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Review Article

Molecular mechanisms for synergistic effect of proteasome inhibitors with platinum-based therapy in solid tumors

Angel Chao [a], Tzu-Hao Wang [a, b, c, *]

[a] Department of Obstetrics and Gynecology, Linkou Medical Center, Taoyuan, Taiwan
[b] Genomic Medicine Research Core Laboratory, Linkou Medical Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
[c] School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan

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ABSTRACT

The successful development of the proteasome inhibitor bortezomib as an anticancer drug has improved survival in patients with multiple myeloma. With the emergence of the newly US Food and Drug Administration-approved proteasome inhibitor carfilzomib, ongoing trials are investigating this compound and other proteasome inhibitors either alone or in combination with other chemotherapy drugs. However, in solid tumors, the efficacy of proteasome inhibitors has not lived up to expectations. Results regarding the potential clinical efficacy of bortezomib combined with other agents in the treatment of solid tumors are eagerly awaited. Recent identification of the molecular mechanisms (involving apoptosis and autophagy) by which bortezomib and cisplatin can overcome chemotherapy resistance and sensitize tumor cells to anticancer therapy can provide insights into the development of novel therapeutic strategies for patients with solid malignancies.

Introduction

The ubiquitin–proteasome system handles 80–90% of intracellular protein catabolism [1]. Proteins to be degraded are initially ubiquinated and subsequently decomposed into peptides in the 26S proteasome for recycling. Dysregulation of the proteasome system can lead to several disorders, including malignancies. Bortezomib was the first proteasome inhibitor approved by the US Food and Drug Administration for treatment of multiple myeloma progressing on prior therapy (in 2003) [2] and relapsed or refractory mantle cell lymphoma (in 2006) (Table 1) [3]. Carfilzomib (the second proteasome inhibitor with higher affinity to proteasome and lower off-target toxicity) was licensed following accelerated approval for treating patients with relapsed and/or refractory multiple myeloma in 2012 (Table 1) [4,5]. However, the modest efficacy of bortezomib in solid malignancies necessitates a study of the mechanisms by which this drug fails in certain cases.

In this review, we focus on the potential usefulness of proteasome inhibitors in solid malignancies. We first summarize clinical trials of newly developed proteasome inhibitors, including carfilzomib, ixazomib (MLN9708), marizomib, oprozomib, and delanzomib (CEP-18770), and then trials involving combinations of bortezomib and platinum-based agents. The use of proteasome inhibitors for hematological malignancies is outside the scope of the present paper and covered in other excellent reviews [4,5].

Proteasome inhibitors

Bortezomib

Bortezomib is a boronic acid derivative that specifically binds to the β5 catalytic subunit of the 26S proteasome (Table 1) [3]. Bortezomib inhibits proteasome activity, inactivates nuclear factor κB (NF-κB), induces cancer cell apoptosis through both p53-dependent and p53-independent mechanisms, and interferes with a number of different cell cycle signaling pathways [6]. Bortezomib has successfully been used as a monotherapy for the treatment of multiple myeloma and mantle cell lymphoma [2]. In some cases, clinical response rates were found to be higher when bortezomib was combined with other drugs, including corticosteroids, alkylating agents, thalidomide, and/or lenalidomide [7]. Despite the clinical usefulness of bortezomib for hematological malignancies, a

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 5 Fushin Street, Guishan, Taoyuan 333, Taiwan.
E-mail address: knoxtn@cgmh.org.tw (T.-H. Wang).

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Table 1
Two FDA-approved proteasome inhibitors.

	Bortezomib	Carfilzomib
Category	First generation	Second generation
Half-life	10–30 h	<30 min
Structural class	Dipeptide boronic acid	Tetrapeptide epoxyketone
Type of inhibition	Reversible, inhibits the chymotryptic-like activity of 20S proteasome	Irreversible, inhibits the chymotryptic-like activity of 20S proteasome
Route of administration	Intravenous	Intravenous
Clinical indications	Approved for multiple myeloma (in 2003) and mantle cell lymphoma (in 2006)	Approved for relapsed and/or refractory multiple myeloma (in 2012)

FDA = US Food and Drug Administration.

proteasome-related off-target effect of peripheral neuropathy has been reported [8].

Second-generation proteasome inhibitors: carfilzomib, ixazomib, marizomib, oprozomib, and delanzomib

Second-generation proteasome inhibitors have been developed with the following goals: (1) to improve treatment efficacy; (2) to overcome drug resistance; and (3) to reduce adverse effects in patients treated with bortezomib [5]. Carfilzomib is the second US Food and Drug Administration-approved proteasome inhibitor for the treatment of recurrent multiple myeloma (Table 1) [5]. A total of four Phase II trials in patients with relapsed and/or refractory multiple myeloma have shown that hematological and nonhematological adverse effects related to the use of carfilzomib as monotherapy are tolerable [4]. Ixazomib (MLN9708) and delanzomib (CEP-18770), two orally bioavailable analogs of bortezomib, are boronate-based molecules that reversibly inhibit the β5 subunit. Oprozomib (ONX-0912), an analog of carfilzomib, is an irreversible epoxyketone inhibitor with high specificity for the β5 subunit. Marizomib is characterized by a β-lactone−γ-lactam backbone that irreversibly inhibits the catalytic activity of all the three 20S proteasomal subunits (namely, β1, β2, and β5) [9].

Proteasome inhibitors in solid malignancies

Several studies have explored the potential value of bortezomib in combination with conventional chemotherapeutic agents in nonhematological malignancies. In general, the therapeutic usefulness of bortezomib combined with cytotoxic drugs in solid malignancies depends on the tumor being treated [9]. The association of bortezomib, camptothecin, and doxorubicin has been shown to improve outcomes and reduce toxicity in patients with oral cancer [10]. Improved survival rates in advanced nonsmall-cell lung cancer have been reported using sequential administration of docetaxel and bortezomib [11]. However, the addition of bortezomib to docetaxel has shown limited therapeutic potential in patients with metastatic head and neck squamous cell carcinoma [12]. Additionally, the combination of bortezomib and irinotecan did not show additional clinical benefits in colorectal cancer [13] or head and neck squamous cell carcinoma [14]. In general, the potential clinical utility of bortezomib has been found to be lower in solid tumors than in hematological malignancies.

Clinical trials of second-generation proteasome inhibitors for the treatment of solid tumors are summarized in Table 2. A Phase I/II study evaluating an escalating dose of carfilzomib in patients with advanced solid neoplasms reported that one-fifth of the study participants achieved stable disease in Phase II cohorts [15]. The addition of other cytotoxic agents to augment proteasome inhibition resulted in a few manageable side effects. Notably, the absence of peripheral neuropathy can favor the use of carfilzomib in combination therapies [15]. Similarly, the efficacy of marizomib combined with vorinostat in patients with melanoma is encouraging [16]. Fatigue, lymphopenia, and anemia have been observed in a Phase I/II study of patients with solid tumors treated with carfilzomib monotherapy [6]. In addition, skin rash has been observed in >50% of patients with solid tumors treated with delanzomib [17]. The optimal dose for avoiding this adverse event remains to be determined.

Special consideration: bortezomib combined with platinum-based chemotherapy and/or radiation in solid tumors

A combination regimen consisting of bortezomib and platinum-based agents has shown promising results in a Phase I study of ovarian cancer [18,19]. Moreover, the use of bortezomib in concurrent chemoradiation regimens is well tolerated in patients with head and neck malignancies [20]. Phase II clinical trials have been conducted to further explore the efficacy of these combinations (Table 3). A survival benefit has been reported in patients with nonsmall-cell lung carcinomas [21–23]. However, a poor clinical response has been observed in malignant pleural mesothelioma [24], metastatic esophageal cancer [25], and metastatic melanoma [26]. The addition of bortezomib to liposomal doxorubicin allowed the achievement of a partial response in 24% of platinum-sensitive patients with ovarian cancer, although no response was observed in chemoresistant patients [27]. Whether tumors are sensitive or resistant to platinum seemingly affects the efficacy of bortezomib combined with other chemotherapy agents, ultimately requiring further scrutiny. Notably, severe adverse effects have been observed with the combined treatment. Grade 3/4 hematological adverse effects included thrombocytopenia (10–63%) and neutropenia (10–71%) [21–27]. The most common nonhematological toxicities were peripheral neuropathy, diarrhea, and fatigue.

Apoptosis and autophagy elicited by bortezomib combined with cisplatin

Phosphorylation of signal transducer and activator of transcription 1 (STAT1) reduces bortezomib-mediated apoptosis in cancer cells. To investigate the signaling pathways elicited by bortezomib in solid malignancies, a panel of 11 reporter assays has been tested in ovarian cancer cells. Although inhibition of the transcription factor NF-κB is believed to be a key mechanism for the antimyeloma effect of bortezomib [28], the NF-κB reporter activity was not found to be affected in ovarian cancer cells [29]. In contrast, bortezomib stimulated STAT1 tyrosine phosphorylation [29]. Dysregulation of STAT1 has been reported in a number of different malignancies [30], but its role remains controversial because it can act either as a proapoptotic [31] or as a prosurvival factor [32]. STAT1 is significantly overexpressed in drug-resistant cancer cells compared with that in drug-sensitive cancer cells or normal cells

Table 2
Completed or ongoing clinical trials of second-generation proteasome inhibitors in patients with solid tumors.[a]

Trial	Phase	Drug(s)	No. of patients	Current status	Response/side effect
NCT02512926	I	Carfilzomib plus (cyclophosphamide, etoposide)	50	Recruiting	NA
NCT02257476	I	Carfilzomib	30	Recruiting	NA
NCT01949545	I	Carfilzomib	40	Recruiting	NA
NCT01941316	I/II	Carfilzomib plus irinotecan	112 (small cell lung cancer)	Recruiting	NA
NCT00667082 [16]	I	Marizomib plus vorinostat	22 (lung cancer, pancreatic cancer, and melanoma)	Completed	Stable disease rate: 61% Nausea and vomiting related to marizomib
NCT00629473	I	Marizomib	86	Completed	NA
NCT00396864	I	Marizomib	51 (solid tumors and lymphoma)	Completed	NA
NCT00572637 [17]	I	Delanzomib (CEP-18770)	30 (evaluable, solid tumors)	Completed	No objective responses 70% of the study patients developed Grade 3 skin rash at a dose of 1.5 mg/m^2
NCT00830869	I	Ixazomib (MLN9708)	116	Completed	NA
NCT01912222	I	Ixazomib	48	Completed	NA
NCT02042989	I	Ixazomib plus vorinostat	56	Recruiting	NA
NCT02384746	I	Ixazomib plus fulvestrant	18 (breast cancer)	Recruiting	NA
NCT02420847	I	Ixazomib plus (gemcitabine, doxorubicin)	57 (bladder cancer)	Recruiting	NA
NCT01129349	I	Oprozomib	44	Completed	NA

NA = not applicable.
[a] The review was updated in October 2015.

Table 3
Phase II trials of bortezomib combined with platinum-based agents in patients with solid tumors.[a]

Trial	No. of patients	Description of the study	Clinical outcome
Phase II study NCT00052338/ NCT00075751 Southwest Oncology Group study (S0339) [21]	114	Advanced NSCLC Gemcitabine 1000 mg/m^2, Days 1 and 8; carboplatin AUC 5.0, Day 1; and bortezomib 1.0 mg/m^2, Days 1, 4, 8, and 11	Notable survival benefits; median OS: 11 mo; 1-y survival rate: 47%; response rate: 23%; disease control rate (response plus stable disease): 68%
Phase I/II study [22]	16	Advanced NSCLC Carboplatin AUC 6 and bevacizumab (15 mg/kg) q 3 wk using a standard Phase I design. Bortezomib doses were 1.3 mg/m^2, 1.6 mg/m^2, and 1.8 mg/m^2 weekly on Days 1 and 8 of q 3-wk cycle	Response rate and OS in the entire study cohort were 37.5% and 9.9 mo, respectively. The response rate and OS for the nine patients in Phase II portion were 44% and 10.9 mo, respectively
Phase I/II study NCCTG-N0321 [23]	27	NSCLC Bortezomib, paclitaxel, and carboplatin concomitantly with thoracic radiation (60 Gy/30 daily fractions)	Median OS: 25.0 mo
NCT00458913 Phase II study European Organisation for Research and Treatment of Cancer 08052 [24]	82	Malignant pleural mesothelioma Cisplatin 75 mg/m^2 on Day 1 and bortezomib 1.3 mg/m^2 on Days 1, 4, 8, and 11 every 3 wk	OS: 13.5 mo; the study did not reach a 50% progression-free survival rate at 18 wk
Phase II study NCCTG-N044B [25]	35	Metastatic esophageal, gastric, and gastroesophageal cancer Bortezomib 1.2 mg/m^2 on Days 1, 4, and 8; paclitaxel 175 mg/m^2 on Day 2; and carboplatin with AUC of 6 on Day 2	RR: 23%, OS: 8.9 mo
Two-stage Phase II study [27]	58	Relapsed ovarian cancer, previously treated with platinum (100%) and taxane (95%), received bortezomib 1.3 mg/m^2 intravenous (Days 1, 4, 8, and 11), and lipodox 30 mg/m^2 intravenous (Day 1), every 3 wk	Platinum-sensitive group; 24% PR Platinum-resistant group; 0%
Two-stage Phase II study [26]	17	Metastatic melanoma, receiving at least one prior cycle of chemotherapy Bortezomib 1.3 mg/m^2 given intravenously on Days 1, 4, and 8, paclitaxel 175 mg/m^2 and carboplatin AUC 6 on Day 2 of a 21-d cycle	Median OS: 7.0 mo

AE = adverse events; AUC = area under the curve; NCCTG = North Central Cancer Treatment Group; NSCLC = nonsmall-cell lung carcinoma; OS = overall survival; PR = partial response; RR = response rate.
[a] The review was updated on October 2015.

[33]. Increased STAT1 phosphorylation has also been associated with reduced sensitivity to bortezomib in ovarian cancer cells [29]. Either knockdown of heat shock factor-1 (HSF1) or pharmacological suppression of Janus kinase (JAK) blocked bortezomib-stimulated STAT1 phosphorylation (Figure 1). These findings are consistent with a report showing that an HSF1 inhibitor enhances the anti-cancer effects of bortezomib in myeloma cells [34]. The results of animal studies also support the notion that the addition of a JAK inhibitor, AG490, to bortezomib treatment can exert synergistic cytotoxic effects on ovarian cancer cells via suppression of STAT1 phosphorylation [29]. Bortezomib has been also used to overcome cisplatin resistance [35,36]. Notably, bortezomib-induced STAT1 phosphorylation seems to be inhibited by cotreatment with cisplatin [29], potentially explaining the synergistic antitumoral effect of the combination of cisplatin and bortezomib [37]. Taken together, a combinatory treatment with bortezomib, cisplatin, a JAK

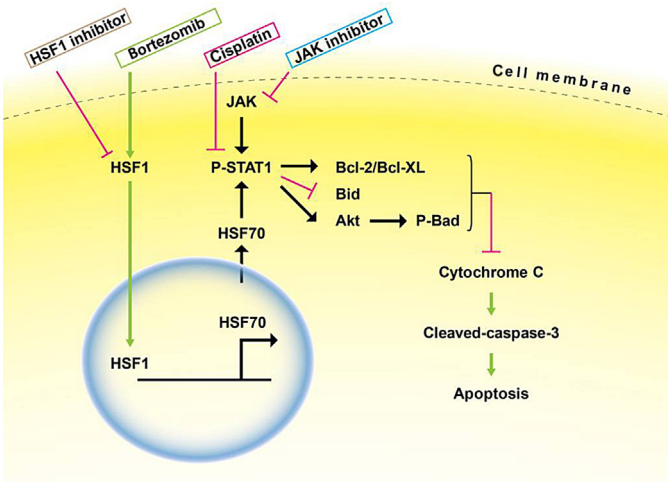

Figure 1. Combination treatment with bortezomib, cisplatin, and a JAK inhibitor provides a chemotherapeutic strategy for treating solid malignancies. Bortezomib increases HSF1 and transcriptionally upregulates HSP70, which subsequently induces STAT1 phosphorylation. Bortezomib can also induce STAT1 phosphorylation through the JAK signaling pathway. Notably, cisplatin and the JAK inhibitor significantly suppress STAT1 phosphorylation and enhance cytotoxicity in bortezomib-treated cells. These results suggest the possibility of overcoming bortezomib resistance in cancer cells through the addition of cisplatin and/or JAK inhibitors. Akt = serine-threonine protein kinase; Bcl-2 = B-cell lymphoma 2; Bcl-XL = B-cell lymphoma-extra large; Bid = BH3 interacting-domain death agonist; HSF = heat shock factor; JAK = Janus kinase; P-Bad = phospho-Bcl2-associated agonist death promoter; P-STAT1 = phosphorylation of signal transducer and activator of transcription 1; STAT1 = signal transducer and activator of transcription 1.

inhibitor, and an HSF1 inhibitor can be a useful chemotherapeutic strategy for solid malignancies (Figure 1).

Bortezomib enhances cancer cell death by inhibiting autophagy through increased phosphorylation of extracellular signal-regulated kinases (ERK)

The role of autophagy in cancer cells is complex and context specific [38]. Upon exposure to chemotherapeutic drugs, cancer

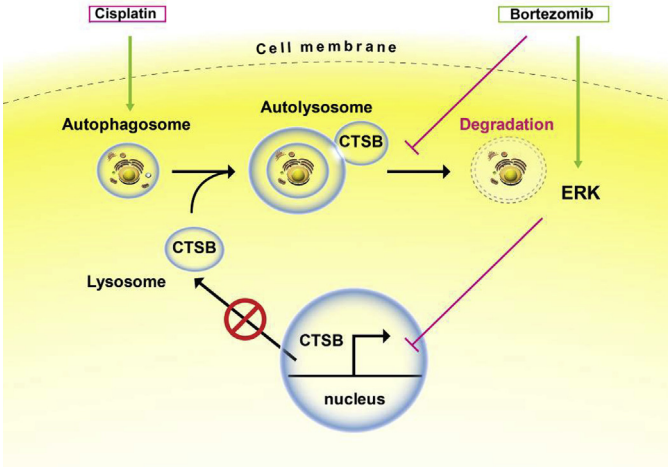

Figure 2. Bortezomib enhances cancer cell death by inhibiting the catabolic process of autophagy through increased phosphorylation of ERK. Cancer cells can use autophagy as a form of self-rescue upon treatment with cisplatin. Increased levels of CTSB are required to complete the autophagy process. Treatment with bortezomib induces phosphorylation of ERK, which decreases CTSB levels and blocks autophagy. When cancer cells are treated with bortezomib and cisplatin-based chemotherapy, self-rescuing autophagy is suppressed in cancer cells, ultimately resulting in enhanced antitumor efficacy. CTSB = cathepsin B; ERK = extracellular signal-regulated kinases.

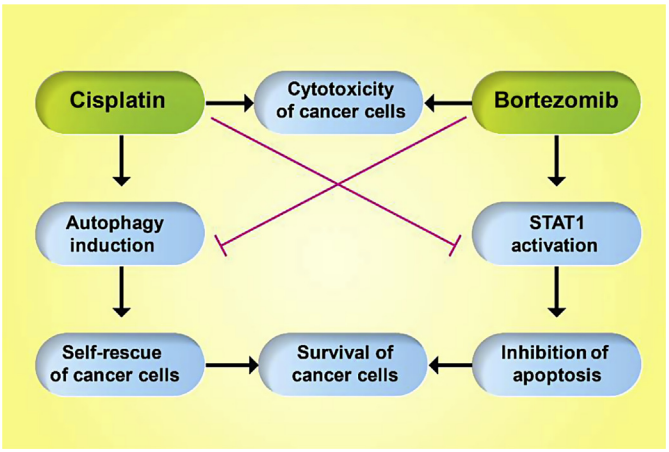

Figure 3. Strategies of integrating proteasome inhibitors and platinum. Proteasome inhibitors as monotherapy did not show major efficacy in treating solid cancers; however, bortezomib in combination with other drugs appears to be a promising strategy in this scenario. STAT1 = signal transducer and activator of transcription 1.

cells can undergo autophagy as a self-rescue process [39]. Moreover, autophagy in cancer cells may be a cause of drug resistance [40]. The process of autophagy begins with the formation of autophagosomes that engulf cytoplasmic material and organelles. Light chain 3-II plays a critical role in the elongation of the autophagosome double membrane [41]. The mature autophagosome subsequently fuses with a lysosome to form an autolysosome (where the autolysosomal components are degraded by lysosomal catalytic enzymes, including cathepsin B) (Figure 2). The autolysosomal components include p62 [also known as sequestosome 1 (SQTM1)], whose degradation indicates that the autophagy process has been completed [42].

Bortezomib has been shown to stimulate autophagy in some [43] but not all studies [44]. Autophagy proteins have recently been shown to regulate the functions of ERK [45], whereas ERK activation is able to induce autophagy [46]. In contrast, sustained activation of ERK inhibits the maturation step of the autophagy process [47]. Recent evidence suggests that bortezomib can block the autophagic flux via the phospho-ERK-mediated inhibition of cathepsin B [48] (Figure 2). The discovery that bortezomib may block chemotherapy-induced autophagy can be clinically important because the commonly used chemotherapeutic agent cisplatin is known to stimulate autophagy of ovarian cancer cells [49]. Accordingly, the combination of bortezomib and cisplatin has been found to exert synergistic antitumor effects in a xenograft mouse model of ovarian cancer. Immunohistochemical studies of xenografted tumor tissues further confirmed that treatment with bortezomib stimulated ERK phosphorylation and inhibited cathepsin B, resulting in the accumulation of p62/sequestosome 1 (an indicator of autophagy blockade) [48].

Conclusions

Bortezomib may exert antitumor effects by regulating two critical cellular processes, i.e., apoptosis [29] and autophagy [48]. From one point of view, bortezomib as a single agent does not appear to be very effective in killing ovarian cancer cells, because STAT1 is activated through phosphorylation (which suppresses apoptosis). The addition of cisplatin, a JAK inhibitor, or an HSF1 inhibitor can block bortezomib-stimulated STAT1 activation (Figure 1). In contrast, chemotherapeutic agents frequently stimulate autophagy in cancer cells, which has evolved as a self-rescuing mechanism in cancer cells. The addition of bortezomib can block

the autophagic flux and may ultimately enhance the cytotoxic effects of chemotherapy (Figure 2). Although proteasome inhibitors as monotherapy do not seem to have major efficacy in solid malignancies, their combination with other therapeutic classes holds significant promise in this scenario (Figure 3).

Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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