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Bortezomib Combination Therapy in Multiple Myeloma

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Abstract

Bortezomib was approved for the treatment of multiple myeloma in 2003. Since then several bortezomib-based combination therapies have emerged. Although some combinations have been preceded by preclinical investigations, most have followed the inevitable process in which active (or potentially active) drugs are combined with each other to create new treatment regimens. Regimens that have combined bortezomib with corticosteroids, alkylating agents, thalidomide, and/or lenalidomide have resulted in high response rates. Despite the higher and often deeper response rates and prolongation of progression-free survival with bortezomib-based multiagent regimens, an overall survival (OS) advantage has not been demonstrated with most combinations compared to the sequential approach of utilizing anti-myeloma agents, particularly in patients less than 65 with newly diagnosed myeloma. The unique properties of some of these regimens can be taken into account when choosing a particular regimen based on the clinical scenario. For example, bortezomib, thalidomide, dexamethasone (VTD) has particular value in renal failure since none of the drugs need dose modification. Similarly, the combination chemotherapy regimen VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) is of particular value in patients presenting with aggressive disease such as extramedullary plasmacytomas or plasma cell leukemia. Ongoing clinical trials are testing combinations of bortezomib with several other classes of agents, including monoclonal antibodies, and inhibitors of deacetylases, heat shock proteins, phosphatidyl inositol 3-kinase/Akt/mammalian target of rapamycin pathway and farnesyl transferase.

Introduction

Bortezomib is boronate-based dipeptide proteasome inhibitor (PI) that primarily targets the chymotrypsin-like activities of the intracellular proteasome enzyme complex.[1] It received accelerated approval by the US Food and Drug Administration in the year 2003 based on a large multicenter phase II clinical trial.[2] This trial demonstrated an overall response in nearly a third of patients with advanced multiple myeloma (MM). Subsequent studies have attributed improvement in overall survival (OS) of MM patients in the last decade to the use of bortezomib, as well as other agents such as thalidomide and lenalidomide that are commonly referred to as immunomodulatory drugs (IMiDs). However, most, if not all, patients inevitably relapse. Each relapse requires salvage therapy, and there is decreasing response duration with successive lines of salvage therapies. Although the activity of bortezomib has been demonstrated with retreatment in prior responders, the median OS of

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patients who become refractory to bortezomib and IMiDs is disappointingly short (~ 9 months).[3]

Bortezomib initially showed activity in a phase 1 trial in which clinical benefit was noted in all 9 heavily pre-treated MM patients.[4] Subsequently, the phase 2 SUMMIT (**S**tudy of **U**ncontrolled **M**ultiple **M**yeloma Managed with Proteasome **I**nhibition **T**herapy) and CREST (**C**linical **R**esponse and **E**fficacy **S**tudy of Bortezomib in the **T**reatment of Relapsing MM) trials demonstrated meaningful benefit in relapsed refractory MM (median TTP 7-11 months and OS 17-60 months).[5,6]. The phase III APEX (**A**ssessment of **P**roteasome Inhibition for **Ex**tending Remissions) trial which led to the full approval of bortezomib in 2005 in patients who have received at least one prior therapy, demonstrated a clear 6-month survival advantage with bortezomib (median OS 29.8 months) compared to dexamethasone despite cross-over from the dexamethasone arm.[7] Here, we review bortezomib-based combination strategies, other than bortezomib-steroid doublets that have been effectively utilized for optimization of clinical response and disease control, particularly in relapsed refractory MM patients who have exhausted the standard therapies or those who are unable to derive ASCT-associated survival benefit owing to their transplant ineligibility status.

Rationale for using bortezomib-based combinations

Although some combinations have been preceded by preclinical investigations, most have followed the inevitable process in which active (or potentially active) drugs in a given malignancy are combined with each other to create new treatment regimens. Nevertheless, a review of possible biological mechanisms through which the activity of bortezomib can be influenced and targeted is worth some discussion. Bortezomib is a prototypical PI that reversibly inhibits the ubiquitin proteasome pathway (UPP) leading to cell-cycle arrest and apoptosis.[1] Combinations should ideally take into account the different mechanisms of action of bortezomib, drug resistance pathways, and incorporate strategies designed to improve sensitivity of myeloma cells to the drug. The molecular mechanisms of proteasome inhibition and the preclinical activity of bortezomib-based combinations have been elucidated in detail elsewhere in this issue of *Seminars*.

Compared to normal cells, neoplastic plasma cells are more dependent on a functional unfolded protein response (UPR) for proper folding of abundantly synthesized immunoglobulins. Bortezomib and other PIs inhibit the UPP which results in the accumulation of misfolded proteins leading to UPR-induced cell death.[8] In addition bortezomib inhibits plasma-cell adhesion to the microenvironmental bone marrow stromal cells (BMSCs) and angiogenesis.[1] The complementary and/or augmenting effects of various agents used in bortezomib-based combinations have been demonstrated in preclinical studies (Table1). The most compelling rationale for many of the combinations is from clinical trials that have exploited the additive or synergistic anti-neoplastic effect that arises when one combines drug classes with impressive independent single-agent activity and unique non-overlapping toxicities. Bortezomib lends itself to multi-drug combinations since its myelosuppressive effect is typically mild, transient and non-cumulative. We have discussed below several bortezomib-based combinations with promising clinical activities.

A. Immunomodulatory Drugs (IMiDs)-Bortezomib-based combinations

a. Lenalidomide-Bortezomib

The mechanism of anti-myeloma activity of lenalidomide is different from that of bortezomib although some degree of overlap exists. The value of this combination has been prospectively assessed in a clinical phase I/II study of bortezomib-lenalidomide-

dexamethasone (VRD) administered as 3-week cycle in newly diagnosed patients).[9] Sensory neuropathy (80%) and fatigue (54%) were commonly seen although the regimen was not associated with any treatment-related deaths. An unprecedented 100% overall response rate (ORR) was seen, with nearly three-fourths of the phase II cohort achieving a very good partial response (VGPR) or better. Despite the impressive initial response rates, a quarter of the patients relapsed within eighteen months.[9] This highly effective regimen has also been studied in the relapsed-refractory setting (Table 2: note that the dose is different in relapsed setting) in which 84% patients achieved minimal response (MR) or better with a median duration of response of 24 weeks (range 6-81).[10] The relatively small sample size of high-risk patients precludes one from drawing definite conclusions about the efficacy of this combination in patients with adverse cytogenetics. The high response rates with VRD have led to the premature adoption of this regimen as a standard front-line treatment outside of clinical trials in the United States. For standard- and intermediate-risk patients with newly diagnosed myeloma, we do not recommend VRD since there are no phase III data to support such therapy. However, in newly diagnosed patients with high-risk features for whom attainment and maintenance of a complete response (CR) is an important therapeutic goal, VRD is a reasonable alternative to other standard regimens. VRD is also of value in patients with relapsed refractory myeloma.[10]

VRD has been compared with two other combinations in the phase 2 EVOLUTION trial.[11] This randomized study concurrently evaluated VRD, bortezomib-cyclophosphamide-dexamethasone (VCD), and bortezomib-dexamethasone-cyclophosphamide-lenaldiomide (VDCR). VCD was later substituted with a modified VCD schedule which added an extra dose of cyclophosphamide on day 15. Initial treatment was followed by four six-week cycles of maintenance bortezomib in all arms. The best response was noted in the modified VCD regimen (PR or better in 100%) with nearly half of the patients achieving CR, although the number of patients enrolled in this arm was small (n=17). One-year OS was 92% for the 4-drug VDCR arm, and 100% for the other three regimens.[11] The study shows that VCD is a reasonable, much less expensive alternative to VRD in terms of highly active 3 drug combinations. Further the study shows that the addition of cyclophosphamide to VRD (or lenalidomide to VCD) to creat a 4-drug combination does not increase efficacy, but results in higher toxicity rates. However, more studies are needed.

The ongoing phase III study (IFM/DFCI2009), designed to evaluate the clinical benefit from VRD, with or without immediate ASCT followed by lenalidomide maintenance, is an important trial attempting to address the usefulness of upfront transplantation in the era of such potent regimens (NCT01208662).

b) Thalidomide-Bortezomib

A recent phase 3 study compared bortezomib-thalidomide-dexamethasone (VTD) versus thalidomide-dexamethasone (TD) as pre-transplant induction therapy and post-double ASCT consolidation therapy (Table 4).[12] The study showed higher CR/nCR rates in the VTD arm (31% vs. 11% with TD; p=0.0001). This improvement translated into superior progression free survival (PFS) rate (3-year PFS 68% vs.12%, respectively). No benefit was apparent in terms of OS.[12] Despite exclusion of patients with ≥grade 2 neuropathy, the improvement in PFS came at a cost of significant neurotoxicity with VTD [10% grade 3 or higher PN similar to that in the Spanish trial (14%)[13] using VTD induction], a significant deterrent to its long-term use. We feel that the use of this potent regimen of two neurotoxic agents is best reserved for clinical scenarios requiring immediate cytoreduction such as MM-induced acute renal failure. There are no randomized trials comparing VTD with either VCD or VRD. In most circumstances, including renal failure, we prefer VCD over VTD.

In order to improve upon the safety profile of VTD while preserving its marked efficacy (i.e. to design a regimen with best efficacy/toxicity ratio), the Intergroupe Francophone du Myelome (IFM) conducted a phase 3 trial comparing reduced dose bortezomib (1mg/m2 IV days 1, 4, 8 and 11 of a 3 week cycle), thalidomide (100mg/day), and dexamethasone (vtD) versus standard full-dose bortezomib-dexamethasone (VD).[14] The dose of dexamethasone was similar in both the arms. An increment in the dosage of bortezomib and thalidomide was permitted if less than PR was achieved with 2 cycles of vtD. However, ninety percent of patients achieved a PR or better after just 2 cycles of vtD. The grade 3-4 peripheral neuropathy was 3% with vTD and 10% with VD. Although no difference in near CR or better responses were seen (31% vs. 22% with VD), a substantial increase in CR+VGPR rates was noted with vtD prior to ASCT (49% vs. 36% with VD). The PFS or OS outcomes between the 2 groups have not shown any difference so far.[14] This study shows that optimizing the dose of bortezomib can alleviate the risk of neuropathy without sacrificing efficacy.

B. Combinations of bortezomib with conventional chemotherapeutic agents

The magnitude of synergy between conventional cytotoxic agents and bortezomib appears to be considerably high.[15] Bortezomib-based combinations such as VCD and bortezomib, melphalan, prednisone (VMP) produce high response rates. However, in most trials, despite significant improvement in the CR rates (considered a surrogate for OS), an improvement in OS has not been seen.

a. Melphalan-Bortezomib based combinations

The landmark, international VISTA (**V**elcade as **I**nitial **S**tandard **T**herapy in Multiple Myeloma: **A**ssessment with melphalan and prednisone) trial established the superiority of VMP (Bortezomib-melphalan and prednisone) compared with MP in transplant-ineligible patients with newly diagnosed myeloma.[16,17] The VISTA trial (Table 4) found a 13-month improvement in the median OS with VMP compared with MP (56.4 versus 43.1 months respectively; HR 0.7, p=0.0004). However, the survival of patients with high-risk cytogenetics (n=46) did not improve with the addition of bortezomib, a reminder of the continued poor outcome in these patients despite several advances in myeloma therapy.[17] No excess risk of second primary malignancies (SPM) was seen between the two arms.[18]

A subsequent Spanish study (Table 4) compared VMP with VTP (bortezomib, thalidomide and prednisone).[19] This trial showed that the grade 3 or worse neurotoxicity of VMP seen in the VISTA trial (13%) could be substantially reduced (~5%) with modification of the bortezomib dose from twice per week to the once per week schedule.[19] Similar observations of significantly reduced grade 3-4 non hematologic adverse effects, including peripheral neuropathy, without a compromise in efficacy were reported in an Italian study of 551 patients in which the schedule of bortezomib was modified from twice weekly to once weekly after enrollment of the first 139 patients (Table 4).[20] A separate phase III trial conducted by the IFM demonstrated that the risk of neurotoxicity can be further reduced by subcutaneous dosing.[21] Unless there is need for rapid control for myeloma (eg., acute renal failure, extramedullary disease, or plasma cell leukemia) we prefer once-weekly subcutaneous bortezomib as the standard schedule when using bortezomib in both newly diagnosed and relapsed settings.

The importance of using a modified bortezomib schedule to minimize neuropathy as much as possible was recently highlighted by the results of a recent community-based phase 3 trial of elderly patients that compared VD, VMP and VTD. This trial found that the overall average quality of life (QOL) of patients with myeloma failed to improve above baseline in any of the 3 arms after one year of therapy.[22,23]

b. Cyclophosphamide-Bortezomib based combinations

Alkylators are particularly effective in MM. Owing to the lack of cumulative stem cell damage, cyclophosphamide, unlike melphalan, preserves the ability to harvest stem cells during induction. The VCD regimen which combines cyclophosphamide and bortezomib is an excellent combination and has become our preferred bortezomib-based combination regimen in the frontline setting, as well as in the maintenance and relapsed settings for selected patients. VCD has shown high response rates (61% ≥VGPR and nearly 40% CR/nCR rates).[24] A modified VCD regimen with weekly bortezomib and low-dose dex (40 mg weekly) is equally effective compared with the original VCD regimen that employed a twice weekly bortezomib schedule and high-dose dex, and is better tolerated.[25] As suggested by the results of the EVOLUTION trial,[11] VCD produces comparable results to VRD in newly diagnosed patients. Although the follow-up of patients in these trials is short to assess the survival outcomes, the regimens incorporating bortezomib and cyclophosphamide show rapid and deep responses and appear to be promising.

c. Anthracyclines-Bortezomib based combinations

Anthracyclines, doxorubicin and pegylated liposomal preparation (PLD) have been shown to enhance MM cell killing when combined with bortezomib in preclinical studies (Table 1). Although statistically significant benefit has been seen with the use of anthracyclines in myeloma, the true clinical benefits have been modest at best. PLD has improved pharmacokinetic and safety profile compared with doxorubicin, but is more expensive, and not easily available.

A phase III international study comparing bortezomib/PLD with bortezomib alone in relapsed, advanced MM, demonstrated improved response quality (27% CR+VGPR vs. 19% with bortezomib alone; p=0.015), response duration (10.2 months vs. 7 months with bortezomib alone, p=0.0008), PFS and OS (Table 4).[26] The improved efficacy comes at a cost of greater toxicity (grade 3-4 myelosuppression, fatigue, diarrhea, hand-foot syndrome) although bortezomib induced neurotoxicity was not increased.[26] Comparatively, a non-randomized study involving VDT ± liposomal doxorubicin (Table 2) showed further improvement in PFS with the four-drug regimen (15 vs. 8 months for VDT) again without any increment in the treatment-emergent neuropathy rate in the doxorubicin containing arm compared to VDT alone. In addition this study registered responses even in patients who were previously anthracycline refractory. The cycle length in the latter study was 4 weeks instead of 3 weeks with bortezomib+ PLD phase III study.[27]

In the frontline setting, 3 published phase 2 studies have reported on the efficacy and tolerability of bortezomib combined with anthracyclines (Table 2). The recently reported outcome with intravenous DVD regimen demonstrated the advantages of using modified metronomic dosing of PLD (5mg/m2 along with dexamethasone 40mg and bortezomib 1 mg/m2 days1, 4, 8 and 11) in a longer four week schedule.[28] This modified regimen retained the high efficacy of a previously reported study of same combination by Jakubowiak et al.[29] with marked improvement in the side-effect profile (reduced fatigue, PN myelosuppression and palmar-plantar erythrodysesthesia).[28] Similarly, Popat et al reported that bortezomib dose reduction from 1.3 mg/m2 to 1.0 mg/m2 improved the toxicity profile of this highly active regimen without adversely affecting the outcome measures.[30] A randomized phase 3 HOVON65/GMMG-HD4 trial (Table 4) compared PAD with VAD (vincristine, Adriamycin and dexamethasone) induction regimen followed high-dose melphalan (HDM) therapy (in both arms) and post-transplant maintenance therapy bortezomib (in PAD arm) or thalidomide (VAD arm).[31,32] Preliminary results suggest that PAD results in a higher ORR compared with VAD (80% for PAD vs. 64% post induction) and that this difference is sustained post HDM (92% vs. 87% for VAD; p=0.01). Out of the seven phase 3 trials of pre-

transplant induction therapy the HOVON65/GMMG-HD4 trial is the only one to show survival advantage of a bortezomib-based regimen.[31] However, the possible unavailability of bortezomib-based salvage therapy at relapse for all patients in the non-bortezomib VAD arm in this study could account for the survival difference. The investigators also analyzed the prognostic value of chromosomal abnormalities in a subgroup of 354 MM patients. Importantly, the patients with del 17p13 appeared to benefit the most from the bortezomib-containing regimen: the median PFS in VAD arm was 12.0 months vs. 26.2 months in PAD ($P = .024$); the 3 year-OS for arm VAD was 17% versus was 69% ($P = .028$) for PAD. After multivariate analysis, del17p13 was an independent predictor for PFS ($P < .0001$) and OS ($P < .0001$) in VAD arm, whereas no statistically significant effect on PFS ($P = .28$) or OS ($P = .12$) was seen with PAD [33].

d. VDT-PACE

The multi-agent chemotherapy regimen VDT-PACE (bortezomib, high dose dexamethasone, thalidomide, cisplatin, doxorubicin (adriamycin), cyclophosphamide and etoposide) has been tested as the standard induction therapy in the total therapy 3 (TT3) trials conducted by the Myeloma Institute for Research and Therapy in Arkansas It is an extremely potent combination that builds by combining the backbone of VTD therapy and the four-day continuous infusion of chemotherapy developed using the components of CAD and DCEP regimens utilized in earlier studies.[34] With similar baseline prognostic features, event-free survival (EFS) and CR duration were markedly superior with TT3 vs. total therapy 2 (TT2) (Table 2), regardless of the addition of thalidomide to one arm of TT2.[34] A recently updated analysis predicted a 5-year OS of 86% (CI 82.2-89.9) in patients with low-risk gene expression profile (GEP), no cytogenetic abnormalities, β2M ≤5.5 mg/L and LDH < 190 U/L vs. only 11.18% (CI 10.15-12.31) with high-risk GEP, cytogenetic abnormalities, β2M > 5.5 mg/L and LDH ≥190 U/L, highlighting the poor prognosis of the very high-risk group despite aggressive treatment.[35] A recent trial (2006-66) replacing VDT/TD consolidation/maintenance during TT3 by VRD for 3 years demonstrated similar results (Table 2).[36]

Patients with t(4;14) on TT3 protocol had similar OS compared to the standard-risk patients, underscoring the efficacy of bortezomib-based combination therapy and ASCT in this high-risk category. The GIMEMA and HOVON-65/GMMG-HD4 protocols utilizing bortezomib with VTD induction plus post-ASCT consolidation and PAD, respectively also confirmed this effect seen with the TT3 protocol on patients harboring t(4;14).

We use VDT-PACE in newly diagnosed patients presenting with agrressive extramedullary disease or plasma cell leukemia, and in selected patients with relapsed refractory myeloma.

C. Experimental Combinations

The combinations listed here have some preclinical rationale. However, most if not all of the agents that are being tested in combination with bortezomib have failed to show significant single-agent activity in myeloma in phase 1/2 studies which is disappointing. The proof of the efficacy of these combinations will need to come from well controlled phase 3 studies. Such data are largely lacking at this juncture. Nevertheless we will review the current status of these combinations in detail since they may provide insight into directions for the future.

a.Bortezomib and Heat Shock Protein Inhibitors (HSPI)

HSP90 is a molecular chaperone for several oncoproteins that are crucial for the cancer cell growth, survival and drug resistance. Preclinical studies have demonstrated marked antitumor effects of HSP90 inhibitors even in MM, a malignancy which is not critically dependent upon the HSP client proteins.[37] The upregulation of HSPs (for example, HSP90)

by bortezomib is a cytoprotective response that leads to resistance to bortezomib. MM cells appear to be exquisitely sensitive to dual inhibition of the proteasome and HSP90. The affinity of HSP90 inhibitor, tanespimycin to tumor-related HSP90 is 100-fold higher compared to HSP from normal cells, making it an attractive therapeutic target. The early reports of clinical efficacy of HSP90 inhibitor-bortezomib combination are shown in Table 3. Interestingly, low rates of neutropenia, anorexia and peripheral neuropathy (PN) compared to historical data with bortezomib monotherapy were noted, and hepatotoxicity was manageable. The low rates of severe PN may be related to the neuroprotective effect of tanespimycin.[38] The TIME-2 randomized study comparing bortezomib plus three different doses of tanespimycin in relapsed-refractory MM patients was truncated early for non-scientific reasons. Prior use of lenalidomide and bortezomib was a prerequisite for eligibility in this study. The preliminary results suggest an overall response rate (ORR) of 14% in this heavily pretreated (median number of therapies=5) population (Table 3).[39] A phase 1/2 trial evaluating another novel HSP inhibitor, KW 2478 in combination with bortezomib is currently ongoing (NCT01063907). The results of a completed phase 3, open-label trial (NCT00546780). for patients with MM in first relapse, comparing tanespimycin plus fixed-dose of bortezomib with bortezomib alone would hopefully shed light on the efficacy of this doublet which has demonstrated modest activity to date.

b. Deacetylase Inhibitors (DACIs) with Bortezomib

In-vitro data suggest that DACIs exhibit potent anti-myeloma activity in combination with bortezomib by inhibiting aggresome formation, or by enhancing the histone acetylation properties of bortezomib (Table 1). Deacetylases (DACs) are enzymes that remove the acetyl groups from several target (both histone and non-histone) proteins including HSP90, HIF-1a, BCL-6, p53, involved in the DNA repair, gene expression and cell growth. DACIs reverse the deacetylated status of MM cells and lead to persistent acetylation. This promotes expression of genes that induce cell cycle arrest and apoptosis.[40] Four clinical trials evaluating the efficacy of DACI in MM as monotherapy have demonstrated modest activity, but acceptable safety profile. The PANORAMA 2 study, a multicenter, phase 2 trial of pan deacetylase inhibitor, panabinostat-bortezomib and dexamethasone in patients who had to be bortezomib-refractory for enrollment showed an ORR of nearly 25%.[41] Another recently reported small phase1/2 study evaluating the combination of bortezomib, dexamethasone and romidepsin (an HDAC inhibitor, currently approved for cutaneous T cell lymphoma) in the relapsed-refractory MM demonstrated a 60% PR rate.[42] A retrospective review of nine patients, refractory to VRD who received vorinostat (Z) additionally (VRDZ) demonstrated 89% disease-control rate (stable disease or better) but disappointingly short median duration of response of 3 months and median OS of 4 (3-21) months.[43]

The above results with Bortezomib-DACI combinations (Table 3) while interesting need confirmation in phase 3 trials to isolate what benefit, if any, is due to the addition of DACI. Two phase III trials: the VANTAGE 088 study[44] (a randomized, double blind placebo controlled phase 3 trial of bortezomib versus vorinostat plus bortezomib) and PANORAMA 1 trial[45] (panabinostat, bortezomib versus bortezomib) are addressing this. Preliminary results of VANTAGE 088 have been reported and are sobering, with no clinically significant improvement in PFS (the median improvement was 26 days), and no improvement in OS (Table 4). The results of PANORAMA 1 trial are awaited.[16]

c. AKT and mTOR Inhibitors plus Bortezomib

The activated PI3-K/AKT/mTOR pathway is a critical cytokine stimulated pro-tumoral pathway[46] that mediates growth and survival of MM cells through their interaction with the BMSCs. TORC1 complex of the downstream mTOR kinase is inhibited by rapalogs. However, TORC1 inhibition-associated feedback activation of the PI3K/AKT pathway

protects against apoptosis, and TORC1 inhibitors can only induce cell-cycle arrest without apoptosis. Dual TORC1/2 complex inhibitors may overcome the activated AKT mediated resistance seen with use of TORC1 inhibitors alone. In fact, a recent preclinical study has shown that TORC1/2 knock-down significantly inhibits the proliferative capacity of MM cells.[47] However the issue of the feedback activation of the MEK/ERK resistance pathway as a result of TORC1 inhibition still remains. Therefore, specific inhibitors of TORC2 alone that inhibit phosphorylation and activation of AKT and are currently under development could potentially be more useful.

The postulation of synergy between PI3K/AKT/mTOR pathway inhibition and bortezomib formed the basis of a recent phase1/2 trial studying the steroid sparing regimen of weekly temsirolimus (a rapalog with anti-TORC1 activity) and bortezomib in heavily-pretreated relapsed and refractory MM patients. In the phase 2 portion, a third of patients (14 out of 43) attained PR or better. Myelosuppression, particularly thrombocytopenia was the most common toxicity observed.[48]

Resistance to bortezomib-induced apoptosis has been demonstrated to be associated with AKT, β-catenin and survivin (a member of inhibitor of apoptosis family) upregulation. Perifosine is a novel, proapoptotic, signal transduction modulator which directly inhibits the constitutively phosphorylated AKT in MM cells. This well-tolerated, oral agent has demonstrated activity in relapsed/refractory MM in combination with both the conventional and novel anti-myeloma agents.[49] Recently, a phase 1/2 study of perifosine in combination with bortezomib with or without dexamethasone evaluated a heavily pretreated cohort of 84 patients with relapsed and /or refractory MM (Table 3).[50] An ORR of 41% (65% in bortezomib–relapsed and 32% in bortezomib refractory) was noted. GI toxicities, fatigue and musculoskeletal pain were the predominant toxicities encountered. A phase III multicenter trial of testing the value of perifosine in relapsed/refractory patients previously treated with bortezomib is ongoing (NCT01002248).

d. Farnesyl transferase inhibitors (FTIs)

A phase 2 trial evaluating the efficacy of single agent FTI, tipifarnib was conducted on the premise that MM patients with mutated Ras exhibit reduced chemosensitivity and targeting farnesylation of oncoprotein Ras would inhibit its membrane association and signaling activity.[51] The study involved forty-three heavily pre-treated patients with advanced MM and demonstrated disease stabilization in 64% of patients independent of farnesyl inhibition. The drug was well tolerated (toxicities included fatigue, diarrhea, myelosuppression and neuropathy) and 40 patients with SD remained stable for 5 months or more.[51] This study along with the demonstration of pre-clinical synergistic activity of combination therapy (Table 1) served as the basis for phase I trial evaluating combination of bortezomib and FTI in relapsed/refractory MM (Table 3). Again, so far only stabilization of disease has been reported in nearly 50% of patients and the optimal dose is yet to be defined.[52] The sequence of drug administration in the combination is important and bortezomib followed by FTI is recommended for optimal efficacy.[52] The combination appears to be effective, but more data are required.

e. Monoclonal Antibodies (MAb)

Potential targets for MAbs in MM include antigens predominantly expressed on MM cells, growth factors, their receptors and signaling proteins although to date only modest clinical activity has been observed with MAb monotherapy in MM.[53] While meaningful responses have been noted with well tolerated bortezomib-based regimens incorporating elotuzumab (chimeric anti-IL6 monoclonal antibody) or siltuximab, a chimeric anti-IL6 monoclonal antibody, (Table 3), the results of a recent randomized phase 2 trial of bortezomib vs.

bortezomib+ mapatumumab (a fully human agonistic antibody activating the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) receptor-1) in relapsed refractory patients were largely disappointing.[54] A phase 2 trial of MPV with or without siltuximab is currently underway (NCT00911859).

Out of the many MAb combination therapies evaluated so far, elotuzumab-based combinations with novel agents, bortezomib or lenalidomide appear to be the most promising in relapsed refractory MM. In a phase 1 study of bortezomib and elotuzumab nearly two-thirds of patients achieved a clinically meaningful response (≥MR) with nearly one-half of all evaluable patients achieving at least PR.[55] The median time to progression was 9.5 months. Infusion-related toxicities and grade 3-4 lymphopenia (25%) were commonly encountered, although adverse effects were largely manageable.[55]

The place of MAb therapy in the current treatment paradigms for MM is still evolving. The results of ongoing trials with MAbs plus existing novel agent-based therapies will define the roles of these agents that have a relatively favorable toxicity profile.

Conclusions and Future Directions

Implicit in our review is the development of numerous potent bortezomib-based combinations that have spawned during the past decade. Importantly, the economic implications of combining expensive agents deserve to be factored into the clinical decision making. The UPFRONT[22] and the PETHEMA trials[19] comparing the efficacy of different bortezomib-based combinations have been unable to establish the superiority of one specific combination. Specifically, the high-risk patients continue to have a poor outcome, although some bortezomib-based regimens appear to be able to overcome the adverse prognostic effects of t(4;14) when bortezomib-based induction and maintenance therapy is incorporated into the treatment plan, particularly in the context of tandem transplantation. With time, neoplastic plasma cells acquire a succession of distinctive features that enable them to proliferate via activation of alternative pathways notwithstanding the plethora of available combination therapies. Several next-generation PIs with molecular characteristics different from bortezomib are being evaluated, and a few that target different proteasome subunits can somewhat overcome bortezomib resistance when used alone or with other effective agents.

While several combinations outlined in this review are frequently being utilized, ongoing trials allow one to envision an optimized approach to proteasome inhibition that incorporates rational use of bortezomib as well as newer second-generation PIs such as carfilzomib, marizomib, and MLN 9708. Desirable properties such as oral route of administration and improved safety profile may make some PIs (e.g., MLN 9708) attractive agents if clinical efficacy is confirmed. The last decade has established a solid foundation upon which many rational bortezomib- and the next-generation PI-based combination regimens can be developed to further improve the outcome of patients afflicted with multiple myeloma.

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Table 1

Rationale for Novel Combinations with Bortezomib (V)

Class	Drug(s)	Rationale for Combination Therapy with Bortezomib
Enzyme Inhibitors		
HSP inhibitors	Tanespimycin	Resistance to V is mediated via upregulation of HSPs. HSPIs sensitize MM cells to V by inhibiting HSP which then leads to increased accumulation of misfolded proteins and further activation of endoplasmic stress response.
Deacetylase Inhibitors (DACi)	Vorinostat Panabinostat Belinostat Romidepsin	Synergy with V has been primarily attributed to the dual inhibition of aggresomes and proteasomes by DACi and V, respectively, thereby blocking protein degradation by different mechanisms. Upregulation of CDK inhibitors such as p21 (vorinostat) or down regulation of antiapoptotic Bcl2 (romidepsin) are some specific mechanisms that have been elucidated.
AKT/mTOR inhibitors	Perifosine Temsirolimus	Treatment with V has been shown to upregulate pAkt in MM cells and perifosine has been shown to inhibit the upregulated pAkt. In addition, perifosine enhances V induced cytotoxicity via activation of JNK (a stress response protein mediating apoptosis by UPR).
Pan-Bcl inhibitors	Obatoclax	Antagonist of BH3 binding groove of Bcl family proteins; induces apoptosis by interfering with the interaction between prov.(e.g.Bak)and anti-apoptotic proteins (e.g.Mcl-1 which accumulates with V therapy a a result of PI) demonstrating augmented cytotoxic responses- against MM cells
Farnesyl Transferase Inhibitors(FTIs)	Tipifarnib Lonafarnib	FTIs in combination with V overcome CAM-DR; induce ER stress-related MM cell apoptosis, downregulation of pAKT and disruption of aggresome complex via inhibition of HDAC6
Immunomodulating Agents (IMiDs)	Thalidomide Lenalidomide Pomalidomide	R, in particular, triggers caspase-8 dependent apoptosis and sensitizes MM cells to death receptor, Fas-mediated apoptosis; disrupts BMSC support, downregulates NFKB by inhibition of IGF-1 and TNF-α (in contrast to IKKB mediated downregulation by V); immunomodulation with improved NK cell- mediated MM cell destruction.
DNA Damaging Agents	Alkylators Anthracyclines Bendamustine	In addition to its proapoptotic effects through decreased expression of Bcl-2, XIAP and other antiapoptotic factors V inhibits the protective cellular response to genotoxic stress thereby restoring the sensitivity to DNA damaging agents. Anthracyclines further demonstrate synergy by suppress V-induced HSP expression
Monoclonal Antibodies	Elotuzumab Mapatumumab Siltuximabb	V enhances activity of monoclonal antibodies by rendering MM cells more vulnerable to NK cell -mediated ADCC

Abbreviations: V=Bortezomib, HSPi = Heat Shock Protein Inhibitor, IGs = Immunoglobulins, PI= Proteasome Inhibitor, JNK= C-Jun N terminal kinase, UPR=Unfolded Protein Response, CAM-DR = Cell-Adhesion Mediated Drug Resistance, R=Lenalidomide, IGF-1 Insulin like Growth Factor, TNF-α = Tumor Necrosis Factor Alpha, ADCC Antibody-Dependent Cellular Cytotoxicity

Table 2

Selected Phase 1 /2 Trials incorporating Bortezomib + IMiDs and/or Cytotoxic agents

Study	Regimen	Cohort	N	ORR	≥VGPR (%)	MTD/Phase 2 dose	Cycle	
							Days	#
EVOLUTION Phase 1[56]	VDCR	NDMM ±ASCT	25	96	56	V 1.3mg/m2 IV d 1,4,8,11 D 40mg PO d 1,8,15 R 15mg (25mg in VDR) PO d 1-14 C 500mg/m2 PO d 1,8 ± d 15 (mod) V maint. 1.3mg/m2 IV d 1,8, 15,22	21	8
EVOLUTION Phase 2[11]	VDCR		132		59			
	VDR				50			
	VDC				41		42	4
	VDC-modified				59			
Phase 2[24,25]	CyBorD	NDMM ±ASCT	33	88	61	V 1.3mg/m2 IV d 1,4,8,11 D 40mg PO d 1-4,9-12,17-20 C 300mg/m2 PO d 1,8 15,22 V 1.5mg/m2 IV d1,8,15,22 (mod) D 40mg d 1,8,15,22 from cycle 3(mod)	28	4
	CyBorD-modified		30	93	60			
		Total	63	90	60			
Phase 1/2[9]	RVD	NDMM ±ASCT	66	100	67	R 25mg PO d 1-14 V 1.3mg/m2 IV d 1,4,8,11 D 20mg PO d 1,2,4,5,8,9,11,12 cycles 1-4 D 10mg PO d 1,2,4,5,8,9,11,12 cycles 5-8	21	8
Phase 1/2[57]	RVDD	NDMM ±ASCT	74	96	67	R 25mg PO d 1-14 V 1.3mg/m2 IV d 1,4,8,11 D 20mg PO d1,2,4,5,8,9,11,12 cycles 1-4 D 10mg PO d 1,2,4,5,8,9,11,12 cycles 5-8 PL**D** 30mg/m2 IV d4	21	8
DSSM XI Phase 1[58]	VDC	NDMM +ASCT	30	77 92 @ MTD	NA	V 1.3mg/m2 IV d 1,4,8,11 D 40mg PO d 1,2,4,5,8,9,11,12 C 900mg/m2 IV d1	21	3
Phase 2[59]	VDT (D=PLD)	NDMM ±ASCT	40	78	35(CR+nCR)	V 1.3mg/m2 IV d 1,4,15,18 PL**D** 20mg/m2 IV d1,15 T 200mg PO daily continuously	28	6 + 2
Phase 2[28]	DVD	NDMM	35	72	29	D 40mg IV d 1,4,8,11 V 1 mg/m2 IV d 1,4,8,11 PLD 5mg/m2 d 1,4,8,11	28	8
Phase 2[29]	VDD	NDMM ±ASCT	40	93	63	V 1.3mg/m2 IV d 1,4,8,11 D 40mg PO d1,2,4,5,8,9,11,12 cycles 1 D 20mg PO d 1,2,4,5,8,9,11,12 cycles 2-8	21	6

Study	Regimen	Cohort	N	ORR	≥VGPR (%)	MTD/Phase 2 dose	Cycle	
							Days	#
						PL**D** 30mg/m2 IV d4		
Phase 2[60]	DBd B=bortezomib	NDMM +ASCT	50	98 ≥MR	27(CR+nCR)	V 1.3mg/m2 IV d 1,4,8,11 D 40mg PO d1-,4, 8-11, 15-18 cycle 1 D 40mg PO d 1-,4, cycles 2-4 PL**D** 30mg/m2 IV d4	21	3-4
Phase 1/2[30]	PAD1	NDMM +ASCT	21	95	62	V 1.3mg/m2 IV d 1,4,8,11 (PAD1) V 1 mg/m2 IV d 1,4,8,11 (PAD1)	21	4
Phase 2	PAD2		20	89	42	D 40mgPO, d1-4,8-11,15-18 cycle1 D 40mgPO, d1-4,cycle2 Dox 9mg/m2 d1-4		
Phase 2	VDT-PACE	NDMM + tandem ASCT	303	92 *	NA	V 1mg/m2/d IV 1,4,8,11 D 40mg PO, d1-4		2(I)
TT3	VTD (1yr) TD (yr 2 & 3)		668	81(+T)		T 200mg PO /d continuously		2(C)
TT2[34]	VAD-DCEP-CAD-DCEP			79(no T)		P 10mg/m2/d CIV 1-4 A 10mg/m2/d CIV 1-4 C 400mg/m2/d CIV 1-4		4 (I)
	DPACE/Interferon ±T					E 40mg/m2/d CIV 1-4 (Interferon± D maintenance in TT2)		4 (C)
Phase 2[36]	VDT-PACE	NDMM + tandem ASCT	303	59 **	NA	V 1mg/m2/d IV 1,4,8,11 D 40mg PO, d1-4	28-42	4
TT3	VTD (1yr) TD (yr 2 & 3)					T 200mg PO /d continuously		
TT3B	VDTPACE VRD (3 yrs)		177	61		P 10mg/m2/d CIV 1-4 A 10mg/m2/d CIV 1-4 C 400mg/m2/d CIV 1-4 E 40mg/m2/d CIV 1-4		
Phase 2[10]	VRD	RR	64	84 ≥MR	21(CR/nCR)	V= 1mg/m2 IVdays 1,4,8,11 V=days 1,8 after cycle 8 R=15mg/day PO days 1-14 D(20-40mg PO days of and afterV D=10mg 1,2, 8,9 after cycle8	8	21
Phase 1/ 2[61]	VCP	RR	37	95 ≥MR	50(CR/nCR)	V 1.3mg/m2 IV d 1,4,8,11 **or** V 1.5mg/m2 IV d 1,8,15 C 300mg/m2 PO d 1,8 15,22 P 100mg PO every other day	28	8
Phase 2[62]	VDC	RR	54	76	15(CR)	V 1.3mg/m2 IV d 1,4,8,11 cycle1-8 D 20mg PO d1,2,4,5,8,9,11,12 C 50mg daily PO continuously V 1.3mg/m2 d1,8,15,22 cycle 9-11)	21 35	8 3
Phase 2[63]	PAd	RR	64	67	25	V 1.3mg/m2 IV d 1,4,8,11 D 40mg d1-4	28	6

Study	Regimen	Cohort	N	ORR	≥VGPR (%)	MTD/Phase 2 dose	Cycle	
							Days	#
						Dox 30mg/m2 IV d1		
Phase 2[27]	VDT	RR	28	36	21	V 1 mg/m2 IV d 1,4,8,11 D 24mg PO d1,2,4,5,8,9,11,12 T 100mg PO continuously	28	6
	VDT+PLD		42	74	52(CR/nCR)			
Phase1/2[64]	V+ Bendamustine	RR	39	48	8	V 1 mg/m2 IV d 1,4,8,11 Benda 90mg/m2 IV d 1,4	28	8

*2-year sustained CR rate I=Induction, C=consolidation

**2-year CR estimate

Abbreviations: N=Number of patients, ORR=Overall Response Rate, VGPR=Very Good Partial Response, MTD=Maximum tolerated dose V/Bor =Bortezomib, D/d=Dexamethasone, C/Cy=Cyclophosphamide, R=lenalidomide,T=thalidomide, PLD/D=Pegylated Liposomal Doxorubicin, P=Prednisone or CisPlatin (in VDTPACE), E=Etoposide, PAD=Bortezomib, Doxorubicin (Adriamycin), Dexamethasone, NDMM=Newly Diagnosed Multiple Myeloma, RR-=Relapsed and/or Refractory, ASCT=Autologous Stem Cell Transplantation, nCR=Near Complete Remission, NA=Not Available, CIV=Continuous Intravenous, PO=Oral, IV= Intravenous,

Table 3

Selected Phase 1 and 2 Trials of Combinations involving Bortezomib (V) and Enzyme Inhibitors or Monoclonal Antibodies in Relapsed and/or Refractory Multiple Myeloma

Class/ Agent(s)	Phase	N	CBR %	CR %	PR %	SD %	PFS mo	OS mo	Comments
Heat Shock Protein 90 Inhibitor									
i) Tanespimycin + V MTD: 340 mg/m2 IV[38]	1/2	72	27	3	12	33	NA	18	Severe PN not noted possibly due to neuroprotective effects of tanespimycin Lower anorexia, constipation & neutropenia rates compared to V alone.
		V naïve	48				7.2	NR	
		V pretreated	22				3.7	17.7	
		V refractory	13				1.6	13.8	
TIME 2 Tanespimycin+V[39]	2	22	14	0	9	45	NA	NA	Study prematurely terminated due to resource-related reasons
Deacetylase Inhibitors									
i) VANTAGE 095[65] Vorinostat+V ± Dex after 4 cycles if SD	2b	143	31	1	16	46	3	11	Activity shown in a heavily pre- treated cohort.(median 4 lines); V refractory and refractory, intolerant, or ineligible for IMiD-based therapy
ii) PANORAMA-2[41] anabinostat+V+Dex	2	55**	49	0	20	NA	NA	NA	A relatively low rate of PN (24%) seen. 2% grade 3/4 PN observed. contrast romidepsin +VD
iii) Panabinostat+V ± Dex (San Miguel) 238	1B	Escalation part 47	76	13	40	15	NA	NA	Common GD3/4 AEs thrombocytopenia, neutropenia, asthenia and anemia
		Expansion part 15							
		V refractory	66						
iv) Romidepsin +V+ Dex[42]	1/2	25	72	8	52	8	7*	76% at 1-yr	PN rates (76%) almost twice that reported in APEX (36%).
AKT/mTOR/Farnesyl Transferase or Serine/Threonine Kinase Inhibitors									
i) Perifosine+V± Dex[50]	1/2	84	41	4	18	41	6	25	Overall well tolerated; side effects, including GI toxicities and fatigue were manageable.
		V relapsed :20	65	10	35	35	9	NR	
		V refractory: 53	32	2	11	43	6	23	
ii) Temsirolimus+V[48]	1	20	20	0	5	60	6	11	3 deaths noted during treatment. Cytopenias commonly seen
	2	43	47	5	19	44	5	NR	

Class/ Agent(s)	Phase	N	CBR %	CR %	PR %	SD %	PFS mo	OS mo	Comments
iii) Tipifarnib+V[52]	1	16	13	NA		32	NA	NA	Commonest AE Gd 2 diarrhea (24%)
iv) Enzastaurin+V[66]	1	23	NA	0	17	39	8*	NA	Commonest AE anemia (70%)
Monoclonal Antibodies									
i) Elotuzumab (E)+V[55]	1	28	63	7	41	NA	10*	NA	E related key toxicities: infusion reactions
ii) Siltuximab+V[67]	2	21	NA	14	43	NA	NA	NA	33% discontinued therapy due to AE

Abbreviations : CBR= Clinical Benefit Rate, CR=Complete Remission, PR=Partial Remission, SD=Stable Disease, PFS=Progression-free survival, OS=Overall Survival, NA=Not Available, NR=Not Reached, Gd =Grade, PN=Peripheral Neuropathy, AE=Adverse Effects, IMiDs=Immunomodulatory Drugs,

Table 4

Phase 3 TRIALS WITH BORTEZOMIB (V)- BASED COMBINATIONS IN MULTIPLE MYELOMA*

	Combination	N	Cohort	ORR (%)	PFS mo	HR for PFS	P value for PFS	OS mo	HR for OS	P value for OS
1	**GIMEMA**[12]				(3-yr)			(3-yr)		
	VTD X 3 +ASCT × 2+ VTD X 2	236	NDMM ASCT eligible	96	68%	0.63	**0.006**	86%	NA	0.30
	TD X 3+ ASCT × 2 + TD X 2	238		89	56%			84%		
2	**IFM 2007-02**[14]									
	VD + ASCT	99	NDMM, ASCT eligible	89	30	NA	0.22	NA	NA	NS
	vtD+ASCT	100		86	26					
3	**PETHEMA**[19]		NDMM ≥ 65 yrs					(3-yr)		
	VMP+ VT or VP maintenance	130		81	34	1.2	0.1	74%	1.2	0.3
	VTP + VT or VP maintenance	130		80	25			65%		
4	**PETHEMA/GEM05MEN0S65**[68]		NDMM <66 ASCT eligible							
	TD	127		NA	27	NA	**0.006**	4-yr	NA	NS
	VTD	130			NR			76%***		
	VBMCP/VBAD/B	129			38					
5	**VISTA**[16]									
	VMP	327	NDMM ASCT ineligible	71	22	0.6	**<0.001**	56	0.7	**<0.001**
	MP	328		35	15			43		
6	**UPFRONT**[22]							(1-yr)		
	VD+ V maintenance	168	NDDM Elderly, ASCT ineligible	73	14	NA	NS	87%	NA	NS
	VTD+ V maintenance	167		80	15			86%		
	VMP+V maintenance	167		69	17			89%		
7	**HOVON 65/GMMG-HD4**[31]		NDMM +ASCT		3-yr			3-yr		
	VAD with T maintenance	305		87	42%	0.8	0.047	71%	0.7	.048
	PAD with V maintenance	308		92	48%			78%		
8	VMP		NDMM ≥ 65 yrs ASCT Ineligible			0.6	**0.008**	3-yr	0.9	0.77

	Combination	N	Cohort	ORR (%)	PFS mo	HR for PFS	P value for PFS	OS mo	HR for OS	P value for OS
	VMPT-VT[20]	257		81	27			89%		
		254		89	NR			87%		
9	**VANTAGE 088**[44]									
	Bortezomib+Vorinostat	347	RR **	56	8	0.8	**0.01**	NR	0.9	0.35
	Bortezomib+placebo	320		41	7			28		
10	**IFM-EBMT**[69]		RR after ASCT					(2-yr)		
	VTD	135		90	19	NA	**0.001**	72%	NA	0.18
	TD	132		69	13			68%		
11	**DOXIL-MMY-3001**[26]							(1.25-yr)	0.7	
	V	322	RR	41	9	0.6	**<0.001**	65%		**0.03**
	PLD+V	324		44	7			76%		

* Bortezomib-dexamethasone doublet excluded

** Patients with prior BTZ resistance excluded

*** No OS difference in 3 arms

Abbreviations : ORR= Overall Response Rate, HR=Hazard Ratio, NDMM=Newly Diagnosed Multiple myeloma, ASCT, Autologous Stem Cell Transplantation, PFS=Progression-Free Survival, OS=Overall Survival, NA=not Available, NR=Not Reached