Tailoring Treatment for Multiple Myeloma Patients With Relapsed and Refractory Disease

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Responses to treatment of relapsed and refractory multiple myeloma are characteristically short, and median survival is as brief as 6 months. Although prognostic factors in the context of relapsed and refractory disease require further characterization, high-risk patients include those with certain cytogenetic abnormalities, high β2-microglobulin, and low serum albumin.

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Survival in multiple myeloma (MM) has improved significantly since 1990,[1] but the disease remains incurable, with most patients responding to therapy but all eventually relapsing. Some have primary refractory disease and do not respond to initial therapy, and those with relapsed and refractory disease constitute a serious and unmet medical need. Overall, the median survival of patients with relapsed and refractory MM is as short as 6 months.[2]TABLE 1

<table>
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<tr>
<th>NCCN-Recommended Salvage Therapies for Multiple Myeloma</th>
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<td>Patients who have received at least two prior therapies and have progressed on therapy or within 60 days of last treatment are usually defined as having “relapsed and refractory” MM. Clinical considerations in caring for these patients include the number of prior therapies, existing and potential toxicities related to treatment, and disease characteristics (eg, aggressiveness of relapse, relapsed disease emerging from prior remission vs disease that is truly both relapsed and refractory, and other high-risk features). Features associated with poor prognosis are t(4;14) or t(14;16), deletion of chromosomes 17 and/or 13, hypodiploidy, high β2-microglobulin, and low serum albumin. Additional challenging clinical scenarios include patients with light-chain and immunoglobulin A (IgA) isotype, renal failure, extramedullary disease, hyposecretory myeloma, and/or advanced bone disease.[2]</td>
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<td>There is no single standard treatment for relapsed and refractory MM; the National Comprehensive Cancer Network (NCCN) recommends a number of agents and combinations as salvage therapy (Table 1).[3] This article reviews recent data on the efficacy and safety of NCCN-recommended therapies that make use of bortezomib and/or lenalidomide, in primarily describing the use of novel agents in the setting.</td>
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Clinical Data on NCCN-Recommended Therapies

Single-Agent Bortezomib

TABLE 2
Clinical Data on Newer NCCN-Recommended Salvage Therapies for Multiple Myeloma

In 2003, bortezomib (Velcade) was granted accelerated approval by the US Food and Drug Administration (FDA) for treatment of relapsed and refractory MM on the basis of results from the phase II trials SUMMIT (Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy) and CREST (Clinical Response and Efficacy Study of bortezomib in the Treatment of relapsing multiple myeloma).[4,5] Subsequently, the phase III APEX trial (Assessment of Proteasome inhibition for EXtending remissions) showed that in comparison with high-dose dexamethasone, bortezomib improved time to progression (TTP), complete response (CR) rate, and overall survival (OS) (Table 2).[3,6-11] Bortezomib received full FDA approval in 2005. With extended follow-up (median, 22 months), response rates further improved to 43% with bortezomib; moreover, 1-year survival was superior with bortezomib, even though 62% of patients in the control arm crossed over to bortezomib.[7] On subgroup analysis of the APEX trial, bortezomib demonstrated substantial clinical activity in patients ≥ 65 years old and those with more than one prior line of therapy, stage II/III myeloma by the International Staging System, or refractoriness to immediate prior therapy.[12] As observed in SUMMIT and CREST, bortezomib-associated thrombocytopenia and neutropenia in APEX were transient and cyclical, with rapid recovery during the treatment-free period in each dosing cycle.[13] Although the rate of grade 3/4 thrombocytopenia was higher with bortezomib than with dexamethasone (30% vs 6%), the incidence of significant bleeding events was comparable in the two treatment groups. Bortezomib-associated thrombocytopenia may not require treatment delays or dose reductions, except in instances of grade 4 toxicity or any situation involving bleeding. In most instances, it can be managed with platelet transfusions as needed to maximize dosing and response to therapy. Similarly, bortezomib-associated neutropenia can typically be managed with growth factor support, with dose delay reserved for patients with febrile neutropenia, which occurred in only 0.3% of bortezomib-treated patients in the APEX, SUMMIT, and CREST studies. Bortezomib-associated peripheral neuropathy (PN) was the most important toxicity, but proved generally reversible in the APEX trial,[14] using a dose-modification guideline that now appears in the bortezomib prescribing information.[15] Overall, 91 of 331 (27%) patients in the bortezomib arm had treatment-emergent PN of grade ≥ 2. Of those, 64% experienced improvement or resolution to baseline at a median of 110 days, and improvement/resolution was more likely for patients who had dose modification. Grade ≥ 2 PN and dose modification did not appear to adversely affect bortezomib efficacy. Fourteen patients discontinued bortezomib due to grade ≥ 2 PN, and of these, 45% did so within the first three cycles. Close monitoring during initial treatment and, if required, prompt dose modification are necessary to prevent progressive PN and aid reversibility. Experience outside clinical trials has confirmed the tolerability and efficacy of bortezomib in relapsed and refractory MM. At one center, among 65 patients who received bortezomib with or without a corticosteroid, the overall response rate (ORR) was 64% among patients with relapsed and refractory MM, and the response rate was even higher (82%) among those with primary refractory disease,[16] Response was better in patients who received bortezomib at first or second relapse than in those treated at later points in the disease course. Four patients developed acute renal failure requiring dialysis, two of them following grade 3 diarrhea, and both of the latter patients subsequently died. Grade 3 PN occurred in 13% of patients, grade 3/4 thrombocytopenia in 42%, and grade 3/4 neutropenia in 31%.

Bortezomib/Dexamethasone

The combination of bortezomib and dexamethasone is at least additive. In an extension trial involving 63 patients from SUMMIT and CREST, retreatment with or continuation of bortezomib ± dexamethasone for a total of 7 to 32 cycles was documented to be safe, with no evidence of new
cumulative toxicity.[18] In total, 75% (n = 47) of patients received bortezomib plus dexamethasone, with 38% (n = 18) achieving at least PR. A multicenter, open-label, phase IIb trial also showed that bortezomib/dexamethasone is safe and effective for heavily pretreated patients with relapsed and refractory MM.[19] The 638 patients (median, three prior therapies) received bortezomib ± dexamethasone for a maximum of eight 3-week cycles (median, five cycles). The ORR was 67%, including 11% CR. Among the 208 patients who received bortezomib/dexamethasone, 70% showed stable disease or improved response compared with their response to bortezomib monotherapy. The most common grade 3/4 adverse events were thrombocytopenia (39% of patients), neutropenia (16%), and anemia (12%). The most common adverse event leading to treatment discontinuation was PN (5%). Bortezomib was also recently prospectively studied by 14 office-based hematologists.[20] Of 46 evaluable patients with relapsed and refractory MM, 22 received concurrent dexamethasone and 1 received prednisone. The ORR was 61%, with a median time to best response of three cycles. Response rates were similar for patients < 70 and > 70 years of age, those with and without renal impairment, and those who did or did not receive concurrent steroid medication. Important grade 3/4 adverse events included thrombocytopenia, PN, fatigue and bone pain, and anemia.

Retreatment With Bortezomib-Based Therapy

Prospective data have become available on patients with relapsed and refractory MM who were heavily pretreated with bortezomib as part of initial or later therapy for their disease. An open-label phase IV trial, performed at 23 community-based centers, assessed retreatment in patients who responded to initial bortezomib therapy for ≥ 4 months and received no interim anti-myeloma therapy before bortezomib retreatment.[21] The median number of prior lines of therapy was 4 (range, 1–8). Of the 32 subjects, 8 were retreated with bortezomib monotherapy and 24 received bortezomib/dexamethasone. The ORR with retreatment was 50%, and the median progression-free interval was 6.6 months. Thirteen patients (41%) had new or worsening PN during bortezomib retreatment, and 4 patients had toxicities that were considered at least possibly related to bortezomib: grade 2 neutropenia, grade 2/3 thrombocytopenia, and one case of reversible grade 3 congestive heart failure. Encouraging responses to bortezomib retreatment, alone or with dexamethasone, have also been observed in an ongoing international phase II trial.[22] Patients were eligible if they responded to a bortezomib-based regimen as most recent treatment and had a treatment-free interval of ≥ 6 months. Fifty-nine percent had received at least three lines of prior therapy. In 97 patients evaluable for efficacy, the ORR was 27%, with 3% CR. The ORR was similar for the 69% of patients treated with bortezomib/dexamethasone and those who received bortezomib alone. Of the 100 patients in the safety analysis, 6% discontinued treatment due to grade 3 PN and 4% due to other treatment-emergent adverse events thought to be bortezomib-related.

Bortezomib/PLD

The combination of bortezomib and pegylated liposomal doxorubicin (PLD; Doxil) was FDA-approved in 2007 for patients who have received at least one prior anti-myeloma therapy and have not received bortezomib. Approval was based on data from the phase III DOXIL-MMY-3001 trial, which demonstrated that the combination reduced the risk of disease progression by 45% over bortezomib alone and resulted in significantly better OS (Table 2).[8] An updated analysis (median follow-up, 11 months) confirmed the improvement in TTP and OS.[23] The safety profile of the combination was consistent with the known toxicities of the two agents, but there was an increase in grade 3/4 adverse events in the bortezomib/PLD group—mostly myelosuppression and gastrointestinal events.[8] Despite prior anthracycline therapy in nearly 70% of patients, the addition of PLD to bortezomib did not significantly increase cardiac toxicity, although a greater frequency of cardiac events was noted. Subgroup analyses showed that TTP was superior with bortezomib/PLD regardless of previous anthracycline exposure, the number of lines of prior therapy, disease stage, or time since initial diagnosis.[24,25] In the early-relapse group (relapse within 12 months after autologous stem cell transplantation [ASCT]), 1-year survival was significantly better with bortezomib/PLD than with bortezomib alone.[26]

Lenalidomide/Dexamethasone
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The phase III registration trials of lenalidomide (Revlimid) for relapsed and refractory MM compared lenalidomide/dexamethasone (len/dex) with high-dose dexamethasone alone.[9,10] Both studies (MM-009, conducted in North America, and MM-010, conducted in Europe, Israel, and Australia) showed that len/dex was superior with respect to response rates, TTP, and OS (Table 2). High ORR, long TTP, and manageable adverse events with len/dex were observed in patients ≥ 65 years old and in those with certain high-risk disease features (IgA subtype, advanced Durie-Salmon stage, or Eastern Cooperative Oncology Group performance status ≥ 1).[27] Len/dex was FDA-approved for relapsed and refractory MM in 2006.

In the phase III trials, the grade 3/4 adverse events of importance with len/dex included venous thromboembolism (VTE), thrombocytopenia, and neutropenia.[9,10] Recent data from an expanded access program showed that among 1,438 patients who received len/dex for relapsed and refractory MM, the most common grade 3 or 4 toxicities were hematologic (45%).[28] Grade ≥ 3 VTE occurred in 6% of patients. The most common nonhematologic serious adverse events included pneumonia (8%) and pyrexia (4%); toxicities proved generally manageable, and rates of PN and constipation were very low.

A pooled update of MM-009/010, with median follow-up of 48 months, showed a significant survival benefit of len/dex even with 48% of patients in the control arm crossing over to lenalidomide at the time of disease progression or study unblinding.[29]

In certain instances, dexamethasone dose adjustments are warranted in patients with relapsed and refractory MM, particularly elderly individuals and those on combination therapy. In MM-009/010, after four cycles, dexamethasone 40 mg was administered only on days 1 to 4. If needed due to toxicities, dexamethasone dose reductions included the following: 40 mg on days 1 to 4 every 2 weeks, 40 mg on days 1 to 4 every 4 weeks, and 20 mg on days 1 to 4 every 4 weeks. Dose reduction resulted in better efficacy and improved tolerability, according to a post hoc analysis of 233 patients.[30]

**Single-Agent Lenalidomide**

Lenalidomide can also be administered as a single agent for patients in whom a steroid-sparing approach is preferred. Lenalidomide monotherapy produced meaningful long-term benefit in patients with relapsed and refractory MM in a single-arm, open-label phase II trial.[31] The primary endpoint of CR plus PR was achieved in 26% of 222 patients. Of note, the ORR was similar regardless of type of prior treatment (thalidomide [Thalomid], bortezomib, or ASCT) and number of prior treatment regimens (≤ 2 vs ≥ 3). The response rates, TTP, and OS were not as promising as in the registration trials of len/dex,[9,10] but those studies enrolled less heavily pretreated patients and excluded dexamethasone-resistant patients. The most common grade 3/4 adverse events in the trial of lenalidomide monotherapy were neutropenia (60%), thrombocytopenia (39%), and anemia (20%), which were manageable with dose reduction.[31] Grade 3/4 febrile neutropenia occurred in 4% of patients and grade 3/4 thrombotic events in 5%. Grade 2 PN occurred in 3% of patients, and there were no cases of grade 3/4 PN, with excellent tolerability of single-agent lenalidomide overall.

**Lenalidomide/Bortezomib/Dexamethasone**

Preclinical studies demonstrating synergy between lenalidomide and bortezomib[32] provided the rationale for the development of lenalidomide/bortezomib/dexamethasone (RVD) in relapsed and refractory MM. In a phase II trial, RVD was highly active in patients with relapsed and refractory MM (Table 2), including ORRs of 73% in patients with adverse cytogenetics, 57% in patients with prior bortezomib therapy, and 57% in patients with prior thalidomide therapy.[11] Toxicities were manageable and included grade 1/2 myelosuppression, grade 3 atrial fibrillation, and grade 3 PN. One patient died on-study from fungal pneumonia, possibly due to dexamethasone, but treatment was otherwise well tolerated. This triplet is now also being investigated in the front-line setting.

**Tailoring Treatment of Relapsed and Refractory Myeloma**

**Influence of TTP and Prior Therapy**

One approach to the treatment of progressive MM is to consider strategies that lengthen TTP, even in the face of more modest ORR. For patients who responded to a first or subsequent line of treatment and have relapsed after > 1 year, it may be worthwhile to reintroduce the same regimen. Formal investigations have documented good results with bortezomib retreatment, as discussed...
above, and with second ASCT when TTP was ≥ 2 years.[33] Patients with TTP < 2 years after ASCT or < 1 year after melphalan (Alkeran)/prednisone have poorer prognosis and are candidates for bortezomib- or lenalidomide-based combination therapy or clinical trials of novel agents.[34]

**TABLE 3**

| Guidance for Using Newer NCCN-Recommended Salvage Therapies in Patients With Multiple Myeloma Depending on Prior Therapy |

Another individualized approach is based on type of prior therapy (Table 3). [6,8-10,18,21,22,26,33,35-40]

**Treating Renal Disease**

The safety and efficacy of bortezomib and bortezomib-based regimens are similar in patients with and without renal impairment; moreover, bortezomib-based therapy rapidly reverses renal dysfunction in up to 40% of patients with relapsed and refractory MM.[41,42]

A subgroup analysis of the APEX trial confirmed that the safety and efficacy of single-agent bortezomib are maintained regardless of renal dysfunction, even with baseline creatinine clearance (CrCl) < 30 mL/min.[43] Reflecting this, the FDA does not suggest bortezomib dosing adjustments for patients with renal insufficiency, including patients on dialysis.[15]

According to a subgroup analysis of DOXIL-MMY-3001, both bortezomib/PLD and single-agent bortezomib can improve renal function among patients with baseline CrCl < 60 mL/min.[44] However, patients with renal dysfunction who received bortezomib/PLD were at increased risk of drug-related serious adverse events (28% vs 19% for CrCl < 60 and ≥ 60 mL/min, respectively). Patients with creatinine > 2.5 g/dL were excluded from the MM-009/010 trials, but those with CrCl < 50 mL/min could receive len/dex. Pooled analysis showed that patients with moderate (30 ≤ CrCl < 50 mL/min) or severe (CrCl < 30 mL/min) renal impairment responded to len/dex as well or better than to high-dose dexamethasone alone.[45] Of 54 patients with renal dysfunction who were treated with len/dex, 78% had improvement in renal function within 4 months.

In the expanded access program, lenalidomide ± dexamethasone or prednisone was safe and effective when given to 23 patients with relapsed and refractory MM and renal impairment.[46] Compared with 46 patients with normal renal function, however, these patients had significantly higher rates of grade 3/4 thrombocytopenia.

**Treating Bone Disease**

The NCCN guidelines on MM management recommend pamidronate (Aredia) or zoledronic acid (Zometa) for all myeloma patients with bone disease, including osteopenia (category 1 recommendation).[3] These bisphosphonates are associated with several important adverse events, so patients must be monitored closely. For instance, intravenous bisphosphonates can cause tubular necrosis and focal segmental glomerulosclerosis, and patients receiving them should undergo regular monitoring of urine creatinine and protein levels. Osteonecrosis of the jaw, a more recently recognized complication, is rare and manageable; the possibility of its development should not preclude judicious use of bisphosphonates, particularly in patients with severe bone disease. The American Society of Clinical Oncology recommends limiting the duration of bisphosphonate use to 2 years in patients with responsive or stable myeloma, with drug resumption if additional skeletal-related events occur.[47] Prior to bisphosphonate initiation, patients should obtain a comprehensive dental examination, with particular attention paid to the presence of active infections and sites at high risk for infection.

The novel agents themselves are important components of the management of bone disease. According to in vivo and correlative clinical studies, bortezomib both inhibits osteoclasts (ie, bone-resorbing cells) and activates osteoblasts (ie, bone-forming cells).[48-52] There is also promising in vitro evidence that lenalidomide inhibits osteoclast differentiation.[53,54]

**Treating Extramedullary Myeloma**
As patients live longer with improved control of their disease, extramedullary myeloma has become an increasingly important challenge. Involvement is usually multifocal, response to conventional chemotherapy is generally poor, and resistance to treatment is frequent.[55] Response of extramedullary disease to thalidomide may be limited,[55-57] but thalidomide can be used successfully in combination with other agents. Bortezomib seems to be active in extramedullary disease, although the numbers of patients formally studied to date has been small[58] and there is preliminary evidence that lenalidomide is active in extramedullary disease when combined with bortezomib and dexamethasone.[59] Extramedullary disease thus remains particularly difficult to treat in the context of advanced myeloma, and clearly more so than extramedullary disease seen at diagnosis. Patients with relapsed and refractory MM who have extramedullary disease should also be strongly encouraged to participate in clinical trials when appropriate, and off protocol typically need combination approaches including both novel agents and chemotherapy when feasible.

Conclusions

The potential to improve responses and survival in patients with relapsed and refractory MM has increased with the introduction of novel therapies. The NCCN-recommended approaches for treating relapsed and refractory MM with bortezomib and/or lenalidomide are single-agent bortezomib, single-agent lenalidomide, bortezomib/dexamethasone, bortezomib/PLD, len/dex, and RVD.

Ongoing research into drug resistance, side-effect management, and optimal sequencing of available therapies should inform decisions about future treatment choices for individual patients with relapsed and refractory MM. Participation in clinical trials remains a key priority in accomplishing these goals and provides patients with options that may be especially effective in the face of resistant disease. In this context, a number of new approaches—such as inhibiting heat shock protein 90, histone deacetylase, AKT, and mammalian target of rapamycin (Figure 1), as well as using monoclonal antibodies—show great promise. The need for continuing research on this patient population — and the continued development of new agents—including second-generation proteasome inhibitors, new immunomodulatory agents, and other small molecules—remain paramount.[60]

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