Tailoring Initial Treatment for Newly Diagnosed, Transplantation-Eligible Multiple Myeloma

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High-dose melphalan (Alkeran) and autologous stem cell transplantation are commonly incorporated into the initial line of therapy for patients newly diagnosed with multiple myeloma.

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In nearly all cases, multiple myeloma is ultimately fatal. However, the 5-year survival rate has improved significantly, from 26% in 1975 through 1977 to 37% in 1999 through 2005 ($P < .05$).[1] Survival has particularly improved in myeloma patients younger than 60 years old, beginning in the mid-1990s.[2] In addition to early deaths, late deaths years after initial treatment have been reduced in this age group.

The improvement in US survival rates began after routine use of autologous stem cell transplantation (ASCT) in the mid-1990s and the advent of thalidomide (Thalomid), bortezomib (Velcade), and lenalidomide (Revlimid).[3] Therefore, consideration of ASCT after induction therapy with one or more of these agents has become the standard of care for front-line myeloma treatment. Transplantation is usually offered to patients younger than 70 years old who have no major comorbidities, but more advanced age and renal dysfunction are not necessarily barriers.[4] Another aspect of eligibility for ASCT, not inconsequential, is the patient's willingness to undergo the procedure after the benefits and risks have been carefully explained. Patients do not need to decide about transplantation upon diagnosis, but those who wish to reserve it as an option for relapsed/refractory disease should either undergo a stem cell harvest early in the course of initial therapy or not be exposed to oral melphalan (Alkeran)-containing regimens or extensive radiation.

There are three goals of induction therapy for transplantation-eligible myeloma patients. The first is to achieve response. Patients who are being considered for treatment have active, symptomatic myeloma, and improvement in symptoms and related organ dysfunction is essential to proceeding to transplantation. A number of studies suggest that the degree (or depth) of response prior to transplantation corresponds to improved outcome. High rates of complete response (CR) or near-CR (nCR) after induction often translate into high CR/nCR rates after transplantation (see, for example, Alegre[5] and Oakervee[6]). Moreover, studies suggest that > 90% disease reduction to induction, ie, very good partial response (VGPR), may predict prolonged event-free survival (EFS)/progression-free survival (PFS) and/or prolonged overall survival (OS) after transplantation.[5,7-9] Indeed, a meta-analysis of 21 studies of transplantation in front-line myeloma showed that the association between response to induction and long-term OS was statistically significant.[10] An important caveat is that if a patient has partial response (PR) to a course of induction therapy, it is not clear that changing or prolonging therapy in an attempt to achieve CR or VGPR is better than simply proceeding to transplantation.

Another consideration in choosing the induction therapy regimen is the need to avoid jeopardizing subsequent stem cell collection. As mentioned above, this requires minimizing alkylating agents, notably melphalan, and minimizing the extent and dose of any radiation therapy. Finally, of course, the regimen must minimize other toxicities that may preclude ASCT, such as cardiac, pulmonary, or renal side effects. Some commentators have suggested that a goal of induction therapy is to provide a less contaminated stem cell product. Although that seems logical, there is little evidence that the degree of bone marrow involvement at the time of stem cell harvest relates to ultimate outcome. Incorporation of the new agents into multidrug combinations has been very encouraging, and a number of promising regimens for induction therapy have been reported in the past few years. What follows is a description of the new standards for induction therapy in transplantation-eligible multiple myeloma patients and a review of the evidence that clinicians can use to choose among the newly established options.

New Standards for Induction Therapy in Transplantation Candidates
TABLE 1

NCCN-Proposed Multiple Myeloma Induction Therapies Prior to Transplantation

The current standard induction regimens for transplantation-eligible patients with myeloma are based on the three newer drugs (thalidomide, lenalidomide, and bortezomib) whose mechanisms of action are complementary to those of existing anti-myeloma agents. These agents have been investigated in combination with established agents and with each other as first-line treatment options for patients proceeding to ASCT. The combinations appear to offer higher rates of CR, higher overall response rates (ORRs), longer duration of response, and longer survival, with lower toxicity, compared with the older regimens. Table 1 lists the regimens that the National Comprehensive Cancer Network proposed as of July 2009 as primary induction therapies for patients with myeloma who are transplantation candidates.[11] A number of trials show that vincristine/doxorubicin (Adriamycin)/dexamethasone (VAD) or single-agent pulse dexamethasone has either higher toxicity or lower efficacy than regimens containing the newer agents, so the older regimens appear to be suboptimal. The next sections of this article describe the studies that established the safety and efficacy of the regimens containing the newest agents, bortezomib and lenalidomide.

Bortezomib/Dexamethasone

TABLE 2

Clinical Trial Data on NCCN-Recommended Multiple Myeloma Induction Therapies Prior to Transplantation

Bortezomib is approved by the US Food and Drug Administration (FDA) for treatment of myeloma in both the up-front and relapsed/refractory settings. In the 2005/01 trial, the Intergroupe Francophone du Mylome (IFM) found that bortezomib/dexamethasone (Vel/dex) significantly improved postinduction response rates compared with VAD (Table 2).[11-18] Vel/dex had superior efficacy regardless of β2-microglobulin > 3 mg/L, presence of del(13), or both conditions. In addition, Vel/dex was well tolerated. During induction, the occurrence of adverse events of grade ≥ 3 was similar to that with VAD, and the incidence of grade 3 peripheral neuropathy (PN) was 7%. The IFM has concluded that Vel/dex could now be considered the standard pre-ASCT induction treatment to which other regimens should be compared.[13]

Bortezomib-Based Triplets

In two randomized trials, thalidomide/dexamethasone (thal/dex) induction therapy showed improved response rate and acceptable toxicity when compared with dexamethasone alone in newly diagnosed myeloma.[12,19] The next logical step was to investigate whether adding thalidomide to Vel/dex might improve survival as well as response rates. The Italian Myeloma Network (GIMEMA) found that compared with thal/dex alone, three 21-day cycles of bortezomib/thalidomide/dexamethasone (VTD) as induction therapy significantly increased the CR/nCR (primary endpoint) and VGPR rates to values previously seen with single or double ASCT preceded by conventional induction (Table 2).[14] The superiority of VTD to thal/dex was maintained across all subgroups examined, as identified according to standard prognostic variables and the cytogenetic abnormalities del(13q), t(4;14), and del(17p). Grade ≥ 3 toxicities significantly higher with VTD than with thal/dex were PN (9%) and skin rash (8%). Four patients in the VTD arm (two in each of the two toxicity subgroups) required early treatment discontinuation. Overall, the rate of treatment discontinuation—whether due to toxicity, disease progression, or other reasons—was
significantly higher in the thal/dex group than in the VTD group (10% vs 4%, \( P < .01 \)). For patients in that trial who underwent double ASCT, induction with VTD resulted in significantly better posttransplantation rates of CR, VGPR or better, and 2-year projected PFS compared with thal/dex.[20] The final CR rates were 44% with VTD vs 32% with thal/dex (\( P = .02 \)), and rates of VGPR or better were 80% vs 65% (\( P = .001 \)). Superior CR and PFS were maintained after double ASCT in patients with high-risk cytogenetics.

Another study of VTD vs thal/dex is being conducted by PETHEMA (Programa para el Estudio de la Teraputica en Hemopata Malign), the Spanish Myeloma Group.[15] Induction with VTD resulted in a significantly higher CR rate compared with thal/dex (Table 2), and the post-ASCT rate of CR was 52% with VTD vs 37% with thal/dex. Among patients with t(4;14), t(14;16), or del(17), the CR rate on the VTD arm was 42%—even higher than the CR rate for patients without high-risk cytogenetics on this arm—and the rate on the thal/dex arm was 0%. The incidence of adverse events and deaths was not significantly different between the arms, but grade 3/4 thrombotic events were significantly more common with thal/dex than with VTD, whereas grade 3/4 PN was significantly more common with VTD than with thal/dex.

In cooperation with the German Multiple Myeloma Group (GMMG), the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) Myeloma Working Party is substituting bortezomib for vincristine in the VAD regimen. The resulting triplet, bortezomib/doxorubicin/dexamethasone, is known as BDD or sometimes PAD (because bortezomib was formerly known as PS-341). According to the first analysis, achievement of CR was not significantly different between the BDD and VAD groups (Table 2).[16] However, the rate of response of VGPR or better was significantly better in the BDD group (42% vs 15%, \( P < .0001 \)), even among patients with del(13q) or t(4;14). Successful stem cell apheresis was achieved in all patients who received BDD, and similar numbers of BDD-treated and VAD-treated patients were able to proceed to transplantation. The primary endpoint of this HOVON-65/GMMG-HD4 study is PFS, and data on that are eagerly awaited. These bortezomib-based triplets have not yet been compared with all, or even most, established doublets in phase III trials. Such studies are ongoing.

**Lenalidomide/Dexamethasone**

Lenalidomide with standard-dose dexamethasone (RD) is FDA-approved for relapsed/refractory myeloma, and phase II trial data suggest that this combination may be even more active in newly diagnosed myeloma.[21] A phase III trial, Southwest Oncology Group S0232, confirmed that RD is a much more active induction therapy than standard-dose dexamethasone alone (dexamethasone dosage 40 mg orally on days 1–4, 9–12, and 17–20 every 28 days for three cycles).[22] The trial was closed after 198 patients were enrolled because the results of the Eastern Cooperative Oncology Group (ECOG) E4A03 trial (see below) suggested that high-dose dexamethasone was not an acceptable control arm.

The E4A03 trial, conducted by the ECOG, compared RD with the combination of lenalidomide and low-dose dexamethasone (Rd, 40 mg orally on days 1, 8, 15, and 22 of each cycle).[23] Neither the CR rate nor the ORR was significantly better with Rd than with RD (Table 2). However, the lower dexamethasone dose was associated with substantially less toxicity and treatment-related mortality. Rates of the following were significantly lower in the Rd arm than in the RD arm: deep-vein thrombosis/pulmonary embolism, infection/pneumonia, any grade ≥ 3 nonhematologic toxicity, any grade 4/5 toxicity, and death within 4 months.[17] These survival data are the most convincing to date regarding the potentially adverse impact of high-dose dexamethasone.

The primary endpoint of the E4A03 study, 1-year OS, was 96% with Rd vs 88% with RD (\( P = .005 \)). The 2-year OS rates were 88% and 78%, respectively (\( P = .007 \).[17] Among patients ≥ 65 years old, the probability of survival also was significantly better in the Rd group than in the RD group at both 1 and 2 years.[23] These observations do not imply that standard-dose dexamethasone should no longer be considered, but it should be used with great caution, especially in older patients.

**Lenalidomide/Bortezomib/Dexamethasone**

Combining bortezomib and lenalidomide is a rational strategy because bortezomib and the immunomodulators have different mechanisms of action and toxicity profiles, and because of the successful combination of bortezomib and thalidomide in the VTD regimen. The combination of lenalidomide/bortezomib/dexamethasone (RVD) as an induction therapy is based on safety results of a phase II trial in the relapsed/refractory setting[24] and safety and efficacy results from a front-line phase II trial (Table 2).[18] In the latter, RVD produced high-quality, durable responses regardless of cytogenetic status or stage, and it was well tolerated. The ORR was 100% overall and at the
maximum planned dose (lenalidomide 25 mg, bortezomib 1.3 mg/m², and dexamethasone 20/10 mg).
Toxicities were manageable, including all grade 3/4 hematologic toxicities (3%-15%), grade 3 hypophosphatemia (8%), and grade 3/4 deep-vein thrombosis/pulmonary embolism (3%, with daily aspirin). Two patients (3%) developed grade 3 PN. Stem cell mobilization was successful in almost all patients, and the transplantation course has been unremarkable to date. According to the latest update on this trial, the results remain encouraging.[25]

Posttransplantation Benefit of Established New Regimens

Achieving CR rates ≥ 30% and ORRs up to 100% is a remarkable advance in the treatment of myeloma. It is important to examine, though, whether deeper remission translates into improved long-term outcomes after ASCT.
Vogl et al retrospectively compared the outcomes of 28 patients who received thal/dex induction and 41 patients who received VAD or doxorubicin/vincristine/dexamethasone (DVD).[26] Despite similar response rates during induction, thal/dex was associated with significantly better PFS after transplantation compared with anthracycline-based induction (hazard ratio = 0.18; 95% confidence interval = 0.04–0.80; P = .011). Overall survival was comparable in the two groups. The results were similar when the investigators considered only the 28 patients who had not received any consolidation or maintenance therapy after transplantation.

For bortezomib-based regimens, data are available from some of the prospective phase III trials described above. In IFM 2005/01, the better response after induction treatment with Vel/dex translated into significantly better response after first ASCT, with CR/nCR rates of 35% vs 23% (P = .006).[13] However, there was no significant difference between treatment arms in OS or PFS at 18 months. In the HOVON-65/GMMG-HD4 trial posttransplant response rates were similar to those observed pretransplant, and as with response to induction, the efficacy of BDD was superior to that of VAD.[16] Specifically, 80% of patients on BDD achieved at least VGPR after transplantation, compared with 50% of those on VAD (P = .002), and the ORR after transplantation was 83% vs 59% (P = .002). In the GIMEMA study, the superiority of VTD to thal/dex as induction therapy translated into significantly higher CR/nCR and VGPR rates after first ASCT, second ASCT, and consolidation therapy.[14] Even more importantly, 2-year PFS was significantly better in the VTD-treated group (90% vs 80%, P = .009). Overall 2-year survival did not differ significantly between the groups. The median follow-up was rather short (15 months) and longer-term survival data will be of great interest.
The ECOG E4A03 trial of Rd was designed to evaluate only induction therapy, not the long-term efficacy of that combination. Intriguingly, though, a subgroup analysis suggests that ASC for myeloma is still pertinent in the era of novel agents. The researchers compared 85 patients who underwent ASC after four cycles of Rd with 142 patients who continued on the regimen. The 2-year OS was 94% for those who underwent ASC vs 70% for those who did not.
Results from studies now underway will yield important information about whether the choice of induction therapy has a bearing on post-ASCT outcomes. Likewise, the role of ASC for eligible patients in the era of newer agents is a question to be examined in future randomized, clinical trials.

Choosing Among the New Standard Regimens

TABLE 3

| Guidance for Using Multiple Myeloma Induction Therapies Prior to Transplantation |
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Table 3 [11,13-16,18,23,27-41] presents information from the myeloma literature that can help clinicians use various induction therapies. It is important to keep in mind that patients with severe renal insufficiency, history of thromboembolism, history of neuropathy, and other relevant comorbidities have generally been excluded from myeloma clinical trials. In addition, relatively few head-to-head trials of newer regimens have been conducted. Longer experience with the newer agents will be necessary before comprehensive evidence-based recommendations are available.

Very recently, an expert panel of the International Myeloma Working Group (IMWG) was convened to review the impact of thalidomide-based, bortezomib-based, and lenalidomide-based regimens on stem cell mobilization and collection. The panel found contradictory data on the impact of thalidomide in this respect, but it concluded that the effect, if any, appears to be relatively small, has limited impact on the ability to proceed with ASCT, and has no effect on the engraftment potential of the collected cells.[42] Phase III trials of bortezomib-based regimens, even those that include lenalidomide or thalidomide, have generally not shown an adverse effect on the ability to collect stem cells.[42] The exception is that in the IFM 2005/01 trial, there was a trend toward lower CD34+ cell numbers in patients receiving Vel/dex than in those receiving VAD.[13] Even so, stem cell collection was adequate in 97% and 99% of the groups, respectively.

Two retrospective analyses have documented that prior treatment with lenalidomide is a risk factor for lower stem cell yields and increased mobilization failure rates when granulocyte colony-stimulating factor (G-CSF) is used alone for stem cell mobilization.[43,44] Patient age and duration of lenalidomide therapy were associated factors.[43] There is no evidence that lenalidomide affects the quality of the stem cells collected. The use of cyclophosphamide in addition to G-CSF lowers back to baseline the incidence of collection failure among lenalidomide-treated patients, independent of the duration of lenalidomide therapy.[45,46] The IMWG panel advises early stem cell mobilization, preferably within the first four cycles of initial therapy, for any patient who may undergo ASCT, whether immediately or later in the disease course.[42]

Conclusions

It is possible that as experience grows with thalidomide, bortezomib, lenalidomide, and agents that are now investigational, the role of ASCT in myeloma treatment will become less routine. For the foreseeable future, however, consideration of ASCT as part of first-line myeloma therapy is appropriate for eligible patients. Numerous induction regimens now meet the goals of achieving CR and allowing subsequent stem cell collection, with acceptable toxicity. Newer combinations, especially those containing bortezomib and/or lenalidomide, are associated with depth and quality of response likely to result in better survival in these patients. Whether one or two of the regimens are superior to all others remains to be determined, but bortezomib-based and/or lenalidomide-based regimens now have adequate level 1 evidence and consensus to be recommended for induction therapy for the transplantation-eligible patient with myeloma. Ongoing studies should provide further guidance for choosing among these regimens based on cytogenetic abnormalities, renal disease, and other prognostic indicators. Additional research is needed to evaluate the optimal use of newer regimens and incorporation of new biologic prognostic factors in the front-line setting.

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