Minireview

Proteasome inhibitor therapy in multiple myeloma

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Abstract

Multiple myeloma remains incurable despite available therapies, and novel therapies that target both tumor cell and bone marrow microenvironment are urgently needed. Preclinical *in vitro* and *in vivo* studies show remarkable anti–multiple myeloma activity of the proteasome inhibitor bortezomib/PS-341 even in multiple myeloma cells refractory to multiple prior therapies, including dexamethasone, melphalan, and thalidomide. Based on these findings, the U.S. Food and Drug Administration recently approved the first proteasome inhibitor bortezomib (Velcade), formerly known as PS-341, for the treatment of relapsed/refractory multiple myeloma. Bortezomib therapy has set an outstanding example of translational research in the field of oncology. Genomics and proteomic studies further provide rationale for combining bortezomib with conventional and novel agents to inhibit multiple myeloma growth, overcome drug resistance, reduce attendant toxicity, and improve patient outcome in multiple myeloma. [Mol Cancer Ther 2005;4(4):686–92]

Introduction

Multiple myeloma cells primarily localize in the bone marrow, where various humoral factors promote multiple myeloma cell growth and survival and prevent the cytotoxic effects of chemotherapy (1, 2). Specifically, adhesion of multiple myeloma cells to bone marrow stromal cells triggers transcription and secretion of cytokines, such as interleukin 6 (IL-6; ref. 3) and insulin-like growth factor I (Fig. 1), or vascular endothelial growth factor, which in turn not only induce proliferation of multiple myeloma cells but also block chemotherapy-induced tumor cell apoptosis (2, 4–10). The bone marrow microenvironment therefore contributes significantly to the pathogenesis and progression of multiple myeloma, and novel anti–multiple myeloma agents that target both multiple myeloma cells and their microenvironment are of immense clinical use.

The successful development of bortezomib/PS-341 therapy for multiple myeloma has established proteasome inhibition as an effective therapeutic strategy (11–13). The dipeptide boronic acid analogue bortezomib is a potent, highly selective, and reversible proteasome inhibitor that targets 26S proteasome complex and inhibits its function (Fig. 1). The 26S proteasome is an ATP-dependent multicatalytic protease mediating intracellular protein degradation. Proteasomal degradation of misfolded or damaged proteins proceeds by recognition of polyubiquitinated proteins by the 19S regulatory subunit of the 26S protease and subsequently hydrolysis to small polypeptides (Fig. 1). Besides eliminating damaged/misfolded proteins, the proteasome also regulate key cellular processes, including modulation of transcription factors, cell cycle progression, growth arrest, and apoptosis. The current article highlights the following: (a) preclinical and clinical data of proteasome inhibition as a therapy in multiple myeloma; (b) cytotoxic activity of combination of bortezomib with other conventional or novel anti–multiple myeloma agents; and (c) strategies to overcome bortezomib resistance in multiple myeloma cells, including genomics and proteomic-based molecular therapies, as well as evaluation of new proteasome inhibitors.

Constitution and Regulation of Proteasome

Proteasomes are key regulators of protein degradation (14). The 26S proteasome complex has two 19S units flanking a barrel-shaped 20S proteasome core (15–17). Four stacked rings comprise the 20S structure: two central β rings are surrounded by two rings, each consisting of seven proteins (Fig. 1). Most action occurs at six sites located in the β rings: two sites act like chymotrypsin, which cleaves after hydrophobic residues; two trypsin-like sites cleave after basic residues; and two are like caspase, cleaving after acidic residues (18, 19). The 19S units regulate entry of only ubiquinated proteins into the 20S core chamber (16, 20). Proteasomal protein degradation occurs via the following events: protein is marked with a chain of small polypeptides or ubiquitin; estrone ubiquitin enzyme then

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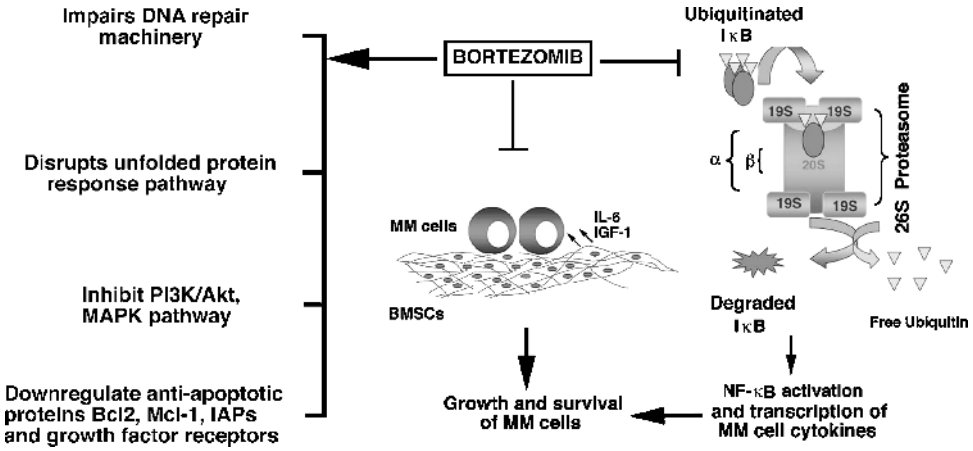

Figure 1. Bortezomib/PS-341 affects various growth and survival pathways in multiple myeloma (*MM*) cells. Treatment of multiple myeloma cells with bortezomib is associated with these events: inhibition of the adhesion of multiple myeloma cells to bone marrow stromal cells (*BMSCs*), resulting in blockade of the adhesion-related transcription and secretion of multiple cytokines; inhibition of NF-κB; impairment of the DNA repair machinery; down-regulation of growth and antiapoptotic signaling pathways and associated proteins, such as mitogen-activated protein kinase (*MAPK*), phosphatidylinositol 3-kinase (*PI3K*)/Akt, Bcl2, or inhibitors of apoptosis proteins (*IAPs*).

activates ubiquitin and links it to the ubiquitin-conjugating enzyme E2 in an ATP-dependent manner; E3 ubiquitin ligase attaches the ubiquitin molecule to the protein; a long polypeptide chain of ubiquitin moieties is formed; and finally, proteasomes degrade protein into small fragments (16, 21). Importantly, blocking proteasome activity leads to stabilization of inhibitory proteins, thereby abrogating growth and survival (Fig. 1).

Protein degradation mediates both normal cellular functioning and cellular response to chemotherapy (22, 23). Multiple studies have shown that protein ubiquitination and degradation via ubiquitin-proteasome pathways regulates cell cycle progression, tumor suppression, transcription, DNA replication, inflammation, and apoptosis (15, 24–27). Mutations or changes in these signaling pathways lead to defective transition from G_1 to S phase (15, 28). Proteasome inhibitors block protein degradation and cause accumulation of misfolded/damaged proteins, which in turn triggers heat shock response and cell death (16, 24). Given that ubiquitin-proteasome pathway affects multiple cellular processes, its inhibition by proteasome inhibitor affects a broader spectrum of proteins with diverse functions.

Proteasome inhibitors fall into three categories: peptide aldehydes, peptide boronates, and nonpeptide inhibitors such as lactacystin. Peptide aldehydes (MG-132, MG-115, ALLN, or PSI) potently, but reversibly, block the chymotrypsin-like activity; however, they also inhibit lysosomal cysteine and serine proteases and calpains. The peptide boronates such as bortezomib are reversible, more potent, and selective than peptide aldehydes. Finally, lactacystin is a natural, irreversible, nonpeptide inhibitor that is more selective than peptide aldehydes but less selective than peptide boronates.

Proteasome and Cancer Therapy

Multiple studies show that proteasome inhibitors are more cytotoxic to proliferating malignant cells than to quiescent normal cells (29–33). It is likely that the malignant cells have altered or defective cell cycle proteins leading to an increased proliferation rate, increased accumulation of damaged proteins, and therefore higher dependency on the proteasomal degradation processes. Importantly, bortezomib triggers apoptosis in multiple myeloma cells at doses that do not affect the viability of normal lymphocytes (12). Furthermore, nuclear factor-κB (NF-κB) is linked to proliferation and drug resistance in cancer cells, including multiple myeloma (34, 35), and bortezomib down-regulates NF-κB activation, thereby enhancing the cytotoxic effects of chemotherapy (refs. 12, 24, 36; Fig. 1). These findings suggest that the proteasome is a valid target for chemotherapy, with tolerable therapeutic index.

Bortezomib-Induced Apoptosis Correlates with Attenuated NF-κB Activity

Constitutive activation of NF-κB is linked to growth/proliferation and drug resistance, thereby conferring differential sensitivity to proteasome inhibitors in cancer versus normal cells (36). NF-κB activation occurs via these sequential events: IκB phosphorylation triggered by an upstream IκBα kinase; ubiquitination and degradation of phosphorylated IκBα resulting in free p50/65 complex; and nuclear translocation and activation of p50/65 NF-κB (37, 38). Once in the nucleus, NF-κB binds to its consensus sequences present in the promoter region of many growth/survival factor–associated genes and triggers their transcription. For example, NF-κB activation promotes the production of cytokines (IL-6 and tumor necrosis factor-α), survival factors (inhibitors of apoptosis proteins and Bcl-Xl), and cell adhesion molecules (intracellular adhesion molecule, vascular cell adhesion molecule, and E-selectin; ref. 38); all of these molecules facilitate growth and survival of cancer cells.

NF-κB mediates key cellular functions, including immune responses as well as growth, survival, and apoptosis in multiple myeloma cells (6, 39). Intrinsic activation of NF-κB is associated with growth/survival of multiple myeloma cells. Adhesion of multiple myeloma cells to bone marrow stromal cells triggers NF-κB–mediated transcription and secretion of IL-6 and insulin-like growth factor I (6, 39, 40); both IL-6 and insulin-like growth factor I

promote the survival of multiple myeloma cells in the bone marrow by blocking apoptosis triggered by conventional agents such as dexamethasone (13). Furthermore, patient multiple myeloma–derived tumor cells and bone marrow stromal cells have up-regulated NF-κB activity relative to normal cells (41). Conversely, drug-sensitive multiple myeloma cells show lower NF-κB activity than drug-resistant multiple myeloma cells, suggesting that NF-κB confers chemoresistance (41). Elevated NF-κB levels have also been reported in multiple myeloma cells derived from patients relapsing after chemotherapy (39). Collectively, these findings indicate that NF-κB is a key regulator of growth and survival of multiple myeloma cells in the bone marrow milieu. Importantly, treatment of multiple myeloma with bortezomib prevents degradation of IκB, thereby blocking not only NF-κB activation but also related cytokine production (Fig. 1). However, NF-κB inhibition alone is unlikely to account for the overall anti–multiple myeloma activity of bortezomib (42, 43). For example, both bortezomib and a specific inhibitor of IκB PS-1145 block NF-κB activation; in contrast to bortezomib, however, PS-1145 only partially inhibits multiple myeloma cell growth (20–40% inhibition by PS-145 versus 80–90% inhibition by bortezomib; ref. 42), suggesting that there are additional targets of bortezomib besides NF-κB in multiple myeloma cells.

Bortezomib Trigger Pleiotropic Signaling Pathways

In vitro biochemical studies have now established that bortezomib-induced apoptosis is associated with these additional events (Fig. 2): (a) activation of classic stress response proteins such as heat shock proteins Hsp27, Hsp70, and Hsp90 (44, 45); (b) up-regulation of c-*jun* NH_2-terminal kinase (46); (c) alteration of mitochondrial membrane potential and production of reactive oxygen species (47–49); (d) induction of intrinsic cell death pathway (i.e., the release of mitochondrial proteins cytochrome *c* and second mitochondrial activator of caspases into cytosol and activation of caspase-9 > caspase-3 cascade; ref. 13); (e) activation of extrinsic apoptotic signaling through Bid and caspase-8 cleavage (44); (f) impairment of DNA repair machinery via inactivation of DNA-dependent protein kinase (50); (g) blockade of adhesion of multiple myeloma cells to bone marrow stromal cells and related cytokine secretion, (51); and (h) down-regulation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt signaling pathways (52). All these signaling events may collectively contribute towards the overall anti–multiple myeloma activity of bortezomib. In particular, our studies have established an obligatory role of c-*jun* NH_2-terminal kinase activation during bortezomib-induced multiple myeloma apoptosis, confirmed by using dominant-negative strategies or specific biochemical inhibitors of c-*jun* NH_2-terminal kinase (46). This finding was recently confirmed by another study in non–small lung cancer cells (53).

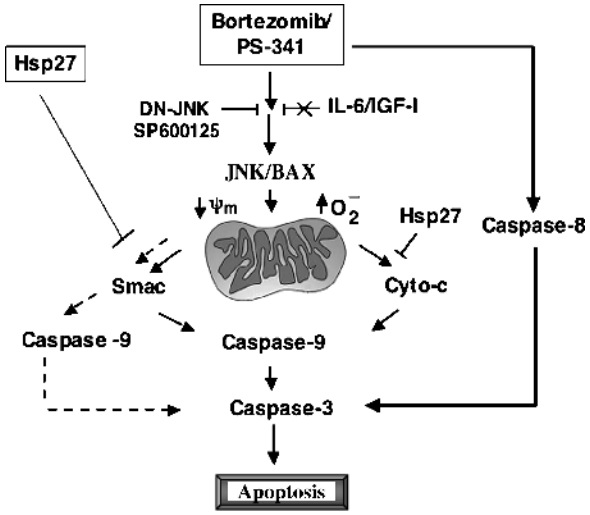

Figure 2. Apoptotic signaling triggered by bortezomib/PS-341. Bortezomib induces activation of c-*jun* NH_2-terminal kinase (*JNK*), which translocates to mitochondria and facilitates the release of cytochrome *c* (*Cyto-c*) and second mitochondrial activator of caspases (*Smac*) from mitochondria to cytosol, followed by caspase-9 activation. Bortezomib also activates caspase-8. Both caspase-8 and caspase-9 induce activation of downstream effector caspase-3 and poly(ADP-ribose) polymerase (*PARP*) cleavage. Blockade of c-*jun* NH_2-terminal kinase using dominant-negative c-*jun* NH_2-terminal kinase (*DN-JNK*) or a biochemical inhibitor SP600125 abrogates cytochrome *c*/Smac release and caspase-9 activation. Bortezomib-induced apoptosis is not blocked by IL-6 or insulin-like growth factor I (*IGF-I*). Ectopic expression of Hsp-27 inhibits bortezomib-triggered release of cytochrome *c* and Smac.

Besides the above-noted signaling events, proteasome inhibition also affect cell cycle regulatory proteins, such as the tumor suppressor gene TP 53 (*p53*). Alterations in p53 lead to genetic instability in a wide variety of cancer cells (54). In the context of multiple myeloma, our recent study showed that bortezomib triggers apoptosis in both wild-type p53 and mutant p53 multiple myeloma cells (12), and these findings are consistent with other studies in colorectal, glioblastoma, and leukemic cells (55–57). Moreover, bortezomib-induced apoptosis in multiple myeloma cells correlates with the phosphorylation of p53 (Ser^{15}; ref. 52). Another study showed that treatment of LNCaP-Pro5 prostrate cancer cells with bortezomib is associated with (a) stabilization of p53 without phosphorylation on Ser^{15} and Ser^{20}, and p53 remains bound to its inhibitor MDM2; (b) translocation of p53 to the nucleus and enhanced p53 DNA binding, accumulation of p53-dependent transcripts, as well as activation of p53-responsive reporter genes; and (c) inhibition of p53 reduced bortezomib-induced cell death (58). Whether mutations in p53 affect bortezomib-induced cytotoxicity is undefined. It is likely that the mutations in the COOH-terminal domain of p53, which contains the main site for ubiquitin ligase, affect bortezomib-induced cytotoxicity. Our findings in multiple myeloma suggest that bortezomib kills cells irrespective of mutational status; however, it remains to be examined whether the sites of p53 mutations in multiple myeloma cells are actually the main sites of ubiquitin ligation or not. A more detailed

study using p53 mutant constructs, in particular, those with mutations in COOH-terminal domain, will provide the data related to the requirement of p53 during bortezomib-induced apoptosis in multiple myeloma cells. Overall, the findings in various cancer types suggest that bortezomib-triggered apoptosis occurs in both p53-dependent and p53-independent manner.

In vivo Antitumor Activity of Bortezomib

Our study examined the efficacy, toxicity, and *in vivo* mechanism of action of bortezomib using a human plasmacytoma xenograft mouse model (59). Marked inhibition of tumor growth was observed in bortezomib-treated mice. The median overall survival was also significantly prolonged compared with controls. Bortezomib was well tolerated at the doses of 0.5 mg/kg (i.v.), but some mice treated at 1.0 mg/kg became moribund and lost weight. Analysis of tumors harvested from treated animals showed that bortezomib induced apoptosis and decreased angiogenesis. Overall, these findings show that bortezomib has significant *in vivo* antimyeloma activity at doses that are well tolerated in a murine model, confirming our *in vitro* data. Another study using LOVO xenografts (55) showed that combined treatment with bortezomib and CPT-11 resulted in marked increase levels of apoptosis and tumor regression when compared with either agent alone, suggesting a significant potential of bortezomib in combination with other chemotherapeutics to enhance antitumor activity, reduce toxicity, and overcome drug resistance.

Clinical Trials of Bortezomib

The preclinical *in vitro* studies demonstrating the anti–multiple myeloma activity of bortezomib was confirmed in phase I trials in hematologic and solid tumors (60, 61). During an initial dose-ranging trial in patients with refractory multiple myeloma, lymphoma, and leukemia, patients received bortezomib by i.v. injections twice a week for 4 weeks followed by 2 weeks of no therapy. The maximum tolerated dose was 1.04 mg/m^2 (60). Dose-limiting toxicities were fatigue and malaise, thrombocytopenia, and electrolyte imbalances. Phase I studies showed encouraging responses in multiple myeloma patients: one complete response (CR), evidenced by immunofixation negativity; and eight responses with reduction in serum monoclonal protein and marrow plasmacytosis. Moreover, bortezomib antitumor activity in these phase I studies was also noted in non-Hodgkin's lymphoma.

Another phase I trial evaluated the efficacy of bortezomib in advanced solid tumors, using a 3-week dose cycle (twice weekly for 2 weeks followed by 1 week of no therapy; ref. 61). The maximum tolerated dose was 1.56 mg/m^2, suggesting that the 3-week cycle may allow administration of higher doses than the 6-week cycle. No hematologic dose-limiting toxicity was observed; and nonhematologic dose-limiting toxicities included grade 3 neuropathy and diarrhea. Furthermore, grade 3 neuropathy was primarily noticed in patients with prior evidence of neuropathy and improved after discontinuation of drug. Finally, bortezomib also showed antitumor activity in other malignancies including non–small cell lung cancer, nasopharyngeal carcinoma, malignant melanoma, and renal cell carcinoma (61).

Phase II Studies in Multiple Myeloma

A phase II bortezomib study included relapsed/refractory multiple myeloma patients (62). Each cycle of therapy included bortezomib (1.3 mg/m^2) given twice weekly for 2 weeks, with 1 week off. Eight cycles of therapy were given to responders and patients with suboptimal responses received oral dexamethasone after initial two cycles with bortezomib. Patients (n = 202) were enrolled, all of whom received corticosteroids, 92% alkylating agents, 81% anthracyclines, 83% thalidomide, and 64% stem cell transplant; the median number of prior therapies was six. Of 193 patients, 4% achieved a CR, evidenced by multiple myeloma protein undetectable by both electrophoresis and immunofixation; 6% achieved a near CR, evidenced by detectable multiple myeloma protein only using immunofixation; 18% and 7% patients showed partial and minimal responses, respectively, for an overall 35% response (CR + PR + MR) rate. Median survival for the entire population was 16 months, and patients achieving a major response (CR + PR) survived significantly longer than those who did not. Of 74 patients who did not achieve at least a MR and therefore received dexamethasone in combination with bortezomib, 18% improved; this included six patients with dexamethasone-refractory disease, providing evidence that bortezomib can overcome resistance to dexamethasone. Commonly associated adverse events were nausea, vomiting, diarrhea, fatigue, loss of appetite including anorexia, constipation, peripheral neuropathy, pyrexia, anemia, and thrombocytopenia.

In another phase II open-label study of bortezomib (63), 54 patients with multiple myeloma who had relapsed after or were refractory to frontline therapy were randomized to receive i.v. 1.0 or 1.3 mg/m^2 bortezomib twice weekly for 2 weeks, every 3 weeks for a maximum of eight cycles. Dexamethasone was permitted in patients with progressive/stable disease after two or four cycles, respectively. The CR + PR rate for bortezomib alone was 30% and 38% in the 1.0 mg/m^2 (8 of 27 patients) and 1.3 mg/m^2 (10 of 26 patients) groups, respectively. The CR + PR rate for patients who received bortezomib alone or in combination with dexamethasone was 37% and 50% for the 1.0 and 1.3 mg/m^2 cohorts, respectively. The most common grade 3 adverse events were thrombocytopenia (24%), neutropenia (17%), lymphopenia (11%), and peripheral neuropathy (9%). Grade 4 events were observed in 9% (5 of 54) patients. Bortezomib alone or in combination with dexamethasone showed anti–multiple myeloma activity in patients who relapsed after frontline therapy.

Recently, the first and largest randomized study (APEX) conducted at 93 sites in North America, Europe, and Israel showed superior efficacy of bortezomib as a single agent compared with high-dose dexamethasone in relapsed multiple myeloma patients (64). A significant

time to progression and survival advantage was observed with bortezomib versus dexamethasone. Superiority was also observed in patients receiving both second-line and later-salvage therapy. The safety profiles of bortezomib and dexamethasone were predictable, relatively balanced with manageable toxicities.

Upfront studies both in combination and as a single agent have shown promising activity and favorable side effect profile. Interestingly, adriamycin + dexamethasone + bortezomib showed high response rate, but with higher toxicity. Conversely, bortezomib as a single agent showed minimal toxicity with lower response rate (64). Preliminary results from Intergroupe Francophone du Myelome Phase II Study show the efficacy of combining bortezomib + dexamethasone as induction regimen before autologous stem cell transplantation in newly diagnosed multiple myeloma patients with little toxicity (65). These results together with those observed in the study by Jagganath et al. confirms that bortezomib/dexamethasone combination is effective and well tolerated in newly diagnosed multiple myeloma patients.

Development of Bortezomib Resistance and Therapeutic Strategies to Overcome Bortezomib Resistance

Bortezomib kills multiple myeloma cells; however, prolonged exposure is associated with toxicity and development of bortezomib resistance. To overcome drug resistance, it is essential to examine its mechanism. We and others have shown that chemoresistance in multiple myeloma cells is conferred by these events: (a) overexpression of P-glycoprotein; (b) antiapoptotic proteins, such as Bcl2 or inhibitors of apoptosis proteins; (c) defects in drug-induced apoptotic signaling pathways, including those that occur at the level of mitochondria or endoplasmic reticulum; (d) up-regulated expression of growth factor receptors and related signaling pathways; and finally, (e) the interaction between multiple myeloma cells and host bone marrow microenvironment. Indeed, it is unlikely that one specific mechanism confers bortezomib resistance and likely that the contribution of diverse factors may lead to the development of drug resistance.

Our gene profiling and proteomic studies using bortezomib and other anti–multiple myeloma agents have provided basis for combining drugs to kill drug-resistant multiple myeloma cells. For example, our *in vitro* studies showed that combining bortezomib with other conventional agents, such as dexamethasone, doxorubicin, melphalan, or mitoxantrone, triggers additive and/or synergistic anti–multiple myeloma activity (12, 41, 50). Moreover, combined treatment of multiple myeloma cells and of multiple myeloma patient cells with bortezomib and novel agents, such as relvimid or triterpenoids CDDO-imidazolide, induces synergistic anti–multiple myeloma activity even in bortezomib-resistant patient multiple myeloma cells from patients (50, 66), thereby providing the basis for clinical protocols using this treatment regimen (66). These combination strategies will reduce attendant toxicity and overcome and/or prevent the development of drug resistance. In the multicenter SUMMIT trial, 35% of heavily pretreated patients with relapsed and refractory multiple myeloma responded to bortezomib monotherapy, and toxicities were manageable. Combining dexamethasone with bortezomib triggered additional responses in patients with suboptimal responses to bortezomib, which confirms similar additive inhibitory effects of these agents on multiple myeloma cells in our *in vitro* studies. Furthermore, based on preclinical data, several ongoing clinical trials are evaluating the antitumor activity of bortezomib in combination with melphalan, pegylated liposomal doxorubicin (Doxil), and thalidomide (67, 68). The data to date show potent anti–multiple myeloma activity of bortezomib combined with other agents in multiple myeloma patients, with manageable toxicities.

Recent mechanistic studies also provide evidence of proteins that confer bortezomib resistance in multiple myeloma cells. For example, our recent study showed that treatment with bortezomib induces apoptosis in SUDHL6 (DHL6) but not in SUDHL4 (DHL4) lymphoma cells (45). Microarray analysis showed high RNA levels for heat shock protein 27 (Hsp27) in DHL4 versus DHL6 cells. Blocking Hsp27 using an antisense strategy restores sensitivity to bortezomib in DHL4 cells; conversely, overexpression of Hsp27 wild type renders bortezomib-sensitive DHL6 cells resistant to bortezomib. These data provide evidence that Hsp27 confers bortezomib resistance. High levels of Hsp-27 are also noted in multiple myeloma cells obtained from patients refractory to bortezomib treatment. Further studies are required to determine whether inhibition of Hsp-27 using clinical grade–specific inhibitors enhances bortezomib anti–multiple myeloma activity and overcomes drug resistance. Nonetheless, based on these findings, we have been able to target p38MAPK, an upstream activator of Hsp27, to inhibit multiple myeloma cell growth. Results show that inhibition of p38MAPK enhances anti–multiple myeloma activity of bortezomib (69). Already, we have derived a clinical protocol using p38MAPK inhibitor with bortezomib in multiple myeloma patients.

It is known that bortezomib mediates its effects by inhibiting cellular proteasomes; however, whether proteasome inhibition is universally required for bortezomib-triggered apoptosis is unclear. Our findings showed that treatment with bortezomib led to 82% and 88% inhibition of proteasome activity in both bortezomib-resistant SUDHL4 and bortezomib-sensitive SUDHL6 lymphoma cells, respectively (45). Together, these data confirm that (a) the proteasome inhibition pathway is not defective in bortezomib-resistant DHL4 cells and (b) proteasome inhibition is not correlated with apoptosis. Direct determination of proteasome inhibition in patient blood and tissue samples was examined in phase I studies. Bortezomib was well tolerated at doses resulting in up to 80% proteasome inhibition (70). Furthermore, extended dosing did not further reduce sensitivity to proteasome inhibition. Together,

these data suggest that proteasome inhibition is the main function of the proteasome inhibitor but that proteasome blockade may not correlate with degree of cytotoxicity in cancer cells.

Besides Hsp-27, Bcl2 protein family members also confer drug resistance in many cell types (71), and bortezomib-triggered apoptosis in multiple myeloma cells is also partially abrogated by Bcl2 expression (44). Up-regulated expression of inhibitors of apoptosis proteins, such as XIAP, may also contribute to bortezomib resistance (44). Ongoing preclinical studies are examining various drugs or specific biochemical inhibitors that block the function of these proteins, thereby triggering apoptosis even in drug-resistant multiple myeloma cells.

Conclusions

Proteasome inhibition has proven a potent therapeutic strategy in the treatment of relapsed/refractory multiple myeloma. Bortezomib is the first treatment in more than a decade to be Food and Drug Administration approved for patients with multiple myeloma and various clinical trials are currently evaluating bortezomib in other cancer types. In addition, clinical trials of bortezomib in combination with other chemotherapeutic agents are helping to design newer therapeutic strategies in multiple myeloma. Finally, the preclinical evaluation of other novel proteasome inhibitor shows significant anti–multiple myeloma activity even against bortezomib-resistant multiple myeloma cells, with lower attendant toxicity to normal cells, providing the framework for clinical protocols to overcome bortezomib resistance and improve patient outcome.

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