Update on the Initial Therapy of Multiple Myeloma

Donna Reece, MD

OVERVIEW

Advances in myeloma biology and the identification of new anti-myeloma agents have resulted in improved management of younger, transplant-eligible, and older patients. The first novel agents—thalidomide, bortezomib, and lenalidomide—have been integrated into induction therapy before autologous stem cell transplant (ASCT) as well as into first-line therapy in elderly individuals; phase III trials have established the superiority of these approaches in terms of better response rates, progression-free survival (PFS), and, in some studies, overall survival. With more experience, improvements in dosing have decreased the toxicity of these regimens. Before ASCT, four phase III studies have shown that bortezomib-based regimens confer better outcomes than older regimens. Posttransplant consolidation and maintenance strategies with novel agents provide additional benefit, particularly in terms of a longer PFS. In the elderly population, novel agents can be combined with melphalan plus prednisone (MP). MP plus thalidomide and MP plus bortezomib are commonly utilized, and the regimen of MP plus lenalidomide with lenalidomide maintenance (MPR + R) produces superior response rates and longer PFS compared with MP alone. Prolonged maintenance with bortezomib plus thalidomide also appears to extend PFS when given following combinations of MP plus bortezomib. Treatment of very elderly patients, however, remains challenging due to comorbidities and side effects. Lenalidomide plus weekly dexamethasone is also effective in elderly patients, and results of a trial comparing this regimen with MP plus thalidomide should be available soon. Finally, better methods of risk stratification and the availability of even newer drugs will allow future refinements in myeloma treatment.

In the previous decade, younger patients with newly diagnosed myeloma were typically treated with induction therapy based on high-dose dexamethasone (dex) (i.e., vincristine/doxorubicin/dexamethasone [VAD] or dex alone) followed by autologous stem cell transplantation (ASCT), whereas older individuals received 6–12 cycles of oral melphalan and prednisone (MP). Results from randomized trials indicated that an approach of VAD and a single ASCT produced an overall response rate (≥ partial remission [PR]) of 80% with up to 20% complete or nearly complete (CR/nCR) remission, a progression-free survival (PFS) rate of around 24 months, and an overall survival rate of 4–5 years. MP in older patients resulted in overall response rates on the order of 50% with few CR/nCRs; a PFS of approximately 12–15 months and an overall survival of 3–4 years could be anticipated.1

More recently, an improved understanding of the biology of myeloma and the identification of new drugs have improved the therapeutic approach to myeloma. Genomic techniques have provided insights into the different molecular subtypes of this disease with differing natural histories. In the clinic, application of the International Staging System (based on the serum levels of beta-2 microglobulin and albumin) and FISH cytogenetics has allowed the definition of different myeloma risk groups with readily available laboratory tests. Several investigators have reported that the presence of t(4; 14), t(14;16) and deletion 17p identifies patients with a poorer outcome. More recently, both 1q gains, as well as deletions of 1p22 and 1p32, have been associated with an adverse prognosis in analyses of patients treated on Intergroupe Francophone du Myelome (IFM) studies involving ASCT.2,3

Following the introduction of the immunomodulatory derivatives (IMiDs) thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib, a series of phase II and III studies in both younger and older patients with myeloma has evaluated the integration of these novel agents into first-line therapy. Other recent developments have included an appreciation of the toxicity of the older schedule of “pulse” dexamethasone (high-dose dex [HD-dex] = 40 mg/day for day 1 through 4, 9–12, and 17–20 of a 28-day cycle) and the benefit of low-dose dex = 40 mg/week (LD-dex).4 In addition, the incidence and severity of peripheral neuropathy associated with bortezomib can be reduced by weekly, rather than twice weekly, dosing as well as by the subcutaneous, rather than intravenous, route of administration.5,6

Finally, various maintenance strategies have been evaluated in both younger and older patients in an attempt to improve the duration of remission and overall survival.5–7

In Europe and Canada, a strategy that maintains the division of newly diagnosed patients into two categories—those who are designated for upfront ASCT and those who are transplant-ineligible on the basis of age and comorbidities—is still in place. In contrast, some U.S. specialists have...
recommended treating younger individuals, particularly those with standard-risk disease, as regimens based on novel agents for variable periods of time; ASCT is considered optional based on patient preference and other unknown factors. Some of these approaches advocate ASCT at the time of relapse. Although delayed ASCT may ultimately be shown to produce results comparable to first-line ASCT, phase III trials evaluating the two strategies have not yet been completed. Moreover, most reports describing the efficacy of 2-, 3- or even 4-drug regimens include a mix of transplant and nontransplant patients, with a focus on response rates; information regarding longer term outcomes such as PFS is often limited and the contribution of ASCT difficult to assess.

To more accurately ascertain the results of different therapeutic strategies, the current discussion will, therefore, emphasize the results of randomized trials in which the distinction between ASCT and nontransplant therapy is determined from the onset of study.

**TABLE 1. Results of Bortezomib-Containing Pre-ASCT Induction Regimens Reported in Phase III Trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Induction Regimen</th>
<th>ASCT + Post-ASCT Therapy</th>
<th>Post-Induction Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau et al.</td>
<td>Bortezomib + dex</td>
<td>1 or 2 (lenalidomide maintenance in some)</td>
<td>≥PR 78% ≥VGPR 38% ≥CR/nCR 15%</td>
</tr>
<tr>
<td>Cavo et al.</td>
<td>VTD</td>
<td>2 + VTD consolidation + dexam maintenance</td>
<td>92% 63% 31%</td>
</tr>
<tr>
<td>Sonneveld et al.</td>
<td>PAD</td>
<td>1 or 2 + bortezomib maintenance</td>
<td>83% 42% 15%</td>
</tr>
<tr>
<td>Rosinol et al.</td>
<td>VTD</td>
<td>1 + VT = bortezomib and thalidomide maintenance</td>
<td>82% 60% 35%</td>
</tr>
</tbody>
</table>

**KEYPOINTS:**

- Bortezomib-based induction regimens before ASCT produce better rates of response, PFS, and OS.
- Post ASCT measures involving novel agents improve PFS with a variable effect on overall survival.
- In elderly patients, the addition of a novel agent to melphalan and prednisone results in a better antitymoma effect, but the incidence of grade 3/4 toxicity is relatively high.
- Lenalidomide plus weekly dexamethasone is also a promising regimen in elderly patients.
- Newer drugs such as carfilzomib are under evaluation in the first-line setting.

Although the inclusion of bortezomib, particularly in a 3-drug regimen, seems important for high-risk disease, as indicated by the recent integrated analysis of the four phase III studies of bortezomib induction described previously, the...
question of whether less intensive induction before ASCT is appropriate for standard-risk patients has not been prospectively addressed. In particular, the oral regimen lenalidomide + LD-dex, as first reported in the ECOG E4A03 trial comparing it with lenalidomide + HD-dex, produces reasonable overall response rates, albeit with comparatively lower CR/nCR rates, and is associated with excellent patient tolerance. Prolonged use can compromise, to some extent, blood stem cell mobilization and collection; stem cell collection is still usually possible by using combination approaches. Details regarding patient outcomes by risk stratification are not available from this study, although newer retrospective reports from the Mayo Clinic have suggested the utility of lenalidomide and LD-dex alone for induction.27 On balance, however, it seems prudent to avoid routine reduction in the intensity of induction therapy in transplant-eligible individuals until further supportive evidence is available.

Post-ASCT Therapy
The two main post-transplant measures include long-term maintenance, usually with either an IMiD or bortezomib as single agents, or consolidation therapy. Thalidomide maintenance has been evaluated in seven phase III trials in which the dose and duration of thalidomide varied, as did the use of concomitant corticosteroids. These trials consistently demonstrated a significantly better PFS—in the range of 6–12 months—in patients receiving thalidomide, with a variable effect on overall survival. A recent meta-analysis of these studies concluded that thalidomide as a single agent or in conjunction with corticosteroids improves both progression-free and overall survival rates.28 Toxicities such as peripheral neuropathy and thrombotic events were increased, not surprisingly, with thalidomide. These and other unpleasant side effects, in turn, negatively affect the quality of life, as highlighted in the recent analysis of the Canadian NCIC randomized study of thalidomide + prednisone compared with observation after ASCT.29

On the other hand, maintenance with lenalidomide avoids many of the toxicities of thalidomide, although it is associated with the potential for myelosuppression. More recently, lenalidomide maintenance has been assessed in two phase III trials—the IFM and CALGB trials—in which patients were randomized post-ASCT to low dose lenalidomide or placebo until disease progression; the IFM trial also included 2 months of full-dose lenalidomide in all patients before beginning the assigned maintenance arm.30,31 The IFM study

### TABLE 2. Summary of Post-ASCT Outcomes in Phase III Trials Using Novel Agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Post ASCT Response Rates</th>
<th>Median PFS</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau et al.</td>
<td>68% CR/nCR 39% VGPR 36 mos 41% NYR 3-yr 86% 3-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavo et al.</td>
<td>89% CR/nCR 71% VGPR 49 mos 68% NYR 3-yr 86% 3-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonneveld et al.</td>
<td>76% VGPR 49% CR/nCR 35 mos 61% 5-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosinol et al.</td>
<td>N/A 46% CR/nCR 56.2 mos 74% 4-yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CR/nCR, complete remission/near CR; mos, months; NYR, not year reached; VGPR, very good partial remission.

### TABLE 3. Summary of Selected 3- or 4-Drug Induction Regimens Reported in Phase I-II Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents</th>
<th>N with ASCT</th>
<th>Post-Induction Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDD</td>
<td>Bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>30 20</td>
<td>93% PR 63% VGPR 40% CR/nCR</td>
</tr>
<tr>
<td>VRD</td>
<td>Bortezomib + lenalidomide + dex</td>
<td>31 31</td>
<td>94% PR 62% VGPR 23% CR/nCR</td>
</tr>
<tr>
<td>RVDD</td>
<td>Lenalidomide + bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>68 24</td>
<td>96% PR 57% VGPR 29% CR/nCR</td>
</tr>
<tr>
<td>VTD</td>
<td>Bortezomib + thalidomide + dex</td>
<td>49 48</td>
<td>96% PR 69% VGPR 44% CR/nCR</td>
</tr>
<tr>
<td>VTDC</td>
<td>Bortezomib + thalidomide + dex + cyclophosphamide</td>
<td>49 40</td>
<td>100% PR 69% VGPR 51% CR/nCR</td>
</tr>
<tr>
<td>CyBorD</td>
<td>Weekly oral cyclophosphamide + weekly bortezomib 1.5 mg/m² + dex</td>
<td>83 83</td>
<td>97% PR 79% VGPR N/A CR/nCR</td>
</tr>
<tr>
<td>CVDD</td>
<td>Cyclophosphamide + bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>49 30</td>
<td>89%/100% (standard/high risk) 69%/69% (standard/high risk) 25%/50% (standard/high risk)</td>
</tr>
<tr>
<td>RVD + vorinostat</td>
<td>Lenalidomide + bortezomib + dex vorinostat</td>
<td>30 10</td>
<td>100% PR 52% VGPR 32% CR/nCR</td>
</tr>
<tr>
<td>CRD</td>
<td>Carfilzomib + lenalidomide + dex</td>
<td>53 7</td>
<td>100% PR 88% VGPR 67% CR/nCR</td>
</tr>
<tr>
<td>CTD</td>
<td>Carfilzomib + thalidomide + dex</td>
<td>39 39</td>
<td>91% PR 61% VGPR 18% CR/nCR</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CR/nCR, complete remission/near CR; dex, dexamethasone; mos, months; N/A, not available; PR, partial remission; VGPR, very good partial remission.

*After 4 cycles.

**After ≥4 cycles.
found a significant prolongation of PFS from 23 to 41 months (p < 0.001), whereas the CALGB trial described a significantly longer time to progression from 27 to 46 months, in the lenalidomide arm (p < 0.001).\textsuperscript{30,31} The latter study also reported a survival benefit (p = 0.03).\textsuperscript{31} Lenalidomide maintenance was generally well-tolerated, although a small but consistent increase in the risk of secondary malignancies has been observed with this agent.\textsuperscript{30,31} Some groups are now advocating the use of lenalidomide maintenance for a shorter, finite period of time (i.e., 1–3 years) in an effort to reduce this risk, although it is currently uncertain whether the same benefit in terms of PFS and survival will be preserved. The introduction of better methods to assay minimal residual disease post-ASCT, such as narrow multiparameter flow cytometry or molecular studies, may help direct the optimal use of maintenance therapy in the future.

The term “consolidation” does not have a standard definition in myeloma but, as in acute leukemia, usually refers to moderately intensive combination therapy given for several cycles after recovery from ASCT. The Arkansas group was with first to report the use of consolidation, which has been a major feature of all of their Total Therapy trials.\textsuperscript{32} Outside of Arkansas, the Italian cooperative group led by Cavo and colleagues has described excellent results with VTD induction, tandem transplantation, and VTD consolidation followed by maintenance with dexamethasone alone, without a novel agent.\textsuperscript{33} Advantages of consolidation compared with long-term maintenance therapy include a finite period of treatment and, potentially, a lower and more predictable cost. It is not known whether the risk of secondary malignancies will be decreased.

The CTN trial (Stamina Trial; BMT-CTN0702) that evaluates different post-transplant strategies will hopefully delineate the optimal approach in the future. In this phase III trial, patients receive induction with RVD followed by ASCT; thereafter, patients are randomized either directly to lenalidomide maintenance for 3 years, to a second ASCT followed by lenalidomide maintenance, or to RVD consolidation and lenalidomide maintenance. This trial has completed accrual, and the results are awaited with considerable interest.

In the interim, many centers like the author’s institution, Princess Margaret Hospital, consider some method of risk stratification for transplant-eligible patients. Given Princess Margaret Hospital’s current Canadian resources, they use weekly CyBorD induction, anticipating a 90% to 95% overall response rate and 45% to 50% CR/nCR rate pre-ASCT.\textsuperscript{17} This is followed by ASCT with melphalan 200 mg/m\textsuperscript{2}. High-risk patients with t(4;14), t(14;16) and/or del 17p or plasma cell leukemia undergo a second ASCT; all patients then received lenalidomide maintenance. Of note, a recent single-center report described a similar approach and observed that high-risk patients undergoing tandem transplantation had outcomes similar to standard-risk patients undergoing a single ASCT.\textsuperscript{34} In the future, consolidation with a 3-drug combination, analogous to the approach of Cavo and colleagues, would ideally be integrated into therapy, particularly in the high-risk setting. Regardless of the choice of induction and post-ASCT regimens, the goal should be a median PFS of 3 or more years, in keeping with the results of the phase III trials discussed above.

**TREATMENT OF TRANSPLANT-INELIGIBLE PATIENTS**

In non-ASCT candidates, the two main approaches to improve results have included: (1) the addition of a novel agent (thalidomide, bortezomib, or lenalidomide) to the MP regimen; (2) the continuous use of an IMiD—without an alkylating agent—and dexamethasone.\textsuperscript{1}

MP has been compared with MPT in six randomized studies, all of which demonstrated an improvement in PFS to approximately 24 months years, compared with MP, which had a PFS of 14 –16 months.\textsuperscript{35,36} Survival outcomes were more variable, but a recent meta-analysis of these trials, including a total of 1685 patients, confirmed a superior 1-year response rate, PFS, and overall survival with MPT.\textsuperscript{35} On the other hand, grade 3 or 4 toxicity occurred in 45% to 50% of patients, with a considerably higher risk of both peripheral neuropathy and venous thromboembolism,\textsuperscript{36} the latter of which requires thromboprophylaxis.\textsuperscript{37} In addition, benefit was most apparent for patients younger than age 65. An appreciation of the effect of poor performance status on outcomes has been recognized, and dose adjustments in very elderly patients (>75 years) and more vulnerable individuals has been proposed.\textsuperscript{38}

VMP (= bortezomib + MP) is the other MP-containing regimen that is commonly used in elderly patients. The VISTA trial demonstrated a substantial improvement in response rates, PFS and overall survival with VMP compared with MP. Similar to MPT, the PFS was 24 months with VMP. However, grade 3–4 toxicities were also noted in a high proportion of patients.\textsuperscript{39} Peripheral neuropathy was not uncommon, although modifications of the regimen, in which bortezomib is given once rather than twice per week, have decreased the incidence of this side effect without compromising the antitumor effect;\textsuperscript{3} the use of subcutaneous bortezomib is anticipated to improve patient tolerance as well.\textsuperscript{6}

The use of prolonged maintenance in subsequent trials, either as VT (bortezomib + thalidomide) or VP (bortezomib + prednisone), has been reported to extend PFS even further than 2 years in patients initially treated with VMP, VTP, or VMPT, but no significant survival improvement has been realized in either of the two trials exploring this strategy.\textsuperscript{5,40} Third, lenalidomide has been combined with MP in MM015 study reported by Palumbo and colleagues. This study compared three treatment arms: MP compared with MPR (MP + lenalidomide) compared with MPR-R (MPR followed by lenalidomide maintenance until disease progression). MPR-R produced a significant prolongation of PFS over MP (p < 0.001), although no significant benefit in overall survival was observed.\textsuperscript{41} Just as in the post-ASCT setting, MPR-R was associated with a small, but measureable, increase in the incidence of secondary cancers.\textsuperscript{42} Additionally, studies of VMP and MPR -R, noted inferior outcomes in patients over the age of 75 years.\textsuperscript{41}

Historically, the first continuous IMiD and corticosteroid regimen used in older patients with myeloma was...
thalidomide + HD dex. However, this regimen produces excessive toxicity\textsuperscript{43} and has been replaced by the combination of lenalidomide + weekly dex, which is better tolerated. As shown by Rajkumar and colleagues in the ECOG E4A03 trial, lenalidomide and LD-dex induces remission in approximately 70\% of patients, with a median PFS of about 2 years.\textsuperscript{4}

This regimen is widely used in the United States, and its efficacy and benignity in an older population will hopefully be illustrated by the results of the MM010 trial, which has completed accrual but has not yet been reported. This large phase III study randomized newly diagnosed patients $\geq$ 65 years of age to a standard regimen of MPT compared with lenalidomide and LD dex until myeloma progression compared with lenalidomide and LD dex for a fixed period of 18 months.

In practice, MPT, VMP, and lenalidomide + LD-dex can each be considered for older patients with myeloma, with the choice based on a variety of disease-related and patient-related factors. Although data are limited regarding the optimal therapy for high-risk patients, particularly those with adverse cytogenetics, many experts recommend a bortezomib-containing regimen in such individuals. Mateos and colleagues has published the results of VMP-based regimens and noted that those with t(4;14) and del 17p have better outcomes with VMP than MP, although the results are less favorable than in the setting of standard-risk disease.\textsuperscript{44}

Given the comorbidities of many older patients with myeloma, the selection of the best approach for those very elderly (>75 years of age) or very frail patients may be challenging. In this population, specific dose reductions have been recommended for the agents in the VMP, MPR, and len + dex regimens, as well as for MPT as mentioned above.\textsuperscript{38}

Newer regimens with less morbidity are also being explored for patients ineligible for ASCT. For example, the combination of weekly oral cyclophosphamide + dexamethasone with carfilzomib has recently been reported to produce $\geq$ PR in 91\% of elderly patients without significant neuropathy and with relatively few grade 3/4 toxicities; equivalent results in patients below and above the age of 75 years have been described.\textsuperscript{39} Trials of 3-drug regimens in which MP is combined with ixazomib and which the monoclonal antibody elotuzumab is combined with len + LD-dex are also in progress in an effort to improve therapeutic options for older individuals with myeloma.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

Employment or Leadership Position: None. Consultant or Advisory Role: None. Stock Ownership: None. Honoraria: Donna Reece, Bristol-Myers Squibb; Celgene; Merck; Novartis; Ortho Biotech; Otsuka. Research Funding: Donna Reece, Bristol-Myers Squibb; Celgene; Merck; Millennium; Ortho Biotech; Otsuka. Expert Testimony: None. Other Remuneration: None.

References


