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Review Article

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

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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.
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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

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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

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