Best Practices in the Management of Newly Diagnosed Multiple Myeloma Patients Who Will Not Undergo Transplant

By Ruben Niesvizky, MD [4], Morton Coleman, MD [5], and Tomer Mark, MD [6]

No survival advantage of autologous stem cell transplantation (ASCT) has been documented for patients older than 65 years, and in the era of thalidomide (Thalomid), bortezomib (Velcade), and lenalidomide (Revlimid), ASCT has a diminished role in the front-line treatment of older patients with myeloma.

Supported by an educational grant from Millennium Pharmaceuticals, Inc.

Multiple myeloma is predominantly a disease of the elderly. In the United States, two-thirds of patients are ≥ 65 years old at diagnosis and 85% of all patients are ≥ 55 years old.[1] Recent studies have documented improved survival of myeloma patients, but mainly in younger patients.[2-4] In the United States, the 5-year survival rate for patients diagnosed at ≥ 65 years old is still unacceptably low: 27%, compared with 49% for patients diagnosed at younger ages.[1] Fortunately, the range of treatment options for older patients has expanded in recent years. This is due to the changing definition of who qualify as “elderly”; the introduction of the novel agents thalidomide (Thalomid), bortezomib (Velcade), and lenalidomide (Revlimid); and the continued safety optimization of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). New guidelines from the International Myeloma Working Group (IMWG) recommend reduced dose intensity ASCT for patients 65 to 70 years of age.[5] National Comprehensive Cancer Network (NCCN) guidelines do not specify an age limit for ASCT in myeloma patients,[6] and patients as old as 80 have participated in trials and institutional protocols of ASCT in the United States. Even so, no survival advantage of ASCT has been documented for patients > 65 years old. Particularly now that thalidomide, bortezomib, and lenalidomide are available, ASCT has a diminished role in the front-line treatment of older patients with myeloma.

TABLE 1

Front-Line Therapies for Patients With Multiple Myeloma Who Will Not Undergo Transplantation

It is well established that chronologic age alone is not reliable in estimating life expectancy, functional reserve, or the risk of complications from cancer chemotherapy. The NCCN guidelines on treating older adults with cancer recommend using Comprehensive Geriatric Assessment tools to assess the patient’s likely tolerance of treatment by formally assessing comorbidities, functional status, geriatric syndromes, polypharmacy, nutrition, socioeconomic status, and personal preferences, in addition to life expectancy.[7] Of these, functional status is perhaps the most important. In elderly persons, dysfunction in instrumental activities of daily living is independently predictive of death, and functional measures contribute prognostic information that is independent of that obtained by evaluating comorbidity.[8,9]

Once a patient with previously untreated myeloma is deemed ineligible or chooses not to undergo ASCT, a number of treatment options are available. The purpose of this review is to compare safety and efficacy data on the standards of care (Table 1)[5,6] as well as several emerging regimens.

Regimens Incorporating Newer Agents

Thalidomide/Dexamethasone
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Published on Cancer Network (http://www.cancernetwork.com)

TABLE 2

Clinical Trial Data on Newer Front-Line Therapies for Multiple Myeloma Patients Who Will Not Undergo Transplantation

For patients unable or unwilling to undergo early ASCT, thalidomide plus dexamethasone (thal/dex) has been compared with dexamethasone monotherapy and with melphalan (Alkeran)/prednisone (MP). When compared with dexamethasone alone, thal/dex resulted in significantly higher response rates (Table 2),[10-19] but grade ≥ 3 adverse events were more common.[10] In the comparison with MP, grade 3/4 toxicity was greater with thal/dex and overall survival (OS) was significantly shorter (Table 2).[11]

The NCCN lists thal/dex among the options for front-line treatment of transplant-ineligible myeloma, although not with its highest level of evidence or consensus (Table 1). The IMWG recommends against using thal/dex as standard therapy for elderly patients ineligible for ASCT, especially at higher doses, mainly due to its major toxicities of peripheral neuropathy (PN) and sedation.[5]

MP + Thalidomide

Three published phase III trials have investigated MP + thalidomide (MPT) regimens of various dose and duration as initial therapy for myeloma (Table 2). All of them have demonstrated improved response rates with MPT compared with MP, but not necessarily improved OS rates.

The first of these, by the Italian Multiple Myeloma Study Group (GIMEMA), found that adding thalidomide to MP significantly improved the complete response (CR) rate and overall response rate (ORR; defined here as at least partial response [PR]) in patients 60 to 85 years old (Table 2).[13] However, there was no significant advantage with respect to OS after a median follow-up of 38 months (Table 2). Survival from progression or relapse was significantly better in patients who received MP at diagnosis and then received thalidomide- or bortezomib-based salvage therapy, compared with those who received MPT initially.[13] Rates of selected grade 3/4 adverse events with MPT in this and the other studies discussed in this article are given in Table 2.

The IFM (Intergroupe Francophone du Mylome) 99-06 trial, on the other hand, showed that MPT significantly extended survival for older patients (65–75 years of age) with previously untreated multiple myeloma.[14] The MPT regimen was better than MP in terms of CR and OS (Table 2) as well as progression-free survival (PFS). Median follow-up (51.5 months) was substantially longer than that in the Italian study discussed above,[13] and other differences included patient age (no patient older than 75 vs 25% patients of advanced age in the Italian study), number of MP cycles (12 vs 6), thalidomide dose (up to 400 mg/d vs 100 mg/d), and use of maintenance thalidomide in the Italian study. At the time of first relapse, about 15% of patients were unable to receive salvage therapy; as the investigators noted, this strongly suggests that optimum front-line treatment is of major importance in elderly patients with myeloma.

In the more recent IFM 01/01 trial, limited to patients ≥ 75 years of age, MPT as initial therapy again significantly prolonged OS and PFS compared with MP.[15] At the time of relapse, 81% of patients in the MP group and 53% of those in the MPT group received thalidomide, bortezomib, and/or lenalidomide, and survival time after progression was similar in the two groups. Again, as the researchers note, this finding emphasizes the need for the best possible front-line treatment in elderly patients.

MP + Bortezomib

The major investigation of MP + bortezomib (VMP) for myeloma patients not undergoing ASCT was VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone).[16] This phase III trial enrolled patients who were ineligible for ASCT due to age ≥ 65 years or coexisting conditions. The trial was stopped by monitoring committee recommendation after the third interim analysis (at median follow-up of 16 months), which determined that VMP was
superior to MP across all prespecified efficacy endpoints: time to progression (TTP) (the primary endpoint), CR, ORR, time to subsequent therapy, and OS (Table 2). Time to response was 1.4 months vs 4.2 months with MP.

Longer follow-up (26 months) confirmed that VMP was superior for all efficacy endpoints.[20] Median OS was not reached in either group; the 3-year OS rate was 72% for VMP and 59% for MP. Overall survival was not affected by renal impairment at baseline or by the prognostically adverse cytogenetic abnormalities t(4;14), t(14;16), or del(17p). Initial treatment with VMP did not preclude successful use of thalidomide- or lenalidomide-based therapy at relapse, or successful retreatment with bortezomib. In a recent update to the VISTA trial which further extended these observations after a median follow-up of 36.7 months, a 35% reduction of risk of death with VMP vs MP (hazard ratio [HR] 0.653, P = .0008) was reported.[21] Based on these findings, the US Food and Drug Administration (FDA) has approved a supplemental new drug application (SNDA) for bortezomib, which expands the label to include these long-term overall survival data and provides specific dosing recommendations for patients with hepatic impairment.[22]

The VISTA investigators determined that quality of response improves with prolonged VMP treatment.[23] Median times to first response, best response, and CR were 1.4, 2.3, and 4.2 months, respectively, vs 4.2, 4.9, and 5.3 months with MP. Prolonged therapy also maximized CR achievement with VMP in that 28% of CRs as best response occurred during cycles 5 to 9. Compared with PR or very good partial response (VGPR), CR was associated with significantly longer TTP, as well as a significantly longer treatment-free interval—a measure of clinical benefit that is important to many patients.

Most recently, the VISTA investigators reported reassuring data about PN, which was grade 3 in 13% of patients and grade 4 in < 1%.[24] Overall, 79% of all events improved by ≥ 1 grade within a median of 2 months, including 60% that completely resolved within a median of 6 months. The only baseline factor associated with worsening of PN was preexisting ≥ grade 1 PN.

No head-to-head study has compared MPT and VMP, but a recent meta-analysis of the phase III studies determined that better response rates could be expected with VMP than with MPT.[25] In comparing data on MP, MPT, and VMP, Yeh and colleagues calculated an 81% probability that VMP was the most efficacious in terms of ORR and > 99% probability that VMP was the most efficacious in terms of CR. The investigators estimated that a patient was twice as likely to achieve CR with VMP than with MPT. The VMP and MPT regimens were similar with regard to OS and PFS.

Noting that it remains to be seen whether an alkylating agent or an immunomodulatory drug is the optimal partner for bortezomib, the Spanish PETHEMA/GEM group is conducting a phase III trial comparing VMP with bortezomib/thalidomide/prednisone (VTP) in patients > 65 years of age.[17] In this study VMP is being modified: patients receive only six cycles and bortezomib is given on a weekly schedule after cycle 1. Patients in the VTP arm receive the same bortezomib and prednisone regimen as patients in the VMP arm, but instead of melphalan, they receive continuous thalidomide at 100 mg/d. On initial analysis, no significant differences between arms were observed with respect to the primary endpoint, ORR, or the CR rate (Table 2).

**Lenalidomide/Low-Dose Dexamethasone**

As with thalidomide, the initial approach to using lenalidomide in the treatment of newly diagnosed patients was to pair it with dexamethasone. In a phase II trial, lenalidomide/dexamethasone (Rev/dex) induced responses in 91% of 34 patients, including CR in 6%, similar to response to thal/dex.[26] This trial was not limited to transplant-ineligible patients, and a more recent analysis distinguishes between the 13 patients who discontinued Rev/dex to proceed to ASCT and the 21 who continued on Rev/dex for a median of 19 cycles.[27] (The latter group included two patients who died before a decision about ASCT could be made.) As in the overall cohort, the depth of remission in the no-transplant group improved over time. After four cycles of therapy, 44% of the entire cohort had at least VGPR; over time, that rate improved to 56% for the entire cohort and 67% for the no-transplant group. TABLE 3
Guidance for Using Front-Line Therapies in Multiple Myeloma Patients Who Will Not Undergo Transplantation

The most common grade 3/4 nonhematologic toxicities with Rev/dex were fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). These toxicities were similar to those noted in the dexamethasone-only arm of a phase III trial that evaluated thal/dex as pretransplant induction therapy.[28] Concerned that high-dose dexamethasone might be greatly contributing to the toxicity of Rev/dex, the Eastern Cooperative Oncology Group (ECOG) initiated the phase III E4A03 trial to compare lenalidomide plus standard high-dose pulse dexamethasone (RD) against lenalidomide plus low-dose weekly dexamethasone (Rd).[19,29] This trial was not limited to transplant-ineligible patients.

In the primary analysis of response and safety after four cycles, neither the CR rate nor the ORR was significantly better with Rd than with RD (Table 2).[19] However, among patients > 65 years of age, the probability of survival in the Rd group was significantly greater than that in the RD group at both 1 and 2 years.[29] Moreover, in the entire cohort, the lower dexamethasone dose was associated with substantially less deep-vein thrombosis/pulmonary embolism, infection/pneumonia, any grade ≥ 3 nonhematologic toxicity, any grade 4/5 toxicity, and risk of death within 4 months.[19] The ECOG investigators performed a landmark analysis of 142 patients in the E4A03 trial, median age 66 years, who did not undergo ASCT and continued on Rd for more than four cycles.[19] Continued Rd was highly active in these patients (Table 2). In fact, the 2-year OS rate was comparable with that of the original intent-to-treat population that received Rd and with that of the patients who received RD or Rd for four cycles before proceeding to ASCT. Table 3[5,10,13,15,16,24,26,29-48] provides guidance for using standard anti-myeloma regimens in the nontransplant setting.

Emerging Induction Therapies

MP + Lenalidomide

In a phase I/II trial by GIMEMA that involved newly diagnosed patients ≥ 65 years, MP + lenalidomide (MPR) resulted in a CR rate of 24% and an ORR of 81%.[47] On exploratory analyses, VGPR or better was linked to significantly better 1-year event-free survival (EFS), and MPR overcame the adverse prognostic effects of del(13) or t(4;14). Myelosuppression with MPR was greater than the rates in most of the phase III studies of MPT. At the maximum tolerated dose of MPR, grade 3/4 neutropenia was detected in 52% of patients, thrombocytopenia in 24%, and anemia in 5%. Peripheral neuropathy did not occur, and the investigators suggest that a lenalidomide-containing regimen may be indicated for patients with preexisting PN.

Based on a subsequent analysis of cytopenia data, the investigators suspect that cytotoxic bone marrow injury with MPR is related to melphalan.[49] They recommend a lower number of MPR cycles or a lower dose of melphalan for patients who experience neutropenia or thrombocytopenia, especially those aged ≥ 75 years and those with previous prolonged exposure to cytotoxic agents. In another phase I/II trial of MPR as initial myeloma therapy, adults of any age were eligible if they were not candidates for ASCT or declined it; the median age was 74 years.[48] The MPR regimen showed substantial activity (CR 12%, ORR 69%) and had a manageable toxicity profile. The most common grade 3/4 toxicities were neutropenia (58% of patients) and thrombocytopenia (27%). No
patient developed PN or thromboembolic complications. A phase III trial has been evaluating 459 patients, ≥ 65 years of age, with newly diagnosed myeloma who were randomly assigned to MPR followed by lenalidomide maintenance, MPR followed by placebo maintenance, or MP followed by placebo maintenance.[50] At a preplanned interim analysis with 50% of information available, the data monitoring committee detected a highly statistically significant improvement in PFS, the primary endpoint, for patients treated with MPR + lenalidomide maintenance compared with those who received MP. There was no significant different in PFS between the group that received MPR + placebo maintenance and the group that received MP.

### Clarithromycin/Lenalidomide/Dexamethasone

Our group is investigating the combination of clarithromycin (Biaxin, 500 mg twice daily), lenalidomide, and low-dose dexamethasone (BiRD) for front-line treatment of myeloma. Clarithromycin has immunomodulatory properties[51] and it may also have a direct antineoplastic effect,[51,52] which suggested to us that BiRD would have excellent efficacy despite the lower corticosteroid dose.

A phase II trial of BiRD involved 72 patients (median 63 years). After a mean time on treatment of 368 days, 31% had achieved stringent CR.[53] An additional 8% achieved CR, and the ORR was 90%. A subset of patients developed atypical serum immunofixation patterns that were correlated with a remarkable 100% ORR and a 71% CR rate.[54] The major grade 3 or higher toxicities were cytopenias, thromboembolic events, myopathy, rash, and diverticular abscess. More than 70% of patients on BiRD who did not undergo ASCT achieved greater than VGPR. Their baseline characteristics did not differ from the overall study population; however, their older age and comorbidities led them to decline high-dose chemotherapy.[53] The responses with BiRD were durable after 48 months of follow-up, with 46% of patients alive and in CR.[55] The 4-year OS rate was 93%. Median PFS and OS were not reached. The median EFS was 40.5 months and the 3-year EFS rate was 59%. Intriguingly, no survival advantage was found for patients who chose to go on to consolidation ASCT compared with those who stayed on BiRD therapy. Like some of the other newest combinations, BiRD is charting new territory in terms of depth and quality of response.

Data from a case-matched study confirm that adding clarithromycin to Rd has significant benefit.[56] We matched the 72 patients, based on age, gender, and transplant status, with Mayo Clinic patients who had received Rd. Rates of CR were 46% with BiRD vs 14% with Rd (P < .001), and at least VGPR occurred in 74% vs 33% of patients (P < .001). BiRD was also significantly superior with regard to PFS and time to next treatment. The principal grade 3/4 toxicities of BiRD were hematologic, especially thrombocytopenia (24% vs 8% with Rd, P = .0012). Rates of neutropenia, infection, dermatologic toxicity, and venous thromboembolism were similar in the two groups. These differences are compelling but are yet to be confirmed by a randomized study.

### Lenalidomide/Bortezomib/Dexamethasone

Another alkylator-free regimen showing promise for newly diagnosed myeloma is lenalidomide/bortezomib/dexamethasone (RVD). Thirty-five patients (median age 59 years; range 22–86 years) were evaluable for both efficacy and safety in the phase II portion of a phase I/II study.[57] After four cycles of therapy (n = 31), the ORR was 78%, with 12% of patients achieving CR/near-CR (nCR) and 12% achieving at least VGPR. Among the 24 patients without CR at cycle 4, response improved between cycles 4 and 8 in 16 (67%) patients and the ORR was 100%, with 33% and 67% achieving CR/nCR or at least VGPR, respectively. After median follow-up of 19.3 months, median TTP, PFS, and OS were not reached; estimated 1-year TTP and PFS were 76%, and estimated 1-year OS was 100%. Deep-vein thrombosis/pulmonary embolism occurred in 6%; there was no PN of at least grade 3 or treatment-related mortality.

### A Word About Maintenance

As reported above, phase III data suggest that MPR is superior to MP only when followed by lenalidomide maintenance.[50] In another phase III study, 511 patients > 65 years were randomly assigned to receive bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide, or to VMP without maintenance.[58] Initially, patients received nine 6-week cycles of either regimen; the protocol was later changed to nine 5-week cycles with weekly bortezomib in all cycles. VMPT plus maintenance was superior with regard to response rates (CR, 34% vs 21%, P < .001; at least VGPR, 55% vs 47%, P = .07) and the primary endpoint, PFS (at 2...
years, 70% vs 58%, \( P = .008 \)). The change from twice-weekly to weekly bortezomib significantly decreased the incidence of grade 3/4 PN in both treatment arms without affecting CR rates or 2-year PFS, and of course, weekly bortezomib will give better dose intensity. This is the first report showing the superiority of a four-drug combination followed by maintenance compared with the most recent standard therapy, VMP.

Conclusions

For myeloma patients who are elderly or have significant comorbidities, the traditional purpose of treatment was palliation. But it is now reasonable to set a goal of achieving CR or nCR. Three highly active, newer combinations—MPT, VMP, and Rd—are recommended by the NCCN and the IMWG: Melphalan/prednisone should no longer be considered the reference treatment, although it may be appropriate for a small number of patients with serious comorbidity and/or poor performance status. Both MPT and VMP have been demonstrated to have superior efficacy compared with MP. Advantages of VMP over MPT include more rapid response and higher rates of CR, which is associated with improved survival in the nontransplant setting.[59,60] Results of VISTA also support use of VMP in patients with high-risk cytogenetics and/or impaired renal function. The IMWG guidelines suggest considering Rd for patients who wish to postpone ASCT.[5]

Data from phase II trials suggest high efficacy rates for MPR, BiRD, and RVD, among other emerging regimens. Toxicity profiles differ among the newly established and emerging regimens, and oncology teams must take care to apply the appropriate risk management measures, including dose reduction where necessary. Additional prospective studies are needed to assess the optimal dosages and combinations in transplant-eligible patients with multiple myeloma.

Acknowledgements: The authors thank medical writer Faith Reidenbach for assistance with drafting the manuscript.

Address all correspondence to: Ruben Niesvizky, MD Weill Cornell Medical College 520 East 70th St Starr 341 New York, NY 10021 e-mail: run9001@med.cornell.edu

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