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New Treatment Approaches for Older Adults with Multiple Myeloma

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Abstract

The incidence of multiple myeloma (MM) increases with age, and with the aging of the population, the number of adults with MM is expected to double in the next 20 years. Novel agents, including the immunomodulatory agents thalidomide and lenalidomide, and the proteasome inhibitor bortezomib have dramatically changed the treatment of multiple myeloma in the past decade. The purpose of this review was to examine the recent clinical therapeutic trials in older adults with MM. A number of trials have evaluated the addition of novel agents to the traditional backbone of melphalan and prednisone. The combination of thalidomide with melphalan and prednisone has been evaluated in 7 randomized trials. The combination improves response rates and, in meta-analyses, survival, but at the expense of increased toxicity. Other combination regimens which include lenalidomide or bortezomib likewise are associated with higher response rates, but at the expense of greater toxicity. High dose dexamethasone is excessively toxic in older adults and should be avoided. The roles for high-dose therapy with autologous stem cell transplant or intermediate-dose melphalan with autologous stem cell transplant in older adults with MM in the era of modern therapy remain to be defined. In summary, there are a number of new therapeutic options for older adults with MM, allowing an individualized treatment strategy based on the patient's comorbidities and goals of care.

Keywords

multiple myeloma; geriatrics; aging; chemotherapy; immunomodulatory agents; proteasome inhibitors

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1. Introduction

With the aging of the population and the increased incidence of multiple myeloma with age, the number of patients over the age of 65 with multiple myeloma in the United States will double by 2030.[1] Almost 40% of cases of multiple myeloma occur in patients over the age of 70.[2] Age is one of the most important negative prognostic factors in multiple myeloma. Over the past decade, there has been a dramatic shift in the treatment of multiple myeloma. The introduction of novel therapeutic agents, including the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib, has been associated with dramatically improved response and survival rates in clinical trials, approaching those seen in trials of high dose therapy and autologous stem cell transplantation in younger patients. [3] However, on a population level, the improvements in survival among older patients have lagged behind younger patients,[4] and have been modest in comparison. [5,6]

Despite the promise of newer therapies, multiple myeloma remains incurable in all but a few patients. Decisions regarding therapy in older adults with multiple myeloma must balance the burden of disease, the risks and benefits of therapy, and the patient's goals of care. Issues of particular importance in the geriatric population, including comorbidities, functional status, cognition, and social support, play an integral role in the decision-making process. Fortunately a number of novel therapeutic strategies have emerged and have been tested in an older population, allowing selection of the regimen to be tailored to an older patient's individual needs and goals. In this article, we will review the efficacy and toxicity of emerging treatment options available to older adults with multiple myeloma.

2. Initial therapy in older adults with multiple myeloma

Melphalan and prednisone have been a mainstay of therapy for multiple myeloma for more than 40 years.[7] With the advent of high dose therapy and autologous stem cell transplantation (HDT/ASCT),[3] there arose the imperative to avoid initial treatment with melphalan, which impairs stem cell mobilization, in patients who were eligible for ASCT. Thus, there is an important distinction between patients who may be candidates for HDT/ASCT and those who are not. Among patients who are not eligible for HDT/ASCT, melphalan remains a central component of initial therapy, the backbone of most novel regimens.

2.1 Thalidomide

2.1.1 Thalidomide and dexamethasone versus melphalan and prednisone—A randomized trial of the orally-administered immunomodulatory and antiangiogenic agent thalidomide plus dexamethasone (TD) versus melphalan plus prednisone (MP) enrolled patients over the age of 65, or younger patients with contraindications or preference not to undergo HDT/ASCT.[8] Patients in the TD arm received thalidomide 50 to 400 mg daily with dexamethasone 40mg on days 1–4 and 15–18 on even cycles and days 1–4 on odd cycles, with cycles every 28 days. Patients in the MP arm received melphalan 0.25 mg/kg days 1–4 and prednisolone 2 mg/kg days 1–4, with cycles every 28–42 days. Patients were scheduled to receive 9 cycles of therapy; those with stable disease were subsequently randomized to maintenance therapy with thalidomide 100mg daily or interferon α -2b. Prophylaxis with low-molecular-weight heparin was added after an increased incidence of thromboembolic complications was noted. The overall response rate was 68% in the TD arm and 50% in the MP arm ($P=0.002$). The median time to progression (TTP) was 21.2 months vs 29.1 months ($p=0.2$) in the TD vs MP arms, disease free survival (DFS) was 16.7 vs. 20.7 months ($p=0.10$), and overall survival (OS) was 41.5 vs. 49.4 months ($p=0.024$), respectively. As expected, toxicities differed in the two groups: cytopenias were more common in patients treated with MP, while constipation, venous thromboembolism,

peripheral neuropathy, and psychological disturbances were more common in patients receiving TD. On subgroup analysis of patients over the age of 75 (N=69), survival was shorter in patients treated with TD (median OS 19.8 months vs 41.3 months with MP, $p=0.071$). Poor performance status and low albumin predicted early non-myeloma related mortality in the TD arm. The authors concluded that, while TD yielded a higher response rate, it was associated with shorter survival, likely attributable to the toxicity of high dose dexamethasone.

2.1.2. Melphalan, Prednisone and Thalidomide—Seven randomized trials[9–16] and two meta-analyses[17,18] have compared melphalan and prednisone (MP) with melphalan and prednisone plus thalidomide (MPT) in patients over the age of 65 or ineligible for HDT/ASCT. These trials differed in doses and duration of therapy, use of maintenance therapy and eligibility criteria. Overall, MPT was associated with improved response rates, improved progression free survival (PFS), and greater toxicity than melphalan and prednisone alone (See Table 1 for summary). Increased toxicities in patients receiving MPT included venous thromboembolism (12%)[11], grade III/IV infection (22%)[15], cytopenias (up to 48% grade III/IV neutropenia)[11], peripheral neuropathy (grade III/IV in up to 23% of patients)[13] and constipation (17% grade III/IV)[16]. Three of the seven trials demonstrated a statistically significant improvement in overall survival with MPT. A meta-analysis which included individual patient data from 6 of these trials found a hazard ratio for death of 0.83 favoring MPT (95% CI 0.73–0.94, $p=0.004$), with a median overall survival of 39.3 months [95% CI 35.6–44.6] in patients receiving MPT versus 32.7 months [95% confidence intervals (CI) 30.5–36.6 months] in patients who received MP.[17] Subgroup analyses suggested that patients with a poor performance status (WHO > 2) and elevated creatinine may not benefit from the addition of thalidomide to MP. MPT may be considered one of the new standard of care treatment regimens for older adults with newly diagnosed multiple myeloma.

2.2 Bortezomib

Bortezomib is a parenterally-administered proteasome inhibitor. Table 2 summarizes randomized trials of regimens containing bortezomib in older adults with multiple myeloma.

2.2.1 Bortezomib, melphalan and prednisone—The proteasome inhibitor bortezomib has been evaluated in combination with melphalan and prednisone. After the initial phase I/II study demonstrated a remarkable 32% complete response rate and a 2-year overall survival (OS) of 86%[19], a randomized phase III study of melphalan and prednisone (MP) versus bortezomib, melphalan and prednisone (VMP) enrolled patients over the age of 65 or otherwise ineligible for HDT/ASCT. There were more complete responses (CR) (30% vs 4%, $P<0.001$), a higher rate of partial response or better (PR) (71% vs 35%, $P<0.001$), longer time to progression (24.0 months vs 16.6 months) and greater 3-year OS (68.5% vs 54%, $P=0.0008$) with VMP vs MP, respectively.[20,21] Patients in the VMP arm did experience a higher rate of serious adverse events, particularly peripheral neuropathy. On subgroup analysis of patients over the age of 75, the disease control benefit was similar to younger patients.

VMP was compared with bortezomib, thalidomide and prednisone (VTP) in a randomized trial of patients over the age of 65.[22] Patients were randomized to either six cycles of VMP or VTP as induction therapy, in which they received one cycle with twice-weekly bortezomib, followed by 5 cycles of once weekly bortezomib with prednisone and either melphalan or thalidomide. Patients completing 6 cycles of induction were then randomized to maintenance therapy with either bortezomib plus prednisone (VP) or bortezomib plus thalidomide (VT). The CR and PR were similar in both groups (20% and 80% for VMP,

28% and 81% for VTD, $p=0.2$ and 0.9 respectively). PFS and OS were also similar between the two groups (PFS 34 months for VMP vs 25 months for VTP, $p=0.1$; 3-year OS 74% for VMP vs 65% for VTP, $p=0.3$). The toxicity profiles of the two regimens differed; VMP caused more hematologic toxicity and more frequent infections, while more cardiac events were reported in the VTP arm (8% vs 0%). Rates of peripheral neuropathy were similar in the two groups (8% grade II and 7% grade III/IV with VMP, 14% and 9% with VTP, respectively, $p=NS$). Overall, patients receiving VTP were more likely to experience serious adverse events and to discontinue therapy due to toxicity of therapy.

2.2.2 Bortezomib, thalidomide and dexamethasone—Preliminary results of a study comparing bortezomib plus steroids alone, with melphalan, or with thalidomide, have been reported.[23] In this trial, patients were randomized to bortezomib, melphalan and prednisone (VMP) versus bortezomib, thalidomide and dexamethasone (VTD) versus bortezomib plus dexamethasone (VD). Regimens included 8 cycles of induction therapy followed by 5 cycles of maintenance bortezomib. Following maintenance, the PR and CR rates were 71% and 31% in the VD arm, respectively, 79% and 38% in the VTD arm and 73% and 34% in the VMP arm. Grade III/IV toxicities, severe peripheral neuropathy and discontinuation of therapy due to toxicities were more common in the VTD arm, while neutropenia was more common in the VMP arm. Rates of severe toxicities were lower in patients under age 75 compared to over 75 years.²³ The study also incorporated serial assessments of quality of life; patients in the VMP and VTD arms had transient decreases in quality of life during the first few cycles, but after 12 cycles, patients in all 3 arms had improved quality of life over baseline.[24]

2.2.3 Bortezomib, melphalan, prednisone and thalidomide—Finally, the four drug combination of bortezomib, melphalan, prednisone and thalidomide (VMPT) was compared with the three drug combination of VMP in a randomized trial of patients ineligible for HDT/ASCT due to age ≥ 65 years or comorbidity.[25] Patients randomized to VMPT received maintenance therapy with bortezomib and thalidomide (VT). The response rates were significantly higher in the VMPT-VT arm compared to the VMP arm (CR 38% vs 24%, $p=0.0008$; PR 89% and 81%, $p=0.01$ in VMPT-VT arm vs VMP arm, respectively). The 3-year progression free survival rate was greater in the VMPT-VT arm (56% vs 41%, $p=0.008$, hazard ratio 0.67), but this did not translate into improved 3-year OS (89% in VMPT-VT arm and 87% in VMP arm, $p=0.77$). Severe neutropenia and cardiac complications were more common in the VMPT-VT arm. After the first 139 patients were enrolled, an interim safety analysis prompted a protocol amendment to reduce the rates of peripheral neuropathy: the bortezomib dosing was changed from twice- to once-weekly. The rate of severe peripheral neuropathy dropped from 28% to 8%, without a decrement in response rate, progression-free or overall survival, subsequent to the dosing change.[26] A subgroup analysis of patients over the age of 75 suggested that patients over the age of 75 may not have same benefit in terms of PFS of VMPT-VT over VMP [Hazard Ratio (HR) 0.81, 95% CI 0.47–1.40].

2.3 Dexamethasone

Several studies have demonstrated the increased risk of severe toxicity and death in older patients receiving high-dose dexamethasone as a component of their initial regimen. The IFM 95-01 study randomized patients aged 65–75 years to one of four regimens: melphalan and prednisone, high-dose dexamethasone alone, melphalan with high-dose dexamethasone and high-dose dexamethasone with interferon α -2b. There was no difference in survival among the four groups (median OS 32–39.6 months), but there were more nonhematologic toxicities and early deaths in the dexamethasone alone group (10.5%) due to both progression of myeloma and infections. Another study evaluated lenalidomide in

combination with either high- or low-dose dexamethasone.[27] Patients in the high-dose arm (RD) received lenalidomide 25 mg daily days 1–21 every 28 days, and dexamethasone 40mg daily on days 1–4, 9–12 and 17–20 q 28 days, while patients in the low-dose arm (Rd) received the same dose of lenalidomide with dexamethasone 40 mg on days 1, 8, 15 and 22 every 28 days; both remained on therapy until progression or proceeding to HDT/ASCT. The response rates were significantly higher in the higher dose dexamethasone group (PR 81% in RD vs 70% in Rd, $p=0.009$). However, the rates of grade 3 or greater nonhematologic toxicity were higher in the RD group, including rates of venous thromboembolic events (26% vs 12%), infection (16% vs 9%) and early mortality (5% vs 0.45%). Older patients appeared particularly vulnerable to toxicity of high-dose dexamethasone. The 1-year OS rate in the subgroup of patients over the age of 65 was 83% in the RD group, and 94% in the Rd group, with a hazard ratio for death of 2.0 ($p=0.02$). These studies suggest that high-dose dexamethasone should be avoided in older patients with newly diagnosed multiple myeloma.

2.4 Lenalidomide

2.4.1 Melphalan, Prednisone and Lenalidomide—The oral immunomodulatory agent lenalidomide has been studied in older patients with multiple myeloma in combination with melphalan and prednisone. Phase I/II data [28] showing an overall response rate of 81% with the combination of melphalan, prednisone and lenalidomide (MPR) led to the MM-015 Phase III trial of MP vs MPR vs MPR with lenalidomide maintenance (MPR-R) in patients over the age of 65 years. All patients received melphalan 0.18 mg/kg days 1–4 and prednisone 2mg/kg days 1–4 q 28 days for 9 cycles. Patients in the MPR and MPR-R arms also received lenalidomide 10mg days 1–21 every 28 days for 9 cycles. Patients in the MP and MPR arms received placebo during the maintenance phase, while the patients in the MPR-R arm received lenalidomide 10mg daily days 1–21. Maintenance therapy continued until progression of disease. Cytopenias were common, with grade III/IV neutropenia rate of 71%, and grade III/IV thrombocytopenia rate of 38% with MPR-R. One-fifth of patients receiving MPR-R discontinued therapy due to adverse events. Preliminary reports of the efficacy demonstrate higher overall response rates in the MPR-R group (77% vs 68% with MPR vs 50% with MP, $p<0.001$) and higher 2-year progression free survival rates with MPR-R (55% with MPR-R vs 24% with MPR and 16% with MP, $p<0.001$). [29–31] With a median follow-up of 30 months, the 3-year OS rates were 73% with MPR-R versus 65% with MP ($p=0.254$).[31]

2.5 Doxil

Regimens containing pegylated liposomal doxorubicin have been employed in older patients with multiple myeloma. A phase II study of thalidomide, pegylated liposomal doxorubicin and dexamethasone (ThaDD) enrolled newly diagnosed patients over the age of 65 years. [32] Treatment consisted of pegylated liposomal doxorubicin 40mg/m² q28 days, dexamethasone 40 mg Days 1–4 and 9–12 every 28 days and thalidomide 100mg daily for 5–6 cycles. Eighty-eight percent of patients had at least a partial response. The projected 3-year OS was 74%. Grade 3 neutropenia occurred in 42% of patients. A high rate of infectious complications (25%) prompted the initiation of fluoroquinolone prophylaxis. The rate of venous thromboembolic events was 14%. A case-match study of patients over the age of 75 with newly diagnosed multiple myeloma compared the combination of ThaDD with MPT; cases were selected from two clinical trials.[9,32] While the PR rate was higher in the ThaDD patients (87.5% with ThaDD vs 61.5% with MPT, $p=0.009$), PFS and OS were similar. Overall, rates of grade III/IV adverse events and treatment discontinuation rates were similar between the two groups. Patient receiving ThaDD had higher rates of DVT and edema, while patients receiving MPT (who received thalidomide maintenance) had higher

rates of neutropenia and neuropathy. ThaDD represents another active and well-tolerated regimen in older patients with newly diagnosed multiple myeloma.

2.6. Cyclophosphamide

The combination of cyclophosphamide, thalidomide and dexamethasone (CTD) was compared with MP in a randomized trial of predominantly older patients deemed unfit for intensive therapy.[33] Patients randomized to the CTD arm received cyclophosphamide 500 mg/week, thalidomide 50mg daily (increased every 4 weeks to a maximum of 200mg/day) plus dexamethasone 20mg/day on days 1–4 and 15–18 every 28 days. Patients randomized to the MP arm received melphalan 7mg/m²/day and prednisolone 40 mg/day on days 1–4 every 28 days. Patients in both arms received 6 to 9 cycles of therapy. There was then a secondary randomization to maintenance with thalidomide versus no maintenance. The PR rate was higher in the CTD group versus the MP group (63.8% vs 32.6%, $p<0.0001$). The median PFS was slightly longer in the CTD group vs the MP group (13.0 months vs 12.4 months, $p=0.01$), but the median OS was similar in the two groups (33.2 months in CTD group vs 30.6 months in MP group, $p=0.24$). CTD was associated with more thromboembolic events, more neuropathy, more constipation and severe infection. The subset of patients with favorable cytogenetics, including hyperdiploidy, deletion(1p32), translocation(11;14) and translocation(6;14), received the greatest benefit.

3. High Dose Therapy and Autologous Stem Cell Transplantation

High-dose melphalan (typically 200mg/m²) and autologous stem cell transplantation improves survival over conventional therapy in patients with multiple myeloma under the age of 65 years.[3] Outside of the United States, age over 65 years essentially excludes patients from HDT/ASCT. A number of single-institution studies have explored the feasibility and toxicity of HDT/ASCT in selected older patients. Early reports of HDT/ASCT in patients over the age of 70 who underwent HDT/ASCT were concerning for excessive treatment related mortality (TRM).[34] In one report, among the first 25 patients who received melphalan 200 mg/m², the TRM was 16%; the dose of melphalan was then decreased to 140mg/m², with a subsequent decline in the TRM rate to 2%. The 3-year OS rate reported in this study was 31%. More recent studies where patients over the age of 70 received melphalan 200mg/m² have shown TRM rates as low as 3%,[35,36] which may reflect improvements in supportive care. The reported 5-year OS rate in one cohort of patients over the age of 70 who underwent HDT/ASCT was 67%[35]; likewise, the higher survival rate compared to earlier reports may reflect improved supportive care, and the impact of novel therapies. Studies report varied results as to whether the toxicity of HDT/ASCT is greater in older individuals than younger.[34,36–39]

Given concerns about toxicity of high dose therapy, several clinical trials have evaluated reduced-intensity, intermediate-dose melphalan with ASCT. One randomized study undertaken prior to the emergence of novel therapies compared intermediate-dose melphalan (100 mg/m²) and ASCT to conventional therapy with MP (melphalan 6mg/m² and prednisone 60 mg/m² days 1–7 every 4 weeks for 6 cycles) in patients aged 50–70 years. [40] Patients with comorbidities were excluded. Patients receiving intermediate-dose melphalan and ASCT had higher response rates and longer overall survival; the benefit extended to the subgroup of patients aged 65–70 years.

However, the benefit of intermediate- dose melphalan and ASCT in the era of modern therapy is not clear. In the IFM99-06 study[11], patients aged 65–75 were randomized to MP, MPT (see table 1) or MEL100. Patients with WHO performance status ≥ 3 or significant comorbidities were excluded. Patients in the MEL100 arm underwent 2 cycles of induction therapy, peripheral blood stem cell collection, followed by melphalan 100mg/m² and stem

cell reinfusion. A second course of melphalan 100mg/m² and stem cell reinfusion was repeated after two months. Even in this fit, selected population, only 65% of patients in the MEL100 arm were able to complete the planned study treatment. Compared to MPT, patients receiving MEL100 had similar response rates (CR:18% for MEL100, 13% for MPT; PR 65% for MEL 100, 76% for MPT). Median PFS was higher in the MPT arm than the MEL100 arm (27.5 vs 19.4 months, $p=0.0002$), as was the median OS in the MPT arm (51.6 vs 38.3 months, $p=0.027$). Thus, intermediate-dose melphalan may not improve outcomes over regimens containing novel agents in older adults with multiple myeloma.

More recently, remarkable results were seen in a phase II study of intermediate-dose melphalan and ASCT following bortezomib-based induction and followed by lenalidomide consolidation and maintenance.[41] Patients aged 65–75 years or under 65 but ineligible for HDT/ASCT received 4 cycles of induction therapy with bortezomib, pegylated liposomal doxorubicin and dexamethasone, followed by stem cell mobilization, then two cycles of melphalan 100 mg/m² (MEL100) with stem-cell reinfusion. This was followed by a consolidation phase of lenalidomide with prednisone for four cycles, then lenalidomide maintenance until relapse. In the per-protocol analysis, 66% of patients achieved a CR following consolidation and maintenance (44% in the intent-to-treat population). The 2-year OS rate was 86%. The regimen was fairly toxic, with 7% treatment-related deaths and 27% grade III/IV infection during MEL100. While the efficacy of this regimen is impressive, the role for intermediate-dose melphalan in the era of novel agents remains to be defined.

4. Maintenance Therapy

While a number of studies have employed maintenance therapy in older patients, only a few studies have addressed the benefit of maintenance therapy after induction therapy in a randomized fashion. In one randomized study, bortezomib, melphalan, prednisone and thalidomide followed by bortezomib and thalidomide maintenance (VMPT-VT) was compared with bortezomib, melphalan and prednisone without maintenance (VMP) in elderly myeloma patients.[25] Landmark analysis among patients assessable for maintenance treatment showed reduced risk for disease progression among patients receiving VT maintenance (HR 0.49, 95% CI 0.33-0.72), though this benefit did not extend to the subgroup of patients over the age of 75 (HR 0.97, 95% CI 0.52–1.78).[42] Continuous therapy with VT was associated with manageable toxicities with 3% grade III/IV hematologic toxicity, 5% grade III/IV peripheral neuropathy and 7% discontinuation due to adverse events.

In the Spanish Myeloma Group's randomized trial of bortezomib, melphalan and prednisone (VMP) versus bortezomib, thalidomide and prednisone (VTP),[22] there was a second randomization to maintenance therapy with bortezomib plus prednisone (VP) versus bortezomib plus thalidomide (VT). Maintenance with either regimen improved response rates over induction alone. Progression free survival from initiation of maintenance therapy were similar in both groups: 30 months with VT vs. 24 months with VP ($p=0.1$). However, nonhematologic toxicities were more frequent with VT, with rates of grade III/IV toxicities including: 7% cardiac events, 11% gastrointestinal events and 9% peripheral neuropathy in the VT arm compared with 1%, 3% and 3%, respectively, in the VP arm. [43]

Lastly, the MM-015 study compared melphalan and prednisone (MP) with melphalan, prednisone and lenalidomide without maintenance (MPR) and melphalan, prednisone and lenalidomide with lenalidomide maintenance (MPR-R).[29–31] Preplanned landmark analysis of PFS from start of maintenance therapy with MPR-R versus MPR showed that lenalidomide maintenance reduced the risk of progression by 68% [Hazard ratio (HR) 0.32 (95% CI 0.20–0.52)]. Toxicities of lenalidomide maintenance were infrequent, with 5%

grade IV thrombocytopenia, 4% grade IV neutropenia and 3% grade IV anemia. Grade III/IV nonhematologic toxicities included 5% bone pain and 5% diarrhea.

Maintenance therapy with either bortezomib-based combinations or lenalidomide clearly improves PFS, though no overall survival benefit has yet been demonstrated. With their acceptable toxicity profiles, maintenance therapy is a viable option for older patients.

5. Depth of Response

With the increasing response rates seen with novel agents, the question arises whether there is prognostic significance to the depth of response achieved. This is particularly relevant in older patients, given that higher response rates are frequently associated with greater toxicity rates. In one extreme case, in the randomized trial of thalidomide and dexamethasone (TD) versus melphalan and prednisolone (MP), TD resulted in a significantly higher overall response rate, but lower survival due to toxicity.[8] In contrast, in an analysis of 3 multi-center trials enrolling patients over age 65,[9,13,25] achievement of CR was associated with improved overall survival when compared to achieving a very good partial response (VGPR) [HR 0.25 (95% CI 0.11–0.55)].[44] Thus, achieving CR with new therapies may yield improved survival, but not if the risk of toxicities and early discontinuation of therapy results in inferior outcomes.

6. Treatment of relapsed/refractory multiple myeloma in older patients

Studies specific to treatment of relapsed/refractory multiple myeloma in older patients are relatively few. A subset analysis of the randomized trial of lenalidomide in combination with high-dose dexamethasone (RD) versus high-dose dexamethasone plus placebo demonstrated that the benefit of lenalidomide extended to older patients.[45] Among patients over the age of 65, the overall response rate was 58.9% in the RD arm versus 20.9% in the dexamethasone alone arm ($p < 0.001$). Time-to-progression and OS were also longer in the older patients treated with RD than dexamethasone alone.

A subset analysis of the randomized trial of bortezomib versus dexamethasone for relapsed multiple myeloma evaluated the benefit of bortezomib in patients over age 65 compared to younger patients. Patients over the age of 65 had similar toxicities, response rates, time to progression and overall survival compared to younger patients.[46]

7. Toxicities of therapy and supportive care

Despite the remarkable advances in response rates and survival with novel regimens, multiple myeloma remains incurable. Thus, the improvements in disease control must be carefully balanced with the increased toxicities of novel regimens. Careful attention to dose selection is essential in this potentially vulnerable population, as evidenced by differences in toxicity and survival among the MPT trials (see Table 1). In the IFM 01–01 trial, with lower doses of melphalan and thalidomide, patients over the age of 75 were successfully treated with MPT, with improved survival.[12] In contrast, in the Nordic study, a vulnerable population, with nearly one-third of the patients having a poor performance status, received higher drug doses, with increased toxic deaths among the patients who received the three-drug combination.[14] Palumbo *et al* have proposed empiric dose-reductions based on age[47] and geriatric syndromes (See Table 3).[48]

7.1. Hematologic

Hematologic toxicities are common in regimens containing melphalan, and tend to be more frequent in combination therapy. These toxicities are manageable, with appropriate dose reductions and supportive care. Lenalidomide is one of the most myelosuppressive novel

agents, particularly in combination with melphalan. The rate of grade III/IV neutropenia with MPR was 70% in the MM-015 trial, with a febrile neutropenia rate of 7%. The rates of grade III/IV anemia and thrombocytopenia were 23% and 37% respectively.[30]

7.2. Peripheral neuropathy

Peripheral neuropathy represents a significant challenge in the treatment of patients with multiple myeloma. It is particularly problematic in older adults, in whom it can affect mobility and functional independence, increase the risk of falls[49] or cause pain[50]. Neuropathy at diagnosis is prevalent, and may be related to the paraprotein itself or comorbidities such as diabetes mellitus. In one prospective cohort of unselected, newly diagnosed patients (which excluded patients with diabetes mellitus or a history of heavy alcohol use), neuropathy was present in 62%; many of these cases were subclinical and diagnosed only by electrophysiologic testing.[51] Treatment with thalidomide or bortezomib may cause or exacerbate peripheral neuropathy, which may be sensory, motor or autonomic. The neurotoxicity due to thalidomide is cumulative,[52,53] dose-dependent, particularly when doses of thalidomide exceed 200mg/day,[54] and may be irreversible. By contrast, the neurotoxicity with bortezomib tends to be reversible. In one study of single-agent bortezomib, peripheral neuropathy developed or worsened in 63% of patients, but had resolved in almost 90% of patients after discontinuation of therapy.[55] Risk factors for development of peripheral neuropathy due to bortezomib include baseline neuropathy due to thalidomide and a history of diabetes mellitus.[56] Guidelines to mitigate bortezomib-induced peripheral neuropathy through dose reductions have been suggested.[57] Additional potential strategies to reduce the incidence of peripheral neuropathy due to bortezomib include weekly intravenous bortezomib[25,26] and the use of subcutaneous bortezomib.[58]

7.3. Venous thromboembolic disease

The increased risk of venous thromboembolism (VTE) with the immunomodulatory agents, particularly when combined with corticosteroids, was recognized soon after their introduction. The risk of VTE appears highest in the first few months on therapy. Risk factors for VTE include treatment with high-dose dexamethasone, comorbidities such as active cardiovascular disease or a history of VTE, and decreased mobility.[59] In a randomized trial of aspirin versus low-dose warfarin versus low-molecular-weight heparin (LMWH) in patients receiving thalidomide, rates of VTE were similar between groups (6.4% vs 8.2% vs. 5.0%, respectively). Post-hoc analyses showed that LMWH appeared more effective than low-dose warfarin in the patients over the age of 65 receiving VMPT (absolute difference +11.3%, $p=0.006$).[60] Interestingly, emerging data on bortezomib in combination with the immunomodulatory agents suggest a protective effect of bortezomib against VTE.[60,61]

7.4. Herpes Zoster

Treatment with bortezomib doubles the risk of development of herpes zoster.[62,63] Older age is a strong risk factor for the development of post-herpetic neuralgia. [64] Prophylaxis with acyclovir is highly effective at preventing herpes zoster and is recommended for patients receiving bortezomib.[65]

8. Summary

In summary, in the past decade, the horizons for treatment for older adults with multiple myeloma have expanded far beyond traditional melphalan and prednisone. New combination regimens have yielded higher response rates and, in some cases, longer survival, but at the expense of greater toxicity. Therapy must be tailored to take into account a patient's underlying comorbidities, functional status, social support, ability to travel for

intravenous therapy and the patient's goals. Table 4 provides a summary of initial treatment considerations for older adults with myeloma. Considerations may include opting to utilize lenalidomide rather than thalidomide or bortezomib in a patient with underlying neuropathy, utilizing bortezomib in patients with a history of VTE, or avoiding bortezomib in patients who prefer to avoid frequent trips to the clinic. While it is an exciting time with more effective therapeutic options, much remains to be learned to optimize the care of older adults with multiple myeloma. Patients should be encouraged to participate in clinical trials whenever feasible. Comprehensive geriatric assessments provide significantly more information about the health status of senior adults with cancer than do traditional oncology assessments of performance status.[66] Further, geriatric assessments predict tolerance of chemotherapy,[67] and should, along with serial quality of life assessments, be incorporated into clinical trials involving older adults with multiple myeloma.

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Table 1
Randomized trials of Melphalan and Prednisone vs. Melphalan, Prednisone and Thalidomide

		Regimen	Maintenance Thalidomide	PR	CR	PFS/DFS (median, months)	OS (median, months)
GIMEMA[9,10]	MPT (N=167)	M 4mg/m ² days 1–7, Q28 days x 6 cycles P 40mg/m ² days 1–7, cycles Q28 days x 6 cycles T 100mg daily continuously	Yes	76%	15.6%	21.8	45.0
	MP (N=164)	M 4mg/m ² days 1–7, Q28 days x 6 cycles P 40mg/m ² days 1–7, cycles Q28 days x 6 cycles	No	47.6%*	3.7%*	14.5*	47.6
IFM 99–06[11]	MPT (N=125)	M 0.25 mg/kg/day days 1–4, Q6 weeks x 12 cycles P 2mg/kg/day days 1–4 Q6 weeks x 12 cycles T Dose at clinician discretion	No	76%	13%	27.5	51.6
	MP (N=196)	M 0.25 mg/kg/day days 1–4, Q6 weeks x 12 cycles P 2mg/kg/day days 1–4 Q6 weeks x 12 cycles	No	35%*	2%*	17.8*	33.2*
IFM 01–01[12]	MPT (N=113)	M 0.2 mg/kg days 1–4, cycles Q6 weeks x 12 cycles P 2mg/kg days 1–4, cycles Q6 weeks x 12 cycles T 100 mg daily x 72 weeks	No	62%	7%	24.1	44.0
	MP (N=116)	M 0.2 mg/kg days 1–4, cycles Q6 weeks x 12 cycles P 2mg/kg days 1–4, cycles Q6 weeks x 12 cycles	No	31%*	1%*	18.5*	29.1*
HOVON49[13]	MPT (N=171)	M 0.25 mg/kg/day days 1–5, Q4 weeks x 8 cycles P 1 mg/kg/day days 1–5, Q4 weeks x 8 cycles T 200mg daily	Yes	66%	NR	15	40
	MP (N=173)	M 0.25 mg/kg/day days 1–5, Q4 weeks x 8 cycles P 1 mg/kg/day days 1–5, Q4 weeks x 8 cycles	No	45%*	NR	11*	31*
Nordic Myeloma Study Group[14]	MPT (N=184)	M 0.25 mg/kg/day days 1–4, Q6 weeks until plateau reached P 100 mg days 1–4 Q 6 weeks until plateau reached T 400 mg daily	Yes	57%	13%	15	29
	MP (N=179)	M 0.25 mg/kg/day days 1–4, Q6 weeks until plateau reached P 100 mg days 1–4 Q 6 weeks until plateau reached	No	40%*	4%*	14	32
Turkish Myeloma Study	MPT (N=58)	M 9mg/m ² days 1–4, Q6 weeks P 60 mg/m ² /day days 1–4 Q6 weeks T 100 mg daily	No	57.9%	8.8%	21	26
Group[15]	MP (N=57)	M 9mg/m ² days 1–4, Q6 weeks P 60 mg/m ² /day days 1–4 Q6 weeks	No	37.5%	8.9%	14	28
Sacchi et al[16]	MPT (N=64)	M 0.25mg/kg days 1–4 Q28 days P 60 mg/m ² days 1–4 Q28 days T 100 mg daily	Planned	79.7%	20.3%	33	52

		Regimen	Maintenance Thalidomide	PR	CR	PFS/DFS (median, months)	OS (median, months)
	MP (N=54)	M 0.25mg/kg days 1–4 Q28 days P 60 mg/m2 days 1–4 Q28 days	No	50%	7.4%	22*	32

PR, partial response; CR, complete response; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; M, melphalan; P, prednisone; T, thalidomide; NR, not reported

* P<0.05 for difference between MP and MPT

Table 2

Randomized trials of Bortezomib-containing regimens

		Regimen	Maintenance	PR	CR	PFS (median, months)	3 Yr OS
VISTA [20,21]	VMP (N=344)	V Cycles 1-4: 1.3 mg/m ² days 1,4,8,11,22,25,32 Q6 weeks; Cycles 5-9: 1.3 mg/m ² days 1,8,22,29 Q6 weeks M 9 mg/m ² days 1-4 Q6 weeks x 9 cycles P 60 mg/m ² days 1-4 Q6 weeks x 9 cycles	No	71%	30%	TTP 24.0	68.5%
	MP (N=338)	M 9 mg/m ² days 1-4 Q6 weeks x 9 cycles P 60 mg/m ² days 1-4 Q6 weeks x 9 cycles	No	35%	4%	TTP 16.6	54%
VMP vs VTP [22]	VMP (N=130)	V Cycle 1(6 weeks): 1.3 mg/m ² days 1,4,8,11,22,25,29,32 Cycles 2-6 (5 week cycles): 1.3 mg/m ² days 1,8,15,22 M 9 mg/m ² Days 1-4 x 6 cycles P 60mg/m ² Days 1-4 x 6 cycles	VP vs VT	80%	20%	34	74%
	VTP (N=130)	V Cycle 1(6 weeks): 1.3 mg/m ² days 1,4,8,11,22,25,29,32 Cycles 2-6 (5 week cycles): 1.3 mg/m ² days 1,8,15,22 T 100 mg daily x 6 cycles P 60mg/m ² days 1-4 x 6 cycles	VP vs VT	81%	28%	25	65%
UPFRONT[23]	VMP	V 1.3 mg/m ² days 1,4,8,11 Q21 days x 8 cycles M 9 mg/m ² days 1-4 every other cycle P 60 mg/m ² days 1-4 every other cycle	V weekly x 5 cycles	73%*	34%**	NR	NR
	VTD	V 1.3 mg/m ² days 1,4,8,11 Q21 days x 8 cycles T 100 mg daily D 20mg days 1, 2, 4, 5, 8, 9, 11, 12 [cycles 1-4] then 30 mg days 1, 2, 4, 5 [cycles 5-8]	V weekly x 5 cycles	79%*	38%**	NR	NR
	VD	V 1.3 mg/m ² days 1,4,8,11 Q21 days x 8 cycles D 20mg days 1, 2, 4, 5, 8, 9, 11, 12 [cycles 1-4] then 30 mg days 1, 2, 4, 5 [cycles 5-8]	V weekly x 5 cycles	71%*	31%**	NR	NR
VMPT-VT vs VMP[25]	VMPT-VT (N=254)	V Cycles 1-4: 1.3 mg/m ² days 1,4,8,11,22,25,29,32 Cycles 5-9: 1.3 mg/m ² days 1,8,22,29 M 9mg/m ² days 1-4 Q6 weeks x 9 cycles P 60 mg/m ² days 1-4 Q6 weeks x 9 cycles T 50 mg daily	V 1.3 mg/m ² q 2 weeks and T 50 mg daily x 2 years	89%	38%	3 Yr PFS 56%	89%
	VMP (N=257)	V Cycles 1-4: 1.3 mg/m ² Days 1,4,8,11,22,25,29,32 Cycles 5-9: 1.3 mg/m ² Days 1,8,22,29 M 9mg/m ² D 1-4 Q6 weeks x 9 cycles P 60 mg/m ² D 1-4 Q6 weeks x 9 cycles	No	81%	24%	3 Yr PFS 41%	87%

PR, partial response; CR, complete response; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; TTP, time to progression; NR, not reported V, bortezomib; M, melphalan; P, prednisone; T, thalidomide; D, dexamethasone

* Response after maintenance;

** CR + near CR rate

Table 3

Treatment algorithm for elderly frail patients[48]

Risk factors	
•	Age over 75 years
•	Mild, moderate or severe frailty: ■ Patients needing help for household tasks and personal care
•	Comorbidities ■ Cardiac dysfunction ■ Pulmonary dysfunction ■ Hepatic dysfunction ■ Renal dysfunction

GO-GO	MODERATE-GO	SLOW-GO
No risk factors ↓ DOSE LEVEL 0	At least one risk factor ↓ DOSE LEVEL -1	At least one risk factor plus occurrence of grade 3–4 non-hematologic AE ↓ DOSE LEVEL -2

Agent	DOSE LEVEL 0	DOSE LEVEL -1	DOSE LEVEL -2
Dexamethasone	40 mg/d days 1,8,15,22 every 4 weeks	20 mg/d days 1,8,15,22 every 4 weeks	10 mg/d days 1,8,15,22 every 4 weeks
Melphalan	0.25 mg/kg or 9 mg/m ² days 1–4 every 4–6 weeks	0.18 mg/kg or 7.5 mg/m ² days 1–4 every 4–6 weeks	0.13 mg/kg or 5 mg/m ² days 1–4 every 4–6 weeks
Thalidomide	100mg daily	50mg daily	50mg every other day
Lenalidomide	25 mg/d days 1–21 every 4 weeks	15 mg/d days 1–21 every 4weeks	10 mg/d days 1–21 every 4 weeks
Bortezomib	1.3 mg/m ² twice weekly days 1,4,8,11 every 3 weeks	1.3 mg/m ² once weekly days 1,8,15, 22 every 5 weeks	1.0 mg/m ² once weekly days 1,8,15, 22 every 5 weeks
Prednisone	60 mg/m ² days 1–4 or 50 mg every other day	30 mg/m ² days 1–4 or 25 mg every other day	15 mg/m ² days 1–4 or 12.5 mg every other day
Cyclophosphamide	100mg/d days 1–21 every 4 weeks or 300 mg/m ² days 1,8,15 every 4 weeks	50mg/d days 1–21 every 4 weeks or 150 mg/m ² days 1,8,15 every 4 weeks	50mg every other day days 1–21 every 4 weeks or 75 mg/m ² days 1,8,15 every 4 weeks

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Table 4

Considerations for initial treatment decision for older adults with multiple myeloma

Patient Factor	Therapeutic Consideration
Potential candidate for high dose therapy and autologous stem cell transplant	■ Avoid treatment with melphalan prior to stem cell collection
	■ Refer to transplant center
Distance to treatment center/ patient preference for oral regimen	■ Consider thalidomide or lenalidomide-based regimen
Pre-existing peripheral neuropathy	■ Consider lenalidomide-based regimen
Renal insufficiency	■ Consider bortezomib-based regimen
History of venous thromboembolism	■ Consider bortezomib-based regimen
Frail, significant comorbidity, age >75	■ Consider two-drug combination over three-drug regimen [68]