a response included 7 patients in whom myeloma protein became undetectable and 12 in whom myeloma protein was detectable only by immunofixation. The median overall survival was 16 months, with a median duration of response of 12 months. Time to progression was increased by a factor of 2 to 4 with bortezomib compared with the last therapy patients received before entering the study. Responses were associated with increased hemoglobin levels and decreased transfusion requirements, improved quality of life, and improved levels of normal immunoglobulins. Although this trial was uncontrolled, several methods were used to reduce bias in assessing the response to therapy. Each patient was used as his or her own control in the assessment of the time to progression of disease relative to that with the last therapy received before enrollment, and a landmark analysis was performed to demonstrate an association between a response to bortezomib alone and survival. In addition, the median duration of survival among patients without a response (8 months) was within the range (6–9 months) that was expected on the basis of the literature. Response to bortezomib did not correlate with most of the standard myeloma prognostic factors, including the deletion of chromosome 13, which predicts a poor outcome with conventional therapy. An international, randomized, multicenter phase III trial comparing bortezomib with high-dose dexamethasone in patients with relapsed multiple myeloma was initiated (7). In 2003, bortezomib was approved for the treatment of refractory multiple myeloma, and in 2005 bortezomib was approved for treatment of patients with multiple myeloma who had received at least one prior therapy. On June 23, 2008, the FDA approved bortezomib for use in patients with multiple myeloma as an initial treatment. In 2006, bortezomib was approved for treatment of relapsed or refractory mantle cell lymphoma, and in 2014 it was approved for previously untreated patients with mantle cell lymphoma.
The success of bortezomib sparked further investigation of the proteasome as a target for anticancer therapy. Carfilzomib (PR-171) is a novel irreversible proteasome inhibitor of the epoxiketone class that is structurally and mechanistically distinct from bortezomib. Consequently, proteasome inhibition is more sustained with carfilzomib than with bortezomib. The epoxiketone pharmacophore of carfilzomib is highly selective for the NH2-terminal threonine residue that catalyzes enzymatic activity in each of the proteolytic active sites within the proteasome. In a phase I trial, reported in 2009, evaluating the safety and efficacy of carfilzomib in relapsed or refractory hematologic malignancies, 29 patients enrolled that were relapsed or refractory after at least two prior therapies. Nonhematologic toxicities included fatigue, nausea, febrile neutropenia, thrombocytopenia, and diarrhea in more than one third of patients. Antitumor activity was observed two prior therapies. MLN2238 had a stronger, more sustained proteasome inhibition in xenograft tumors, and a weaker, less sustained effect in whole blood than did bortezomib. MLN2238 inhibited growth and induced apoptosis in multiple myeloma cells resistant to conventional and bortezomib therapies without affecting the viability of normal cells.

MLN9708 (ixazomib citrate), a novel orally bioactive proteasome inhibitor, hydrolyzes to the biologically active compound MLN2238 (ixazomib), which preferentially and reversibly inhibits the proteasome chymotryptic–like subunit, resulting in the accumulation of ubiquitinated proteins. MLN2238 had a stronger, more sustained proteasome inhibition than xenograft tumors, and a weaker, less sustained effect in whole blood than did bortezomib. MLN2238 inhibited growth and induced apoptosis in multiple myeloma cells resistant to conventional and bortezomib therapies without affecting the viability of normal cells. In animal tumor models, MLN2238 inhibited tumor growth with significantly reduced tumor recurrence. A head-to-head analysis of MLN2238 versus bortezomib showed a significantly longer survival time in mice treated with MLN2238 than mice receiving bortezomib. Immunosuppression of tumors from MLN2238-treated mice showed growth inhibition, apoptosis, and decreased angiogenesis. Mechanistic studies showed that MLN2238 triggered apoptosis was associated with inhibition of NF-kB activation. Combining MLN2238 with lenalidomide, histone deacetylase inhibitor suberoylanilide hydroxamic acid, or dexamethasone increased antimaloma activity. Bortezomib slows progression of myeloma bone disease. This beneficial impact of bortezomib on bone metabolism is not due to antimyeloma activity; bortezomib directly interferes with osteoclastogenesis and resorption and promotes osteoblast formation and function. Clinical trials of orally administered MLN9708 (now in phase III) indicate that the agent is tolerable, with infrequent peripheral neuropathy and clinical antimaloma activity reported either when it is used alone or in combination with other antimyeloma drugs, as well as signs of additional beneficial bone effects (10, 11).

Six of the nine reports highlighted in this short history of proteasome inhibitor anticancer agents were published in CCR. The 20-year history of proteasome inhibitors in cancer coincides with the 20 years of CCR. It is an honor to be part of the story.

Disclosure of Potential Conflicts of Interest

K.C. Anderson is a consultant/advisory board member for Millennium Pharmaceuticals. No potential conflicts of interest were disclosed by the other author.

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