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Targeting the ubiquitin-proteasome pathway to overcome anti-cancer drug resistance

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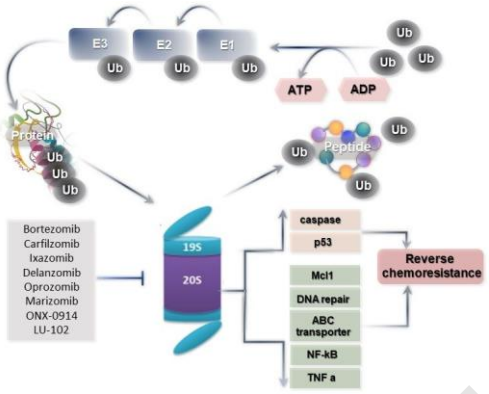
Graphical abstract



Abstract

Drug resistance is a major obstacle in the field of pre-clinical and clinical therapeutics. The development of novel technologies and targeted therapies have yielded new modalities to overcome drug resistance, but multidrug resistance (MDR) remains one of the major challenges in the treatment of cancer. The ubiquitin-proteasome system (UPS) has a central role in regulating the levels and activities of a multitude of proteins as well as regulation of cell cycle, gene expression, response to oxidative stress, cell survival, cell proliferation and apoptosis. Therefore, inhibition of the UPS could represent a novel strategy for the treatment and overcoming of drug

resistance in chemoresistant malignancies. In 2003, bortezomib was approved by the FDA for the treatment of multiple myeloma (MM). However, due to its limitations, second generation proteasome inhibitors (PIs) like carfilzomib, ixazomib, oprozomib, delanzomib and marizomib were introduced which displayed clinical activity in bortezomib-resistant tumors. Past studies have demonstrated that proteasome inhibition potentiates the anti-cancer efficacy of other chemotherapeutic drugs by: i) decreasing the expression of anti-apoptotic proteins such as TNF-α and NF-kB, ii) increasing the levels of Noxa, a pro-apoptotic protein, iii) activating caspases and inducing apoptosis, iv) degrading the pro-survival protein, induced myeloid leukemia cell differentiation protein **(**MCL1), and v) inhibiting drug efflux transporters. In addition, the mechanism of action of the immunoproteasome inhibitors, ONX-0914 and LU-102, suggested their therapeutic role in the combination treatment with PIs. In the current review, we discuss various PIs and their underlying mechanisms in surmounting anti-tumor drug resistance when used in combination with conventional chemotherapeutic agents.

Keywords

Cancer chemotherapy; multidrug resistance; ubiquitin-proteasome system; sensitizing compounds; overcoming chemoresistance; proteasome inhibitors; immunoproteasome

Introduction

Globally, cancer is the second leading cause of mortality, causing an estimated 600,000 deaths in United States in 2018 (Siegel et al., 2018). One of the hallmarks of cancer is the dysregulated and uncontrolled cell proliferation (Collaborators, 2016). The major clinical impediment in the

treatment of cancer remains the development of multidrug resistance (MDR) that occurs primarily during chemotherapy (Assaraf et al., 2019; Bar-Zeev et al., 2017; Coppola et al., 2017; Cui et al., 2018; Gonen and Assaraf, 2012; Leonetti et al., 2019; Levin et al., 2019; Livney and Assaraf, 2013; Mansoori et al., 2017; Niewerth et al., 2015; Zhitomirsky and Assaraf, 2016). MDR is defined as the survival of cancer cells during or following exposure to a broad spectrum of anti-cancer drugs (Amawi et al., 2019; Li et al., 2016; Zahreddine and Borden, 2013; Zhitomirsky and Assaraf, 2016). Cancer cells display resistance to anti-cancer drugs via a plethora of molecular mechanisms including: 1) Overexpression of ATP-binding cassette (ABC) efflux transporters which extrude a multitude of structurally and functionally distinct cytotoxic drugs from cancer cells (Sun et al., 2012); 2) Impaired drug uptake via qualitative (i.e. inactivating mutations) or quantitative alterations (i.e. downregulation) of influx transporters, thereby decreasing the intracellular concentration of drugs (Consortium et al., 2010); 3) Evasion of apoptosis via distinct anti-apoptotic mechanisms (Chen et al., 2018); 4) Enhanced DNA damage response and repair (Broustas and Lieberman, 2014); 5) Enhanced tolerability of stressful tumor microenvironment (TME) cues or conditions (Quail and Joyce, 2013); 6) Increasing the biotransformation and metabolism of drugs to less active or inactive congeners(Inaba et al., 2013); 7) Mutations in drug target proteins that diminish or abolish the interaction of drugs with their specific cellular targets(Jones et al., 2009), and 8) Drug sequestration within organelles away from their cellular targets (Fig. 1) (Aleksakhina et al., 2019; Cree and Charlton, 2017; Gottesman et al., 2002; Mashouri et al., 2019; Zahreddine and Borden, 2013).

The ubiquitin proteasome system (UPS) and the immunoproteasomes have been postulated to be *bona fide* targets for novel anti-cancer drugs and chemosensitizers that block the proteolytic activities in this central cellular system (Adams, 2004; Cloos et al., 2017; Gandolfi et al., 2017;

King et al., 1996; Landis-Piwowar et al., 2006; Niewerth et al., 2015; Roeten et al., 2018). Specifically, proteasome inhibitors (PIs) constitute one of the most important classes of chemotherapeutic drugs to have emerged for the treatment of MM and mantle cell lymphoma in the past two decades, and currently form the foundational drugs in the treatment of these hematological malignancies (Fricker, 2019; Gandolfi et al., 2017). Three antitumor drugs in this class of PIs have been approved by the United States Food and Drug Administration (FDA), the first-in-class is bortezomib (Velcade), the second-generation chemotherapeutic being carfilzomib (Kyprolis), an irreversible inhibitor of the chymotrypsin activity of the proteasome, whereas the first oral PI was ixazomib (Ninlaro) (Fricker, 2019; Gandolfi et al., 2017). The remarkable antitumor efficacy of this class of antitumor drugs is due to the hypersensitivity of myeloma cells to the inhibition of the 26S proteasome, which plays a critical role in the pathogenesis and proliferation of the disease. Proteasome inhibition results in multiple deleterious downstream effects, including inhibition of NF-κB signaling, the accumulation of misfolded and unfolded proteins, leading to endoplasmic reticulum (ER) stress and unfolded protein response (UPR), downregulation of growth factor receptors, suppression of adhesion molecule expression, and inhibition of angiogenesis; resistance to PIs may arise through cellular responses mediating these downstream effects (Gandolfi et al., 2017; Thibaudeau and Smith, 2019)

Numerous studies have shown that the UPS modulates or degrades the majority of cellular proteins and plays a critical role in maintaining protein homeostasis (Ciechanover, 1994; Jana, 2012; Sun et al., 2016). Furthermore, the UPS regulates the cell cycle, apoptosis, cell differentiation, angiogenesis, and drug resistance (Ciechanover, 1994; Hochstrasser, 1995; Orlowski and Dees, 2003). As such, decreased proteasome activity has been linked to aging and several age-related neurodegenerative pathologies, thereby highlighting the importance of the regulation of the UPS.

While the proteasome has been traditionally viewed as a constitutive machinery of proteolysis, recent studies revealed that distinct regulatory mechanisms can affect its activity (Ciechanover, 2017; Mayor et al., 2016).

The interaction of a molecular substrate with the proteasome requires a prior enzymatic conjugation to ubiquitin, a 76 amino acid protein, which results in degradation of the ubiquitinated protein by the 26S proteasome (Ciechanover, 2017; Ciehanover et al., 1978; Hershko et al., 1980, 1979; Mayor et al., 2016). Ubiquitination involves the ubiquitin activating enzymes, E1, the ubiquitin conjugating enzyme, E2 and ubiquitin ligases known as E3 (Wolf and Hilt, 2004). The 26S proteasome is a large multi-subunit protein complex and the UPS is a major pathway that regulates the degradation of a multitude of proteins in eukaryotes (Mani and Gelmann, 2005) (Fig. 2). Proteins are ubiquitinated by these series of enzymes and are recognized by the proteasome (Almond and Cohen, 2002; Voutsadakis, 2007). The 26S proteasome is a large complex composed of a 20S catalytic core and one or two regulatory subunits (Groll et al., 1997; Unno et al., 2002). The regulatory subunit recognizes the ubiquitinated proteins and the target molecule dissociates from ubiquitin and is transferred to the core 20S proteasome (Wolf and Hilt, 2004). The 20S proteasome consists of 4 rings, comprised of two sets of α and β subunits, that are arranged symmetrically with the α rings surrounding the inside of the β rings (Winter et al., 2017). Each α and β rings is formed by seven different subunits, α 1-7 and β 1-7 (Ciechanover, 1994; Goldberg et al., 1997; Hochstrasser, 1995; Satoh et al., 2019)

These subunits have proteolytic activity, including the β-1, which has a caspase-like activity. The β-1 subunit cleaves acidic residues and the β-2 is endowed with a trypsin-like activity and cleaves basic residues, whereas the β-5 subunit has a chymotrypsin-like activity and cleaves hydrophobic residues (Glickman and Ciechanover, 2002). The regulatory subunit has a lid and a base that is

attached to both ends of the 20S core subunit and the 19S proteasome lid plays a role in deubiquitination, an enzymatic reaction that catalyzes the removal of the target molecule from the polyubiquitin chain by 9 or more non-ATPase subunits (Tanaka, 2009). The 19S base has 6 ATPase as well as 4 non-ATPase subunits and is a multifunctional complex that recruits, and unfolds the target proteins and directs them into the core 20S proteasome (Bai et al., 2019; Bochtler et al., 1999; Livneh et al., 2016; Schmidt et al., 2005).

The UPS plays a central role in regulating key cellular functions. For example, during the cell cycle, progression of cells from the G2 phase to the M phase requires cyclin-dependent protein kinase, cdc2, that phosphorylates mitosis-regulating proteins and their regulatory partners, cyclin B, which are considered to be cell cycle checkpoints (An et al., 2018; Rosamond, 1995; Venuto and Merla, 2019; J.-H. Wang et al., 2019). Once the cell completes mitosis, the anaphase promoting complex (APC), an E3 ligase, ubiquitinates these promoting factors which are then degraded by the proteasome, allowing the cell to reenter the G1 phase (Hershko, 1999; Vodermaier, 2004). Another important cellular mechanism that is regulated by the UPS is apoptosis. For cell growth and survival, UPS is crucial, whereas for apoptosis to occur, there needs to be an inhibition of UPS. For example, p53 activity is tightly regulated by UPS and it plays a crucial role in the suppression of tumors (Adrain et al., 2004; Friedman and Xue, 2004; Gupta et al., 2018; Sun et al., 2004). Another example is that PIs can induce endoplasmic reticulum (ER) stress and produce apoptosis in many cancers (Best et al., 2019).

Previous studies have shown that UPS plays an important role in oncogenesis, cancer development and chemoresistance (Cao and Mao, 2011; Gandhi et al., 2014; Huang et al., 2017; Lu et al., 2014; Micel et al., 2013; Wu et al., 2015; Yontem, 2013). E3 ligases determine the fate of each protein by binding to the target protein and transferring ubiquitin from the E2 enzyme to a

lysine residue in the target protein (David et al., 2011). Thus, E3 ligases play an important role in the final process of the UPS cascade (Liu et al., 2015). Although the survival rate of patients has been increased with the availability of novel anti-cancer drugs, chemoresistance remains a major impediment towards the achievement of curative treatment of various human malignancies (Assaraf et al., 2019; Cree and Charlton, 2017; Gacche and Assaraf, 2018; Gonen and Assaraf, 2012; Li et al., 2016; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). As E3 ligases have been shown to play a role in oncogenesis, researchers have begun to determine the role of E3 ligases in cancer chemoresistance, as well as the underlying mechanisms mediating chemoresistance (de Wilt et al., 2012; Franke et al., 2016, 2012; Jeon et al., 2016; Nelson et al., 2016; Niewerth et al., 2015, 2014a, 2014b; Oerlemans et al., 2008; Petzold et al., 2016; Tanaka et al., 2016; Xu et al., 2016; Yoshino et al., 2016; Zhang et al., 2016).

Human E3 ligases contain more than 600 members and based on characteristic domains and are classified into 3 types:1) HECT E3 (homologous to the E6-associated protein carboxyl terminus) with about 28 members; 2) RING finger E3s, the largest class with approximately 600 members, and 3) RBR (RING between RING) type E3s with 18 members (Berndsen and Wolberger, 2014; Sluimer and Distel, 2018; Weber et al., 2019). HECT E3s determine the specificity of ubiquitination (Sluimer and Distel, 2018). E3 ligases catalyze the transfer of ubiquitin to the substrate protein by a two-step reaction where ubiquitin is transferred to E3 and then from E3 to the substrate protein (Thibaudeau and Smith, 2019). Studies have reported that RING-finger E3 ubiquitin ligases are the most abundant type of E3 ligases (Metzger et al., 2012). They have a zinc-binding domain called RING (also known as the U-box domain) and a ring domain that mediates the direct transfer of ubiquitin to the substrate protein (Lipkowitz and Weissman, 2011). The U-box family of ubiquitin ligase E3 in eukaryotes is required for protein synthesis and it contains

about 70 amino acids (Hatakeyama and Nakayama, 2003). U-box proteins mediate ubiquitination in the absence of the HECT and RING domains (Hatakeyama and Nakayama, 2003). E3 ligases play a crucial role in the ubiquitin-proteasome pathway (Yang et al., 2018).

The process of ubiquitination can be reversed by a specific group of enzymes called deubiquitinases (DUBs) and there are 100 human DUBs that are members of the cysteine protease family (Dou and Zonder, 2014; Kapadia and Gartenhaus, 2019; Kaushal et al., 2018). The mechanism of deubiquitinase includes cleavage of the bond between the ε-amino group of the lysine residue on the target protein and C-terminal glycine of the ubiquitin molecule (Komander et al., 2009). DUBs can be subdivided into 6 classes: 1) ubiquitin-specific proteases (USPs); 2) ubiquitin carboxy-terminal hydrolases (UCHs); 3) ovarian-tumor proteases (OTUs); 4) Machado-Joseph disease protein domain proteases; 5) JAMM/MPN domain-associated metallopeptidases, where the MPN domain containing proteins are metallopeptidases (Zn^{++} ion metalloproteinases) that display JAMM motif which has a catalytic center for the hydrolysis of the linkage between ubiquitin and the target protein (Echalier, 2014), and 6) monocyte chemotactic protein-induced protein (MCPIP) (Fortelny et al., 2014; Fraile et al., 2011).

The USPs exist in various forms and the DUBs catalytically release the target protein that is attached to the ubiquitin molecule, thereby preventing its proteasomal degradation (Clague et al., 2012). DUBs play an important role in balancing receptor degradation (Sowa et al., 2009), the endocytic pathway (Bowers et al., 2006) and various signaling pathways (Buus et al., 2009).

The current review discusses the effect of clinically approved UPS inhibitors and their role in surmounting resistance to conventional anti-cancer drugs (Table 1) and the structures of these PI drugs discussed in the current review, are shown in the Fig. 3.

Proteasome Inhibitors (PIs)-Detailed description

1. Bortezomib (Velcade)

Bortezomib (Fig. 1A), the first in-class dipeptide boronate PI, was approved by the FDA in 2003 for the treatment of MM (Teicher et al., 1999). Bortezomib is a boronic dipeptide which reversibly inhibits the chymotrypsin-like activity of the β5 subunit and partially inhibits the trypsin-like activity of the β1 subunit of the 20S proteasome, especially at high concentrations (Lü and Wang, 2013). However, bortezomib does not inhibit the β2 subunit (de Bruin et al., 2016). Inhibition of the proteasome suppresses the proteasome-mediated degradation of ubiquitin-conjugated inhibitory proteins of the kappa-beta (kB) family, IkB (Chen et al., 2011); IkB binds to phosphorylated nuclear factor kappa-light-chain-enhancer in activated B cells (NF-kB), preventing its translocation to the nucleus, where it functions as a TF (Hideshima et al., 2001b). Bortezomib indirectly suppresses NF-kB signaling (Rajkumar et al., 2005). Indeed, NF-kB was shown to induce resistance to platinum-based drugs (e.g., cisplatin) in pancreatic cancer (Almoguera et al., 1988), prostate cancer (Newmark et al., 1992) and SCLC (Bassères et al., 2010). The phosphorylated form of NF-kB is sequestered by IkB in the cytoplasm and this complex is degraded by the UPS (Oeckinghaus and Ghosh, 2009). Thus, PIs that block the UPS would be hypothesized to decrease NF-kB expression and thereby promote apoptosis. Overall, by increasing the degradation of NF-kB, bortezomib down-regulates the expression of certain proteins that produce anti-apoptotic effects, thereby decreasing cell survival by enhancing apoptosis. The anti-cancer efficacy of bortezomib may also result from an increase in the pro-apoptotic protein, Noxa (Qin et al., 2005). This protein can induce apoptosis by: 1) augmenting the activation of caspases (Suzuki et al., 2009; Zhang et al., 2010); 2) producing changes in the mitochondrial membrane that bring about the release of apoptogenic proteins from the mitochondria (Letai et al., 2002); 3) interacting with, and promoting the degradation of the pro-survival protein, myeloid leukemia cell

differentiation protein (Mcl1) (Czabotar et al., 2013; Moldoveanu et al., 2014) and 4) inducing the phosphorylation of the anti-apoptotic protein, B-cell lymphoma-extra-large (Bcl-xL (Qin et al., 2005)**,** which may be disabled in its capacity to bind Bax, resulting in apoptosis upon Ser 62 phosphorylation (PMID:18974096). The anti-cancer efficacy of the conventional chemotherapeutic drugs 5-fluorouracil, cisplatin, paclitaxel and doxorubicin was significantly increased by bortezomib, when compared to bortezomib monotherapy (Orlowski et al., 2016; Yerlikaya et al., 2013; Zhao et al., 2015); this experiment was performed in a Lewis rat lung carcinoma model. Bortezomib was administered intraperitoneally (i.p.; 1 mg/kg/day) on days 0, 4, 7 and 18, in combination with 5-fluorouracil (30 mg/kg i.p.) on days 7 and 11 and this treatment regimen produced a significant delay (the treatment group had 0% large lung metastases compared to 45% in the control group) in tumor growth (Teicher et al., 1999). Bortezomib, *in vitro* and *in vivo*, has efficacy in MM cells resistant to mammalian target of rapamycin (mTOR), phosphoinositide-3-kinase (PI3K) and serine/threonine-specific protein kinase (Akt) inhibitors (Varga et al., 2014). *In vitro* data indicated that incubation of MM cells with 2 nM bortezomib for 72 hours increased the cytotoxicity of doxorubicin and melphalan by inducing DNA damage (Richardson et al., 2003). Bortezomib also significantly downregulated the expression of apoptosis inhibitors such as NF-kB and tumor necrosis factor-alpha (TNF-α) (Hideshima et al., 2001a) and suppressed the genotoxic stress response pathway proteins, mut S homologues 2 and 6 (involved in DNA mismatch repair) and uracil DNA glycosylase (involved in base-excision repair and protection from oxidative DNA damage) (Mitsiades et al., 2003). Despite the efficacy of bortezomib in treating patients with MM, there have been reports of drug resistance (Kumar and Rajkumar, 2008; Robak et al., 2018; Shah and Orlowski, 2009). Since bortezomib interacts with the proteasome β5 core particle to inhibit its chymotrypsin-like activity, mutations in the β subunits

impair the binding of bortezomib to the β5 subunit, resulting in bortezomib resistance both *in vitro* as well as in MM patients (de Wilt et al., 2012; Franke et al., 2012; Lü et al., 2008; Verbrugge et al., 2012). Clonal sublines of HT-29 colon adenocarcinoma cells, selected for resistance to bortezomib upon long term exposure, harbored point mutations in the β5 subunit, and displayed 30-fold resistance to bortezomib, compared to wild type HT29 cells. In 2014, bortezomib was also approved by the FDA for the treatment of previously untreated patients with mantle cell lymphoma (Raedler, 2015). Clinical data indicated that in MM patients, bortezomib can produce peripheral neuropathy, fluid retention, thrombocytopenia, fatigue, nausea, vomiting, and diarrhea (Schwartz and Davidson, 2005). Overall, bortezomib monotherapy was efficacious in treating MM and mantle cell lymphoma and data suggest that it may be useful in combination with other anti-cancer drugs including 5-flurouracil (Wang et al., 2016) cisplatin, cyclophosphamide, doxorubicin, and thalidomide (Gerecke et al., 2016; Konac et al., 2015).

The protein human anterior gradient 2 (AGR2) belongs to the disulfide isomerase family and is highly expressed in estrogen receptor-positive breast cancer cells (Thompson and Weigel, 1998), lung cancer (Chung et al., 2012), prostate cancer (Hu et al., 2012) and pancreatic cancer (Dumartin et al., 2011). Moreover, the expression level of AGR2 can modulate the response to chemotherapeutic drugs and it has been considered to be a potential tumor marker (Hrstka et al., 2010; Zhao et al., 2009). AGR2 binds to vascular endothelial growth factor (VEGF) and increases vascular endothelial growth factor receptor (VEGFR) signaling, thereby decreasing the efficacy of bevacizumab (Avastin), a humanized monoclonal antibody that has been approved for colon cancer treatment, by binding to VEGF, and preventing it from interacting with its receptor VEGFR (Jia et al., 2018). In male athymic mice (tumors were generated by the subcutaneous inoculation of NSCLC A549 cells), the i.p. injection of 0.4 mg/kg of bortezomib and 10 mg/kg of bevacizumab

(every week for three weeks) significantly decreased tumor weight and volume compared to animals that received bevacizumab monotherapy (D. Wang et al., 2019).

2. Carfilzomib

Carfilzomib (Fig. 1B) is a second generation, irreversible epoxyketone PI which is also used in the treatment of MM (Leleu et al., 2019). Carfilzomib covalently attacks the active site Thr1 residue of the β5 subunit under the formation of a morpholine ring, resulting in inhibition of the chymotrypsin-like activity of the proteasome (Kuhn et al., 2007). Carfilzomib induces programmed cell death by 1) activating c-Jun-N-terminal kinase; 2) producing mitochondrial membrane depolarization; 3) eliciting the release of cytochrome c from mitochondria, 4) increasing the levels of Noxa, a pro-apoptotic, member of the Bcl-2 protein family, and 5) activating caspase-3/caspase-7 (Etlinger and Goldberg, 1977; Hershko et al., 1982; Parlati et al., 2009). In a randomized, phase 3, open-label study, one group of patients with refractory MM received bortezomib (1.3 mg/m^2, s.c.) and 20 mg p.o. dexamethasone and the other group received carfilzomib (20 mg/m^2, s.c.) and 20 mg p.o. dexamethasone. The end point of the study was progression-free survival (PFS); remarkably, the median PFS was 18.7 months in the carfilzomib group and 9.4 months in the bortezomib group (Dimopoulos et al., 2017). Carfilzomib significantly decreased mortality compared to bortezomib and it was the first drug to increase the overall survival of MM patients (Dimopoulos et al., 2017).

Mechanistic studies indicate that carfilzomib was more efficacious than bortezomib in increasing the phosphorylation of Janus kinase and caspase activity in acute lymphoblastic leukemia cell lines (Kuhn et al., 2007). Carfilzomib was 2-fold more potent than bortezomib in inducing caspase activity, which may explain the increased sensitivity of a MM cell line to carfilzomib (Kuhn et al.,

2007). Importantly, carfilzomib (3 mg/kg i.v. given twice weekly for 42 days) surmounted bortezomib resistance in a human Lagk-1A MM severe combined immunodeficient (SCID) mouse model (Sanchez et al., 2014). Carfilzomib significantly reversed the resistance to the alkylating drug, melphalan, in melphalan-resistant MM 8226.LR5 cells and also reversed the resistance to dexamethasone in dexamethasone-resistant MM1.R cells (Kuhn et al., 2007). Although carfilzomib is an option for refractory MM patients (Siegel et al., 2012), a large number of these patients displays resistance to carfilzomib treatment (Shah et al., 2018). The upregulation of P-glycoprotein and the overexpression of the catalytic subunits of proteasome are the main causes of resistance to carfilzomib therapy (Ao et al., 2012; Zang et al., 2014). To delineate the molecular mechanism underlying carfilzomib resistance, human H727 bronchial carcinoid tumor cells (which have high levels of β1i and β5 subunits, whereas β1 expression is undetectable) were incubated with 20 nM carfilzomib for 4 hours. The results indicated that the activities of the catalytic subunits, β5, β5i and β1i were blocked by carfilzomib, whereas β1 activity remained intact, suggesting that differences in catalytic subunit expression and sensitivity to PIs are associated with the development of resistance to carfilzomib (Lee et al., 2019).

Carfilzomib (27 mg/m^2 i.v.) significantly increased the efficacy of lenalidomide (25 mg p.o.) and dexamethasone (40 mg p.o.) in patients with relapsed or progressive myeloma (Jakubowiak et al., 2012; Niesvizky et al., 2013). Lenalidomide is a thalidomide derivative which has direct anti-tumor efficacy, via inhibition of angiogenesis, and exerts an immunomodulatory activity. *In vivo*, lenalidomide induces tumor cell apoptosis directly, as well as indirectly via inhibition of bone marrow stromal cell support, through anti-angiogenic and anti-osteoclastogenic activities, and via immunomodulatory activity. The protein cereblon (an E3 ligase) is expressed at low levels in patients with MM tumors that are resistant to lenalidomide and the levels of cereblon may be

regulated by the UPS and thus, inhibition of the proteasome would be poised to increase cereblon levels, thereby increasing the efficacy of lenalidomide (Lopez-Girona et al., 2012). Furthermore, the activation of the wingless-related integration site (Wnt)/β-catenin signaling pathway is positively correlated with resistance to lenalidomide (Bjorklund et al., 2011). Therefore, lenalidomide resistance could be surmounted by increasing proteasome-mediated degradation of proteins in the Wnt/β-catenin pathway (Bjorklund et al., 2011). In 2012, carfilzomib was approved by the FDA for use as monotherapy or in combination with dexamethasone or lenalidomide plus dexamethasone, for the treatment of patients with relapsed or refractory MM who have failed to respond to one or more previous drug regimens (Jakubowiak et al., 2012). However, the use of carfilzomib is limited due to adverse effects that include cardiac toxicity, acute renal failure, pulmonary toxicity, pulmonary hypertension, liver toxicity and teratogenicity (Perel et al., 2016).

3. Ixazomib

Although bortezomib and carfilzomib displayed efficacy in MM treatment, the use of these drugs is limited by their routes of administration (i.v. or s.c.). Thus, ixazomib (Fig. 1C) was developed as the first oral PI for the treatment of relapsed or refractory MM(Moreau, 2014; Raedler, 2016). Ixazomib is a dipeptidyl leucine boronic acid that reversibly blocks the chymotrypsin-like activity of the β5 subunit of the 20S proteasome (Chauhan et al., 2011; Lee et al., 2011). The proteasome dissociation half-life for ixazomib is relatively short (18 min) and is ultimately re-available to re-enter tumor cells and other tissues (Kupperman et al., 2010); hence, when compared to bortezomib, this shorter 20S proteasome dissociation half-life is believed to play an important role in its improved tumor and tissue distribution. Direct comparison with bortezomib revealed that ixazomib has improved pharmacokinetic and pharmacodynamic profiles and showed superior antitumor activity in both solid tumors and hematologic xenograft mouse models when compared to

bortezomib (Kupperman et al., 2010). Ixazomib (dose ranging from 1-125 mg/m^2 given i.v. on day 1, 8 and 15 of a 28 day cycle for up to 12 cycles), compared to bortezomib, produced a longer duration of tumor proteasome inhibition and increased the antitumor efficacy in OCI-Ly10 and PHTX22L mouse models of lymphoma (Assouline et al., 2011). In the human MM cell line 1S, incubation with 12.5 nM ixazomib for 48 hours significantly induced apoptosis and inhibited growth in both drug sensitive 1S cells and the OPM1 cell line that is resistant to conventional cytotoxic compounds including bortezomib, without significantly affecting the viability of normal non-malignant cells (Chauhan et al., 2011). The incubation of MM cells from patients who were resistant to lenalidomide, vorinostat or dexamethasone, with 50 nM ixazomib for 48 hours, significantly increased the cytotoxicity and anti-cancer efficacy of these cytotoxic drugs (Chauhan et al., 2011). Ixazomib was approved by the FDA in 2015 for use in combination with lenalidomide and dexamethasone for the treatment of MM patients (Shirley, 2016). Clinical data indicated that ixazomib has untoward side effects including nausea, vomiting, diarrhea, constipation, rashes and thrombocytopenia (Kumar et al., 2017).

4. Delanzomib

Delanzomib (Fig. 1D) is an orally active, P2 threonine boronic acid PI that can reversibly inhibit chymotrypsin-like and caspase-like activities of the proteasome (Dorsey et al., 2008). *In vitro*, bortezomib (10 nM) and delanzomib (20 nM) were equipotent in inhibiting distinct proteasome subunits (β5 and β1), albeit when compared to bortezomib, delanzomib displayed a more favorable cytotoxicity profile in normal human epithelial bone marrow progenitor and bone marrow-derived stromal cells (Piva et al., 2008). However, phase I and II trials with delanzomib indicated that it did not significantly inhibit disease progression in MM patients and the trials were terminated (Vogl et al., 2017). Thus, delanzomib monotherapy is unlikely to be used for the treatment of MM.

However, delanzomib in combination with conventional anti-cancer drugs or along with bortezomib may be efficacious in treating MM patients. For example, delanzomib (3 mg/kg i.v. twice a week for a period of 70 days) increased the efficacy of dexamethasone (1.25 mg/kg i.p. daily) or lenalidomide (30 mg/kg p.o. daily) in a xenograft CB17 SCID multiple myeloma mouse model (Sanchez et al., 2010). The inhibition of MM cell viability by melphalan (10 mg/kg i.p. once weekly for 3 weeks) or bortezomib (1.2 mg/kg i.v. once a week for 4 weeks) was synergistically increased by delanzomib (3 mg/kg i.v. twice weekly for 4 weeks) (Piva et al., 2008). Moreover, data suggest that the use of a combination of delanzomib with melphalan or delanzomib with bortezomib prevents the growth of melphalan-resistant as well as bortezomib-resistant tumors (Sanchez et al., 2010). Therefore, it is possible that clinical studies could be conducted to determine the efficacy of delanzomib for the treatment of MM in combination with specific anti-cancer drugs. The adverse effects of delanzomib include nausea, vomiting, anorexia, neutropenia and pyrexia (Vogl et al., 2017).

5. Oprozomib

Oprozomib (Fig. 1E) is an oral tripeptide epoxyketone that irreversibly inhibits the chymotrypsin-like activity of the proteasome (Rajan and Kumar, 2016). It has a longer duration of action compared to bortezomib and induces apoptosis through the activation of caspase 3, 8 and 9 (Chauhan et al., n.d.). It has been reported that angiogenesis plays a very important role in the progression of MM (Giuliani et al., 2011; Podar et al., 2001). *In vitro*, oprozomib (10 nM) blocked angiogenesis in human umbilical vein endothelial cells (Chauhan et al., 2010). In a human MM xenograft mouse model with severe combined immunodeficiency, a combination of oprozomib (40 mg/kg p.o.), dexamethasone (1 mg/kg i.p.) and pomalidomide (10 mg/kg p.o.) for 77 days was significantly more potent than oprozomib monotherapy or a combination of any duo of the drugs

(Sanchez et al., 2015). The major adverse effects produced by oprozomib were anemia, nausea, thrombocytopenia, hypotension, diarrhea and vomiting (Vij et al., 2014). The unfolded protein response (UPR), a cellular stress response associated with endoplasmic reticulum (ER) stress, may induce apoptosis if it is unmitigated (Walter and Ron, 2011). It is possible that the proteasome may be a negative UPR regulator, and this was reversed by oprozomib in human hepatocellular cancer HepG2 cells treated with 400 nM oprozomib for 48 hours (Vandewynckel et al., 2016). In two experimental models of hepatocellular carcinoma, the administration of both nelfinavir (250 mg/kg/day i.p.), a protease inhibitor and antiretroviral drug currently used in the treatment of human immunodeficiency virus-based AIDS, and salubrinal (1 mg/kg/day i.p.), a specific inhibitor of dephosphorylation of the eukaryotic translation initiation factor 2 alpha (eIF2α), for 4 weeks, significantly increased the anti-cancer efficacy of oprozomib (30 mg/kg p.o. given three times a week). These results suggest that oprozomib may be used in combination regimens to treat certain cancers (Vandewynckel et al., 2016). In addition, oprozomib can induce apoptosis in lung cancer cells by activating caspase 3 and poly ADP ribose polymerase (PARP) cleavage, independent of p53 activity (Zhu et al., 2019).

6. Marizomib (Salinosporamide A)

Marizomib (Fig.1F), a novel β-lactone-γ-lactam PI which underwent phase I and II clinical trials for the treatment of solid tumors and hematological malignancies (Feling et al., 2003), is currently undergoing phase III clinical trials for the treatment of newly diagnosed glioblastoma multiforme (NCT03345095). It is the first natural PI derived from the marine actinomycete bacteria *Salinosporamide tropica* (Feling et al., 2003). Remarkably, marizomib is a next generation inhibitor that produces a prolonged inhibition (≥72 h) of the proteasome compared to other PIs

(Potts et al., 2011). It irreversibly inhibits the β1, β2 and β5 subunits which are responsible for the proteolytic activity of the proteasome.

Immunoproteasomes mediate the formation of antigenic peptides that are bound to major histocompatibility class I (MHC class I) proteins (Strehl et al., 2005). There are data indicating that high levels of immunoproteasomes are present in MM cells (Singh et al., 2011). Marizomib (10 nM) induced apoptosis in D-54 human glioma cells (Di et al., 2016) by activating caspase-8 (Potts et al., 2011). This induction decreased the expression of NF-kB, which repressed cell growth and survival pathways (Ahn et al., 2007) Furthermore, marizomib also decreased the levels of IL-6, TNF-α and IL-1β (Chauhan et al., 2005). Incubation of the MM cell line, 1S, with marizomib (1.25 nM) along with the immunomodulatory and anti-angiogenic drug, pomalidomide (2.5 μM), for 24 hours, induced apoptosis and produced a synergistic effect compared to either drug alone at these concentrations (Das et al., 2015). Clinical data indicated that colorectal cancers (CRC) express high levels of NF-kB, inducing resistance to irinotecan and 5-fluorouracil (Cusack et al., 2000; Kojima et al., n.d.; Voboril et al., 2004). In refractory cases of CRC, *in vitro* studies indicated that marizomib (200 nM for 4 hours) decreased NF-kB levels by increasing the level of IkB (Cusack et al., 2006). Thus, marizomib resensitizes CRC to the anti-tumor drugs, SN-38, 5-flurouracil, oxaliplatin and avastin. The incubation of the human pancreatic cell line, Panc-1, with marizomib (200 nM for 24 hours) also reversed resistance to gemcitabine (1 μM) (Sloss et al., 2008). The major adverse effects produced by marizomib were fatigue, infusion site pain, nausea and diarrhea (Harrison et al., 2016) (Townsend et al., 2009).

Recent studies indicated that cancer cells can acquire resistance to PIs (Zheng et al., 2017). The factors that cause this drug resistance include: 1) proteasome complex mutations (Soriano et al., 2016); 2) increased expression of drug efflux transporters (Gupta et al., 2015); 3) formation of

alternative pathways (Riz et al., 2015). Another mechanism of drug resistance involves certain microRNAs (miRNAs). miRNAs are noncoding RNAs that regulate cell proliferation, differentiation, development and apoptosis (Ha and Kim, 2014; Maimaiti et al., 2015). Furthermore, miRNAs play an important role in the development of drug resistance by targeting the genes that modulate the response to chemotherapeutic drugs (Allen and Weiss, 2010; Just et al., 2019; Ma et al., 2010; Si et al., 2019). For example, the miRNA precursors Let-7A2, Let-7D, Let-7E, Let-7F2 were downregulated in MM cells resistant to bortezomib, carfilzomib and ixazomib (Malek et al., 2016). Compared to the drug-sensitive counterpart cell line, RPMI8226 (Malek et al., 2016), the X-box binding protein (XBP), a bZIP (Basic Leucine Zipper Domain) transcription factor, can regulate stress-induced apoptosis of cancer cells (Gambella et al., 2014) in MM patients and loss of this transcription factor is involved in the development of resistance to bortezomib (Leung-Hagesteijn et al., 2013). The levels of the unspliced transcript of XBP1 were significantly lower in ixazomib-resistant cells compared to ixazomib-sensitive parental cells (Mitra et al., 2017). As described above, mutations in PSMB5 (encoding for the β5 subunit of the proteasome) are one of the important mechanisms of acquired resistance to PIs (de Wilt et al., 2012; Franke et al., 2012; Lü et al., 2008; Verbrugge et al., 2012). It has been shown that mutations in PSMB5 and PSMB7 occur in bortezomib-resistant CRC HT 29 cells (Suzuki et al., 2011). Another mechanism of drug resistance is the overexpression of MDR efflux pumps e.g., ABCB1, and ABCC1 (Kale and Moore, 2012). There is a report showing that ABCB1 [P-glycoprotein (P-gp)] overexpression significantly decreases the accumulation of bortezomib and carfilzomib in acute lymphocytic leukemia CEM/VLB cells (Verbrugge et al., 2012). Tariquidar, an ABCB1/P-gp inhibitor (5 μM for 24 hours) markedly increased the *in vitro* sensitivity of resistant MM cells to the PIs, bortezomib and carfilzomib (Muz et al., 2017).

Immunoproteasomes

Immunoproteasomes are predominantly present in cells of hematopoietic origin (McCarthy and Weinberg, 2015) and are derived from the constitutive proteasomes (Kloetzel and Ossendorp, 2004; Tanaka, 1994). Constitutive proteasomes are present in all cell types and are involved in degradation of target proteins (Cromm and Crews, 2017; Ichihara and Tanaka, 1995; Morozov and Karpov, 2019; Tanaka, 2009). The expression of immunoproteasomes is enhanced by cytokines (e.g., TNFα and interferon α) which are produced and secreted during inflammation and certain types of infections (Shachar and Karin, 2013). Immunoproteasomes generate various peptides for the MHC class I complexes that are presented to lymphocytes by antigen presenting cells (Fehling et al., 1994). The constitutive proteasome has a 20S core that consists of α- and β- rings (7 subunits in each) and the β subunits (β 1, 2 and 5) have proteolytic activities (DeMartino and Slaughter, 1999). The overall structure of the constitutive and immunoproteasome are similar, but the immunoproteasome has different catalytic subunits (Ferrington and Gregerson, 2012). Immunoproteasomes contain 3 distinct pairs of active sites, β5i, β1i, and β2i, which are different from their constitutive β5, β1, and β2 counterparts.

Immunoproteasomes are present in antigen presenting cells (Haorah et al., 2004) and the presence of inflammatory cytokines such as interferon-γ elicits the replacement of the regular β subunits with different subunits as abovementioned, including LMP2(β1i), MECL-1 (β2i) and LMP7(β5i) (Ahn et al., 1995; Basler et al., 2019; Glynne et al., 1991; Kelly et al., 1991; Ortiz-Navarrete et al., 1991; Pletinckx et al., 2019; Realini et al., 1994; Tanahashi et al., 1997; Xie et al., 2019).

It has been reported that transplant rejection occurred in mice lacking immunoproteasomes, suggesting that they are involved in regulating the immune response (Kincaid et al., 2011). The inhibition of the catalytic subunits of proteasomes is an important mechanism for the treatment of

cancer and an increased expression of immunoproteasomes occurs in several cancers, including prostate, MM and lung cancer (Ho et al., 2007; Wehenkel et al., 2012).

FDA-approved PIs do not display specificity for constitutive proteasomes when compared to immunoproteasomes (Kisselev et al., 2012). Interestingly however, the decreased expression of immunoproteasomes can enhance the response to bortezomib in MM patients (Zhang et al., 2016). It has been postulated that the development of immunoproteasome selective inhibitors may have efficacy in the treatment of certain cancers and autoimmune diseases as other nonselective inhibitors can produce adverse effects due to their lack of selectivity (Dubiella et al., 2015; Johnson et al., 2017).

ONX-0914 is a tripeptide epoxyketone that selectively inhibits the β5i subunit of the immunoproteasome (Miller et al., 2013). The progression of nephritis was significantly decreased in an MRL/lpr mouse model of systemic lupus erythematosus, following the administration of 10 mg/kg i.v. (once daily) for 13 weeks (Ichikawa et al., 2012). KZR-616, a derivative of ONX-0914, has already completed a phase I study and is being developed for the treatment of autoimmune diseases (Lickliter et al., 2018). The administration of 15 mg/kg s.c. of ONX-0914 and 0.5 mg/kg s.c. of bortezomib twice weekly for 60 days, significantly increased the overall survival of animals in an NSG mouse model compared to treatment with only bortezomib (Downey-Kopyscinski et al., 2018).

Apart from its selective β5i inhibitory action, ONX-0914 can inhibit the catalytic subunit, trypsin–like activity-bearing β2i subunit, at concentrations significantly greater than those required to inhibit the β5i subunit (Muchamuel et al., 2009). The s.c. administration of 10 mg/kg of ONX-0914, once a day for 35 days, to five week old Apc Min/+ and LMP 7-/- mice (colon cancer models), significantly decreased: 1) the incidence of CRC tumors, as well as 2) tumor initiation

and growth (Koerner et al., 2017). The incubation of MM MM1.S cells with ONX-0914 (500 nM) significantly increased the sensitivity of these cells to 100 nM bortezomib or carfilzomib (Downey-Kopyscinski et al., 2018).

LU-102 is a peptide epoxyketone that inhibits the β2 subunit (which has the trypsin-like activity) of the proteasome and sensitized cancer cells to both bortezomib and carfilzomib (Mirabella et al., 2011). Based on the increased expression of β2 subunit in cells that are resistant to bortezomib (a β5 inhibitor) (Rückrich et al., 2009), β2 was identified as a crucial factor in regulating the activity of β5-targeted PIs (Britton et al., 2009). LU-102 is the first irreversible, β2-selective PI (Geurink et al., 2013) and it enhanced the cytotoxicity of β5 inhibitors in MM cells (Britton et al., 2009; Mirabella et al., 2011). This is an important observation as bortezomib, carfilzomib and ixazomib primarily inhibit the β5 subunit of the proteasome, which is the catalytically active site in protein degradation (Arendt and Hochstrasser, 1997; Chen and Hochstrasser, 1996). The incubation of the triple negative breast cancer (TNBC) cell lines, MDA-MB-231 MDA-MB-468, SUM149, HCC38, HCC1187 and HCC1937, with 3 μM LU-102 for 48 hours, significantly increased the cytotoxic efficacy of bortezomib and carfilzomib in these TNBC cells (Weyburne et al., 2017). The incubation of MM 1.S cell lines with 0.9 μM ONX-0914 for 1 hour, followed by incubation with 1 μM LU-102 for 47 hours, produced a 3-8-fold decrease in the IC_{50} values of ONX-0914 (i.e. cells were sensitized to ONX-0914) (Downey-Kopyscinski et al., 2018).

Nuclear factor erythroid derived 2-related factor 1 (Nrf1) is a transcriptional activator of proteasomes that increases proteasome synthesis upon proteasome inhibition, thereby restoring proteasome activity (Radhakrishnan et al., 2010; Steffen et al., 2010). MG132, a PI (1 μM for 10 h), the boronation of which yielded bortezomib, induced the expression of proteasomal subunit genes (PSM) in wild type mouse embryonic fibroblasts (MEF) but not in $Nrf1^{-/-}$ MEF cell lines

(Chan et al., 1998), suggesting that Nrf1 upregulates PSM gene expression in cells incubated with a PI (Radhakrishnan et al., 2010). Upon complete inhibition of β2 subunit of the proteasome, Nrf1 became inactive and insoluble, preventing the recovery of proteasomal activity and increasing the sensitivity to β5 inhibitors (Sha and Goldberg, 2016).

Conclusion

Proteasome activity is associated with various cellular mechanisms and human diseases. Cumulative data indicated that increased proteasome activity can occur in certain cancers (Voutsadakis, 2017), whereas decreased proteasome activity facilitates the development of neurodegeneration and other underlying disorders (Tomaru et al., 2012). Expression of immunoproteasomes has been reported for various cancers, including prostate, MM and lung cancer. Therefore, the use of PIs represents a proven potent strategy for the treatment of cancer. The present article focused on the role of the UPS in cancer drug resistance, the mechanism of action of specific UPS inhibitors and their efficacy in restoring the chemosensitivity of cancer cells to specific chemotherapeutic drugs. Data from numerous studies indicate that UPS inhibition can restore the sensitivity of cancer cells to conventional chemotherapeutic drugs. The first UPS inhibitor, bortezomib, was approved by FDA for the treatment of MM and mantle cell lymphoma. However, due to limitations including potency and drug resistance, researchers developed next generation PIs including carfilzomib, ixazomib, oprozomib, delanzomib and marizomib, which display more favorable pharmacokinetic and pharmacodynamics profiles, greater potency and specificity. Since immunoproteasomes also play a vital role in cancer, the development of immunoproteasome inhibitors such as ONX-0914 and LU-102, are essential for cancer chemotherapy. The combination of UPS inhibitors reviewed in this paper with conventional anti-

cancer drugs, produced synergistic activity that may significantly improve patient outcomes during chemotherapy.

Conflict of interest

The authors declare no potential conflicts of interest.

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Figure legends

Fig.1. Multiple drug resistance mechanisms in cancer (as shown in blue rectangles)

Mechanisms that produce MDR in cancer cells include decreased drug uptake, enhanced DNA repair, metabolism and inactivation of drugs, evasion of apoptosis, mutations in the drug target proteins, drug sequestration in other organelles away from the target, enhanced tolerability to tumor environment, and overexpression of ABC efflux transporters.

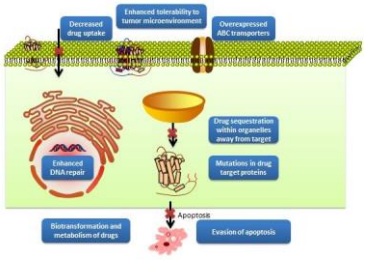

Fig. 1. Multiple drug resistance mechanisms in cancer

Fig.2. An illustration of the multi-subunit structure and functions of the ubiquitin proteasome system (UPS)

Ub, ubiquitin. E1, ubiquitin activating enzyme. E2, ubiquitin conjugating enzyme. E3, ubiquitin ligases. 20S, catalytic core of proteasome. 19S, regulatory subunits of proteasome. 2 sets of α and β rings each, formed by 7 different subunits.

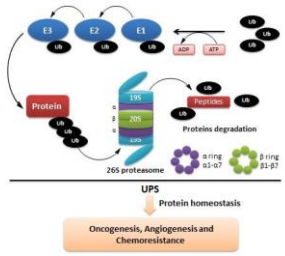

Fig. 2. Multi-subunit structure and functions of UPS

Fig.3. The structures of proteasome inhibitors that sensitize cancer cells to conventional chemotherapeutic drugs

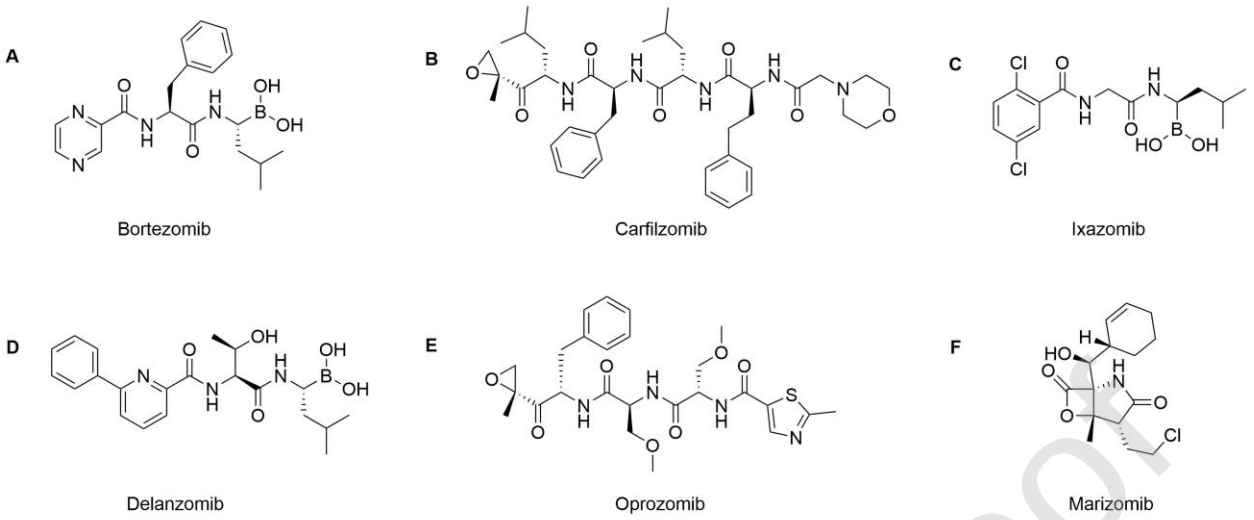

Fig. 3. PI inhibitors with efficacy as sensitizing compounds

Table. Mechanism of action, uses and ADR of various UPS inhibitors.

Compound	Structural Class	Target of interaction	Binding kinetics	FDA status	Doses	Routes	Adverse effects
Bortezomib	Peptide boronic acid	Inhibits B5 and partial inhibition of β1	reversible	Approved for MM	1.3mg/m²/dose IV twice weekly for 2 weeks	IV	peripheral neuropathy, fluid retention, thrombocytopenia, fatigue
Carfilzomib	Peptide epoxyketone	Inhibits β5 subunit	irreversible	Phase II	20 mg/m² in Cycle 1 on Day 1,8 and 15	IV	Cardiac toxicity, acute renal failure, pulmonary toxicity
Ixazomib	Dipeptidyl leucine boronic acid	Inhibits chymotrypsin- like activity of β5 subunit	reversible	Phase I	4 mg PO on days 1, 8, and 15 of a 28-day cycle	IV/oral	diarrhea, constipation, rashes, thrombocytopenia
Delanzomib	Peptide boronic acid	Inhibits chymotrypsin and caspase-like activity	reversible	Phase I	1.5 mg/m2. I.V. administration on days1,8, 15 of a 28-day cycle	IV	nausea, vomiting, anorexia, neutropenia and pyrexia
Oprozomib	Peptide epoxyketone	Inhibits chymotrypsin like activity of β 5 subunit	irreversible	Phase I	150 to 330 mg/d for 2 of every 7 days (2/7 schedule)	oral	anemia, nausea, thrombocytopenia, hypotension
Marizomib	β-lactone-γ-lactam	Inhibits β1, β2 and β 5	Irreversible	Phase I	0.7 mg/m^2	IV	fatigue, infusion site pain, nausea and diarrhea

					On days 1, 4, 8, 11 of 28-day cycle		