Management of Newly Diagnosed Myeloma

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Multiple myeloma (MM) accounts for approximately 10\% of hematologic malignancies [1,2]. Many patients evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of unknown significance (MGUS). MGUS is present in approximately 3\% of the population older than 50 years, and progresses to myeloma or related malignancy at a rate of 1\% per year [3,4]. In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as smoldering multiple myeloma can be recognized. At diagnosis, most patients are older than 65 years; about 35\% of myeloma patients are younger than 65 years, 28\% are 65 to 74 years, and 37\% are older than 75 [5]. The current changes of the demographic curves will probably increase the incidence of elderly patients in the near future. In newly diagnosed myeloma patients younger than 65 years, high-dose melphalan followed by autologous stem cell transplantation (ASCT) is considered the standard of care. In elderly patients, usually older than 65 years, oral melphalan and prednisone (MP) has been considered the standard until recently.

The discovery of new drugs, such as thalidomide, lenalidomide, and the proteasome inhibitor bortezomib, targeting the myeloma cells and the bone marrow microenvironment have significantly increased the clinical efficacy of the old chemotherapy regimens. The challenge is now to define the optimal sequence and combination of these drugs to significantly impact the natural history of the disease.

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DIAGNOSIS
A monoclonal (M) protein can be detected by serum protein electrophoresis alone in 82% of patients and by serum immunofixation in 93%; a combination of serum and urine protein immunofixation studies improve the sensitivity to 97% [6]. In the work-up of a patient who has suspected myeloma, screening urine electrophoresis and immunofixation can be eliminated by using the serum free light chain assay instead. Less than 3% of patients have no evidence of monoclonal paraproteins (nonsecretory myeloma). The diagnosis of myeloma requires 10% or more plasma cells on bone marrow examination (or biopsy-proven plasmacytoma), M protein in the serum or urine (except in patients who have true nonsecretory myeloma), and evidence of organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) believed secondary to the underlying plasma cell disorder.

RISK STRATIFICATION
The specific prognostic factors used to stratify patients at the Mayo Clinic into high-risk and standard-risk myeloma to guide therapeutic strategy are deletion 13 or hypodiploidy on metaphase cytogenetic studies, deletion 17p- or immunoglobulin heavy chain (IgH) translocations t(4;14) or t(14;16), or plasma cell labeling index of 3% or higher. Presence of any one or more of the above high-risk factors classifies a patient as having high-risk MM. The median survival of high-risk MM is less than 2 to 3 years even with tandem stem cell transplantation, compared with more than 6 to 7 years in patients who have average-risk MM [2].

TREATMENT
There is no evidence that early treatment of patients who have asymptomatic (smoldering) multiple myeloma prolongs survival compared with therapy at the time of symptoms. Clinical trials are ongoing to determine if newer agents can delay progression, however. An approach to treatment of symptomatic newly diagnosed multiple myeloma at Mayo Clinic is outlined in Fig. 1. It is not clear if high-risk patients need to be treated differently from standard-risk patients as outlined in this approach, however, and this requires further study. New regimens for myeloma are given in Table 1.

Treatment of Myeloma in Patients Eligible for Transplantation
Initial therapy for patients who have standard-risk disease depends on eligibility for ASCT. Eligibility is determined by age, performance status, and coexisting comorbidities. Protracted melphalan-based therapy should be avoided in patients who have newly diagnosed myeloma who are considered eligible for ASCT, because it can interfere with adequate stem cell mobilization. Typically patients are treated with approximately two to four cycles of induction therapy before stem cell harvest. This treatment includes patients who are transplant candidates but who wish to reserve ASCT as a delayed option for relapsed refractory disease. Such patients can resume induction therapy following stem cell collection until a plateau phase is reached, reserving ASCT for relapse.
Vincristine, doxorubicin, dexamethasone (VAD) was used for many years as pretransplant induction therapy for patients considered candidates for ASCT. VAD has drawbacks, however, such as needing an intravenous indwelling catheter, and neurotoxicity from vincristine, which can limit the future use of thalidomide and bortezomib. Recently, Cavo and colleagues [7] in a matched
Table 1
New regimens for the treatment of newly diagnosed multiple myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide-dexamethasone (Thal/Dex) [13]</td>
<td>Thalidomide 200 mg oral d 1–28</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Repeated every 4 wk × 4 cycles as pretransplant</td>
</tr>
<tr>
<td></td>
<td>induction therapy; or continued until plateau</td>
</tr>
<tr>
<td></td>
<td>or progression if used as primary therapy</td>
</tr>
<tr>
<td>Lenalidomide-dexamethasone (Rev/low-dose dexamethasone) [21]</td>
<td>Lenalidomide 25 mg oral d 1–21 every 28 d</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg oral d 1, 8, 15, 22</td>
</tr>
<tr>
<td></td>
<td>Repeated every 4 wk × 4 cycles as pretransplant</td>
</tr>
<tr>
<td></td>
<td>induction therapy; or continued until plateau</td>
</tr>
<tr>
<td></td>
<td>or progression if used as primary therapy</td>
</tr>
<tr>
<td>Bortezomib-dex (Vel/Dex) [24]</td>
<td>Bortezomib 1.3 mg/m² intravenous d 1, 4, 8, 11</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Repeated every 3 wk × 4 cycles as pretransplant</td>
</tr>
<tr>
<td></td>
<td>induction therapy</td>
</tr>
<tr>
<td>Melphalan-prednisone-thalidomide (MPT) [27]</td>
<td>Melphalan 0.25 mg/kg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Prednisone 2 mg/kg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Thalidomide 100–200 mg oral d 1–28</td>
</tr>
<tr>
<td></td>
<td>Repeated every 6 wk × 12 cycles</td>
</tr>
<tr>
<td>Melphalan-prednisone-bortezomib (MPV) [28]</td>
<td>Melphalan 9 mg/m² oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Prednisone 60 mg/m² oral d 1 to 4</td>
</tr>
<tr>
<td></td>
<td>Bortezomib 1.3 mg/m² intravenous d 1, 4, 8, 11</td>
</tr>
<tr>
<td></td>
<td>Repeated every 42 d × 4 cycles followed by</td>
</tr>
<tr>
<td></td>
<td>maintenance therapy as given below:</td>
</tr>
<tr>
<td></td>
<td>Melphalan 9 mg/m² oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Prednisone 60 mg/m² oral d 1 to 4</td>
</tr>
<tr>
<td></td>
<td>Bortezomib 1.3 mg/m² intravenous d 1, 8, 15, 22</td>
</tr>
<tr>
<td></td>
<td>Repeated every 35 d × 5 cycles</td>
</tr>
<tr>
<td>Melphalan-prednisone-lenalidomide (MPR) [39]</td>
<td>Melphalan 0.18 mg/kg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Prednisone 2 mg/kg oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide 10 mg oral d 1–21</td>
</tr>
<tr>
<td></td>
<td>Repeated every 4–6 wk × 9 cycles</td>
</tr>
<tr>
<td>Bortezomib-thalidomide-dexamethasone (VTD) [32]</td>
<td>Bortezomib 1.3 mg/m² intravenous d 1, 4, 8, 11</td>
</tr>
<tr>
<td></td>
<td>Thalidomide 100–200 mg oral d 1–21</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg/m² oral d 1–4</td>
</tr>
<tr>
<td></td>
<td>Repeated every 4 wk × 4 cycles as pretransplant</td>
</tr>
<tr>
<td></td>
<td>induction therapy</td>
</tr>
</tbody>
</table>

*Starting and subsequent doses need to be adjusted for performance status, renal function, blood counts, and other toxicities. Recommended dose of dexamethasone has been reduced from the published series to no more than four doses per month based on recent results of a trial comparing lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone.
case-control study of 200 patients demonstrated that response rates with VAD were significantly lower compared with Thal/Dex; 76% versus 52%, respectively. Preliminary results from randomized trials confirm these findings [8,9]. As a result, VAD is no longer recommended as initial therapy. Thalidomide-dexamethasone (Thal/Dex) has increasingly been used in place of VAD. When thalidomide was incorporated into the high-dose therapy followed by autologous transplantation, a higher CR rate (62% versus 43%) and improved 5-year event-free survival (56% versus 44%) was observed compared with high-dose therapy without thalidomide [10]. Unfortunately, the 5-year overall survival was similar in both groups (P = .9). In the thalidomide group, a higher rate of thromboembolism (30% versus 17%) and peripheral neuropathy (27% versus 17%) were reported.

Dexamethasone alone has also been used as induction therapy. Objective response rates are approximately 45% [11], significantly lower compared with newer induction regimens. In randomized trials the early mortality rate associated with dexamethasone is more than 10% in the first 4 months of therapy, reflecting the toxicity and ineffectiveness of this regimen. Consequently, single-agent dexamethasone is no longer recommended as initial therapy.

The main choices for initial therapy are thalidomide-dexamethasone (Thal/Dex), bortezomib-based regimens, and lenalidomide-dexamethasone (Rev/Dex) (Table 2). All of these regimens act rapidly, and are associated with high response rates; Thal/Dex and Rev/Dex have the added advantage of being orally administered. Thal/Dex and Rev/Dex are associated with an increased risk for deep vein thrombosis (DVT), necessitating routine thromboprophylaxis.

**Thalidomide-dexamethasone**

The first clinical trial with thalidomide demonstrated a response rate of 25% in heavily pretreated patients who had relapsed refractory disease [12]. Response rates in relapsed disease are about 25% to 35% with single-agent thalidomide, 50% with thalidomide plus corticosteroids, and more than 65% with a three-drug combination of thalidomide, corticosteroids, and alkylators.

The use of Thal/Dex in newly diagnosed myeloma was initially based on three phase II clinical trials [13–15]. The Eastern Cooperative Oncology Group (ECOG) recently compared Thal/Dex to dexamethasone in 207 patients [11]. The best response within four cycles of therapy was significantly higher with Thal/Dex compared with dexamethasone alone: 63% versus 41%, respectively, P = .0017. Stem cell harvest was successful in 90% of patients in each arm. DVT was more frequent with Thal/Dex (17% versus 3%). Overall, grade 3 or higher nonhematologic toxicities were seen in 67% of patients within four cycles with Thal/Dex and 43% with dexamethasone alone (P < .001). Early mortality (first 4 months) was 7% with Thal/Dex and 11% with dexamethasone alone. Based on this trial, the US Food and Drug Administration (FDA) granted accelerated approval for Thal/Dex for the treatment of newly diagnosed myeloma.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of patients</th>
<th>Median age (range)</th>
<th>≥PR (%)</th>
<th>CR (%)</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Peripheral neuropathy, grade 3–4 (%)</th>
<th>DVT/embolism, grade 3–4 (%)</th>
<th>Infection, grade 3–4 (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>103</td>
<td>65 (38–83)</td>
<td>63</td>
<td>4</td>
<td>50% at 22 mo</td>
<td>72% at 2 y</td>
<td>7</td>
<td>17</td>
<td>6</td>
<td>[11]</td>
</tr>
<tr>
<td>TD</td>
<td>100</td>
<td>54 (49–59)</td>
<td>76</td>
<td>10</td>
<td>ND</td>
<td>ND</td>
<td>4</td>
<td>15</td>
<td>4</td>
<td>[7]</td>
</tr>
<tr>
<td>ASCT-T</td>
<td>323</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>62% at 5 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65% at 5 y</td>
<td>27&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND</td>
<td>[10]</td>
</tr>
<tr>
<td>RD</td>
<td>34</td>
<td>64 (32–78)</td>
<td>91</td>
<td>18</td>
<td>74% at 2 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91% at 2 y</td>
<td>ND</td>
<td>3</td>
<td>6</td>
<td>[21]</td>
</tr>
<tr>
<td>VD</td>
<td>79</td>
<td>55 (ND)</td>
<td>82</td>
<td>9</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>[28]</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT-T, autologous stem cell transplant + thalidomide; CR, complete response; DVT, deep vein thrombosis; ND, not determined; PR, partial response; RD, lenalidomide + dexamethasone; TD, thalidomide + dexamethasone; VD, bortezomib + dexamethasone.

<sup>a</sup>Event-free survival.

<sup>b</sup>Greater than grade 2.
Preliminary results are available from a separate randomized, double-blind, placebo-controlled study comparing Thal/Dex versus dexamethasone alone as primary therapy in 470 patients who had newly diagnosed myeloma (MM) [16]. Among 470 patients enrolled, time to progression (TTP) was significantly superior with Thal/Dex, \( P < .001 \). As in the ECOG trial, DVT and other grade 3 to 4 events were more frequent with Thal/Dex.

Patients receiving thalidomide in combination with high-dose steroids or chemotherapy need routine thromboprophylaxis with Coumadin (target INR 2–3) or low–molecular weight heparin (equivalent of enoxaparin 40 mg once daily). Aspirin can be used instead in patients receiving only low doses of dexamethasone (40 mg, 4 days a month or lower) or prednisone in combination with thalidomide, provided no concomitant erythropoietic agents are used.

Lenalidomide–dexamethasone

Richardson and colleagues [17] tested lenalidomide in a multicenter randomized phase II trial of 102 patients who had relapsed/refractory myeloma. Overall response rate with single-agent lenalidomide was 17%. Two large phase III trials have since shown significantly superior time to progression with Rev/Dex compared with placebo plus dexamethasone in relapsed myeloma [18,19]. Rev/Dex is currently approved by the FDA for the treatment of myeloma in patients who have received one prior therapy.

In newly diagnosed myeloma, a phase II trial conducted at the Mayo Clinic demonstrated remarkably high activity with the Rev/Dex regimen. Thirty-one of 34 patients (91%) achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for very good partial response (VGPR) [20]. With longer follow-up, 56% of patients achieved VGPR or better. In the subset of 21 patients receiving Rev/Dex as primary therapy without ASCT, 67% achieved VGPR or better [21]. Approximately 50% of patients experienced grade 3 or higher nonhematologic toxicity.

ECOG tested Rev/Dex as administered in the Mayo Phase II trial (and in the regulatory relapsed refractory myeloma studies) versus Rev/low-dose dexamethasone (40 mg dexamethasone once weekly) [22]. Results so far show that toxicity rates are significantly higher with Rev/high-dose dexamethasone compared with Rev/low-dose dexamethasone. Early (first 4 months) mortality rates were low in both arms, 5% and 0.5%, respectively. The early mortality rate in the Rev/low-dose dexamethasone arm is probably the lowest reported in any large phase III newly diagnosed trial in which enrollment was not restricted by age or eligibility for stem cell transplantation; DVT rates are also low, making this one of the safest pretransplant induction regimens for myeloma. Based on this Rev/low-dose dexamethasone is currently the regimen of choice at Mayo Clinic outside the setting of a clinical trial. This ECOG study was recently closed by the data monitoring committee because of significantly superior overall survival in patients receiving Rev/low-dose dexamethasone compared with Rev/high-dose dexamethasone. As a result, doses of dexamethasone in excess of 40 mg for 4 days each month should be avoided in patients...
who have newly diagnosed myeloma, either as a single agent or in combination with other agents.

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but increases markedly when the agent is combined with high-dose dexamethasone. Recommendations for thromboprophylaxis are similar to those discussed previously with Thal/Dex; aspirin alone is probably sufficient for patients receiving lenalidomide plus low-dose dexamethasone.

**Bortezomib-based regimens**

Bortezomib is a novel proteasome inhibitor approved for the treatment of patients who have relapsed and refractory multiple myeloma. In relapsed/refractory MM, approximately one third of patients respond to bortezomib therapy with an average response duration of 1 year [23]. Progression-free survival (PFS) is superior with bortezomib compared with dexamethasone alone in patients who have relapsed, refractory MM [24]. Bortezomib is currently approved by the FDA for the treatment of myeloma in patients who have failed one prior therapy.

In newly diagnosed myeloma, bortezomib has shown response rates of approximately 40% as a single agent [25]. Significantly higher response rates (approximately 70%–90%) have been observed with bortezomib plus dexamethasone (Vel/Dex) [26,27], bortezomib, thalidomide, dexamethasone (VTD), and other bortezomib-based combinations. The CR plus VGPR rate is approximately 25% to 30% with Vel/Dex in one study. No adverse effect on stem cell mobilization has been noted. The most common grade 2 or higher adverse events in one study were sensory neuropathy (31%), constipation (28%), myalgia (28%), and fatigue (25%) [26]. Harousseau and colleagues [28] recently reported preliminary results of a randomized trial comparing VAD versus Vel/Dex as pretransplant induction therapy. With more than 400 patients enrolled, preliminary results show superior response rates and long-term outcome with Vel/Dex compared with VAD. DVT risk is low with bortezomib (<5%).

The main drawback of bortezomib-based regimens is the need for intravenous therapy. Bortezomib-based regimens may be of value in patients who have renal failure, however, and in patients who have high-risk myeloma (see later discussion).

**Other induction regimens**

The role of other pretransplant induction regimens, such as those containing doxorubicin or liposomal doxorubicin, need to be weighed in terms of the added side effects that can affect quality of life and should be considered investigational until future studies show that the addition of these agents improves long-term outcome compared with the regimens discussed previously.

**Transplantation in Newly Diagnosed Myeloma**

The role of transplantation (autologous and allogeneic) in myeloma is discussed elsewhere in this issue. An increasing number of patients are opting
for delayed transplantation. There is also new interest in allografting. In a recent trial, patients who had newly diagnosed multiple myeloma received an ASCT followed by an allograft from an HLA-identical sibling or a tandem ASCT. Patients who had an HLA-identical sibling then received nonmyeloablative total-body irradiation and stem cells from the sibling. Patients who did not have an HLA-identical sibling received two consecutive myeloablative doses of melphalan, each of which was followed by autologous stem cell rescue. The median overall survival and event-free survival were longer in patients who had HLA-identical siblings than in those who did not have HLA-identical siblings (80 months versus 54 months, \(P = .01\); and 35 months versus 29 months, \(P = .02\), respectively). These data suggest that survival in recipients of a hematopoietic stem cell autograft followed by a stem cell allograft from an HLA-identical sibling may be superior to that in recipients of tandem stem cell autografts [29]. Further studies are needed to confirm these findings in the context of improved initial therapeutic approaches discussed later in this article.

**New Maintenance Approaches**

The role of maintenance therapy remains controversial in myeloma. After conventional or high-dose therapy, maintenance with interferon alpha provided marginal benefits. In patients who responded to conventional chemotherapy, maintenance therapy with 50 mg alternate-day prednisone significantly improved progression-free and overall survival compared with 10 mg alternate-day prednisone [30].

In a large randomized study conducted by the IFM group, patients younger than 65 years were randomly assigned to receive no maintenance, pamidronate, or pamidronate plus thalidomide [31]. The 3-year post-randomization probability of event-free survival \((P < .009)\) and the 4-year overall survival \((P < .04)\) were significantly prolonged in patients who received thalidomide. The proportion of patients who had skeletal events was not influenced by the administration of pamidronate. Grade 3 to 4 neuropathy (7%), fatigue (6%), and constipation (1%) were more prominent in the thalidomide group. The incidence of thromboembolic events was not significantly different in the three arms. More recently, a randomized trial compared thalidomide-prednisone versus prednisone alone as maintenance therapy after autologous stem cell transplantation: the 1-year progression-free survival was 91% versus 69%, and the 2-year overall survival was 90% versus 81%, respectively. Neurologic side effects were more common with thalidomide, but no differences were observed in the incidence of thromboembolic events [32]. Additional studies are needed to determine the role of routine maintenance in myeloma, especially the use of lenalidomide, which has a better safety profile than thalidomide for long-term maintenance.

**Treatment of Myeloma in Patients Not Eligible for Autologous Stem Cell Transplantation**

Patients who are not transplant candidates are treated with standard alkylating agent therapy. For decades this has meant therapy with melphalan plus
prednisone (MP) [1]. Over the years, despite better response rates, no survival benefit has been reported with any of the more aggressive combination chemotherapy regimens compared with MP. In a recent randomized trial, four treatment regimens have been evaluated: MP, melphalan and dexamethasone, high-dose dexamethasone, and high-dose dexamethasone plus interferon alpha [33]. Response rate was significantly higher among patients receiving melphalan-dexamethasone. Median progression-free survival was 21 and 23 months after MP or melphalan and dexamethasone, but only 12 and 15 months after high-dose dexamethasone or high-dose dexamethasone plus interferon alpha, respectively. No difference in overall survival was reported among the four different groups, however. Melphalan should be incorporated in the induction regimen for elderly patients who are not candidates for autologous transplant.

In patients older than 65 years, melphalan 200 mg/m² followed by autologous transplant is too toxic, whereas intermediate-dose melphalan (100–140 mg/m²) seems more suitable. In one study, patients were aged 65 to 70 years and melphalan 100 mg/m² was superior to MP [34]. In another study, patients were aged 65 to 75 years and melphalan 100 mg/m² was superior to MP in response rate but not in progression-free and overall survival [35]. In the first study, 22% of patients did not complete the assigned treatment; in the second trial, 37% of patients did not complete it. According to these data, the age of 70 years may be suggested as the age limit for intermediate-dose melphalan.

Recently three new combinations have emerged: melphalan, prednisone, thalidomide; melphalan, prednisone, lenalidomide; and melphalan, prednisone, bortezomib (Table 3).

Melphalan, prednisone, thalidomide
Two randomized studies show that melphalan, prednisone, thalidomide (MPT) improves response and event-free survival compared with MP [35,36]; an overall survival advantage has been reported in one of the two trials [35]. Although results with melphalan, prednisone, lenalidomide (MPR) and melphalan, prednisone, bortezomib (MPV) are promising, randomized trials are needed to determine if MPR or MPV is superior to MPT.

In the Italian randomized trial, oral MPT was compared with MP in patients aged 60 to 85 years [36]. The partial response (PR) rates were 76% in patients treated with MPT and 47.6% in those treated with MP; near-CR or CR rates were 27.9% and 7.2%, respectively. The 2-year event-free survival rates were 54% for MPT and 27% for MP ($P = .0006$). The 3-year survival rates were 80% and 64%, respectively ($P = .19$). Compared with the MP regimen MPT was associated with a higher risk for grade 3 to 4 neurologic adverse events (10% versus 1%), infections (10% versus 2%, $P = .001$), cardiac toxicity (7% versus 4%), and thromboembolism (12% versus 2%). Introduction of enoxaparin prophylaxis significantly reduced the rate of thromboembolism from 20% to 3% ($P = .005$).

In the French phase III trial, MPT was compared with MP and with intermediate-dose melphalan (100 mg/m²) followed by ASCT. A higher PR rate
Table 3
New induction regimens tested in patients older than 65 years of age who had myeloma

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of patients</th>
<th>Median age (range)</th>
<th>&gt;65 years (%)</th>
<th>≥PR (%)</th>
<th>CR (%)</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
<th>Peripheral neuropathy, grade 3–4 (%)</th>
<th>DVT/embolism, grade 3–4 (%)</th>
<th>Infection, grade 3–4 (%)</th>
<th>References</th>
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<tbody>
<tr>
<td>MPT</td>
<td>124</td>
<td>ND (65–75)</td>
<td>100</td>
<td>81</td>
<td>16</td>
<td>50% at 28 mo</td>
<td>78% at 2 y</td>
<td>6</td>
<td>12</td>
<td>13</td>
<td>[35]</td>
</tr>
<tr>
<td>MPT</td>
<td>129</td>
<td>72 (60–85)</td>
<td>97</td>
<td>76</td>
<td>16</td>
<td>54% at 2 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80% at 3 y</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>[36]</td>
</tr>
<tr>
<td>MPR</td>
<td>54</td>
<td>71 (57–77)</td>
<td>96</td>
<td>85</td>
<td>24</td>
<td>91% at 2 y</td>
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<td>8</td>
<td>[39]</td>
</tr>
<tr>
<td>VMP</td>
<td>60</td>
<td>75 (65–85)</td>
<td>100</td>
<td>89</td>
<td>32</td>
<td>91% at 16 mo</td>
<td>90% at 16 mo</td>
<td>17</td>
<td>ND</td>
<td>16</td>
<td>[38]</td>
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Abbreviations: CR, complete response; DVT, deep vein thrombosis; MPR, melphalan + prednisone + lenalidomide; MPT, melphalan + prednisone + thalidomide; ND, not determined; PR, partial response; VMP, bortezomib + melphalan + prednisone.

<sup>a</sup>Event-free survival.
was seen in the MPT and in the melphalan 100 mg/m² arms, compared with MP (81% versus 73% versus 40%, respectively) [35]. Similarly, the CR rates were significantly higher with MPT and intermediate-dose melphalan compared with MP. Progression-free survival was superior in the patients treated with MPT compared with MP ($P < .001$) and autologous transplantation ($P = .001$). Furthermore, overall survival was significantly improved in the MPT group in comparison with MP ($P = .001$) and autologous transplantation ($P = .004$).

MPT was associated with a higher risk for grade 3 to 4 neutropenia, infections, thrombocytopenia, thromboembolic complications, peripheral neuropathy, constipation, and cardiac events. These data, along with the Italian study, strongly support the use of MPT as standard of care in elderly patients who have newly diagnosed myeloma.

Antithrombotic prophylaxis is recommended when using MPT. At present there is no evidence of the best prophylaxis: low–molecular weight heparin, therapeutic doses of warfarin, or daily aspirin are the preferred options [37].

**Melphalan, prednisone, bortezomib**

The Spanish cooperative group conducted a large phase I/II trial of MPV [38]. The association showed encouraging results: PR rate was 89%, including 32% immunofixation-negative CR, and half achieved immunophenotypic remission (no detectable plasma cells at $10^{-4}$ to $10^{-5}$ sensitivity). Progression-free survival at 16 months of patients treated with bortezomib, melphalan, and prednisone (VMP) was significantly prolonged in comparison with historical controls treated with MP only (91% versus 66%); similarly, overall survival at 16 months was improved (90% versus 62%). Interestingly, response rate, progression-free survival, and overall survival were similar among patients who did or did not have chromosome 13 deletion or IgH translocations. Grade 3 to 4 adverse events were thrombocytopenia, neutropenia, peripheral neuropathy, infections, and diarrhea. The treatment seemed more toxic in patients older than 75 years and during early cycles. Bortezomib may induce transient thrombocytopenia and peripheral neuropathy. Pre-existing neuropathy or previous neurotoxic therapy increases the risk for peripheral neuropathy, which can be reduced or resolved by timely dose adjustment of the drug. Bortezomib may enhance the incidence of infections, in particular herpes zoster reactivation, and prophylactic antiviral medications are highly recommended.

**Melphalan, prednisone, lenalidomide**

In a phase I/II trial dosing, safety, and efficacy of MPR were studied in newly diagnosed elderly patients who had myeloma [39]. Aspirin was administered as antithrombotic prophylaxis. At the maximum tolerated dose (lenalidomide 10 mg plus melphalan 0.18 mg/kg), 85% of patients achieved at least a PR and 23.8% immunofixation-negative CR. The 1-year event-free and overall survivals were 92% and 100%, respectively. The corresponding 1-year event-free and overall survivals were 78% and 87.4%, respectively, in historical MPT-treated control patients. Grade 3 to 4 adverse events were mainly related to hematologic toxicities (neutropenia 66%). Severe nonhematologic side effects
were less frequent and included febrile neutropenia (8%), cutaneous rash (10%), and thromboembolism (6%). Preliminary results showed that the event-free survival of patients who had deletion of chromosome 13 or chromosomal translocation (4;14) was not significantly different from those who did not have such abnormalities. By contrast, patients who had high levels of serum β2-microglobulin experienced a shorter event-free survival compared with those who showed low levels of β2-microglobulin.

Neutropenia and DVT are the major complications with lenalidomide; the addition of aspirin markedly reduced the risk for thromboembolic events in newly diagnosed patients treated with lenalidomide in association with dexamethasone or chemotherapy. Although the optimal prophylaxis strategy has not been established, aspirin seems to be the preferred choice.

**Treatment of High-Risk Myeloma**

Patients who have high-risk myeloma tend to do poorly with median overall survival of approximately 2 years even with tandem ASCT. One option for these patients is novel therapeutic strategies [2]. For example, bortezomib-containing regimens can be considered early in the disease course as primary therapy, with stem cell transplantation reserved for relapse. In at least three separate studies, bortezomib seems to overcome the adverse effect of deletion 13 [40,41].

Allogeneic approaches may be an option in selected patients (eg, ASCT followed by nonmyeloablative allogeneic transplantation). The recent IFM 99 trial in patients who had deletion 13 and high β2-microglobulin levels has not shown significant benefit with this strategy compared with tandem ASCT [42]. In case patients are treated similar to standard-risk patients, routine maintenance therapy should be considered (eg, thalidomide plus prednisone), given the high risk for relapse. Clearly clinical trials and new agents specifically designed for high-risk myeloma are needed.

**SUMMARY**

High-dose melphalan followed by ASCT in younger patients and oral MPT in the elderly are the standard of care for the initial therapy of myeloma. Survival after transplant seems to be related to the achievement of CR or VGPR. Improved response rate after induction treatment, before transplant, could translate into better results after high-dose therapy and into a prolonged survival. In younger patients, combinations incorporating thalidomide or lenalidomide or bortezomib significantly increase the pretransplant CR rate before high-dose melphalan and autologous transplantation. These combinations may further improve the CR rate achieved after transplant.

Cytogenetic abnormalities, such as deletion of chromosome 13 or chromosomal translocation (4;14), are considered negative prognostic factors. Unfortunately, most of the studies reported to date have not prospectively stratified patients based on cytogenetic abnormalities, making a firm conclusion difficult. In patients treated with MPV, and in a smaller cohort of patients treated with MPR, the event-free survival of patients who had deletion of chromosome
13 or chromosomal translocation (4;14) was not significantly different from those who did not show such abnormalities. If these data are confirmed, it seems likely that a cytogenetically adapted strategy will represent the most rational, molecularly targeted approach to myeloma therapy.

References


