Proteasome inhibitors: beyond NFKB inhibition alone and the emerging role of combination therapy in the treatment of multiple myeloma

Introduction

The emerging role of novel agents has dramatically increased treatment options for patients with multiple myeloma (MM), with new agents including thalidomide, bortezomib and lenalidomide significantly improving outcomes for patients with both newly diagnosed and relapsed and refractory MM.\textsuperscript{1-5} Studies in early relapse suggest that both bortezomib and lenalidomide are more effective in patients who have received fewer prior therapies and provide a rationale to investigate their use in the frontline setting.\textsuperscript{6,7} As an example, the ability to safely combine bortezomib with other combinations and the consistent signal provided by informative pre-clinical studies has led to a number of important combination strategies in both the upfront and the relapsed and relapsed/refractory settings (Figure 1). The role of NFKB as a key therapeutic target has thus been validated, and beyond NFKB the importance of other downstream targets has become established, as combination therapies have shown activity even in highly resistant MM.\textsuperscript{8,9} Early clinical studies with small molecules and monoclonal antibodies have likewise demonstrated that there are a number of promising new agents in clinical development that when combined with established platforms of bortezomib-based therapies may provide additional treatment options for patients with relapsed and refractory disease.

The impact of bortezomib – based therapy in the upfront treatment of multiple myeloma

The phase III VISTA trial reported 682 newly diagnosed elderly patients were randomized to VMP (n=344) or MP (n=338).\textsuperscript{10} The trial was halted early because VMP showed a statistically significant benefit in the TTP (the primary endpoint) and all secondary endpoints.

The overall CR (immunofixation negative) rate by M protein was 35% for VMP and 5% for MP (p<0.000001). VMP was superior to MP regardless of age, renal status, or cytogenetics (t[4;14], t[14;16], 17p deletion). The median time to next therapy (TNT), defined as the interval between the start of the study therapy (VMP or MP) and the start of next therapy, has not been reached in the VMP arm; TNT in the MP arm was 20.8 months (p=0.000009).

VMP had higher rates of grade 3
gastrointestinal toxicities (19% vs. 5%), peripheral neuropathy (13% vs. 0%), and fatigue (7% vs. 2%). Peripheral neuropathy resolved or improved in 75% of cases in a median of 64 days. Grade 4 nonhematologic toxicities were rare in both groups, and treatment-related mortality was low at 1% in the VMP arm and 2% in the MP arm.

The median age of this population was 71 years. Approximately one third were 75 years or older, had stage III disease, or had a β2-microglobulin level greater than 5.5 mg/L.

In the updated analysis of IFM2005/01, 482 newly diagnosed MM patients were randomized to VD or VAD induction. VD resulted in a statistically significant improvement over VAD in the primary endpoint, CR+nCR rate. VD was superior to VAD regardless of the presence or absence of adverse risk factors (chromosome 13 deletion, high β2-microglobulin levels [≥3.0 mg/L]). By TTT analysis, posttransplant, pts treated with VD induction had superior CR+nCR rates (35.0% vs. 23.6%; \( p=0.0056 \)) and VGPR or better rates (61.7% vs. 41.7%; \( p<0.0001 \)) than patients treated with VAD induction. Importantly, in patients who actually received transplant, response rates were higher, and DCEP consolidation which was given prior to first transplant in a second randomization in both arms did not appear to add benefit. Furthermore, the need for second transplant was significantly reduced for those patients receiving bortezomib–based induction.

In terms of toxicity, VD resulted in a greater incidence of thrombocytopenia (10.1% vs. 5% with VAD), herpes zoster infection (8.4% vs. 2.1%, pts in this trial were not required to receive acyclovir prophylaxis), fatigue (21.4% vs. 16.7%), rash (10.1% vs. 5.4%), and peripheral neuropathy (35.3% vs. 22.6%), but less anemia (12.2% vs. 21.8% with VAD), neutropenia (5% vs. 10.9%), infection (5% vs. 7.5%), and thrombosis (3.8% vs. 8.4%). Rates of grade 3 or 4 peripheral neuropathy were 6.3% with VD and 1.3% with VAD. Moreover, VD had no detrimental impact on stem cell collection.

The median age of the study population was 57 years. Approximately 22% of the pts had stage III disease, approximately 58% had a β2-microglobulin level of 3 mg/L or higher, and about 40% had chromosome 13 deletion (determined by FISH).

In the MMY-3006 trial, 351 newly diagnosed patients were randomized to VTD (n=176) or TD (n=175). In this interim analysis, 129 patients in the VTD arm and 127 patients in the TD arm were evaluable for response. VTD resulted in a statistically superior CR+nCR rate. VTD also resulted in a superior rate of patients achieving a VGPR or better.

In patients with chromosome 13 deletion, the CR+nCR rate was 43% in patients treated with VTD and 4% in patients treated with TD (\( p<\)}
In patients with t(4;14) translocation, the CR+nCR rate was 47% in patients treated with VTD and 8% in patients treated with TD (p=0.002). Stem cell collection was not impaired by VTD.

A total of 74 patients in the VTD arm and 79 patients in the TD arm went on to transplant. VTD resulted in statistically significant improvement in posttransplant CR+nCR rates (57% vs. 28%; p<0.001) and in posttransplant rates of VGPR or better (77% vs. 54%; p=0.003).

VTD resulted in more peripheral neuropathy (7% vs. 2% with TD) and skin rash (6.5% vs. 1%), but less DVT (3% vs. 6.5%).

In this patient population, approximately half the patients had stage I disease. Median β2-microglobulin was about 3 mg/L. There were no statistically significant differences in baseline demographics between treatment arms.

**Novel bortezomib–based combinations in multiple myeloma**

In a phase I study, lenalidomide and bortezomib (MTD: 15 mg/1.0 mg/m²) ± dexamethasone (RVD) at 20-40 mg achieved a 58% response rate in relapsed/refractory MM pts.13 A subsequent study evaluating RVD at the phase I MTD in up to 65 pts with relapsed/refractory MM following 1-3 prior lines of therapy was reported at the 2008 ASCO meeting.14 This phase II study showed that the combination of RVD is active and well tolerated in relapsed/refractory MM pts, including those who received prior lenalidomide, bortezomib, thalidomide, and SCT. Responses were assessed by modified EBMT and Uniform Criteria. In 33 evaluable pts, the overall response rate (ORR) (≥ minimal response (MR)) was 73% (95% CI 55.6-85.1%), including 55% ≥ partial response (PR) and 36% very good PR (VGPR)/ near complete response (nCR)/ complete response (CR). Median duration of response (DOR) was 39 weeks (95% CI 13.5-63 weeks) with median time to progression (TTP), progression free survival (PFS), and overall survival (OS) not yet reached. Toxicities (NCI CTCAE v3.0) were manageable, consisting mainly of grade (G) 1/2 myelosuppression. Attributable non-hematologic toxicities include deep vein thrombosis (DVT) (2 pts), G3 peripheral neuropathy (PN) (1 pt), and G3 atrial fibrillation (2 pts). Dose reductions were required for lenalidomide (9 pts), bortezomib (5 pts), and dexamethasone (14 pts).

A phase I/II study of RVD in the upfront setting for MM patients was also reported at ASCO 2008.15 Patients received lenalidomide 15-25 mg on d 1-14, bortezomib 1.0-1.3 mg/m² on d 1, 4, 8, 11, and dexamethasone (dex) 40/20 mg (cycles 1-4/5-8) on day of and after bortezomib for up to eight 21-d cycles, initially at 4 planned dose levels. Dose escalation proceeded depending on dose-limiting toxicities (DLTs) and based on safety data, dose level 4M was added with a reduced dex starting dose (20/10 mg). Patients with >PR could proceed to SCT after > 4 cycles. Encouragingly, RVD at the maximum planned dose resulted in PR or better in 100%, with 71% of pts having high-quality response (VGPR or better) and 36% nCR/CR in the trial overall.15

Whilst the numbers in this study are small for those going to SCT to date, there were no significant difficulties with stem cell mobilization reported.15 Tolerability has been good, with 2 DLTs of G3 hyperglycemia due to high-dose dex (40 mg) seen in dose level 4. Dose reductions in cycle 2 and beyond have occurred for lenalidomide in 12 pts, bortezomib in 11 pts, and dex in 18 pts, mostly in dose levels 1-4. Toxicities have thus been manageable, with no grade 4 PN, only 2
DVTs, and no treatment-related mortality.\textsuperscript{15}

Preclinical evaluation has shown that the combination of RVD and doxorubicin is highly active. Based on these observations, a phase I/II study of a 4-drug combination, using the RVD platform with the addition of liposomal doxorubicin – so called RVDD – has been developed. The primary objective is to improve CR/nCR rates in newly diagnosed MM, and the study has recently been activated in the Multiple Myeloma Research Consortium (MMRC) with co-sponsorship between 3 pharmaceutical companies.

Preclinical studies have shown that heat shock protein 90 (Hsp 90) inhibition has potent anti-MM activity, especially in combination with bortezomib.\textsuperscript{16} At the ASH 2007 meeting in Atlanta, GA, a phase II trial assessing two formulations of the Hsp 90 inhibitor, tanespimycin, used in combination with bortezomib was reported.\textsuperscript{17} Patients had a median of 5 prior lines of therapy, and most had received prior bortezomib. Response rates and toxicity were similar with both formulations, though efficacy data in pts treated with the suspension was limited to 9 pts (vs. 25 with the Cremophor formulation). Response rates in bortezomib-naïve and bortezomib-pretreated pts were about the same at approximately 50%. However, pts with confirmed evidence of being refractory to bortezomib (defined as no response to, or disease progression with 60 days of being treated with a bortezomib-containing regimen) were less likely to respond to the tanespimycin-bortezomib combination (with PR or better reported in 3 of 18 (17%) patients), although this group were both relapsed and refractory, and had very advanced disease. Primary toxicities were gastrointestinal (diarrhea), fatigue, elevated liver enzymes, and thrombocytopenia. Interestingly, significant PN did not occur, potentially as a result of up-regulation of Hsp70 by tanespimycin, which may be neuroprotective, an observation that has been confirmed in a rat model.\textsuperscript{18}

Three early phase clinical trials assessing perifosine in heavily pretreated populations with relapsed/refractory MM have also been reported.\textsuperscript{19-21} Perifosine, an orally bioavailable AKT inhibitor, appears limited in its efficacy as a single agent in MM, but has much better activity when combined with dexamethasone, bortezomib or lenalidomide.\textsuperscript{19-21} In a phase I/II trial, the combination of perifosine-bortezomib resulted in an ORR (CR +PR + MR) of 56% (n=16). G3/4 toxicities were primarily thrombocytopenia, anemia, and fatigue. No cases of DVT and/or significant PN were reported. Pts had received a median of 5 prior lines of therapy, and all had received prior bortezomib, with 83% of pts being relapsed and refractory. The activity of this regimen was thus notable, and further benefit was seen with the addition of dex. The dose escalation portion of this trial is complete, and accrual continues at a dose level of perifosine 50 mg/day and bortezomib 1.3 mg/m\textsuperscript{2} on days 1, 4, 8, and 11, given in 21-day cycles.\textsuperscript{20}

Early phase clinical studies of 3 HDAC inhibitors given to patients with relapsed/refractory myeloma, including vorinostat, romidepsin, and ITF257 are encouraging. Vorinostat and romidepsin were assessed in combination with other drugs, whereas ITF257 was given alone.

Two phase 1 studies of vorinostat given in combination with bortezomib showed promising activity in about half the patients treated.\textsuperscript{22,23} In the study performed by Badros and colleagues,\textsuperscript{22} most dose levels used bortezomib 1.3 mg/m\textsuperscript{2} on days 1, 4, 8, and 11, with escalating doses of vorinostat given twice or once daily on days 4 through 11 (100-200 mg bid, for a total of 200-500 mg daily). Patients were heavily pretreated, with a median of 6 prior lines of therapy and the majority of patients had received a median of 2 prior bortezomib-based regimens. In the study conducted by
Donna Weber and her team, 4 dose levels of bortezomib ranging from 0.7-1.3 mg/m\(^2\) were studied in combination with vorinostat 200 or 400 mg/day. Cycles were 21 days, with vorinostat given on days 1 through 14 and bortezomib on days 1, 4, 8, and 11. Median number of prior therapies was 3, and relatively few patients had received prior bortezomib treatment. Interestingly, more activity was seen in the Badros study. This population had received more prior therapies and more prior bortezomib-based therapies, though they also received maximal doses of bortezomib (1.3 mg/m\(^2\)). Ten of 23 (43%) patients achieved a PR or better. Hematologic toxicity in this study was cumulative toxicity with QTc prolongation, noted in the first cycle, was not seen in subsequent cycles. These preliminary data are encouraging and suggest that phase 2 trials are warranted.

In the phase 1 trial of romidepsin, with the MTD of romidepsin was 10 mg/m\(^2\) on days 1, 8, and 15, combined with bortezomib 1.3 mg/m\(^2\) on days 1, 4, 8, 11 and dexamethasone 20 mg/day on the day of and the day after bortezomib administration, and an ORR of 70% (including 1 CR and 6 PRs in 10 patients). Although the response rates in this trial are promising, it should be noted that this population had relatively few prior regimens (≤2), and all patients were bortezomib naïve. Given that bortezomib alone results in objective response rates (PR or better) of about 28% in a heavily pretreated relapsed and refractory population, these promising response rates with this combination regimen need to be confirmed in additional studies.

Bortezomib plus tipifarnib has been shown to be synergistic preclinically, through the down regulation of HDAC-6 and inhibition of aggresome formation. This has prompted a phase I combination study of the two agents. To date, 14 pts have enrolled. Major toxicities have included GI and hematologic effects, and there have been at least 2 responses among bortezomib resistant pts so far.

Although monoclonal antibodies typically have not played a substantial role in the treatment of myeloma, that may change in the future. Several phase 1 trials have shown that monoclonal antibodies against insulin-like growth factor receptor (CP-751,87125 and AVE1642\(^a\)), CD56 receptor (hu901-DM1),\(^b\) and CS1 (HuLuc63)\(^c\) can be safely administered. Although responses have been rare to date, disease stabilization with single-agent treatment has occurred in many of these trials, suggesting that further development of monoclonal antibodies in combination is likely. In a phase 2 trial of an anti-IL-6 monoclonal antibody (CNTO 328), CNTO 328 was administered at a dose of 6 mg/kg IV every 2 weeks in combination with bortezomib. Of 21 evaluable patients, one patient achieved a CR and 5 achieved a PR. All patients were bortezomib naïve. Patients were eligible if they had documented disease progression after at least 1 prior therapy, although the number of prior therapies was not described.

Second generation proteasome inhibitors in the treatment of multiple myeloma

Two phase 1 trials of the novel and potent proteasome inhibitor carfilzomib have been reported.\(^{30,31}\) A trial employing a 4-week cycle in which carfilzomib is given on days 1, 2, 8, 9, 15, and 16, with 12 days’ rest showed better tolerability and more activity than a regimen given on days 1 through 5 in a 14-day cycle. Carfilzomib was generally well tolerated. Carfilzomib was associated with transient increases in serum creatinine in cycle 1, one episode of renal failure, and mild to moderate peripheral neuropathy as well as thrombocytopenia. This study included both myeloma and lymphoma patients, and neuropathy
appeared to be more common in myeloma patients. Encouragingly, responses in patients who were refractory to bortezomib were seen, and this molecule is currently being further evaluated in phase 2 trials. A second proteasome inhibitor, NPI0052, with promising preclinical activity, is also undergoing early clinical evaluation.32

Evolving clinical endpoints

The majority of these bortezomib-based combination trials have been performed in the relapsed and refractory population. Clinical endpoints have included toxicity and response rate (MR+PR+CR/nCR/VGPR), as well as PFS, TTP and OS, recognizing that in this heavily treated population, MR or better is associated with clinical benefit.33 As these combinations move into phase III study, primary endpoints will include PFS and TTP, with secondary endpoints including RR, toxicity and OS.33

Summary and future directions

In conclusion, the results yielded to date using novel bortezomib combination-based therapies have been encouraging, with high response rates (including CR) and manageable toxicity. Second generation proteasome inhibitors are now in clinical trial and show promise. Further studies are ongoing incorporating rational, biologically-derived combinations of novel agents and other small molecules (e.g. bortezomib and SAHA) with the goal of further optimizing the regimens to ensure that pts receive more effective and well-tolerated treatment.

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References

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