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Review Article

Proteasome inhibitors for multiple myeloma

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Abstract

Therapeutic strategies for multiple myeloma have dramatically changed in the last two decades, especially after the introduction of proteasome inhibitors. The first-in-class proteasome inhibitor, bortezomib, was approved by the US Food and Drug Administration in 2003. Since then, it has been a backbone therapy for not only relapsed or refractory myeloma patients but also newly diagnosed multiple myeloma patients. Second-generation proteasome inhibitors, such as carfilzomib and ixazomib, have been approved, and three proteasome inhibitors were incorporated into several regimens with other cytotoxic agents, such as alkylating agents, immunomodulatory drugs and monoclonal antibodies. Because each proteasome inhibitor shows different properties with respect to adverse events, understanding and managing each adverse event of proteasome inhibitors are necessary for the continuation of therapy with minimal interruption of treatment. This review summarizes the recent advances in proteasome inhibitors used in the treatment of multiple myeloma.

Key words: multiple myeloma, proteasome inhibitor, bortezomib, carfilzomib, ixazomib

Introduction

Proteasome inhibitors (PIs) have become one of the necessary agents to treat patients with multiple myeloma (MM) over the past two decades. Bortezomib has emerged as the primary backbone of combined therapy and demonstrated significant results in clinical trials with several types of new agents, such as immunomodulatory drugs, monoclonal antibodies and small molecules. Although bortezomib showed efficacy in patients with both newly diagnosed (NDMM) and relapse and/or refractory multiple myeloma (RRMM), many patients develop resistance to bortezomib after several courses of chemotherapy. Moreover, adverse events (AEs), such as peripheral neuropathy (PN), could lead to treatment discontinuation. Therefore, other second-generation PIs, which exhibit more robust responses and different profiles with respect to AEs, are necessary. Several promising new drugs such as carfilzomib and ixazomib have been approved and incorporated into not only salvage regimens but also frontline regimens. These new drugs have improved progression-free survival (PFS) and overall survival (OS) across all ages (1,2). Optimal treatment selection and the management of toxicities will result in fewer patients requiring dose reductions and treatment discontinuations, ultimately leading to improved outcomes. Thus, the features of each PI need to be understood. In this review, the roles of PIs in MM treatment are outlined.

Proteasome and PIs

Ubiquitination and the proteasome degradation pathway are important for the maintenance of cell cycle progression, DNA repair, apoptosis and stress response for eukaryotes. In the first step, a single ubiquitin-activating enzyme 1 (E1), and multiple ubiquitin-conjugating enzymes (E2) and ubiquitin–protein ligases (E3) mediate polyubiquitination of the target proteins that are unnecessary or misfolded. Next, the ubiquitinated protein is degraded by the 26 S proteasome, which consists of a 20 S core proteolytic particle and 19 S regulatory particles. The 20 S core consists of α and β rings arranged into four rings composed of different polypeptides, enclosed by a central catalytic chamber with proteolytic active sites. Additionally, the β ring consists of seven different β subunits with three proteolytic units, such as caspase-like (C-L) in the β1 subunit, trypsin-like (T-L) in the β2 subunit, and chymotrypsin-like (CT-L) in the β5 subunit. The 19 S regulatory particles recognize substrates that are ubiquitin-like at Lys48, which enables substrates to enter the 20 S core particle. Subsequently, the 20 S core particle

degrades the ubiquitinated intracellular proteins to maintain cell homeostasis. Previous studies demonstrated that malignant cells were more susceptible to PIs than normal cells (3). Because most malignant cells proliferate highly compared with normal cells, malignant cells have an increased requirement for protein synthesis and clearance of misfolded and/or unfolded proteins to maintain cell proliferation. PIs showed remarkable effects in patients with MM. The mechanism of action of PIs has been well characterized. PIs exert their biological activities via various mechanisms, such as direct effects on myeloma cells, inhibition of cytokines, suppression of several adhesion molecules and angiogenesis. Bortezomib exhibited an inhibitory effect on NF-kB that plays a key role in the survival and proliferation of myeloma cells. IκB, which shows inhibitory effects on NF-κB activity, is a substrate of PIs. Thus, the accumulation of IκB induced by PIs results in a blockage of NF-κB. Additionally, the interaction between myeloma cells and bone marrow stromal cells (BMSCs) has been clarified. The adhesion molecules ICAM1 and VCAM1 on myeloma cells and BMSC is upregulated by NF-kB. Bortezomib also inhibited the expression and secretion of vascular endothelial growth factor, leading to the inhibition of angiogenesis in the bone marrow microenvironment. Therefore, proteasome inhibition by bortezomib results in myeloma cell death via various action mechanisms (4). In addition, the efficacy of PIs in osteolytic lesions has been established. Although the bone lesions, which occur in up to 90% of myeloma patients, rarely heal with conventional chemotherapy even in patients with complete remission (CR) (5), there have been several preclinical and clinical reports that PIs improved osteolytic lesions. An imbalance in bone remodeling because of myeloma resulted in increased osteolytic bone destruction. The regulation of bone metabolism is controlled by several cytokines, such as the NF-κB ligand (RANKL), its cellular receptor (RANK) and osteoprotegerin (OPG). In brief, maturation and activation of osteoclasts are activated by the binding of RANKL to RANK expressed on the surface of osteoclasts. RANKL expressed on the surface of osteoblasts can be inhibited by OPG. Bortezomib has been found to exert a direct inhibitory effect on the activation of osteoclasts because of inhibition of NF-κB (6). In addition, bortezomib directly affects osteoblast proliferation and differentiation (7).

Bortezomib

Bortezomib is the first-in-class, boronic acid-based PI, which inhibits β5(CT-L) and to a lesser extent β1(C-L) of the proteasome (Table 1). Because bortezomib has a half-life independent of renal insufficiency, dose modification of bortezomib is unnecessary for myeloma patients with renal insufficiency (8). Thus, rapid initiation of treatment with bortezomib in such cases improves renal function (9,10).

Relapse and refractory patients

The first phase 1 study demonstrated feasible toxicities and efficacy in patients with advanced solid tumor malignancies, with dose-limiting AEs of PN and gastrointestinal effects (11). Subsequently, the phase II CREST study was conducted to explore the efficacy and safety of two doses of bortezomib, 1.0 and 1.3 mg/m^2, in patients with RRMM (12). The rate of a response better than the partial response (PR) for bortezomib alone was 30 and 38% in the 1.0 and 1.3 mg/m^2 groups, respectively, whereas that for 1.3 mg/m^2 of bortezomib and dexamethasone was 50%. The phase II SUMMIT study also demonstrated an overall response rate (ORR) of 27% in patients with RRMM with feasible AEs, including thrombocytopenia, neutropenia and PN (13). The phase 3 APEX trial, in which bortezomib at 1.3 mg/m^2 was administered intravenously on days 1, 4, 8 and 11 of cycle 1 through 8 (21-day cycles) for RRMM, demonstrated the superior effects of bortezomib with respect to PFS and OS compared with that of high-dose dexamethasone (14). As the doublet regimen led to a durable remission and longer PFS, triplet regimens were determined for patients with RRMM. A phase 3 study compared bortezomib, thalidomide and dexamethasone (BTD) and thalidomide and dexamethasone (TD) in patients relapsing following autologous stem cell transplantation (15). A total of 269 patients were randomly assigned to receive BTD or TD for 1 year. Median time to progression was significantly longer with BTD than with TD (19.5 vs 13.8 months, P = 0.001). The CR and near-CR were 45 and 25% with BTD and TD, respectively. BTD was more effective than TD in patients relapsing after autologous stem cell transplantation. However, PN of grade 3 or higher severity was more frequently documented in the BTD arm (29% vs 12%, P = 0.001). Because vorinostat, a pan-deacetylase inhibitor that targets class I and II histone deacetylase, showed efficacy in a preclinical study, a phase 3 trial comparing vorinostat and bortezomib with bortezomib alone was conducted. However, this regimen failed to show significant differences in PFS (16). Thus, another oral pan-deacetylase inhibitor, panobinostat, which showed more potent *in vitro* inhibitory activity than vorinostat, was combined with BD (17). Median PFS in the panobinostat group was significantly longer than that in the BD group (11.99 months vs 8.08 months). Severe AEs were observed in the panobinostat group (60%) and BD group (42%). Common grade 3 or 4 AEs were more frequently observed in the panobinostat group, including diarrhea (26% vs 8%), thrombocytopenia (67% vs 31%) and lymphopenia (53% vs 40%).

Newly diagnosed patients

The efficacy of bortezomib for NDMM was established with or without dexamethasone (18). The synergistic effects of bortezomib with dexamethasone (BD) have been established; patients who had suboptimal responses to bortezomib alone showed improved responses with BD (19). Additionally, the addition of dexamethasone to bortezomib was associated with an improvement in responses without severe toxicities. Subsequently, phase III trials of triplet regimens utilizing bortezomib with other anticancer agents were conducted. Major key studies of triplet regimens are shown in Table 2. The efficacy of BD as an induction therapy relative to the vincristine, doxorubicin and dexamethasone (VAD) regimen, which was regarded as the standard regimen at that time, was investigated in patients with NDMM (20). In this randomized study, the rate of very good partial response (VGPR) or better was significantly higher with BD than with VAD (37.7% vs 15.1%; P < 0.001) and the ORR was also significantly higher. Post-transplant CR and VGPR rates remained significantly higher in the BD group (35.0 and 54.3%). Although the incidence of severe AEs appeared similar between both groups, the rate of grade 2 and grade 3 PNs during induction therapy was significantly higher in the BD group (29.7%). The standard regimen for elderly patients was melphalan-prednisolone (MP). Because the combination of bortezomib and melphalan was reported to show synergistic effects, bortezomib has also been combined with MP. The phase 3 VISTA trial that compared BMP and MP for NDMM ineligible for ASCT was reported in 2008 (21). The ORR was 71% vs 35% for BMP vs MP, and the CR rates were 30 and 4%, respectively. Results were published in 2010 and demonstrated statistically significant OS benefits with BMP vs MP

Table 1. PIs in clinical use and their interaction with the proteasome target

	Bortezomib	Carfilzomib	Ixazomib
structure	Boronate	Epoxyketone	Boronate
Binding	Reversible	Irreversible	Reversible
Half-life (min)	110	<30	18
Target			
Constitutive proteasome	β5 and β1	β5	b5 and b1
Route of administration	IV/SC	IV	Oral

PIs, proteasome inhibitor; IV, intravenous; SC, subcutaneous.

(22). Additionally, use of bortezomib as first-line therapy did not induce more resistant relapse for subsequent therapy (22). These data led to the approval of BMP for transplant-ineligible NDMM patients. However, grade 3 or higher PN was documented more frequently in the BMP arm. Thus, one-third of patients discontinued treatment. An Italian group incorporated thalidomide into the BMP regimen in a phase 3 study. A total of 511 elderly NDMM were assigned to receive nine cycles of BMPT followed by continuous BT as maintenance, or nine cycles of BMP with no maintenance (23). BMPT followed by BT maintenance showed superior 3-year PFS compared with that of BMP alone. Updated follow-up analysis with a median follow-up of 54 months demonstrated that the BMPT-BT therapy improved OS significantly (24). However, PN of severity > grade 3 was noted with BMPT (38%) and BMP (28%), respectively. Because of the high incidence, 28%, of PN, the protocol was amended and patients in both BMPT and BMP arms received once-weekly bortezomib instead of the initial twice-weekly infusion (25). The incidence of grade 3 or 4 PN decreased to 8% with bortezomib, and weekly administration of bortezomib reduced the rate of discontinuation compared with that observed for the twice-weekly schedule with similar cumulative bortezomib doses in both groups without a decrease in efficacy. Bortezomib was also combined with cytotoxic agents, such as doxorubicin or cyclophosphamide. Several phase 2 studies of bortezomib, cyclophosphamide and dexamethasone (BCD) have demonstrated the efficacy of this combination with manageable AEs (26,27), and subsequently, a German group conducted a phase 3 trial to compare BCD and bortezomib, doxorubicin and dexamethasone (PAd) in NDMM (28). The rate of VGPR was better than or comparable (37.0% vs 34.3%, 0.58) to that of the BCD group and PAd group, respectively. Although leukocytopenia occurred more frequently in the BCD arm (35.2% vs 11.3%), neuropathy and thromboembolic events were significantly more frequent with PAd than with BCD. Additional analyses revealed that progression disease (PD) rate in the BCD arm was lower, especially in patients with gain of 1q21 at diagnosis. BCD showed a favorable toxicity profile with comparable ORR to that of PAd. BLd therapy consisted of bortezomib, lenalidomide and dexamethasone, which has been one of the standard induction therapies in recent years. A phase 3 trial comparing the efficacy of the BLd and Ld demonstrated significantly improved PFS in the BLd arm (43 months vs 30 months) (29). Median OS also improved in the BLd arm (75 months vs 64 months). AEs of severity > grade 3 were higher in the BLd arm (82% vs 75% in Ld arm), and 23 and 10% of patients treated with BLd and Ld, respectively, discontinued treatment because of AEs. The higher efficacy of induction therapy prompted the question of whether upfront transplant was still necessary after BLd. Another phase 3 study was conducted to compare the efficacy and safety of BLd alone and BLd plus autologous stem cell transplantation (30). Median PFS was 50 months in the transplantation group and 36 months in the BLd without transplantation group and the hazard ratio for disease progression or death was 0.65 ($P < 0.001$). This benefit was observed across all patient subgroups, including ISS stage and high-risk cytogenetics. However, OS at 4 years was not significantly different, because 136 out of 172 symptomatic relapsed patients (79%) received second-line salvage transplantation. The consolidation therapy with high-dose chemotherapy and transplantation resulted in longer PFS than BLd alone, but not in OS, because later transplantation might be as effective as early transplantation. In addition to being studied in induction regimens, bortezomib has been studied in maintenance regimens after autologous stem cell transplantation. The results from a phase 3 HOVON-65/GMMG-HD4 trial demonstrated that maintenance therapy with 1.3 mg/m^2 of bortezomib alone once every 2 weeks after

Table 2. Effectiveness in the major phase 3 trial

Study name	Regimen	*N*		Indication for transplant	Primary endpoint	Response rate (%)	Median OS/PFS (months)	Reference
Bortezomib								
VISTA	BMP	344	NDMM	Inegible	TTP (24.0 vs 16.6 months)	ORR:71, CR:30	Not reached/ND	(21,22)
	MP	338				ORR:35, CR:4	43.1/ND	
GIMEMA	BMPT-BT	254	NDMM	Ineligible	3y-PFS (56% vs 41%)	ORR:89, ≥VGPR:59	Not reached/Not reached	(23,24)
	BMP	257				ORR:81, ≥VGPR:50	Not reached/27.3	
MM5	BCD	251	NDMM	Eligible	Non-inferiority of BCD to PAd	ORR:78.1, ≥VGPR:37.0	ND/ND	(28)
	PAd	251			PFS	ORR:72.1, ≥VGPR:34.3	ND/ND	
SWOG S0777	BLD	264	NDMM	Eligible and ineligible	PFS	ORR:81.5, ≥VGPR:27.8	Not reached/43	(29)
	Ld	261				ORR:71.5, ≥VGPR:23.4	63/31	
MMVAR/IFM 2005-04	BTD	135	RRMM		PFS	CR+near-CR: 45	Not reached/19.5	(15)
	TD	134				CR+near-CR: 25	Not reached/13.8	
PANORAMA1	Panobinostat-BD	387	RRMM		PFS	ORR:60.7	33.64/11.99	(17)
	BD	381				ORR:54.6	30.39/8.08	
Carfilzomib								
ASPIRE	KLd	396	RRMM		PFS	ORR:87.1, CR:31.8	Not reached/26.3	(36,37)
	Ld	396				ORR:66.7, CR:9.3	Not reached/17.6	
ENDEAVOR	Kd	381	RRMM		PFS	ORR:77, CR:13	47.6/18.7	(38,39,40)
	Bd	404				ORR:63, CR:6	40.0/9.4	
CLARION	KMP	478	NDMM		PFS	ORR:84.3, CR:25.9	Not reached/22.3	
	BMP	477				ORR:78.8, CR:23.1	Not reached/22.1	
A.R.R.O.W.	Once-weekly KRd	240	RRMM		PFS	ORR:62.9, CR:7	Not reached/11.2	(42)
	twice a week KRd	238				ORR:40.8, CR:2	Not reached/7.6	
Ixazomib								
TOURMALINE	ILd	360	RRMM		PFS	ORR:78, CR:12	Not reached/20.6	(46,47)
	Ld	362				ORR:72, CR:7	Not reached/14.7	

B, bortezomib; K, carfilzomib; I, ixazomib; T, thalidomide; L, lenalidomide; P, prednisolone; D(d), dexamethasone; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed and/or refractory multiple myeloma; TTP, time to progression; PFS, progression-free survival; ORR, overall response; CR, complete response; VGPR, very good partial response.

autologous stem cell transplantation was well tolerated, and maintenance treatment with bortezomib improved PFS and OS (31). In this trial, adverse impacts of del(17p) on PFS and OS were significantly reduced (21).

Notably, PN is one of the most problematic adverse effects interfering with bortezomib continuation. Moreau et al. reported that subcutaneous administration of bortezomib showed non-inferiority with respect to ORR and the incidence of PN was significantly less common in the subcutaneous administration group (32). Based on this result, most clinical trials have used bortezomib subcutaneously.

Carfilzomib

Bortezomib demonstrated efficacy and safety in NDMM and RRMM. Despite these promising results, many patients treated with bortezomib show resistance eventually after several courses of chemotherapies, indicating an ongoing need for new therapeutic approaches. A next-generation PI, carfilzomib (Kyprolis®), is an epoxyketone PI binding irreversibly to the β 5 subunit (Table 1). In a preclinical study, carfilzomib demonstrated increased efficacy against bortezomib-resistant MM cell lines (33). The pharmacokinetics and safety of carfilzomib were not influenced by renal impairment, including in patients on hemodialysis (34).

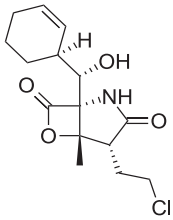
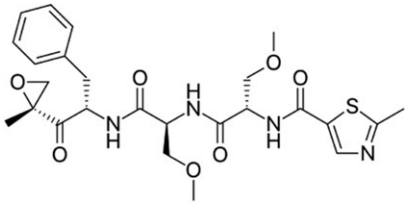
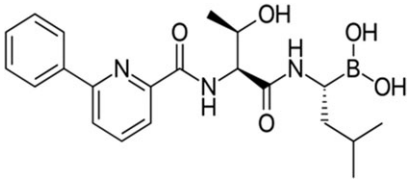
Relapse and refractory patients

In a phase 2 study, which was conducted in 266 RRMM patients using an initial dose of 20 mg/m^2 with subsequent escalation to 27 mg/m^2, demonstrated an ORR of 23.7% with a median duration of response of 7.8 months (35). Because the combination therapy with bortezomib showed a superior effect, carfilzomib was also combined with dexamethasone and/or lenalidomide. A randomized phase 3 ASPIRE trial was conducted in patients with RRMM with one to three prior regimens[36] (Table 2). A total of 792 patients with RRMM were randomly assigned to KLd (n = 396) or Ld (n = 396) groups. PFS significantly improved with KLd (26.3 months vs 17.6 months in the Ld group), and median OS was not reached in either group at interim analysis. The 24-month OS rate was 73.3% in the KLd and 65.0% in the Ld group. The rate of grade 3 or higher AEs was 83.7 and 80.7% in the KLd and Ld group, respectively. Additionally, the rates of discontinuation of treatment due to AEs were comparable, 15.3 and 17.7% for KLd and Ld, respectively. The data from the ASPIRE study were updated in 2018, in which KLd demonstrated a statistically significant and clinically meaningful reduction in the risk of death compared with Ld, extending survival by 7.9 months (37). The randomized ENDEAVOR trial demonstrated a superior PFS with carfilzomib and dexamethasone (Kd) compared with BD in patients with relapsed MM (38). In this phase 3 study, carfilzomib was administered at 20 mg/m^2 on days 1 and 2 as in the ASPIRE trial described above, and the dose was escalated to 56 mg/m^2 from day 8. Median PFS was 18.7 months in the Kd vs 9.4 months in the BD group (38). The updated analysis (3 January 2017) showed median OS to be 47.6 months in the carfilzomib group and 40.0 months in the bortezomib group (HR 0.791, P = 0.010) (39). A superior ORR was reported in the high-risk chromosome group (72.2% in Kd vs 58.4% in BD), and a better CR was observed (15.5% in Kd vs 4.4% in BD), regardless of cytogenetic risk, in the subgroup analysis (40). As described above, all regimens consisting of carfilzomib are twice-weekly dosing regimens. The phase 1/2 CHAMPION-1, the first study investigating once-weekly carfilzomib dosing, demonstrated 70 mg/m^2 to be the maximum tolerated dose in combination with dexamethasone (41). In this study, the most common grade 3 AEs were fatigue (11%) and hypertension (7%). Subsequently, the phase 3 study, A.R.R.O.W., investigated the efficacy of once-weekly carfilzomib and dexamethasone (42). In this trial, once-weekly carfilzomib at 70 mg/m^2 or twice-weekly carfilzomib at 27 mg/m^2 was combined with 40 mg of dexamethasone on days 1, 8, 15 (all cycles) and 22 (cycles 1–9 only). This trial demonstrated a higher median PFS in the once-weekly group than in the twice-weekly group (11.2 months vs 7.6 months, CI 0.54–0.83, P = 0.0029). Although grade 3 or higher AEs were observed more frequently in the once-weekly group (68% vs 62%), the grade 3 or higher cardiac AE was lower in the once-weekly group (3% vs 4%). This study demonstrated a significantly longer PFS in the once-weekly arm than in the twice-weekly arm with comparable overall safety.

Newly diagnosed patients

Because BMP showed significant efficacy for transplant-ineligible patients, carfilzomib was also incorporated into MP in the phase 3 CLARION trial. CLARION, which compared KMP with VMP in untreated transplant-ineligible patients, did not demonstrate significant differences in PFS (22.1 months vs 22.3 months; KMP and BMP, HR 0.91). The rate of fatal AEs of KMP and BMP was 6.5 and 4.3%, respectively. Although carfilzomib demonstrated significant

Table 3. PIs under clinical development

	Marizomib	Oprozomib	Delanzomib
Structure	β-lactone	Epoxyketone	Boronate
			
Binding	Irreversible	Irreversible	Reversible
Target			
Constitutive proteasome	b5, b1 and b2	b5	b5
Route of administration	IV	Oral	Oral/IV
Half-life in plasma	<10 min	<10 min	62 hours
Major clinical trials	50, 51	52, 53	54

efficacy in a second-line setting, KMP showed no favorable PFS in NDMM. Another phase 3 trial to compare the efficacy of KRd and VRd is in progress. In the other trial, weekly carfilzomib was administered at a starting dose of 20 and 56 mg/m^2 thereafter with lenalidomide for 21 days and with 40 mg of dexamethasone on days 1, 8, 15 and 22. Although further follow-up is necessary to confirm the results, ORR was 93% with 89% of VGPR or better (43).

Although PN is not reported frequently with carfilzomib, there have been several reports of a higher rate of carfilzomib-associated cardiovascular adverse events (CVAEs), such as heart failure, hypertension, arrhythmias and ischemic events. So far, the etiology and pathophysiology of CVAE are largely unknown. A systematic review and meta-analysis revealed that grade 3 and higher CVAE were seen in 8.2% of patients treated with carfilzomib (44). A subgroup analysis revealed that 45 mg/m^2 or higher doses of carfilzomib were associated with high-grade CVAE. However, a median age of >65 years, duration of carfilzomib exposure and number of prior myeloma therapies were not associated with the rate of CVAE. The addition of carfilzomib to the standard Ld salvage regimen did not limit the potential benefit of KLd, because of the impressive improved result for RRMM patients (36). Attention needs to be paid to cardiac toxicity especially in patients who have baseline pre-existing cardiac disease.

Ixazomib

Ixazomib is an analog of boric acid and the first oral second-generation PI (Table 1). In a preclinical study, ixazomib (MLN9708) was immediately hydrolyzed to MLN2238, which is the active form, on exposure to plasma. MLN2238 binds and inhibits the β5 subunit (CT-L) reversibly and also inhibits β 1(C-L) at a high concentration. In a preclinical xenograft mice model, ixazomib showed a significantly longer survival time than that in mice treated with bortezomib (45). Additionally, ixazomib alone or in combination with lenalidomide and dexamethasone showed synergistic anti-MM activity. Based on this result, a randomized phase 3 trial (TOURMALINE-MM1) was conducted to compare the efficacy and safety of ixazomib, lenalidomide and dexamethasone with those of placebo plus Ld in patients with RRMM (Table 2) (46). PFS was significantly longer in the ixazomib group (20.6 months vs 14.7 months). ORR was 78.3% in the ILd group and 71.5% in the Ld group ($P = 0.03$). Additionally, this response increased with increasing cycles of treatments. The rate of severe AEs was comparable in ixazomib and placebo groups, and the rate of death during the study was similar in the two groups (5 and 4%). In subgroup analysis, ILd demonstrated PFS benefit in RRMM with high-risk cytogenetic abnormalities (47) ILd as an induction therapy for patients with NDMM has been ongoing in the TOURMALIN-MM2 study. Ixazomib also has been used for maintenance therapy in a phase 1/2 study. A total of 121 patients in these studies received maintenance therapy with ixazomib, and the median PFS was 21.4 months from the start of maintenance. The best response rate was better than VGPR after induction and was 57% (22% CR), which increased to 63% (35% CR/sCR) after maintenance. Although the follow-up period was still short, single-agent ixazomib contributed to a durable response with limited toxicity (5% of drug-related SAE) and was expected to improve PFS. In the TOURMALINE study, patients with creatine clearance ≥30 ml/min were enrolled because ixazomib was administered with lenalidomide. Subsequently, the pharmacokinetics and safety of 3 mg of ixazomib were studied in patients with severe renal sufficiency, including hemodialysis in a phase 1/1b study (48). This study demonstrated similar pharmacokinetics with similar AEs across all groups.

Marizomib

The three PIs described above demonstrated inhibitory activity especially against the β5 subunit (CT-L). Marizomib, which is a broad-spectrum PI, binds to 3 major catalytic sites on β5, β1 and β2, irreversibly (Table 3), and demonstrates efficacy in RRMM patients who are resistant to bortezomib, carfilzomib and ixazomib. Moreover, marizomib activates a variety of the caspases and reactive oxygen species and thus induces apoptosis. In a phase two study, marizomib was administered to 68 patients who were refractory to prior carfilzomib (49). Six patients (8.8%) demonstrated an IMWG response of minor or better, and PR was observed in five patients (7.4%). The most common AEs were fatigue, headache, nausea, anemia, and increased blood creatinine. Although bortezomib has been shown to have efficacy in glioma cell lines, the appropriate method of drug delivery is inevitable to circumvent the blood–brain barrier (50). Marizomib was distributed in the brain at a 30% blood drug concentration in rats (51). This preclinical result supports the efficacy of marizomib in patients with intracranial myeloma lesions.

Oprozomib

Oprozomib, which is known as ONX 0912, is an oral analog of carfilzomib, demonstrating an equivalent antitumor activity as carfilzomib *in vitro* and in animal models (52). Oprozomib has an epoxyketone, which inhibits the β5 subunit like carfilzomib (Table 3). A phase 1b/2 study with the single-agent oprozomib for myeloma and Waldenstrom macroglobulinemia was reported in 201 6 (53). Although most patients were treated with other PIs, such as bortezomib, carfilzomib and lenalidomide, single-agent oprozomib showed durable responses. Most common AEs were gastrointestinal events, such as diarrhea, nausea and vomiting.

Delanzomib

Delanzomib, which is known as CEP-18 770, is an oral PI that inhibits the β5 subunit reversibly (Table 3). A single-center phase I/II study was conducted, in which the most prominent AEs at the MTD were nausea, vomiting, fatigue and pyrexia. Additionally, PN was limited to grade 1 or 2. Dose-limiting toxicities were rashes and thrombocytopenia (54). Results of a phase 3 study have not been reported yet.

Conclusion

In the past two decades, a variety of new agents to treat MM have been launched and studied in several phase 3 trials. Bortezomib has been one of the groundbreaking treatments for MM with other anticancer agents. Currently, three PIs, which have been utilized in clinical setting, have demonstrated superior efficacy in several phase 3 trials and showed different profiles of AEs. The understanding of AEs for their better management could lead to a more effective way of conducting chemotherapy more safely, which might result in a better outcome.

Conflicts of Interest statement

T.I.: Takeda, Ono pharma, Jannsen and Celgen.

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