Evolving Paradigms in the Treatment of Newly Diagnosed Multiple Myeloma

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Key Words
Multiple myeloma, new drugs, induction, consolidation, maintenance

Abstract
The treatment of multiple myeloma has undergone significant changes in the past few years. The introduction of novel agents, such as the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib, has dramatically improved the outcome of this disease and considerably increased the treatment options available. Several trials have shown the advantages linked to the use of novel agents both in young patients, who are considered eligible for transplantation, and elderly patients, for whom a conventional therapy should be considered. These novel agents may increase the efficacy of autologous stem cell transplantation with deeper and long-lasting response. In the transplant setting, different novel agent combinations have proved to be superior to the traditional vincristine-doxorubicin-dexamethasone. Similarly, novel agents have also changed the treatment paradigm of patients not eligible for transplantation, thus replacing the traditional melphalan-prednisone approach. Preliminary data also support the role of consolidation and maintenance therapy to further improve outcomes. This article provides an overview of the latest strategies, including novel agents used to treat patients with multiple myeloma, both in the transplant and nontransplant settings. (JNCCN 2011;9:1186–1196)

Multiple myeloma (MM) is the second most common hematologic malignancy. It accounts for 1% of all cancers and 13% of hematologic neoplasms. The median age at diagnosis is 70 years, with 37% of patients younger than 65 years, 26% aged 65 to 74 years, and 37% older than 75 years.1–3

The diagnosis of MM is based on the presence of at least 10% clonal bone marrow plasma cells and serum and/or urinary monoclonal protein.4,5 Symptomatic MM is characterized by evidence of end-organ damage caused by plasma cell proliferation, defined as CRAB features (hypercalcemia, renal failure, anemia, bone disease). Recognizing organ damage is the first step to correctly identifying symptomatic disease and subsequently starting appropriate treatment.4,5 Symptomatic MM should be treated immediately, whereas asymptomatic disease requires clinical observation because early treatment has shown no benefit.6,7 Staging of the disease according to the International Staging System (ISS), defines 3 risk groups based on serum β₂-microglobulin and albumin levels at diagnosis.8 High-risk diseases and poor prognosis are defined with the presence of high levels of serum β₂-microglobulin (stage III). Any chromosomal abnormality detected on standard cytogenetic analysis is associated with a worse outcome.9 The presence of del(17p13) or t(4;14), t(14;16), or chromosome 1 abnormalities detected on fluorescent in situ hybridization is associated with a poor prognosis (Table 1).9,10

Patients with MM can be further classified based on patient characteristics. Patients younger than 65 years without severe comorbidities who are able to undergo intensive treatments are considered eligible for autologous stem cell transplantation (ASCT). Patients aged 65 years or older or with serious comorbidities are usually not considered ASCT candidates and need a gentler approach. Because the biologic age may differ from the chronologic age, comorbidities must be considered when determining eligibility of patients for ASCT.11

The introduction of novel agents, such as the first in-class proteasome inhibitor bortezomib and the im-
munomodulatory drugs (IMIDs) thalidomide and lenalidomide, that target MM cells and bone marrow microenvironment led to great advances in the treatment of MM. Prolongation of progression-free survival (PFS) and overall survival remains the ultimate goal, but newer and more efficacious therapies enabled a complete response in a larger proportion of patients. In the transplant setting, complete response was found to be closely related to overall survival. With the availability of novel agents, a greater number of elderly patients are now able to experience complete response. A recent analysis of 1175 elderly patients showed a significant association between the achievement of complete response and long-term outcome, thus supporting the use of novel agents to achieve maximal response also in patients older than 75 years. Stringent complete response is associated with better outcome. Definition of minimal residual disease using multiparameter flow cytometry is one of the most important prognostic factors for survival.

This article provides an overview of novel-agent–based regimens for the initial treatment of patients with MM.

### Treatment of Young Patients

A variety of strategies have been proposed to achieve higher complete response rates in the first-line therapeutic setting, including ASCT. A systematic meta-analysis of randomized trials involving 2411 patients treated with ASCT versus conventional chemotherapy showed a significantly longer PFS among those treated with ASCT. The source studies were markedly heterogeneous, and no overall survival benefit was detected with single ASCT performed early.

For many years, standard induction treatment consisted of vincristine-doxorubicin-dexamethasone (VAD). Ten years ago, patients who were candidates for transplant would receive VAD for 4 to 6 cycles, leading to a partial response rate of 52% to 63%, and a complete response rate of 3% to 13%. Conventional induction followed by a single or double ASCT resulted in a 30% to 40% complete response rate and a median survival of 6 years but, unfortunately, without a survival plateau.

Recently, novel agents in combination with established antimyeloma drugs, such as dexamethasone, doxorubicin, and cyclophosphamide, provided physicians with more effective combinations that have replaced the VAD regimen.

### New Induction Treatments Including Novel Agents

#### Two-Drug Regimens

Several trials showed good feasibility and efficacy with thalidomide, lenalidomide, and bortezomib combined with dexamethasone (Table 2). The combination thalidomide-dexamethasone (TD) proved to be superior to dexamethasone alone. TD improved the response rate and time-to-progression (22.6 vs. 6.5 months; \( P < .001 \)), but a low complete response rate and no survival advantage were reported. Grade 4 adverse events were more frequent with TD compared with dexamethasone (30% vs. 23%). Deep vein thrombosis (DVT) was a major drawback and occurred in 11.5% to 17% of patients in the TD arm, and in 2% to 3% in the dexamethasone arm. Nevertheless, TD remains a possible induction option for young patients.

Lenalidomide showed a higher potency than its analogue thalidomide, and the advantage of less neurotoxicity, particularly peripheral neuropa-
<table>
<thead>
<tr>
<th>Combination</th>
<th>No. of Patients</th>
<th>Schedule</th>
<th>At Least PR</th>
<th>CR</th>
<th>PFS/EFS/TTP</th>
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<tr>
<td><strong>Two-drug regimens</strong></td>
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<tr>
<td>TD</td>
<td>235</td>
<td>T: 50 mg/d, escalated to 100 mg on day 15, and to 200 from day 1 of cycle 2; D: 40 mg on days 1–4, 9–12, and 17–20 during cycles 1–4 and on day 1–4 from cycle 5 onward</td>
<td>63%</td>
<td>8%</td>
<td>NA</td>
<td>NA</td>
<td>Rajkumar et al.19</td>
</tr>
<tr>
<td>RD</td>
<td>97</td>
<td>R: 25 mg/d for 28 days; D: 40 mg on day 1–4, 9–12, and 17–20 For three 35-day cycles</td>
<td>77%</td>
<td>NA</td>
<td>52% at 36 mo</td>
<td>79% at 36 mo</td>
<td>Zonder et al.20</td>
</tr>
<tr>
<td>RD*</td>
<td>223</td>
<td>R: 25 mg/d on days 1–21; D: 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle</td>
<td>81%</td>
<td>17%</td>
<td>63% at 24 mo</td>
<td>75% at 24 mo</td>
<td>Rajkumar et al.21</td>
</tr>
<tr>
<td>Rd*</td>
<td>222</td>
<td>R: 25 mg/d on days 1–21; D: 40 mg on days 1, 8, 15, and 22 of a 28-day cycle</td>
<td>70%</td>
<td>14%</td>
<td>65% at 24 mo</td>
<td>87% at 24 mo</td>
<td>Rajkumar et al.21</td>
</tr>
<tr>
<td>VD</td>
<td>32</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks for up to 6 cycles; D: 40 mg on the day of/after V administration</td>
<td>88%</td>
<td>6%</td>
<td>NA</td>
<td>87% at 12 mo</td>
<td>Jagannath et al.25</td>
</tr>
<tr>
<td>VD</td>
<td>240</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks for up to 6 cycles; D: 40 mg on the day of/after V administration</td>
<td>79%</td>
<td>6%</td>
<td>50% at 36 mo</td>
<td>81% at 36 mo</td>
<td>Harousseau et al.24</td>
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<td><strong>Three-drug regimens</strong></td>
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<tr>
<td>TAD</td>
<td>201</td>
<td>T: 100–200 mg on days 1–28; A: 9 mg/m² on days 1–4; D: 40 mg on days 1–4, 9–12, 17–20, plus days 8–11, 15–18, cycle 1 only</td>
<td>72%</td>
<td>4%</td>
<td>NA</td>
<td>NA</td>
<td>Lokhorst et al.25</td>
</tr>
<tr>
<td>PAD</td>
<td>21</td>
<td>P: 1.3 mg/m² on days 1, 4, 8, and 11; A: 9 mg/m² on days 1–4; D: 40 mg on days 1–4, plus days 8–11, 15–18, cycle 1 only</td>
<td>95%</td>
<td>24%</td>
<td>50% at 29 mo</td>
<td>95% at 24 mo</td>
<td>Popat et al.26</td>
</tr>
<tr>
<td>VTD</td>
<td>241</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11; T: 100 mg/d for the first 14 days, 200 mg/d thereafter; D: 40 mg on day 8 of the first 12 days (not consecutively) for three 21-day cycles</td>
<td>93%</td>
<td>19%</td>
<td>68% at 36 mo</td>
<td>86% at 36 mo</td>
<td>Cavo et al.28</td>
</tr>
<tr>
<td>VRD</td>
<td>66</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11; R: 25 mg on days 1–14; D: 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12</td>
<td>100%</td>
<td>29%</td>
<td>75% at 18 mo</td>
<td>97% at 18 mo</td>
<td>Richardson et al.21</td>
</tr>
<tr>
<td>VCD</td>
<td>200</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11; C: 900 mg/m² on day 1; D: 40 mg on days 1, 5, 8, 11, and 12</td>
<td>84%</td>
<td>13%</td>
<td>NA</td>
<td>NA</td>
<td>Knop et al.32</td>
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<td><strong>More intense regimens</strong></td>
<td></td>
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<tr>
<td>VDCR</td>
<td>28</td>
<td>V: 1.3 mg/m² on days 1, 4, 8, and 11; D: 40 mg on days 1, 8, and 15; C: 500 mg/m² on days 1 and 8; R: 15 mg on days 1–14 for eight 21-day cycles</td>
<td>96%</td>
<td>40%1</td>
<td>NA</td>
<td>NA</td>
<td>Kumar et al.34</td>
</tr>
<tr>
<td>VTD-PACE</td>
<td>303</td>
<td>V: 1.0 mg/m² on days 1, 4, 8, and 11; T: 200 mg/d on days 4–7; P: 10 mg/m² on days 4–7; A: 10 mg/m² on days 4–7; C: 400 mg/m² on days 4–7; E: 40 mg/m² on days 4–7</td>
<td>NA</td>
<td>56%1</td>
<td>84% at 24 mo</td>
<td>86% at 24 mo</td>
<td>Barlogie et al.37</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; EFS, event-free survival; NA, not available; OS, overall survival; PAD, bortezomib-adriamycin-dexamethasone; PFS, progression-free survival; PR, partial response; RD, lenalidomide-dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; TAD, thalidomide-adriamycin-dexamethasone; TD, thalidomide-dexamethasone; TTP, time to progression; VCD, bortezomib-cyclophosphamide-dexamethasone; VD, bortezomib-dexamethasone; VDCR, bortezomib-dexamethasone-cyclophosphamide-lenalidomide; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone; VTD-PACE, bortezomib-thalidomide-dexamethasone and cisplatin-doxorubicin-cyclophosphamide-etoposide.

1 The study included both young and elderly patients.
2 CR/marrow CR.
3 Percentage at 2 years.
thy. Lenalidomide in combination with high-dose dexamethasone (RD) led to improved response rates compared with dexamethasone alone. In particular, rates of at least a partial response and a very good partial response (VGPR) were particularly higher with RD, as was 1-year PFS. However, this improvement did not translate into an overall survival advantage. The incidences of grade 3/4 neutropenia (21% vs. 5%) and thromboembolic events (24% vs. 5%) were more pronounced with RD. A phase III trial showed superior overall survival and lower toxicity with lenalidomide plus low-dose dexamethasone (RD). Toxicity rates were significantly higher with RD, particularly those for DVT or pulmonary embolism (26% vs. 12%), and infections (16% vs. 9%). Almost all recent trials are now using the reduced dose of dexamethasone (40 mg once weekly or equivalent), and high-dose dexamethasone is no longer recommended in newly diagnosed MM. High-dose dexamethasone remains indicated in particular settings, such as when hypercalcemia, spinal cord compression, renal failure, and pain occur at diagnosis. Antithrombotic prophylaxis is highly recommended in patients receiving lenalidomide or thalidomide as induction therapies.

The combination bortezomib-dexamethasone (VD) is another possible option for patients eligible for transplantation. VD proved to be more effective than VAD as pretransplant induction. Responses pre- and posttransplantation were considerably better with VD, particularly at least VGPR. This benefit did not translate into a survival advantage, and the PFS improvement associated with VD was modest and not statistically significant.

Three-Drug Regimens

Several investigators postulated that response rates could be further increased by adding a third drug, without a burden of toxicities. IMIDs and bortezomib are being used in combination with dexamethasone and anthracyclines, resulting in a triple regimen. Three-drug combinations led to improved response, particularly complete response, and survival compared with 2-drug associations.

The combination of thalidomide-doxorubicin-dexamethasone (TAD) led to a significantly higher response rate posttransplant and a superior at least VGPR rate posttransplant (49% vs. 32%) compared with VAD, with a comparable toxicity profile.

The addition of doxorubicin to bortezomib and dexamethasone (PAD) resulted in a pretransplantation overall response rate of 95%, with a 24% complete response rate, associated with impressive outcomes after long-term follow-up. Another phase II study confirmed the efficacy of this regimen, reporting a complete response/near-complete response rate of 38%, a median 1-year PFS rate of 93%, and an overall survival rate of 98%.

Novel agents with different mechanisms of action combined in the bortezomib-thalidomide-dexamethasone (VTD) regimen proved to be superior to TD as induction therapy pre-ASCT. The Italian group showed improved response and PFS with VTD, but no survival advantage was yet seen. Grade 3 to 4 adverse events were significantly higher in patients treated with VTD (56%) than in those treated with TD (33%; P < .0001), and peripheral neuropathy was most frequently observed in patients treated with VTD (10% vs. 2%; P = .0004). The Spanish and French groups confirmed the superiority of VTD over TD in terms of response rate and PFS.

Considering the positive results obtained with this induction regimen, particularly in terms of complete response/near-complete response rates, VTD represents an excellent option, able to maximize the degree and speed of tumor reduction in patients with MM eligible for transplant.

Richardson et al. performed a phase I/II study to evaluate the role of bortezomib-lenalidomide-dexamethasone (VRD) in front-line treatment. VRD was shown to be highly effective, with favorable tolerability. Most common grade 3/4 hematologic toxicities included lymphopenia (14%), neutropenia (9%), and thrombocytopenia (6%). Thrombosis was less common (6%) and no treatment-related mortality was reported. Based on these data, VRD should be further evaluated as an alternative induction regimen pre-ASCT.

An open-label, prospective, multicenter, phase II clinical trial explored the combination bortezomib-cyclophosphamide-dexamethasone (VCD). Data from the first 200 patients confirm that VCD is highly effective, regardless of cytogenetic risk factors. Of the patients enrolled, 53% had grade 3/4 adverse events, including serious infections (2%) and grade 3 paresthesia (2%).

The combination cyclophosphamide-thalidomide-dexamethasone (CTD) with reduced doses of thalidomide and dexamethasone was compared with
Hematopoietic Stem Cell Transplantation

ASCT is considered the gold standard for patients with MM younger than 65 years. Long-term results of autologous and allogeneic transplantation, before the addition of new drugs, show that several patients experience prolonged PFS, and a small proportion of them can achieve cure.

Two trials compared the efficacy of single versus double ASCT. The IFM group reported a prolonged survival by 10 months with tandem transplantation, and 42% and 21% overall survival at 7 years for tandem and single ASCT, respectively. A non-preplanned analysis of these data showed that the patients who benefited from a second ASCT were those for whom the first transplantation failed to produce at least a VGPR (overall survival rates at 7 years were 43% and 11% with tandem and single transplantation, respectively). In the Italian study, tandem versus single ASCT showed significant prolonged event-free survival with no impact on overall survival. Patients not experiencing at least near-complete response after the first ASCT derived the most benefit from the second transplant. Recently, the achievement of at least a VGPR after high-dose therapy was shown to be a simple prognostic factor, with a significant impact in intermediate- and high-risk patients with ISS stage II to III MM and high-risk cytogenetics [t(4;14) or del(17p)].

The recent addition of new drugs provides response rates similar to those achieved with ASCT. These favorable results obtained with long-term novel combinations are challenging the role of upfront transplantation. Ongoing trials are evaluating the role of delayed versus frontline ASCT.

Novel agents have also renewed the role of maintenance. Different randomized trials showed a benefit in terms of PFS and overall survival with thalidomide maintenance. These encouraging results have led to the design of several trials exploring the role of maintenance with lenalidomide or bortezomib.

Future studies should compare the best chemotherapeutic approach with ASCT strategies to assess the impact of complete response on long-term survival, define the benefit of single versus tandem transplant, define the role of maintenance treatment, and identify the optimal dose and schedule and the subgroups of patients who may benefit from maintenance.

Treatment of Elderly Patients

For more than 40 years, MP was considered the standard treatment. A meta-analysis of 27 randomized trials compared different chemotherapy regimens...
with MP. Chemotherapy induced higher response rates (60.0% vs. 53.2%; P < .0001) but similar overall survival, and MP was better tolerated. The role of MP has been challenged by newer combinations (Table 3). TD was more effective than MP, but toxicity and treatment discontinuation were higher with dexamethasone, whereas MP was better tolerated and associated with longer survival. During the first year of therapy, non–disease-related deaths in the TD group were twice as high compared with those in the MP group, with infections being the primary cause. In patients older than 72 years with poor performance status, this trend was even more evident.

New Approaches With Novel Agents

Two- and Three-Drug Therapies

Six randomized phase III studies have shown that the combination melphalan-prednisone-thalidomide (MPT) is superior to MP in terms of response and PFS. The PFS advantage achieved with MPT translated into improved survival in the 2 IFM studies, but this trend was not observed in the 3 other trials comparing MPT with MP. Grade 3/4 neutropenia was the main adverse event associated with MPT (16%–48%), mainly related to melphalan. Peripheral neuropathy (6%–23%) and venous thromboembolism (3%–12%) were the main adverse events associated with thalidomide.

Individual data of these trials were pooled together in a meta-analysis of 1682 patients. Median PFS was 20 months in the MPT arm and 15 months in the MP arm, and median overall survival times were 39 months (95% CI, 35.6–39.0) and 33 months (95% CI, 30.4–36.5), respectively. This meta-analysis further confirmed the PFS advantage achieved with MPT.

Data reported suggest that the addition of thalidomide considerably improves the results achieved with MP, and MPT is now considered a new standard of care for elderly patients with MM. Concomitant antithrombotic prophylaxis with aspirin, warfarin, or low-molecular-weight heparin is suggested.

The addition of bortezomib to MP (VMP) proved to be a valid alternative option in this setting. The phase III VISTA study found that responses, particularly complete response, time to progression, and survival, were significantly higher with VMP compared with MP. A recent update of the trial further confirmed the survival benefits of VMP after longer follow-up. Hematologic toxicity was similar in the 2 groups. Grade 3/4 peripheral sensory neuropathy and neuralgia were more frequent in the VMP group, as were grade 3/4 gastrointestinal events (19% vs. 5%). Rates of adverse events were higher with VMP versus MP during the first 4 cycles of therapy when bortezomib was administered twice weekly. In light of the impressive results, VMP has become the new standard of care for patients with untreated newly diagnosed MM.

A randomized trial by Mateos et al. compared the VMP regimen along with bortezomib with the combination of bortezomib, thalidomide, and prednisone (VTP) as induction therapy. Response rates were similar and no significant differences in 2-year time to progression and overall survival were observed between the arms. Nevertheless, VMP was better tolerated than VTP. The incidence of grade 3/4 cardiac toxicity was 8.5% versus 0% (P = .01), thromboembolic events was 2% versus 1% (P = .5), and peripheral neuropathy was 9% versus 5% (P = .6) with VTP and VMP, respectively. Patients receiving VMP had higher rates of neutropenia (39% vs. 22%; P = .008), thrombocytopenia (27% vs. 12%; P = .0001), and infections (7% vs. 1%; P = .01). The rates of discontinuation (17% vs. 12%; P = .03) and serious adverse events (31% vs. 15%; P = .01) were higher among patients treated with VTP. The reduced VMP regimen was associated with a reduction of peripheral neuropathy and gastrointestinal toxicity compared with the conventional VMP of the VISTA trial. These data confirm the role of VMP in the treatment of elderly patients, and suggest that VMP, considering its toxicity profile, should be preferred to VTP.

Promising results were seen in a phase II study of lenalidomide in combination with MP (MPR). Grade 3/4 adverse events were neutropenia (67.9%), thrombocytopenia (32%), anemia (17%), infections (9.4%), and dermatologic reactions (7.5%). Aspirin was administered as antithrombotic prophylaxis, and the incidence of thromboembolic events was 5.7%. An ongoing phase III study is comparing MPR, MPR followed by lenalidomide maintenance (MPR-R), and MP. MPR-R reduced the risk of disease progression by 58% compared with MP. A landmark analysis proved the benefit of lenalidomide maintenance: the risk of progression in the MPR-R arm was re-
Table 3  Novel-Agent Containing Induction Regimens for Elderly Patients With Multiple Myeloma

<table>
<thead>
<tr>
<th>Combination</th>
<th>No. of Patients</th>
<th>Schedule</th>
<th>At Least PR</th>
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<tr>
<td>TD</td>
<td>145</td>
<td>T: 200 mg/dl D: 40 mg, days 1–4 and 15–18 on even cycles and days 1–4 on odd cycles, during a 28-day cycle</td>
<td>68%</td>
<td>2%</td>
<td>41% at 16 mo</td>
<td>61% at 41 mo</td>
<td>Ludwig et al. 14</td>
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<tr>
<td>Three-drug regimens</td>
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<tr>
<td>MPT</td>
<td>125</td>
<td>M: 0.25 mg/kg days 1–4 P: 2 mg/kg days 1–4 T: 400 mg/dl for twelve 6-week cycles</td>
<td>76%</td>
<td>13%</td>
<td>50% at 28 mo</td>
<td>50% at 52 mo</td>
<td>Facon et al. 15</td>
</tr>
<tr>
<td>MPT</td>
<td>113</td>
<td>M: 0.25 mg/kg days 1–4 P: 2 mg/kg days 1–4 T: 100 mg/dl for twelve 6-week cycles</td>
<td>62%</td>
<td>7%</td>
<td>50% at 24 mo</td>
<td>50% at 44 mo</td>
<td>Hulin et al. 16</td>
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<tr>
<td>MPT</td>
<td>60</td>
<td>M: 9 mg/m² days 1–4 P: 60 mg/m² days 1–4 T: 100 mg/dl for eight 6-week cycles, followed by T: 100 mg/dl until relapse</td>
<td>58%</td>
<td>9%</td>
<td>50% at 21 mo</td>
<td>50% at 26 mo</td>
<td>Beksaç et al. 17</td>
</tr>
<tr>
<td>MPT</td>
<td>182</td>
<td>M: 0.25 mg/kg days 1–4 P: 2 mg/kg days 1–4 T: 100 mg/d for twelve 6-week cycles until plateau T: 400 mg/dl until plateau, reduced to 200 mg/dl until progression</td>
<td>57%</td>
<td>13%</td>
<td>50% at 15 mo</td>
<td>50% at 29 mo</td>
<td>Waage et al. 18</td>
</tr>
<tr>
<td>MPT</td>
<td>165</td>
<td>M: 0.25 mg/kg P: 1 mg/kg days 1–5 T: 200 mg/dl for eight 4-week cycles, followed by T: 50 mg/dl until relapse</td>
<td>66%</td>
<td>23%</td>
<td>67% at 24 mo</td>
<td>50% at 24 mo</td>
<td>Wijermans et al. 19</td>
</tr>
<tr>
<td>MPT</td>
<td>167</td>
<td>M: 4 mg/m² days 1–7 P: 40 mg/m² days 1–7 for six 4-week cycles T: 100 mg/dl until relapse</td>
<td>76%</td>
<td>15%</td>
<td>50% at 22 mo</td>
<td>50% at 45 mo</td>
<td>Palumbo et al. 20</td>
</tr>
<tr>
<td>MPR</td>
<td>54</td>
<td>M: 0.18–0.25 mg/kg days 1–4 P: 2 mg/kg days 1–4 R: 5–10 mg days 1–21 for nine 4-week cycles</td>
<td>81%</td>
<td>24%</td>
<td>92% at 12 mo</td>
<td>100% at 12 mo</td>
<td>Palumbo et al. 21</td>
</tr>
<tr>
<td>MPR-R</td>
<td>152</td>
<td>M: 0.18 mg/kg days 1–4 P: 1 mg/kg days 1–4 R: 10 mg days 1–21 for nine 4-week cycles Maintenance R: 10 mg/dl until relapse</td>
<td>77%</td>
<td>16%</td>
<td>50% at 31 mo</td>
<td>92% at 12 mo</td>
<td>Palumbo et al. 20</td>
</tr>
<tr>
<td>VMP</td>
<td>344</td>
<td>M: 9 mg/m² days 1–4 P: 60 mg/m² days 1–4 V: 1.3 mg/m² days 1, 4, 8, 11, 22, 25, 29, and 32 for first four 6-week cycles; days 1, 8, 15, and 22 for subsequent five 6-week cycles</td>
<td>71%</td>
<td>30%</td>
<td>50% at 22 mo</td>
<td>41% at 36 mo</td>
<td>San Miguel et al. 22 Mateos et al. 23</td>
</tr>
<tr>
<td>VMP</td>
<td>257</td>
<td>M: 9 mg/m² days 1–4 P: 60 mg/m² days 1–4 V: 1.3 mg/m² days 1, 4, 8, 15, and 22</td>
<td>81%</td>
<td>24%</td>
<td>41% at 36 mo</td>
<td>87% at 36 mo</td>
<td>Palumbo et al. 20</td>
</tr>
<tr>
<td>VMP</td>
<td>130</td>
<td>M: 9 mg/m² days 1–4 P: 60 mg/m² days 1–4 V: 1.3 mg/m² twice weekly (days 1, 4, 8, 11; 22, 25, 29, and 32) for one 6-week cycle, followed by once weekly (day 1, 8, 15, and 22) for five 5-week cycles</td>
<td>89%</td>
<td>20%</td>
<td>50% at 36 mo</td>
<td>74% at 36 mo</td>
<td>Mateos et al. 24</td>
</tr>
<tr>
<td>VTP</td>
<td>130</td>
<td>T: 100 mg/dl P: 60 mg/m² days 1–4 V: 1.3 mg/m² twice weekly (days 1, 4, 8, 11, 22, 25, 29, and 32) for one 6-week cycle, followed by once weekly (day 1, 8, 15, and 22) for five 5-week cycles</td>
<td>81%</td>
<td>28%</td>
<td>50% at 25 mo</td>
<td>65% at 36 mo</td>
<td>Mateos et al. 24</td>
</tr>
<tr>
<td>Four-drug regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMPT/VT</td>
<td>254</td>
<td>M: 9 mg/m² days 1–4 P: 60 mg/m² days 1–4 V: 1.3 mg/m² days 1, 8, 15, and 22 T: 50 mg/dl 12</td>
<td>89%</td>
<td>38%</td>
<td>56% at 36 mo</td>
<td>89% at 36 mo</td>
<td>Palumbo et al. 20</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; EFS, event-free survival; MPR, melphalan-prednisone-lenalidomide; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide maintenance; MPT, melphalan-prednisone-thalidomide; OS, overall survival; PFS, PR, partial response; TD, thalidomide-dexamethasone; TTP, time to progression; VMP, bortezomib-melphalan-prednisone; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance; VTP, bortezomib-thalidomide-prednisone.

*Disease-free survival.*

CR plus very good partial response.
duced by 69% compared with MPR. Grade 3/4 hematologic adverse events were more frequent with MPR-R than with MP (neutropenia, 71% vs. 30%; thrombocytopenia, 38% vs. 14%). Lenalidomide maintenance was well tolerated, with few reported incidences of grade 3/4 adverse events and second cancer.35,36,56

The 2-drug combination Rd was shown to be a possible alternative option also for elderly patients, considering its low toxicity profile.21 However, further studies are needed to compare Rd with the new standards MPT and VMP, and to validate its role.

A More Intense Approach
The triplets MPT and VMP are now considered the new standards of care for elderly patients with MM. Recently, an Italian phase III study compared the role of a more complex approach involving both thalidomide and bortezomib in combination with MP followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus the standard VMP.37 Response rates were significantly superior with the 4-drug regimen, and this translated into a better PFS. No differences in overall survival were detected between the groups, but follow-up is still short to draw definitive conclusion. Grade 3/4 neutropenia (38% vs. 28%; \( P = .02 \)), cardiac complications (10% vs. 5%; \( P = .04 \)), and thromboembolic events (5% vs. 2%; \( P = .08 \)) were more common among patients treated with VMPT-VT.

Intermediate-dose regimens were proposed to adapt ASCT to older patients and reduce potentially lethal side effects. Before the introduction of novel agents, a randomized study on patients aged 65 to 70 years found that melphalan, 100 mg/m² (Mel100), followed by ASCT was well tolerated and led to better responses and outcomes than standard MP (3-year event-free survival, 31% vs. 18%, respectively; 3-year overall survival, 73% vs. 58%, respectively; \( P = .01 \)).58 The role of Mel100 in patients aged 65 to 75 years was further evaluated in comparison with both MPT and MP in another randomized trial. PFS and overall survival were significantly better in patients treated with MPT compared with Mel100 and MP, and no differences were detected between Mel100 and MP.45 A phase II trial investigated the effect of bortezomib before tandem Mel100, followed by posttransplant consolidation and maintenance with lenalidomide, in patients between 65 and 75 years of age. This sequential approach lead to a progressive improvement and quality of response. Patients younger than 70 years showed a slightly better outcome than patients older than 70, although the difference was not significant.59 The incidences of adverse events, early mortality, and drop-out rates suggest that Mel100 has high toxicity in patients aged 71 to 75 years and should be considered in patients younger than 70 years.

Treatment of Patients Older Than 75 Years
In an elderly population, a precise age cutoff to guide physicians in the choice of treatment is difficult to define. The efficacy should carefully be balanced against drug toxicity, and age-adjusted dose modifications are highly suggested to improve tolerability and consequently outcome (Table 4). Various studies tested the role of reduced-dose regimens in patients older than 75 years. The French MPT study investigated reduced-dose melphalan (0.2 mg/kg) and thalidomide (100 mg/d) in patients older than 75 years.46 Median PFS was 24.1 months with MPT, and overall survival was equally remarkable at 44.0 months. Toxicity from MPT was acceptable, with a median thalidomide treatment duration longer than 1 year. No increase in thrombosis was noted, possibly related to the more frequent use of antithrombotic treatments for comorbidities in this age group.

Similarly, the study conducted by the Spanish group compared VMP versus VTP with bortezomib administered twice weekly for the first cycle, and once weekly for the following 5 cycles. This approach proved to be effective and well tolerated: grade 3 or worse peripheral neuropathy was 8% in this study versus 13% in VISTA study, and the rate of gastrointestinal symptoms was 4% in this study versus 19% in VISTA trial.52-54

The benefit of reduced-dose bortezomib was also evident in the Italian study comparing VMPT-VT with VMP. To optimize treatment the protocol was amended, and the bortezomib schedule was decreased from twice- to once-weekly in both arms. A post hoc analysis showed that patients receiving once-weekly bortezomib had a significantly lower incidence of adverse events, without affecting efficacy. No significant differences in terms of complete response, PFS, and overall survival were observed. A significant reduction of nonhematologic grade 3/4
adverse events, particularly peripheral neuropathy (from 28% to 8%; \( P < .001 \)), and a subsequent treatment discontinuation rate were detected with the once-weekly schedule.60

## Conclusions

Today, a wider variety of treatment options is available for both young and elderly patients with MM. This enables physicians to tailor and better personalize therapies according to patient characteristics by balancing efficacy and toxicity of each drug.

Patients younger than 65 years appear to benefit from ASCT. Induction treatment with new drugs is the most suitable preparatory regimen before transplant, leading to improved outcome as compared with the old standard VAD. In particular, the 3-drug combinations VTD and PAD seem more effective than 2-drug combinations, and are likely to become the new standard induction therapies for young patients. Other combinations such as VRD are being explored with promising results. Although ASCT is considered an essential strategy for the treatment of young patients, whether to perform ASCT, either single or double, in all patients remains an open issue.

In elderly patients, the combination of an alkylating drug with a novel agent should be considered the standard approach. Randomized phase III studies have shown that MPT and MPV were more effective than traditional MP, and therefore can be considered the new standards of care for patients ineligible for ASCT. The newer MPR is providing promising results in this setting. The more-intense VMPT combination recently led to improved response rates compared with standard VMP, but longer follow-up is needed to detect a survival advantage. Reducing the bortezomib schedule further improved outcome through decreasing treatment-related toxicity without negatively affecting efficacy. Recent data also showed the advantage of reduced-dose dexamethasone, and Rd proved to be effective and well tolerated also by elderly patients.

In the past few years, much progress has been made in the treatment of MM, but there is still a long way ahead. A key challenge in the management of this rare disease will require a careful integration of the optimal sequence of therapy with the risk/benefit ratio of each agent.

## Acknowledgments

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