The role of histone deacetylase inhibitors in patients with relapsed/refractory multiple myeloma

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ABSTRACT

Clinical outcomes for patients with multiple myeloma (MM) have improved substantially since the introduction of novel agents including the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide. However, most patients with MM eventually relapse, and prognosis remains poor among patients with relapsed and/or refractory disease. Combination therapy using agents with different mechanisms of action is emerging as an attractive treatment approach in oncology to increase efficacy and/or overcome resistance to standard treatment regimens. This review discusses unmet needs in the treatment of MM and the development of histone deacetylase inhibitors as a treatment modality for MM.

Keywords: Multiple myeloma, histone deacetylase inhibitor, proteasome inhibitor, immunomodulatory drug, bortezomib

Introduction

Over the past 50 years, clinical management and supportive care for patients with multiple myeloma (MM) has improved significantly [1]. The introduction of novel agents (i.e. proteasome inhibitors [PIs] and immunomodulatory drugs [IMiDs]) has dramatically improved clinical outcomes for patients with MM, including patients with poor prognostic factors [2,3]. Despite progress in MM treatment the disease remains incurable, and prognosis remains relatively poor among patients with relapsed and/or refractory disease. New therapeutic options are urgently needed to improve outcomes in this patient population. Histone deacetylase inhibitors (HDACi) in combination with bortezomib or lenalidomide are currently being investigated in relapsed/refractory MM, and have shown promising preliminary safety and efficacy [4–6]. We review the unmet medical needs of patients with relapsed or refractory MM and examine the rationale for using HDACi in this patient population.

Clinical need in relapsed or refractory multiple myeloma

The clinical landscape in MM has been evolving. In the mid-1990s, autologous stem cell transplant (ASCT) became a key treatment option [7]. However, unsatisfactory outcomes with conventional approaches (e.g. ASCT) led to the introduction of regimens containing PIs (e.g. bortezomib) and/or IMiDs (e.g. thalidomide) [8]. Subsequently, MM treatment has been influenced by the approval and increased availability of these agents. In the USA, bortezomib was first approved in 2003 as third-line therapy, in 2005 as second-line therapy, in 2007 as second-line therapy with pegylated liposomal doxorubicin and in 2008 as first-line therapy. In Europe, bortezomib was approved in 2005 as second-line therapy and in 2008 as first-line therapy with prednisone and melphalan. In the USA, thalidomide was first available in 1998 for the treatment of erythema nodosum leprosum; in 2006, it was approved for use in combination with dexamethasone for newly diagnosed patients with MM. In Europe, thalidomide was approved in 2008 for use in combination with melphalan and prednisone in newly diagnosed patients with MM (> 65 years) who are not candidates for ASCT. Lenalidomide was approved for use with dexamethasone as second-line therapy in the USA in 2006 and in Europe in 2007.

Since the introduction and widespread use of PIs and IMiDs, response rates and median survival have considerably improved [2,3,9]. Survival trends of 26 523 patients diagnosed with MM in the USA between 1980 and 2004 from the Surveillance, Epidemiology and End Results (SEER) database show that the 5-year relative survival increased by 5.9% and the 10-year relative survival increased by 6.3% between 1990–1992 and 2002–2004 [9]. This improvement was likely due to expanded use of ASCT and the development of thalidomide. In a Mayo Clinic study of newly treated patients with MM who relapsed after SCT, patients who relapsed or were diagnosed when novel agents were available demonstrated better outcomes [2]. In patients who relapsed after SCT was a treatment option (n = 387), median overall survival (OS) was longer in those who relapsed after 31 December 2000 (23.9 vs. 11.8 months, $p < 0.001$). Patients who were treated with newer drugs (bortezomib, lenalidomide or thalidomide) also had an increased OS after relapse (30.9 vs. 14.8 months, $p < 0.001$). Similarly, in a group of 2981 patients newly diagnosed with myeloma from 1971 to 2006, those diagnosed between 1997 and 2006 had an increase in median OS compared with those diagnosed before 1997 (44.8 vs. 29.9 months, $p < 0.001$), and the OS improvement was significantly better in patients aged 65 years or younger. In another study of patients with MM treated with ASCT between 1988 and 2008, of the 306 relapsed patients, those who relapsed after 2004 had significant improvements in OS (71.8 months vs. 32.0 months, $p < 0.001$) and post-relapse survival (PRS; 42.8 months vs. 15.2 months, $p < 0.001$) [3]. Higher PRS rates correlated with treatment with novel agents (35.7 months for patients exposed to newer drugs vs. 9.1 months for those who were not treated with novel agents, $p < 0.001$). Furthermore, patients treated with bortezomib or lenalidomide demonstrated greater benefit in PRS compared with thalidomide (43.0 months vs. 16.8 months, $p < 0.001$). Although early relapse within 1 year after ASCT predicted a worse outcome, improvement in OS was still observed in the cohort of patients who relapsed after 2004 and who were treated with newer agents.

Historically, lower response rates have been observed in patients who have received increasing numbers of prior treatment regimens [10]. This is supported by recent International Myeloma Working Group (IMWG) outcomes research data demonstrating that survival rates in heavily pretreated patients remain disappointing [11]. In patients with MM refractory to bortezomib, lenalidomide or thalidomide, the median OS was found to be 11, 22 and 16 months, respectively. Median OS was found to be 9 months in patients with bortezomib-refractory MM who were relapsed, refractory or ineligible for IMiDs; median event-free survival (EFS) was found to be 5 months (Figure 1). These data are consistent with what has been observed with regard to poorer outcomes seen in patients who had received prior thalidomide in bortezomib and lenalidomide

registration trials [12,13]. In an Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial post hoc subgroup analysis, prior thalidomide treatment predicted worse outcomes with bortezomib, including a lower response rate (30% vs. 46%), shorter time-to-progression (TTP) and shorter OS [12]. A subgroup analysis of two phase 3 lenalidomide trials in relapsed/refractory MM also demonstrated that prior thalidomide predicted worse outcomes with lenalidomide and dexamethasone, including lower response rate and shorter TTP and progression-free survival (PFS), with no change in OS [13].

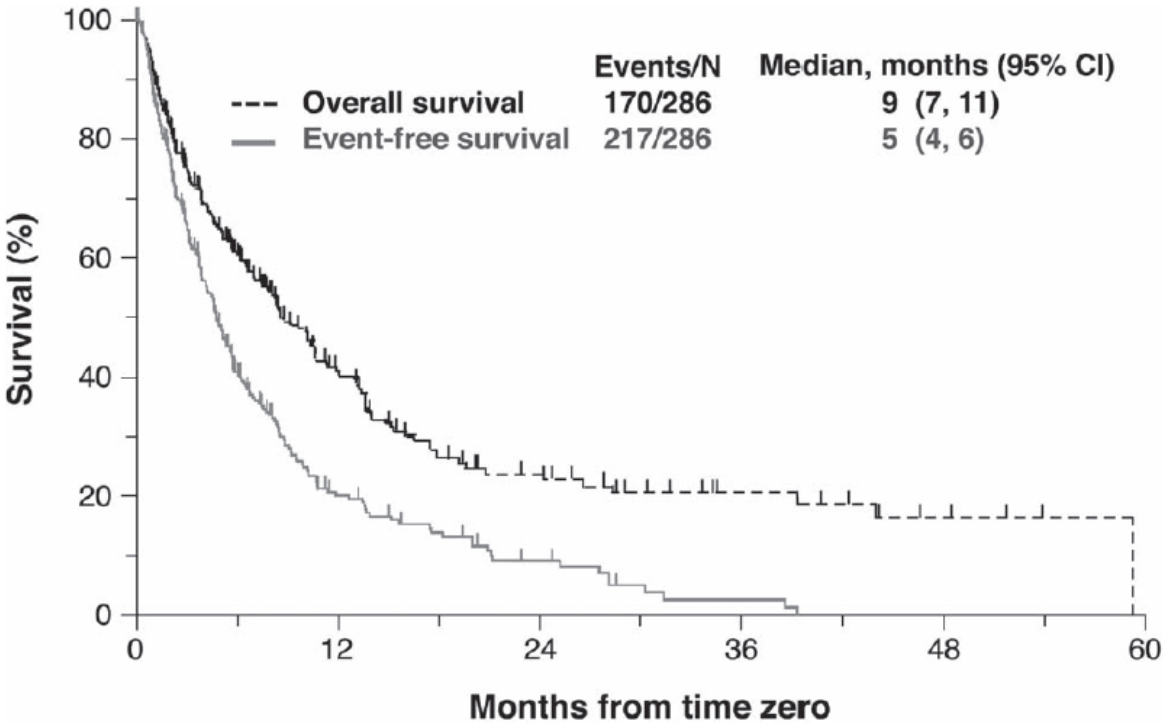

Figure 1. Overall and event-free survival for patients who were refractory or ineligible for treatment with novel agents. 95% CI, 95% confidence interval. Adapted with permission from: Macmillan Publishers Ltd: [Leukemia]. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012;26:149–157, copyright (2012) [11].

Various approaches have been investigated in an effort to improve treatment efficacy with reduced toxicity, including lowered dosage, once-weekly versus twice-weekly dosing, and subcutaneous versus intravenous (IV) dosing. For instance, low-dose dexamethasone with lenalidomide has demonstrated superior OS outcomes relative to high-dose dexamethasone with lenalidomide in newly treated patients [14]. In patients treated with thalidomide at the reduced dose of 100 mg/day, the observed OS was the same as that seen with a 400 mg/day dose; there were also fewer toxicities in patients who had received at least two prior lines of therapy [15]. With regard to dosing schedules, one trial compared bortezomib plus melphalan and prednisone with bortezomib plus thalidomide and prednisone in newly treated patients 65 years and older; after the first cycle, bortezomib once weekly showed promising efficacy in both regimens [16]. In a trial comparing different administration routes of bortezomib, subcutaneous administration demonstrated an equivalent overall response rate (ORR) to the IV therapy in patients who had received 1–3 prior lines of treatment [7]. Subcutaneous bortezomib also showed an improved safety profile.

Despite new therapies and advances in care, patients with MM still frequently relapse. Regional considerations may also affect treatment outcomes. For instance, due to different drug approval processes, the availability of novel agents varies by region, which could contribute to differential outcomes. However, IMWG findings do not suggest a significant difference in outcomes among US patients versus all patients studied (USA, European Union [EU], Asia) with respect to ORR for next line of therapy, EFS and OS [11]. These studies suggest that new agents and/or treatment approaches that enhance the efficacy of existing treatments are still needed, particularly after failure of prior IMiD- or PI-based regimens.

Preclinical rationale for use of histone deacetylase inhibitors in multiple myeloma

The regulation of protein acetylation through inhibition of histone deacetylases (HDACs) has been considered a feasible approach to improve outcomes in relapsed/refractory patients with MM [17]. Many normal cellular processes are modulated by the balance between acetylation and deacetylation, which often function abnormally in tumor cells because of increased HDAC activity. As such, HDACi affect multiple processes (Figure 2) [18]. In normal and malignant cells, both the proteasome and aggresome pathways are involved in the degradation of misfolded proteins. When PIs are used to block the proteasome pathway, aggresome activity increases to compensate and remove toxic misfolded proteins from the cell. Blockade of the aggresome pathway with HDACi appears to prevent this compensatory mechanism, and the resulting buildup of misfolded proteins induces cell stress and leads to apoptosis [19–22]. Therefore, HDACi and PIs are thought to each inhibit separate but complementary pathways involved in the removal of misfolded proteins from the cell.

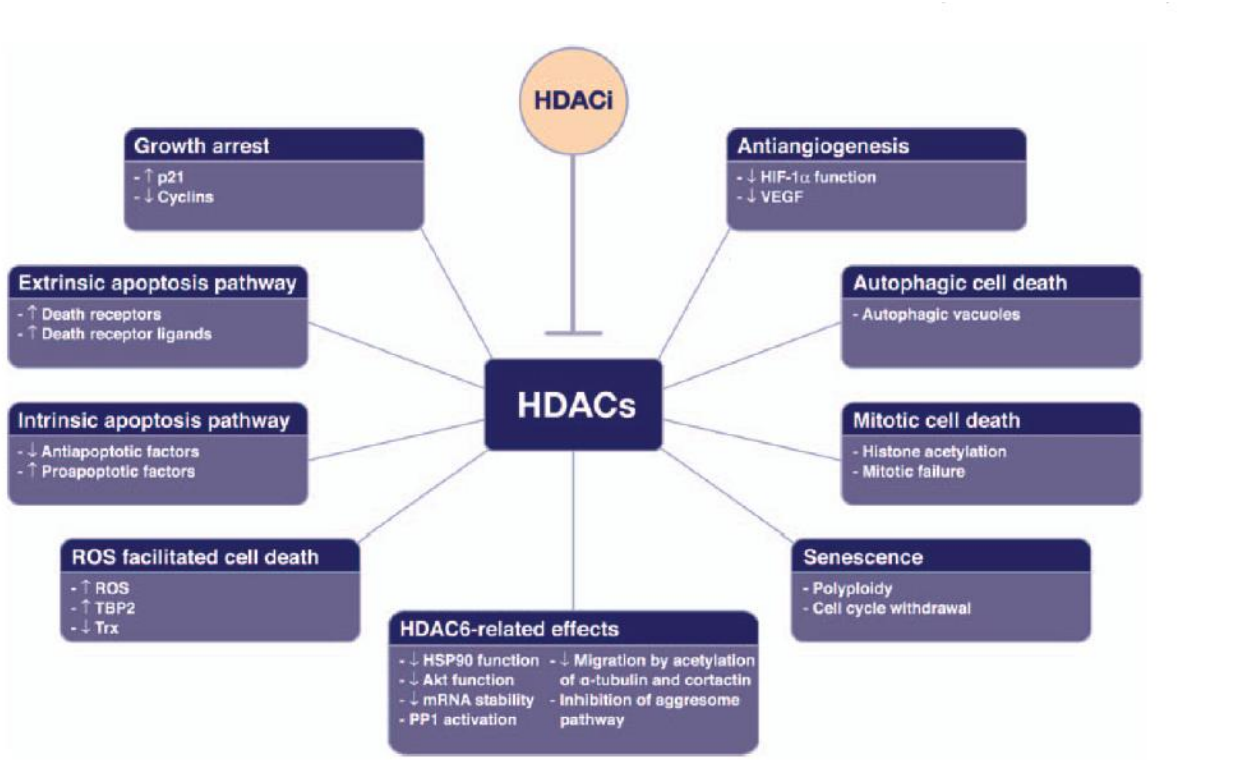

Figure 2. Multiple effects of histone deacetylase inhibitors affecting tumor cell growth. HDACi, histone deacetylase inhibitor; HIF-1α, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; HSP90, heat shock protein 90; PP1, protein phosphatase 1; ROS, reactive oxygen

species; TBP2, thioredoxin binding protein 2; Trx, thioredoxin; p21, cyclin-dependent kinase inhibitor 1. Adapted with permission from: Marks PA, Xu WS. Histone deacetylase inhibitors: Potential in cancer therapy. J Cell Biochem 2009;107:600–608 [18].

Histone deacetylase inhibitors have also been shown to up-regulate proapoptotic and down-regulate antiapoptotic signaling pathways in MM cell lines, both directly and through downstream transcriptional effects [19,23]. Such inhibitors exhibit synergistic effects with bortezomib or enable cells to overcome resistance to bortezomib. In particular, a number of HDACi (e.g. vorinostat, panobinostat, romidepsin, belinostat, tubacin and ACY-1215) have demonstrated synergistic cytotoxicity with bortezomib, inducing apoptosis in MM cell lines and primary cells from patients with MM [19,23–28]. Romidepsin has also been shown to restore sensitivity to bortezomib in HDAC1-overexpressing cells both in vivo and in vitro [24]. Additionally, several other HDACi have demonstrated promising preclinical data in myeloma or malignant hematologic cell lines [29–31]. Although generally all inhibition of HDACs results in inhibition of tumor growth and apoptosis, HDACi display differential properties, both in target specificity and in effective inhibitory concentrations. Table I summarizes the characteristics of selected HDACi being evaluated for activity in MM.

Table I. Characteristics of HDAC inhibitors that have been evaluated for multiple myeloma.

HDAC inhibitor	Target(s)	IC_{50}	Key cellular effects	References
Vorinostat (SAHA)	HDAC1–4, 6, 7, 9 HDAC8	48–164 nM 1.5 μM	Accumulation of acetylated histones; induces apoptosis, cell cycle arrest and differentiation	Dell'Aversana, 2012 [55]
Panobinostat (LBH589)	HDAC1–11	< 40 nM	Promotes histone and HSP90 acetylation; induces apoptosis and blocks cell cycle progression	Maiso, 2006 [23]
Belinostat (PXD-101)	HDAC1–3, 6	27 nM	Promotes histone acetylation; inhibits cell growth and induces apoptosis	Plumb, 2003 [56]; Bantscheff, 2011 [57]
Entinostat (MS-275)	HDAC1 HDAC3	300 nM 8 μM	Promotes histone acetylation; induces apoptosis and differentiation through gene modulation	Hu, 2003 [58]
Mocetinostat (MGCD0103)	HDAC1, 2 HDAC3 HDAC11	34 nM 1 μM 2 μM	Hyperacetylation of histones, selectively induced apoptosis and cell cycle blockade	Fournel, 2008 [59]; Dell'Aversana, 2012 [55]
Romidepsin (FR901228/FK228)	HDAC1 HDAC2 HDAC4 HDAC6	36 nM 47 nM 510 nM 14 μM	Induces differentiation, growth arrest, apoptosis; inhibits metastasis and angiogenesis	Furumai, 2002 [60]
ACY-1215	HDAC6	5 nM	Promotes α-tubulin acetylation; histone acetylation at higher doses	Santo, 2012 [61]

HDAC, histone deacetylase; IC_{50}, half maximal inhibitory concentration; SAHA, suberoylanilide hydroxamic acid; HSP90, heat shock protein 90.

The activity of HDACi has also been examined in combination with IMiDs, such as lenalidomide and thalidomide [32–34]. Ocio et al. examined antimyeloma activity associated with exposure to the HDACi panobinostat in MM cell lines [33]. Cells were treated with antimyeloma agents (dexamethasone, the proteasome inhibitor bortezomib and/or the IMiD lenalidomide) individually or in combination with panobinostat (i.e. as monotherapy or double and triple combinations). Bortezomib/lenalidomide triple combinations (panobinostat with dexamethasone and either bortezomib or lenalidomide) resulted in clear potentiation in a MM cell line (i.e. superior efficacy with synergistic effects compared with other combinations), increased antiproliferative activity, decreased tumor growth and altered expression of a unique set of genes (e.g. apoptotic, cell-cycle and chemokine factors).

The activity of HDACi has also been investigated in combination with other drugs [23,32–36]. Both vorinostat and panobinostat have been investigated in combination with dexamethasone [23] and conventional cytotoxic agents (e.g. melphalan and pegylated liposomal doxorubicin) [23,32–36]. Results from these studies have shown that the addition of HDACi enhances the anti-MM activity of these agents.

Clinical experience with histone deacetylase inhibitors in relapsed/refractory multiple myeloma

New agents, in combination or as single-agent therapy, for patients with relapsed/refractory MM include novel PIs (carfilzomib) and IMiDs (pomalidomide), HDACi (panobinostat, vorinostat and ACY-1215), antibodies (anti-CS-1 elotuzumab), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus) and kinase inhibitors (CDK inhibitor AT7519M, JAK-2 inhibitor INCB018424 and Akt inhibitor), as well as other agents (Hedgehog antagonist GDC-0449 and peptide vaccines against myeloma cells MAGE-A3 and NY-ESO-1). As this review focuses on clinical results with HDACi (as single-agent or in combination therapy) in relapsed/refractory patients with MM, key data are summarized in Table II [37].

Table II. Summary of clinical data for histone deacetylase combination therapy in relapsed/refractory multiple myeloma**.

Phase	HDACi	Combination	*n*	ORR*	Most common AEs	Reference
1	VOR	BOR	23	42%	Myelosuppression, fatigue, diarrhea	Badros, 2009 [4]
1	VOR	BOR	24	24%	Nausea, thrombocytopenia, diarrhea	Weber, 2008 [62]
1	VOR	BOR	13†	38%	Nausea, diarrhea, thrombocytopenia	Weber, 2008 [44]
1b	PAN	BOR	38	68%	Neutropenia, thrombocytopenia	San-Miguel, 2010 [51]
1/2	ROM	BOR + DEX	25	72%	Thrombocytopenia, fatigue, peripheral neuropathy	Harrison, 2011 [53]
1	VOR	BOR + PLD	20	70%‡	Diarrhea, nausea, peripheral neuropathy	Voorhees, 2010 [36]
1b	PAN	LEN + DEX	46	37%	Hematologic, gastrointestinal, muscular	Mateos, 2010 [5]
1	VOR	LEN + DEX	12	27%	Fatigue, thrombocytopenia	Siegel, 2009 [63]
1	VOR	LEN + DEX	30	53%	Neutropenia, thrombocytopenia, diarrhea	Richardson, 2010 [46]
1	PAN	MEL	15	27%	Thrombocytopenia, neutropenia	Berenson, 2009 [32]
1/2	PAN	MEL + THAL + PRED	24	38.5%	Gastrointestinal, thrombocytopenia, neutropenia	Offidani, 2012 [64]
2	PAN	BOR + DEX	55§	29%	Thrombocytopenia, fatigue, nausea	Richardson, 2011 [65]
2b	VOR	BOR	142¶	18%	Thrombocytopenia, nausea, anemia	Siegel, 2011 [6]
3	VOR	BOR	637	54%	Nausea, diarrhea, thrombocytopenia	Dimopoulos, 2011 [45]

HDACi, histone deacetylase inhibitor; ORR, objective response rate; AE, adverse event; VOR, vorinostat; BOR, bortezomib; PAN, panobinostat; ROM, romidepsin; DEX, dexamethasone; PLD, pegylated liposomal doxorubicin; LEN, lenalidomide; MEL, melphalan; THAL, thalidomide; PRED, prednisone.
*Based on number of evaluable patients.
†All patients were previously exposed to bortezomib.
‡Only patients with relapsed disease.
§Eligible patients had relapsed from two or more prior lines of therapy and were refractory to BOR.
¶Eligible patients had relapsed from two or more prior lines of therapy, were refractory to BOR, and were refractory to or ineligible for THAL and/or LEN.
**Adapted with permission from: Ocio EM, San Miguel JF. Deacetylase inhibitors in multiple myeloma. Presented at 13th International Myeloma Workshop. 3–6 May 2011. Paris, France [37].

Single-agent therapy with histone deacetylase inhibitors in MM

Both vorinostat and panobinostat have demonstrated modest activity in the single-agent setting. In a phase 1 trial of oral vorinostat (n = 13), the maximum tolerated dose (MTD) was not determined [38]. Common adverse events (AEs) included fatigue, anorexia and dehydration; one patient experienced a dose-limiting toxicity (DLT; grade 3 fatigue). Of the 10 evaluable patients, one experienced a minimal response and nine experienced stable disease (SD). Vorinostat received US approval in 2006 for the treatment of cutaneous T-cell lymphoma. A pooled safety analysis of 341 patients with solid or hematologic malignancies who were treated with vorinostat monotherapy demonstrated that vorinostat was generally well tolerated. Treatment-related AEs of all grades occurring in greater than 20% of patients were fatigue (62%), nausea (56%), diarrhea (49%), anorexia (48%), vomiting (33%), increased blood creatinine (26%), weight loss (25%), hyperglycemia (23%) and thrombocytopenia (21%) [39]. A phase 1/2 study examined oral panobinostat in patients with refractory MM (≥ 2 prior therapies; n = 38). Common AEs were nausea, fatigue and asthenia; grade 3/4 cytopenias, infections, hypercalcemia and hypokalemia were also reported [40]. Although the study did not meet its objective, a durable very good partial response (VGPR) and a durable marginal response (MR) in one patient each, as well as three patients with SD, were observed. Another HDACi, romidepsin, was evaluated in a phase 2 trial of refractory patients with MM (n = 13) [41]. The most common AEs reported included nausea, fatigue and taste alteration; grade 3 thrombocytopenia was reported in three patients. No objective

responses were observed, although four out of 12 patients with secretory myeloma exhibited evidence of M-protein stabilization.

Other novel HDACi have been investigated, including belinostat and ITF2357. Belinostat was examined in a phase 1 trial in patients with hematological malignancies (n = 16) [42]. The most common AEs were nausea, vomiting, fatigue and flushing; one patient experienced grade 3 lymphopenia and two patients experienced grade 4 renal failure. Although no objective responses were observed, five patients experienced disease stabilization, including one patient with MM. In a phase 2 study that evaluated the MTD of ITF2357 alone or with dexamethasone in patients with relapsed or progressive MM (n = 19), the MTD of ITF2357 was determined to be 100 mg twice daily for 4 consecutive days every week for 4 weeks [43]. Four patients experienced serious AEs, while three patients experienced grade 3/4 gastrointestinal toxicity, three had transient electrocardiographic abnormalities, and all but one patient experienced thrombocytopenia (grade 3/4 in 10 patients). Five patients experienced SD as their best response. Collectively, early clinical trials with HDACi as single agents have demonstrated modest response rates. Based on preclinical results suggesting that HDACi may have synergistic effects with PIs, a number of combination therapy trials are being conducted and are discussed in the following section.

Histone deacetylase inhibitors in combination therapy in MM

Early phase clinical trials have investigated vorinostat in combination with antimyeloma agents and have shown encouraging results. Results with the combination of vorinostat and bortezomib have been promising. A phase 1, dose-finding study in patients with at least three prior therapies identified the MTD of vorinostat as 400 mg daily for 8 days every 21 days, with bortezomib administered on days 1, 4, 8 and 11 [4]. Observed DLTs included prolonged QT interval and fatigue; the most common grade 3 and above toxicities were myelosuppression, fatigue and diarrhea. Nine out of 21 patients achieved objective responses (two VGPR, seven partial response [PR]); three patients were bortezomib-refractory. In a phase 1, dose-finding study, escalating doses of vorinostat and bortezomib were evaluated in patients with relapsed/refractory MM (n = 34) [44]. The MTD was not determined; the most common AEs included nausea and diarrhea. Best responses included PR in nine patients, MR in seven patients and SD in 18 patients.

Two recently completed trials further investigated the combination of vorinostat and bortezomib in different MM patient populations. The first trial was a single-arm, open-label, phase 2b trial that examined this combination (with dexamethasone added for non-responders) in bortezomib-refractory patients with MM who were refractory to, or ineligible for, an IMiD, and had received at least two prior regimens (n = 143) [6]. This combination was active in these patients (17% ORR and 31% clinical benefit rate [CBR; minor response or better based on IMWG criteria]). Observed OS was 11.2 months, with a 2-year OS rate of 32%. This treatment was generally well tolerated, with 27% of patients completing eight or more cycles, and the most common grade 3/4 AEs were hematologic: thrombocytopenia, anemia and neutropenia. Interestingly, grade 3/4 peripheral neuropathy was infrequent, occurring in only two patients (2%). The second study was a large, global, randomized, placebo-controlled, phase 3 trial assessing the combination of vorinostat and bortezomib in patients with relapsed/refractory MM who received 1–3 prior lines of therapy (n = 637) [45]. The combination was active in patients with MM: the ORRs were 54% and 41% and the CBRs were 71% and 53% in the combination (bortezomib and vorinostat) and bortezomib arms, respectively, demonstrating a significant improvement in response with the addition of vorinostat. Progression-free survival was modestly, but statistically significantly, increased in the combination arm versus the control arm (7.6 months [95% confidence interval (CI): 6.9–8.4] vs. 6.8 months [95% CI: 5.7–7.7]), and TTP was prolonged in the combination arm compared with the bortezomib arm. Both the PFS hazard ratio and TTP hazard ratio were reduced, by 23% ($p = 0.01$) and 21% (p

= 0.02), respectively. A transient response to the combination treatment may explain the more significant increase in ORR/CBR and the modest increase observed in PFS. The combination was generally well tolerated and the side effects were manageable. The most common grade 3/4 AEs were hematologic (neutropenia, thrombocytopenia and anemia), and few drug-related deaths were observed.

Vorinostat has also been examined in combination with other agents. A phase 1 trial evaluated vorinostat in combination with lenalidomide and dexamethasone in patients with relapsed/refractory MM (n = 30) [46]. Although the MTD was not reached, one DLT was identified (grade 3 diarrhea). The most common grade 3/4 AEs included neutropenia, thrombocytopenia and diarrhea. Twenty-six of 30 evaluable patients (87%) experienced SD or better (two complete response [CR], three VGPR, 11 PR, five MR, five SD and four progressive disease [PD; response rate (RR) including MR = 53%]). Of 13 patients who had received prior lenalidomide, nine experienced SD or better, including two VGPR, three PR, one MR and three SD (RR including MR = 38%). Vorinostat has also been evaluated in combination with pegylated liposomal doxorubicin in a phase 1 study that enrolled 20 patients with relapsed/refractory MM [36]. The MTD for vorinostat was determined to be 400 mg daily when administered on days 4–11 of a 3-week cycle, and the DLTs identified included atrial flutter and thrombocytopenia. The most common AEs were diarrhea, nausea and peripheral neuropathy. Preliminary efficacy findings showed that seven patients had VGPR or better and 11 had PR or better. Three out of nine patients with bortezomib-refractory disease had PR or better, and three additional patients experienced a MR.

Vorinostat is also being evaluated in combination with a standard MM treatment regimen consisting of bortezomib/lenalidomide/dexamethasone in newly diagnosed patients with symptomatic MM [47]. Eleven patients were enrolled at three dose levels, and two DLTs occurred (syncope and asymptomatic grade 3 alanine aminotransferase elevation). Treatment-emergent peripheral neuropathy occurred in six patients. Eight patients were evaluable for response: three patients had a CR, one had a VGPR and four experienced a PR. In addition to the recently presented results from the phase 2 and 3 trials of vorinostat in combination with bortezomib in relapsed/refractory MM, a chart review of patients with MM who were relapsed or refractory to lenalidomide/dexamethasone and/or bortezomib indicates that the addition of vorinostat is a viable approach to regain disease control in this population. For nine patients with lenalidomide/dexamethasone/bortezomib-relapsed/refractory disease, four patients achieved a PR or better and eight patients achieved a MR or better (89%) with vorinostat (300 or 400 mg) [48]. The most common toxicities were gastrointestinal, including diarrhea and cramping. Cytopenias occurred at an incidence similar to that of patients treated with lenalidomide-based therapy alone. The ORR was 43%, with eight patients achieving a PR, four achieving VGPR or better, five achieving MR and eight maintaining SD.

Panobinostat has shown promising early clinical signs of efficacy in combination with other myeloma agents. In a phase 1b dose-finding study of panobinostat in combination with bortezomib in patients with relapsed/refractory MM, the most common non-hematologic AEs observed were diarrhea and nausea; frequent grade 3/4 AEs included thrombocytopenia and neutropenia. Dose-limiting toxicities identified were mostly hematologic [49]. Twenty-six out of 38 patients experienced MR or better, as did eight of 13 bortezomib-refractory patients. Moreover, an ongoing phase 2 study of panobinostat in combination with bortezomib and dexamethasone in patients who had received at least two prior therapies (including an IMiD) and were bortezomib-refractory (n = 24) is proceeding to stage 2, based on at least four responses of PR or better occurring during stage 1 [50]. A randomized, phase 3 trial evaluating the efficacy and safety of the combination of panobinostat and bortezomib in patients with relapsed/refractory MM who had received 1–3 prior lines of therapy has enrolled 270 patients out of a projected accrual of 672 [51]. In a phase 1b study

of panobinostat in combination with lenalidomide/dexamethasone, 46 patients with relapsed/refractory MM were treated [5]. Dose-limiting toxicities occurred in nine out of 36 evaluable patients, and common AEs included grade 3/4 hematologic events, as well as gastrointestinal and muscular events. The panobinostat 20 mg dose was expanded to determine MTD. Amongst the 30 evaluable patients, 17 responses were reported (one stringent complete response [sCR], one CR, seven VGPRs and eight PRs), seven patients had SD and six experienced PD.

Panobinostat has also been investigated in combination with the alkylating agent melphalan with or without prednisone and thalidomide. In a phase 1 study of melphalan plus panobinostat in relapsed/refractory MM, in which 14 of the 15 patients had previously been treated with melphalan, significant hematologic events led to a decrease in the time that panobinostat was administered [32]. Of 12 patients evaluable for response, four patients (33%) who had previously received melphalan at higher doses achieved a response, including one CR and three PR; four patients had SD. In a phase 2 study of melphalan, prednisone, thalidomide and panobinostat in relapsed/refractory MM, 50% of the first 13 enrolled patients experienced grade 3/4 toxicities, leading to a panobinostat dose reduction to 10 mg from 15 mg (three times a week) [52]. Of 24 patients enrolled, a response of PR or better was seen in 12 patients (four VGPR, eight PR), two patients showed MR, eight had SD and two experienced PD; responses were observed in two out of seven patients who progressed on IMiDs or bortezomib.

Romidepsin has been investigated in combination with bortezomib and dexamethasone in a phase 1/2 trial that enrolled 25 patients with relapsed/refractory MM and more than one prior therapy [53]. The MTD for romidepsin was determined to be 10 mg/m^2 on days 1, 8 and 15, every 28 days. Dose-limiting toxicities included thrombocytopenia, febrile neutropenia, intracerebral hemorrhage and bowel obstruction. Eighteen out of 25 patients experienced an objective response, including two CR, 13 PR and seven VGPR. Median TTP was 7.2 months (95% CI: 5.5–19.6) and median OS was greater than 36 months. A phase 2 study of belinostat in combination with bortezomib in patients with relapsed/refractory MM was terminated due to DLTs, while another phase 2 study of belinostat alone and in combination with dexamethasone was completed [54]. Of the 12 patients evaluable for two or more cycles, one patient had a minor response for 6 weeks; five patients had SD. Together, trials assessing the combination of HDACi and PIs or other antimyeloma agents have demonstrated promising clinical activity, and the results from larger phase 2/3 trials are anticipated to further support the use of combination therapy in this patient population.

Summary and future challenges

Although clinical outcomes for patients with MM have improved substantially since the introduction of novel agents that include bortezomib and the IMiDs thalidomide and lenalidomide, as well as the expanded use of SCT, prognosis remains poor among patients with relapsed or refractory disease. There is a need for novel therapies that can be tolerated in combination with existing therapies and can overcome resistance to bortezomib, thalidomide or lenalidomide. Histone deacetylase inhibitors have demonstrated cytotoxic effects synergistic with bortezomib in MM cells and tumor models, as well as an ability to overcome resistance to bortezomib. Early-phase clinical trials for HDACi in MM have shown promising efficacy and tolerability results. Although the recently completed late-stage (phase 2b and 3) trials with vorinostat did not clearly establish a clinically meaningful benefit of the combination with bortezomib, further analysis of the data in different patient populations with relapsed/refractory MM (e.g. based on number of prior therapies, types of prior therapy) may shed light on the utility of these agents in clinical practice. In addition, there are ongoing clinical trials in relapsed/refractory MM involving HDACi and approved IMiDs, as well as the potential for combining HDACi with carfilzomib, pomalidomide, elotuzumab and

other newer novel agents, all of which should provide additional experience with HDACi to help clinicians make informed decisions on the value of HDACi in caring for patients with MM.

Along with improved outcomes, the introduction of novel therapies has raised a number of questions related to the improved survival observed with novel therapies. Will the use of novel agents as maintenance therapy delay initiation of second-line therapy? What are the criteria for switching from maintenance therapy to a second-line agent in terms of relapse (i.e. full-blown relapse vs. early signs of relapse)? Will second SCTs be a part of the treatment paradigm going forward? What is the impact of PFS on physicians switching their patients to other therapies earlier in cases of suboptimal response because of the expanded list of new treatment options? Some of these questions will be answered as more data are generated from clinical trials as newer agents are evaluated for the treatment of patients with MM, ultimately improving the care of these patients.

Potential conflict of interest:

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