Part II: Role of Maintenance Therapy in Transplant-Ineligible Patients

Antonio Palumbo, MD, and Roberto Mina, MD

Abstract
Many advances were made in the treatment of multiple myeloma since the introduction of the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib. An increasing number of clinical trials have examined consolidation/maintenance therapy as part of a sequential approach after induction therapy and demonstrated benefit in patients eligible and ineligible for transplantation. This outcome improvement reported with consolidation/maintenance therapy should be balanced against the toxicity profile, and prompt management of adverse events is necessary. This article provides an overview of the main trials including consolidation/maintenance therapy after induction for transplant-ineligible patients. Recommendations on how to manage treatment-related toxicities are also provided. (JNCCN 2013;11:43–49)

Multiple myeloma is a malignant neoplasm accounting for 1% of all cancers and 10% of hematologic neoplasms. Its incidence increases with age: the median age at diagnosis is 70 years, with only 37% of patients younger than 65 years, 26% between the ages of 65 and 74 years, and 37% aged 75 years or older.1 In patients older than 70 years from 2002 through 2004, 10-year survival was approximately 5% to 10%.2 In the past few decades, treatment efficacy was improved by the use of autologous stem cell transplantation (ASCT), and subsequently by the introduction of the immunomodulators thalidomide and lenalidomide, and the proteasome inhibitor bortezomib.2 Consolidation (2–4 cycles of combination therapies) and maintenance (continuous therapy, usually with single agents, until disease progression) are commonly used in the clinical practice to improve outcome after induction therapy.3 Different trials have assessed the benefits associated with consolidation and maintenance treatment with thalidomide, lenalidomide, and bortezomib, although no clinical study has directly compared the advantages of one approach over the other. Despite the benefits associated with consolidation/maintenance therapy, prolonged exposure to new drugs may increase toxicities; thus, appropriate and prompt management of treatment-related adverse events is needed (Table 1).

Transplant-Ineligible Patients
Patients older than 65 years are usually not considered eligible for high-dose therapy followed by ASCT. However, this age cutoff may vary because the chronologic age does not always correspond to the biologic age of patients. For these patients, and for younger patients with comorbidities who would not tolerate ASCT, gentler approaches are needed. For patients aged 65 to 75 years with no comorbidities, full-dose treatments should be selected. Elderly patients with comorbidities or those older than 75 years are considered frail and may benefit more from adjusted-dose therapies.4 The goal of treatment in elderly patients is to achieve the maximal depth of response that controls disease and prolongs survival while preserving quality of life, thus minimizing treatment-related toxicity and patient discomfort. The combination of melphalan and prednisone (MP) was considered to be the standard treatment for more than 30 years, but the introduction of thalidomide, lenalidomide, and bortezomib revolutionized the treatment paradigm of multiple myeloma. Previous trials
have assessed the role of adding thalidomide or bortezomib to MP (MPT and VMP, respectively), and these combinations are now considered standard induction therapies for elderly patients.\(^5\sim7\) Given the equivalence of cyclophosphamide to melphalan, the combination of bortezomib, cyclophosphamide, and dexamethasone (VCD) can also be a possible alternative in this setting.\(^8\) The 4-drug combination of VMP plus thalidomide (VMPT) is an effective therapeutic strategy for fit elderly subjects.\(^9\) Recently, MP plus lenalidomide (MPR) proved to be a valid option in elderly patients,\(^10\) although no significant

<table>
<thead>
<tr>
<th>AE</th>
<th>Novel Agent</th>
<th>Management</th>
<th>Dose Modifications Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>R, V</td>
<td>G-CSF until neutrophil recovery in case of uncomplicated grade 4 AE or grade 2/3 AE complicated by fever or infection</td>
<td>25%–50% drug reduction</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>R, V</td>
<td>Platelet transfusion in case of occurrence of grade 4 AE</td>
<td>25%–50% drug reduction</td>
</tr>
<tr>
<td>Anemia</td>
<td>R, V</td>
<td>Erythropoietin or darbepoietin if hemoglobin level is ≤10g/dL</td>
<td>25%–50% drug reduction</td>
</tr>
<tr>
<td>Infection</td>
<td>T, R, V</td>
<td>Trimethoprim/cotrimoxazole for <em>Pneumocystis carinii</em> prophylaxis during high-dose dexamethasone; acyclovir or valacyclovir for HVZ prophylaxis during bortezomib-containing therapy</td>
<td>25%–50% drug reduction</td>
</tr>
<tr>
<td>Neurologic</td>
<td>T, V</td>
<td>Neurologic assessment before and during treatment. Prompt dose reduction is recommended</td>
<td>T: 50% reduction for grade 2 neuropathy; discontinuation for grade 3; resume at a decreased dose if neuropathy improves to grade 1 V: 25%–50% reduction for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves to grade 1 or better with restart at 50% dose reduction for grade 2 with pain or grade 3 peripheral neuropathy; treatment discontinuation for grade 4 peripheral neuropathy</td>
</tr>
<tr>
<td>Skin</td>
<td>T, R</td>
<td>Steroids and antihistamines</td>
<td>Interruption in case of grade 3/4 AE 50% reduction in case of grade 2 AE</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>T, R, V</td>
<td>Appropriate diet, laxatives, physical exercise, hydration, antidiarrheals</td>
<td>Interruption in case of grade 3/4 AE 50% reduction in case of grade 2 AE</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>T, R</td>
<td>Aspirin, 100–325 mg, if no or 1 individual/myeloma thrombotic risk factor is present; LMWH or full-dose warfarin if there are ≥2 individual/myeloma risk factors and in all patients with thalidomide-related risk factors</td>
<td>Drug temporary interruption and full anticoagulation, then resume treatment</td>
</tr>
<tr>
<td>Renal</td>
<td>R</td>
<td>Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections, and concomitant use of nephrotoxic drugs)</td>
<td>Reductions based on creatinine clearance: • 30–60 mL/min → R: 10 mg/d • &lt;30 mL/min and no dialysis needed → R: 15 mg every other day • &lt;30 mL/min with dialysis required → R: 5 mg on dialysis days after dialysis</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; G-CSF, granulocyte-colony stimulating factor; HVZ, herpes varicella zoster; LMWH, low-molecular-weight heparin; R, lenalidomide; T, thalidomide; V, bortezomib.
Maintenance Therapy in Transplant-Ineligible Patients

Advantage was seen with MPR in patients older than 75 years compared with MP. Lenalidomide plus low-dose dexamethasone (Rd) also proved to be effective and well tolerated in elderly patients. In frail patients, less-intensive approaches, such as the combination Rd or bortezomib plus low-dose dexamethasone (Vd), seem to be appropriate strategies to reduce toxicities and discontinuations, thus enabling patients to benefit more from treatment.

**Maintenance Approaches**

The high efficacy of thalidomide, lenalidomide, and bortezomib, both upfront and at relapse, has provided the rationale for testing these agents as maintenance therapy after induction treatment. The main goal of this approach is to preserve outcome after induction, prolong remission duration, and ultimately extend survival. The very first attempts at maintenance therapies date back to 1975, and simply consisted of continuing chemotherapy after successful induction treatment with MP. Despite prolonging remission, no survival benefit was detected, thus this strategy was no longer adopted. Single-agent interferon was also assessed as maintenance therapy in the past. Although 2 meta-analyses found a survival improvement of approximately 6 months with continuous interferon administration, results from trials were controversial, and this approach was not pursued further because of its high toxicity.

In the era of novel agents, different trials have assessed the role of maintenance therapy in elderly patients, and results are promising.

**Thalidomide-Based Maintenance**

Thalidomide is a favourable option for maintenance therapy in the elderly because of its oral administration. However, its specific toxicity profile, particularly neurotoxicity, should be taken into account. Seven trials have compared MPT with MP in this setting, and in 4 of them thalidomide was administered continuously (Table 2). In the Italian study, thalidomide was administered continuously at a dose of 100 mg/d. Median progression-free survival (PFS) for patients treated with thalidomide was 25 months compared with 15 months for those who did not receive thalidomide (P < .001). The respective median overall survival (OS) was 47.6 versus 45 months (P = .79), with 10% and 1% of patients, respectively, experiencing a neurologic toxicity. In the Dutch study, the dose of thalidomide was decreased from 200 mg/d during induction therapy to 50 mg/d during maintenance. Median duration of thalidomide maintenance was 7.5 months, and median event-free survival was 13 months with MPT versus 9 months with MP alone (P < .001). Notably, this trial found a borderline significant OS advantage with MPT followed by thalidomide maintenance (40 vs. 31 months; P = .05), although the incidences of grade 3/4 neurologic events were high (23% vs. 4%). The Nordic study also used thalidomide at the dose of 200 mg/d until relapse. In this trial, no significant improvement was seen in median PFS in the thalidomide group compared with MP (15 vs. 14 months; P = .84), nor was a significant OS difference between the arms detected (29 vs. 32 months; P = .16). Grade 3/4 peripheral neuropathy was 6% for MPT and 1% for MP.

Two other studies explored the role of thalidomide maintenance after conventional therapy, demonstrating an improvement in PFS but not OS, probably because of a slight increase in toxicity. In the first trial, patients had received induction with either thalidomide plus dexamethasone (TD) or MP and were then randomized to receive thalidomide with interferon or interferon alone as maintenance. Median PFS was improved with thalidomide (27.7 vs. 13.2 months; P = .0068), but OS was similar in both groups (52.6 vs. 51.4 months; P = .81). Patients on thalidomide/interferon reported a higher incidence of grade 3/4 neuropathy (7% vs. 0%; P = .0015). In the MRC Myeloma IX trial, patients who received cyclophosphamide, thalidomide, and dexamethasone (CTD); cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD); MP; or CTD attenuated (CTDa) were then randomized to receive thalidomide maintenance or no maintenance. Thalidomide maintenance improved PFS (23 vs. 15 months; P < .001), particularly in patients who also received thalidomide during induction. No significant difference was seen in median OS (P = .40).

These data suggest that the optimal dose of thalidomide in elderly patients with myeloma should range between 50 and 100 mg/d. Recommending a specific length of thalidomide therapy is difficult; however, limiting the duration of thalidomide exposure may be preferable to reduce peripheral neuropathy. Despite the PFS advantage associated with continuous administration of thalidomide, longer
### Table 2 Main Maintenance Approaches in Elderly Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Schedule</th>
<th>CR</th>
<th>PFS/TTP/EFS</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>T: 100 mg/d until relapse</td>
<td>16%</td>
<td>50% at 22 mo</td>
<td>50% at 45 mo</td>
<td>19, 20a</td>
</tr>
<tr>
<td></td>
<td>T: 50 mg/d until relapse</td>
<td>23%</td>
<td>50% at 13 mo</td>
<td>50% at 40 mo</td>
<td>21a</td>
</tr>
<tr>
<td></td>
<td>T: 200 mg/d until progression</td>
<td>13%</td>
<td>50% at 15 mo</td>
<td>50% at 29 mo</td>
<td>22a</td>
</tr>
<tr>
<td></td>
<td>T: 100 mg/d until relapse</td>
<td>9%</td>
<td>50% at 21 mo</td>
<td>50% at 26 mo</td>
<td>23a</td>
</tr>
<tr>
<td></td>
<td>T: 200 mg/d until progression or intolerance</td>
<td>---</td>
<td>50% at 28 mo</td>
<td>50% at 53 mo</td>
<td>27a</td>
</tr>
<tr>
<td></td>
<td>T: 50 mg/d increased to 100 mg/d after 4 cycles if tolerated</td>
<td>---</td>
<td>50% at 23 mo</td>
<td>---</td>
<td>28c</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>R: 10 mg days 1–21 until disease progression</td>
<td>33%</td>
<td>50% at 31 mo</td>
<td>70% at 36 mo</td>
<td>10d</td>
</tr>
<tr>
<td></td>
<td>R: 25 mg days 1–21 P: 50 mg qod for four 28-d cycles followed by</td>
<td>40%</td>
<td>66% at 36 mo</td>
<td>85% at 36 mo</td>
<td>30e</td>
</tr>
<tr>
<td></td>
<td>R: 25 mg days 1–21 until disease progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>V: 1.3 mg/m² twice weekly on days 1, 4, 8, 11 every 3 mo P: 50 mg qod for up to 3 y</td>
<td>39%</td>
<td>50% at 32 mo</td>
<td>---</td>
<td>31f</td>
</tr>
<tr>
<td></td>
<td>V: 1.3 mg/m² twice weekly on days 1, 4, 8, 11 every 3 mo T: 50 mg/d for up to 3 y</td>
<td>44%</td>
<td>50% at 24 mo</td>
<td>---</td>
<td>31f</td>
</tr>
<tr>
<td></td>
<td>V: 1.3 mg/m² every 14 d T: 50 mg/d for 2 y</td>
<td>42%</td>
<td>56% at 36 mo</td>
<td>89% at 36 mo</td>
<td>9g</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; EFS, event-free survival; I, interferon α-2b; OS, overall survival; P, prednisone; PFS, progression-free survival; qod, every other day; R, lenalidomide; T, thalidomide; TTP, time to progression; V, bortezomib; VGPR, very good partial response.

*a Maintenance after melphalan/prednisone/thalidomide induction.

*b Maintenance after melphalan/prednisone or thalidomide/dexamethasone inductions.

*c Maintenance after cyclophosphamide/thalidomide/dexamethasone, cyclophosphamide/vincristine/doxorubicin/dexamethasone, or melphalan/prednisone inductions.

*d Maintenance after melphalan/prednisone/lenalidomide.

*e Consolidation/maintenance therapy after bortezomib/doxorubicin/dexamethasone induction and reduced-intensity transplantation.

*f Maintenance after bortezomib/melphalan/prednisone or bortezomib/thalidomide/prednisone inductions.

*g Maintenance after bortezomib/melphalan/prednisone/thalidomide induction.
follow-up may be required to detect any significant OS advantage.

**Lenalidomide-Based Maintenance**

Lenalidomide is also administered orally and proved to be well tolerated and active in multiple myeloma. A recent phase III study assessed the role of lenalidomide after MPR (MPR-R) versus no maintenance (MPR or MP). After a median follow-up of 27 months, PFS was significantly longer with lenalidomide maintenance (31 months with MPR-R vs. 14 months with MPR vs. 13 months with MP). A landmark analysis from the start of maintenance confirmed that lenalidomide maintenance after MPR significantly extended median PFS compared with MPR alone (26 vs. 7 months; \( P < .001 \)), regardless of age. The influence on OS remains uncertain, and the 4-year OS rate was similar between the treatment groups (58%–59%). Neutropenia is one of the major toxicities associated with lenalidomide administration, and grade 3/4 events were reported in 7% of patients receiving lenalidomide continuously. In these patients, the rate of thrombocytopenia was 6%, and no extrahematologic grade 3/4 toxicity with an incidence rate greater than 5% was observed. The rate of second primary malignancies was higher in the lenalidomide arms; 7% in both MPR-R and MPR patients versus 3% in MP patients. However, the PFS advantage associated with MPR-R seems to outweigh the increased risk of second primary malignancy.

A phase II study assessed the role of lenalidomide maintenance in patients aged 65 to 75 years as part of a sequential approach consisting of bortezomib, doxorubicin, dexamethasone (PAD) induction followed by tandem melphalan at 100 mg/m\(^2\), ASCT, lenalidomide/prednisone consolidation, and lenalidomide maintenance. This approach induced a 2-year PFS rate of 69% and a 2-year OS rate of 86%. Notably, consolidation and maintenance with lenalidomide considerably increased the complete response rate achieved after induction, from 12% to 40%. Sixteen percent of patients who received consolidation and maintenance therapy experienced grade 3/4 neutropenia.

A phase III study also compared lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus Rd, and both young and elderly patients were included. After 4 cycles, patients could discontinue therapy to pursue stem cell transplantation or continue treatment until disease progression. A landmark analysis at 4 months was performed. Among the 248 patients who continued on primary therapy (108 in the RD group and 140 in the Rd group), the 3-year OS was 79%. The 3-year PFS was 46% with RD and 50% with Rd. The complete response rate was 39%, and grade 3/4 toxicities occurred in 7% of subjects who continued either RD or Rd therapy. These results showed that lenalidomide plus dexamethasone may also be suitable for prolonged therapy for elderly patients.

Overall, the available data suggest that lenalidomide is a good maintenance approach in this setting, and may be preferred to thalidomide because of the lack of neurologic side effects.

**Bortezomib-Based Maintenance**

Bortezomib as maintenance therapy in combination with either thalidomide (VT) or prednisone (VP) improved outcome after induction therapy with VMP or bortezomib/thalidomide/prednisone. During maintenance, bortezomib at 1.3 mg/m\(^2\) was administered with the conventional day 1, 4, 8, and 11 schedule for 3 years. After a median follow-up of 38 months from start of maintenance, the complete response rate increased from 24% at the end of induction (mean value obtained after VMP and bortezomib/thalidomide/prednisone inductions) to 42%, with a slightly higher rate with VT versus VP (46% vs. 39%). Median PFS was also longer with VT than VP (39 vs. 32 months), although this advantage was not statistically significant (\( P = .1 \)). Similarly, OS was only slightly longer with VT than with VP (5-year OS, 69% vs. 50%; \( P = .1 \)). Peripheral neuropathy is a major concern associated with bortezomib administration, and was the major toxicity associated with both approaches (9% with VT vs. 3% with VP).

In another study, VT maintenance after VMPT induction (VMPT-VT) was compared with VMP without maintenance. To decrease neurologic toxicity, the study was amended, and patients received once-weekly bortezomib instead of the twice-weekly schedule. During maintenance, bortezomib at 1.3 mg/m\(^2\) was given every 14 days for 2 years or until progression. The 3-year PFS was longer in patients assigned to the VMPT-VT than VMP arms (56% vs. 41%; \( P = .008 \)), but longer follow-up is needed to detect any OS advantage. Grade 3/4 sensory neuropathy was slightly higher with VMPT-VT (8% vs. 5%; \( P = .19 \)), and did not increase during VT maintenance.
The preliminary results of a phase III study evaluated the benefits of bortezomib alone as maintenance therapy after induction with bortezomib/dexamethasone (VD), bortezomib/thalidomide/dexamethasone (VTD), or VMP. Bortezomib maintenance was administered at 1.6 mg/m² twice weekly. This strategy improved response obtained after induction and slightly increased toxicity across all 3 treatment arms, with 5% of patients experiencing grade 3/4 peripheral neuropathy during bortezomib maintenance therapy.

Based on the available trials, bortezomib maintenance seems beneficial and well tolerated in elderly patients, with a neurologic toxicity lower than thalidomide, particularly when a reduced schedule of bortezomib is used, and is a valuable maintenance option when combined with thalidomide. In addition to the weekly schedule, the recent use of subcutaneous administration rather than intravenous administration was shown to be a feasible and equally effective option. Therefore, subcutaneous bortezomib may be considered for prolonged treatment.

Conclusions

Maintenance therapy is an effective strategy to prolong remission and survival in both young and elderly patients. In the era of novel agents, various maintenance approaches have been tested and associated with a PFS advantage. In elderly patients, continuous thalidomide is preferred after thalidomide-based regimens, such as MPT induction, although peripheral neuropathy may be a major concern. Lenalidomide has the advantage of the lack of neurologic toxicity, and it seems to be a good option after MPR induction. Bortezomib maintenance has been tested either alone or in combination with thalidomide or prednisone in elderly patients. The major advantages have been detected when bortezomib is used with the reduced schedule to decrease peripheral neuropathy. Quality of life is a major goal of maintenance therapy; therefore, this approach should not lead to excessive toxicity, treatment delay, and discontinuation. The choice of the most appropriate maintenance treatment should carefully balance the potential benefits and risks associated with this strategy, because none of the new drugs is currently approved for maintenance therapy.

Acknowledgments

The authors wish to thank the editorial assistant Giorgio Schirripa.

References


