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Summary

Many advances have been made in the treatment of patients with multiple myeloma, including elderly subjects. The introduction of novel agents thalidomide, lenalidomide, bortezomib has revolutionized the treatment paradigm of this neoplasm, and second-generation molecules are currently being tested to offer patients a wider variety of treatment options and to improve outcome.

The efficacy of a regimen should be carefully balanced against its toxicity profile. Elderly patients are particularly susceptible to adverse events that may lead to early treatment discontinuation. Thus a more accurate distinction within the elderly population and a more appropriate treatment allocation is necessary. Here we describe the major and more recent treatment options available today for elderly patients with multiple myeloma.

Keywords

Multiple myeloma, elderly, novel agents, diagnosis, relapse

INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 10% of all hematologic malignancies. In the Western countries the incidence is about 5/100.000 cases per year, with a median age at diagnosis of 65 years.[1] MM is typical of the elderly: 37% of patients are younger than 65 years, 26% aged 65 to 74 years, and 37% older than 75 years.[2] Life expectancy has increased over the past few decades, consequently also the incidence of MM is expected to rise over time.

The diagnosis of myeloma requires the presence of at least 10% clonal plasma cells on bone marrow examination and/or a biopsy-proven plasmacytoma, as well as evidence of end-organ damage that can be attributed to the disease, defined by the CRAB symptoms: hypercalcemia, renal insufficiency, anemia, or bone lesions.[3] Treatment should be started only in the presence of symptomatic disease, as no benefit has been observed with early intervention. In addition, some authors also consider the presence of at least 60% bone marrow involvement or rapidly climbing paraprotein, independently of CRAB criteria, as a criterion to start therapy.[4]

Novel agents, such as the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, have dramatically changed the treatment of MM, and they are now routinely used.

Patients older than 65 years of age are generally considered ineligible for high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). These patients usually need gentler approaches.[1] Within the elderly population, different strategies including novel agents should be adopted based on patients characteristics. Thus, a careful assessment of patient status is needed before choosing treatment. This should be based on age, organ dysfunctions (cardiac, pulmonary, hepatic, gastrointestinal, renal) and presence of co-morbidities. Different instruments, such as the Charlson score for co-morbidity and the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), can be used to carefully assess a patient's status.[5, 6] Very fit patients in excellent clinical status are able to tolerate more intense approaches and may receive reduced-dose ASCT. Fit patients in good clinical status can be safely treated with full-dose three- or four-drug regimens including at least one novel agent: 3-drug regimens melphalan-prednisone-thalidomide (MPT),[7] bortezomib-melphalan-prednisone (VMP),[8] bortezomib-cyclophosphamide-dexamethasone (VCD)[9] and bortezomib-lenalidomide-dexamethasone (VRD)[10] are now considered the standards of care in this setting, although the 2-drug regimen lenalidomide plus low-dose dexamethasone (Rd)[11] represents a valuable

therapeutic option, also considering its oral administration. Unfit patients are characterized by older age, organ dysfunctions, co-morbidity and limits in mental/mobility functions, thus reduced-dose regimens or less intense approaches with two-drug combinations are suggested. Indeed, in unfit patients, less is more, because gentler approaches enable these patients to stay longer on treatment and benefit from it.

Patient's characteristics have a fundamental role in the prognosis. Patients with International Staging System stage III have a poor prognosis.[12] In addition, chromosomal abnormalities t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, and del17p detected by Fluorescence In Situ Hybridization (FISH) are associated with poor prognosis, while the presence of 13q deletion with no other abnormality is not considered a high-risk feature.[13–16] An abnormal k/λ FLC ratio (rFLC) at diagnosis is also associated with poor prognosis.[17]

Recently, the combination of cytogenetics abnormalities such as t(4;14) and deletion17p detected by FISH and the ISS stage assessment showed to further improve the prognostic evaluation of MM patients in terms of progression-free survival (PFS) and overall survival (OS).[14]

In the era of novel agents, attaining a complete response (CR) has become a more easily achievable goal also in the elderly, and several studies found that the achievement of CR after initial treatment is associated with PFS and OS.[18, 19]

In this paper we present the most recent therapies for the treatment of elderly MM patients, both at diagnosis and relapse. At diagnosis, the presence of sensitive disease is associated with deep, long-lasting responses and decreased risk of toxicity, with consequent improved quality of life and lower health care costs;[20] conversely, in later phases, when the disease becomes more resistant, the proportion of responses is considerably decreased and the risk of adverse events higher, with a negative impact on both quality of life and health care costs.[21]

The efficacy of a regimen should be carefully balanced against its toxicity profile, particularly in elderly patients, as they are more susceptible to adverse events. Thus a prompt and appropriate management of treatment related side effects is necessary also to enable patients to stay longer on treatment and benefit from it (Table 1).

Definition of fit and unfit patients

Patient's eligibility to ASCT is normally evaluated with the cut-off age of 65 years, but chronological and biological age may be deeply different. A patient's overall physical

condition and organ function should be assessed to determine his or her ability to tolerate treatment. Of note, comorbidities (defined as the concurrent presence of ≥ 2 medically diagnosed diseases), frailty (critical mass of ≥ 3 core elements of frailty: weakness, poor endurance, weight loss, low physical activity and slow gait speed) and disability (defined as difficulty or dependency in carrying out activities essential to independent living, both essential personal care and household tasks) also have to be considered when choosing the optimal treatment schedule for patients: all these factors are associated with high risk of therapy-related adverse events and consequently treatment discontinuation.[6]

Patient's clinical conditions, organ functions, weakness, poor endurance, need for help for household activities should be always considered. Cardiac performance, pulmonary and hepatic functions, renal function and peripheral neuropathy should be evaluated. Afterwards, it is possible to stratify patients into those suitable for full-dose therapy or drug-combination treatment and those requiring adjusted-dose treatment strategies.

A recent study by the European Myeloma Network proposed recommendations to choose the best approach for all patients;[6] patients with more than 1 risk factor (age ≥ 75 years, frailty, comorbidities, disability, or grade 3-4 non hematologic adverse events) should be considered for a reduced-dose treatment strategy. Patients without risk factors should receive full-dose treatment.

THERAPY AT DIAGNOSIS

Very fit patients

For elderly patients, with an excellent performance status, reduced-regimen of melphalan (Mel 100) followed by ASCT could be considered.

Two trials were conducted to evaluate the efficacy of Mel 100 compared with the standard melphalan-prednisone (MP).

In the first one, 194 patients aged 65 to 70 years were randomized to receive either 6 courses of oral MP or two courses of Mel 100. Near-complete response rate was higher in Mel 100 arm: 6% after MP and 25% after MEL100 ($P = 0.0002$). The OS in patients that received Mel 100 followed by ASCT was longer (58 months vs 37,2 months $p<0.001$), and, at 3 years, Mel 100 increased event-free survival (EFS) from 16% to 37%.[22]

The second one compared MP, MPT and Mel 100 followed by ASCT in patients aged 65-75. After a median follow-up of 51.5 months, median overall survival times were 33.2 months (13.8-54.8) for MP, 51.6 months (26.6-not reached) for MPT, and 38.3 months

(13.0-61.6) for MEL100, but results showed no differences between the MP and the Mel 100 groups.[23]

Rd followed by an intermediate dose of melphalan (140 mg/m2) before ASCT was evaluated; Rd induction therapy was associated with an acceptable tolerability and feasibility in elderly myeloma patients. Stem cell mobilization was successful in 97% of patients.[24]

A sequential approach including novel agents as induction followed by reduced-intensity transplantation and novel agent-based consolidation/maintenance showed to be a sensible strategy in this setting. A phase II trial was conducted to evaluate the effect of bortezomib with doxorubicin and dexamethasone (PAD) as induction therapy before autologous transplantation (Mel 100), followed by lenalidomide-prednisone consolidation and lenalidomide maintenance (LP-L). After PAD, 58% of patients obtained very good partial response (VGPR) or better; after Mel 100, 82% of patients had at least VGPR and 38% had CR; and after LP-L, 86% of patients had at least VGPR and 66% had CR.

After median follow-up time of 21 months, the 2-year PFS rate was 69%, and the 2-year OS rate was 86%.[25]

Fit patients

IMiDs-based regimens

For many years, MP was considered the standard of care for elderly patients with MM.[1] The introduction of novel agents has challenged this combination and new and more effective combinations are available also in this setting.

MM patients ineligible for transplantation were included in a randomized, phase III trial, in order to compare MP with the combination of thalidomide and high dose of dexamethasone (TD).[26] TD combination was associated with a higher overall response rate (ORR): 68% vs 50% (P = 0.002), but no differences in terms of time to progression (TTP) (21.2 vs 29.1 months; P = 0.2) and PFS (16.7 vs 20.7 months; P = 0.1) were observed. Data show a higher incidence of non-myeloma related deaths due to infection and cardiovascular events in the TD arm; this regimen is too toxic for elderly patients. Reduced-dose schedule, with low-dose dexamethasone can probably increase treatment tolerability.

Six randomized trials evaluated the efficacy of the standard MP with the combination MPT, where thalidomide was given at different doses (100-400 mg) in transplant ineligible, newly diagnosed MM patients.[23, 27–31]

A meta-analysis pooled data from 1,685 patients included in these trials to evaluate MPT efficacy.[7] Best response were higher in the MPT group: at least VGPR rate was 25% for MPT vs 9% for MP. The 2-year PFS was 42.5% with MPT and 28.4% with MP, median OS was 39.3 months with MPT vs 32.7 months with MP (Table 2).

Data obtained from this meta-analysis confirmed that MPT improved OS and PFS in previously untreated MM patients.

A safety meta-analysis based on the same trials was conducted on 1,680 patient data.[32] The incidence of grade 3-4 adverse events was higher (at least 75%) during the first six months of treatment for both MPT and MP. Hematologic toxicity was increased with MPT (the rate of grade 3-4 adverse events was 28% vs 22%). Similarly more non-hematologic adverse events occurred with MPT than MP (39% vs 17%). Grade 3-4 non-hematologic adverse events negatively impacted PFS and OS. Beside toxicities, advanced International Staging System stage, high creatinine levels and, Performance Status and patient's age had a negative impact on survival.

The positive results obtained with MPT in the six studies confirmed the role of this combination as standard of care for elderly patients.

A phase III trial also assessed the role of attenuated regimen of cyclophosphamide-thalidomide-dexamethasone (CTD) as compared with MP in 849 newly diagnosed MM elderly patients.[33] The ORR was primary aim and it was significantly higher with CTD than MP (63.8% vs 32.6%; P <0.0001), mainly due to the higher rate of CR (13.1% vs 2.4%) and VGPR (16.9% vs 1.7%). However, no differences in terms of median PFS (13 months vs 12.4; P = 0.1) and OS (33.2 months vs 30.6 months; P = 0.24) were observed between the two treatment arms, thus showing that the regimen with the highest response rate may not necessarily translate into either improve survival or improved quality of life. CTD was particularly beneficial in subjects with a good cytogenetic profile by FISH. Toxicities were higher with CTD than MP and were mainly constipation (41% vs 18%), infection (32% vs 26%), sensory neuropathy (24% vs 6%), and thromboembolic events (16% vs 5%). CTD can be considered a possible option in selected elderly patients, particularly for standard-risk patients by FISH.

Lenalidomide is a potent IMiD derived from thalidomide. An open label, non inferiority, phase III trial was conducted to evaluate lenalidomide plus high-dose of dexamethasone

(RD) in comparison with lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed MM patients, both eligible and ineligible for ASCT.[11] After four cycles, patients could discontinue therapy to pursue ASCT or continue treatment until disease progression. Seventy-nine percent of 214 patients receiving high-dose therapy and 68% of 205 patients receiving low-dose therapy had CR or PR within four cycles (P = 0.008).

The survival benefit of the combination Rd was particularly evident in patients older than 65 years (1-year OS: 83% with RD vs 94% with Rd).

In a subgroup analysis including patients older than 70 years, the 3-year OS was better in the Rd arm (73%) than in the RD arm (61%), while the incidence of non-hematologic toxicities was 78% with high-dose dexamethasone and 59% with low-dose dexamethasone.

Because more adverse events occurred when RD was given compared with Rd (DVT or pulmonary embolism; 26% vs 12%; infections: 16% vs 9%), Rd seems preferable in the elderly setting.

However, high-dose dexamethasone remains a good option for patients with renal failure, hypercalcemia, pain and spinal cord compression.

Another recent phase III trial evaluated the role of lenalidomide. Four-hundred and fifty-nine patients were randomized to receive induction therapy with nine cycles of MPR, followed by either lenalidomide maintenance or placebo, or standard MP.[34] The ORR was higher with MPR-R and MPR compared with MP (77%, 68%, 50% respectively). PFS was longer with MPR-R compared with MPR and MP (31 vs 14 vs 13 months; P < 0.001). Yet, in patients older than 75 years of age, MPR induction did not improve PFS as compared with MP, due to the increased incidence of toxicities with MPR, which led to more frequent dose adjustments in elderly patients. The 3-year OS was similar between the three treatment arms (70% vs 62% vs 66%).

Neutropenia is common with lenalidomide, and grade 4 neutropenia occurred in 35% of MPR-R patients and 32% of MPR patients. The most frequent non-hematologic grade 3 adverse events consisted of infections (9% with MPR-R, 13% with MPR 7% with MP), while deep vein thrombosis was not so frequent due to thromboprophylaxis with aspirin. Recently, there have been some concerns about lenalidomide-related occurrence of second primary malignancies (SPMs): 3-year SPM rate was 7% with both MPR-R and MPR, and 3% with MP. However, in patients younger than 75 years of age, the benefits associated with MPR-R appear to outweigh the increased risk of SPMs.

In patients with renal impairment, lenalidomide dose-adjustments are recommended because this drug is mainly excreted by the kidneys (Table 3). In these patients, full-dose bortezomib and thalidomide can be safely used .

A phase 2 study including both young and elderly patients evaluated the combination of lenalidomide with cyclophosphamide and dexamethasone (CRD): fifty-three patients with previously untreated symptomatic MM were enrolled.[35] The median PFS was 28 months (22.7-32.6), while the 2-year OS rate was 87%. Neutropenia was common but easily manageable through cyclophosphamide dose adjustments. Fatigue was the most frequent non-hematologic adverse event.

Bortezomib-based regimens

The combination of bortezomib associated with melphalan and prednisone (VMP) was compared with the standard MP in the international phase III VISTA trial.[8, 36]
TTP was 24 months with VMP and 16.6 months with MP ($P < 0.001$). The 3-year OS was 69% with VMP and 54% with MP. These results were confirmed in different subgroups of patients, but not in those with high-risk cytogenetic profile. Toxicities were higher with the three-drug combination: the rate of grades 3-4 peripheral sensory neuropathy was 14% with VMP and 0% with MP. Gastrointestinal complications were more frequent with VMP (19%) than with MP (5%). The rate of treatment-related deaths was unchanged in the two groups (2%). When bortezomib schedule was changed from twice-weekly (cycle 1 to 4) to once weekly (cycle 5 to 8), the rate of adverse events was lower in both VMP and MP groups, while no negative impact on outcome was noticed. Based on these positive results, VMP is today considered one of the standard strategies to treat elderly patients with myeloma.
VMP combination has also been compared with bortezomib-thalidomide-dexamethasone (VTD) and bortezomib-dexamethasone (VD).[37] After a median follow up of 21.8 months, the ORR response rate was equivalent in the three regimens (69-80%) and no differences in PFS and OS were observed. A higher rate of grade 3-4 Adverse events and discontinuation were observed in the VTD arm.
Bortezomib was also evaluated in combination with cyclophosphamide and dexamethasone (VCD) in newly diagnosed MM patients, both eligible and not eligible for ASCT.[9] Two cohorts received different schedule of bortezomib: the first one received

twice-weekly bortezomib, the second one received once-weekly bortezomib. After 4 cycles of induction, the ORR was 90% and the CR/ near CR rate was 41% with no differences in terms of response between the two cohorts.

Bortezomib plus IMiDs-based regimens

The Spanish PATHEMA trial evaluated patients ineligible for ASCT who were allocated to 6 cycles of either bortezomib-thalidomide-prednisone (VTP) or VMP induction.[38] Patients of both groups obtained high ORR rates (81 and 80% respectively), but VTP regimen was associated with higher rate of cardiac events (31% vs 15%; P = 0.01) and discontinuation rate (17% vs 12%; P = 0.03). A higher rate of grade 3-4 hematologic adverse events was observed in the VMP group (39% vs 22%; P = 0.008). Therefore, a careful assessment of the risks and benefits of both treatments is needed. To evaluate the role of continuous treatment with bortezomib, patients were randomized to receive bortezomib maintenance with either thalidomide (VT) or prednisone (VP).[39] After 38 months, an increase in the CR rate after induction was observed both in the VT and VP groups (up to 46% with VT and up to 39% with VP). The VT combination led to an advantage in terms of PFS (39 months vs 32 months), and 5-years OS (69% vs 50%), although these differences were not statistically significant (P=0.1). The incidence of grade 3-4 non-hematologic adverse events was significantly higher in patients receiving VT (17% vs 5%). Rate of discontinuation was 57% in the VT arm and 59% in the VP arm, most frequently due to disease progression.

A more intense regimen with the four-drug combination bortezomib-melphalan-prednisone-thalidomide followed by VT maintenance (VMPT-VT) for two years (or until progression or relapse) was evaluated as compared with standard VMP.[40, 41] VMPT induction was associated with higher CR rate (38% vs 24%). After nine 6-weeks cycles of VMPT induction, bortezomib was administrated at the dose of 1,3 mg/m2, while no maintenance was planned for patients assigned to VMP induction. VT maintenance increased the CR rate to 42%. Five-years OS was 59.3% for VMPT-VT and 45.9% for VMP, after 47 months of follow up. VT maintenance therapy induced a low rate of adverse events, with peripheral neuropathy occurring in 7% of patients.

A phase I/II study assessed safety and efficacy of the combination bortezomib-lenalidomide-dexamethasone (VRD) in both young and elderly newly diagnosed patients.[10]

Patients who did not proceed to ASCT received eight 3-week cycles of VRD. This combination led to a PR rate of 100% and a CR/ near CR rate of 37%. Treatment-related toxicities were low, with 9% of patients experiencing neutropenia and 6% thrombocytopenia.

Finally, a phase II trial compared the combination bortezomib-cyclophosphamide-dexamethasone (VCD) with VRD and VRD associated with cyclophosphamide (VDCR).[42] All the three arms induced similar 1-year OS (100%, 100% and 92%, respectively), as well as 1-year PFS (97%,68% and 83%, respectively).

In conclusion, VMP, VCD or VRD are the current standards of care for elderly MM patients. Bortezomib is commonly given at 1.3 mg/m^2 twice weekly. If needed, it can be administered once-weekly or the dose can be reduced to 1.0 mg/m^2 .to reduce toxicity and thus to keep patients on treatment The subcutaneous administration of bortezomib is another recently introduced strategy to reduce the risk of peripheral neuropathy.

Unfit patients

Unfit elderly MM patients are more susceptible to side effects and are often unable to tolerate full-drug doses. Lower dose-intensity regimens could improve the safety profile and consequently optimize treatment outcomes. Appropriate screening for vulnerability and an assessment of cardiac, pulmonary, renal, hepatic, and neurologic functions allow to provide effective individualized treatment strategies and to adjust drug doses in order to improve tolerability and efficacy.

A phase II trial, enrolled patients with a median age of 75 years, with a rate of 60% affected with at least one comorbidity. The aim was to evaluate the efficacy of induction with lenalidomide and prednisone (RP) followed by consolidation with MPR and RP maintenance.[43] Hematologic toxicities were significantly reduced. PR rate was 80%, including 29% VGPR. Median PFS was 18.4 months and 2-year OS was 80%. The most frequent grade 3 adverse events were neutropenia (36.4%), anemia (12.1%). RP induction followed by MPR consolidation and RP maintenance showed a manageable safety profile, and reduced the risk of severe hematological toxicity in unfit elderly myeloma patients. The positive results suggest that starting with a gentler approach with a 2-drug induction regimen and then intensifying with a 3-drug combination treatment, if tolerated, may be a valid option in unfit patients. Yet, this should be confirmed in future phase III trials.

In this setting, VD and Rd are the suggested 2-drug approaches. The first one is less toxic than VMP and VTD with no differences in terms of efficacy in an elderly population.[37] Rd was also better tolerated than RD.[11]

Dose reductions are recommended when age ≥75, presence of comorbidities, frailty or disability occur (Table 3); thalidomide can me administrated at dose of 100 mg or even 50 mg per day, while lenalidomide can be given from 25 mg to 15-10 mg on days 1-21.

Concerning to the use of bortezomib, patients could receive once weekly administration of 1.3 mg/m2 or even 1.0 mg/m2; low-dose dexamethasone is usually better than the high-dose schedule and melphalan may be decreased from 0.25 mg to 0.18 or 0.13 mg per kilogram of body weight on days 1-4.

THERAPY AT RELAPSE

Although many steps forward have been made in the last decade, MM still remains an incurable disease which eventually relapses and becomes refractory to the available drugs, despite the depth and the duration of response obtained with first line therapy.

The introduction of novel agents such as IMiDs (thalidomide and lenalidomide) and the proteasome inhibitor (bortezomib) represented a major improvement in the treatment of myeloma, extending survival as compared to conventional chemotherapies.[44] However, a new challenge is now emerging in the treatment of patients relapsed and refractory after novel agents: these patients have limited treatment options and poor outcome. Kumar et al evaluated 286 patients refractory to bortezomib and IMiDs (or unable to receive IMiDs): median event-free survival (EFS) and OS in the study population were 5 and 9 months, respectively. This study highlighted the poor outcome of patients failing novel agents and the clinical need for newer effective drugs.[21]

The recent availability of newer compounds, such as the third generation IMiD pomalidomide and the oral proteasome inhibitor carfilzomib, upgraded the treatment armamentarium for relapsed/refractory MM patients.

The choice of treatment at relapse should be based on several factors: patient's clinical conditions and comorbidities; type of prior therapies and depth and duration of response to prior therapies; treatment related toxicities.

Relapse is defined as the recurrence or the progression of the disease after the patient has experienced the best response to therapy; refractory myeloma progresses under treatment or within 60 days after its completion.[45]

When biochemical relapse occurs, asymptomatic increment in monoclonal protein > 25% and >500 mg/L in urine, early treatment may allow to delay disease recurrence and clinical relapse.

Retreatment with the same drug performed at induction may be considered in patients in whom the previous therapy induced a durable response (longer than 24 months at induction, 9-12 months at relapse); in patients relapsed after 6-9 months or refractory to previous therapy a different class of drug is recommended.[46]

In elderly patients with relapsed/refractory MM, 2-drug regimens combining lenalidomide or bortezomib and dexamethasone are the treatments of choice.

The APEX trial showed the superiority of bortezomib over dexamethasone in 669 patients relapsed/refractory after 1-3 prior lines of treatment.[47] The higher ORR (38% vs 18%; P < 0.001), CR rate (6% vs 1%; P< 0.001) and the prolonged DOR (8 vs 5.6 months) obtained with bortezomib as compared to dexamethasone alone translated in higher time to progression (TTP; median, 6.2 vs 3.5 months; P < 0.001) and OS (median, 80 vs. 66 months; P = 0.003), despite a 44% crossover of patients to bortezomib arm. An updated analysis showed an increase in the ORR (43%) and CR rate (9%) and confirmed the OS advantage (median, 29.8 vs 23.7 months; P = 0.027) with bortezomib.[48] Despite a higher rate of grade 3 toxicities in the bortezomib arm, grade 4 adverse events, serious adverse events and discontinuation rate were similar between the two groups.

The role of lenalidomide in the relapse setting has been explored in two phase III trials (MM009 – MM010).[49, 50] Patients were randomized to receive dexamethasone with either lenalidomide or placebo. In the lenalidomide arm, both ORR (60% vs. 20-24%) and CR rate (14-16% vs. 1-3%) were higher in comparison with those observed in the placebo arm. Furthermore, patients receiving lenalidomide had a significantly prolonged TTP (median, 11.4 vs. 4.7 months) and OS (median, 29.6 vs. 20.2-20.6 months) compared to those treated with placebo. Results reported in these studies led to the FDA and EMA approval of lenalidomide for relapsed/refractory MM patients.

Lenalidomide has shown a significant activity also in patients previously exposed to thalidomide, though responses and survival may be lower than those observed in thalidomide naïve patients.[50]

Since lenalidomide lacks in neurotoxicity, it is recommended in patients suffering from thalidomide- or bortezomib-related peripheral neuropathy. In patients with renal insufficiency or with a history of thrombosis, bortezomib is indicated.

In the relapse setting, the orally available proteasome inhibitor carfilzomib and the third generation IMiD pomalidomide showed promising results and have been recently approved by FDA for relapsed/refractory MM patients.

Carfilzomib has shown remarkable efficacy and safety in the relapse setting; its approval by the FDA for the treatment of RRMM patients, after at least two prior therapies, was based on results from the phase II, single arm PX-171-003 study.[51] The efficacy analysis performed on 257 patients showed an ORR of 23.7%, a median DOR of 7.8 months and a median OS of 15.4 months. A prospective analysis conducted over 229 patients receiving single agent carfilzomib in the PX-171-003-A1 study, evaluated responses and outcomes of patients divided into a cohort at high risk, defined by the presence of at least one of the following abnormalities: t(4;14); t(14;16), del17p13, del13 or hypodiploydy, and a cohort at low-risk patients. Results showed that carfilzomib induced similar ORR (25.8% vs 24.6%, respectively) within the two groups, although a trend toward a shorter PFS and OS in high-risk patients was observed. Furthermore, among cytogenetics abnormalities, t(4;14) was associated with the highest ORR (38.9%) and the longest median OS (11.8 months).[52]

Carfilzomib showed to be effective even in bortezomib-treated patients, though its activity resulted in lower ORR and shorter TTP in comparison with bortezomib naïve patients.[53]

In the phase II PX-171-003-A1 trial, patients received single agent carfilzomib, and the ORR was lower in refractory patients who had received bortezomib as their last line of treatment in comparison with those who had received a different drug.[51] The phase Ib PX-171-006 trial explored the combination of carfilzomib and lenalidomide (CRd), at different doses, with low-dose dexamethasone in relapsed/refractory MM patients; at the highest dosage, CRd resulted in a promising 75% ORR.[54] Results from the phase III, randomized clinical trial ASPIRE, comparing lenalidomide plus low-dose dexamethasone with or without carfilzomib, are awaited.

Pomalidomide, a thalidomide analogue, has been tested both alone or in combination with dexamethasone in relapsed/refractory patients showing safe toxicity profile and excellent clinical efficacy. Several phase I/II studies evaluated the safety and efficacy of pomalidomide combined with low-dose dexamethasone in heavily pre-treated patients: this combination induced a significant ≥PR rate (21-65%) with a manageable toxicity profile.[55] Furthermore, the ≥PR rate (26-32%) reported in patients refractory to lenalidomide suggests that pomalidomide may be effective in these patients as well. In the phase III, randomized MM-003 clinical trial, both median PFS (15.7 vs 8 weeks; $P < 0.001$) and median OS (NR vs 34 weeks; $P < 0.001$) were significantly longer in patients receiving

pomalidomide and low-dose dexamethasone as compared to those treated with high-dose dexamethasone alone.[56] These findings led to the recent FDA approval of pomalidomide plus low-dose dexamethasone in MM patients after at least 2 prior therapies, including lenalidomide and bortezomib. Recently, the addition of a third drug (cyclophosphamide or clarithromycin) to the combination of pomalidomide and steroid has shown to increase the ≥PR rate (54%) and to prolong PFS.[57, 58] Three-drug regimens combining pomalidomide plus steroid and conventional chemotherapy or novel agents are currently under investigation in phase I/II trials.

Newer classes of drugs such as histone deacetylase (panobinostat and vorinostat), monoclonal antibodies (elotuzumab and daratumumab) and proteasome inhibitors (MLN 9708) are currently under investigation, either alone or in combination with currently available novel agents in the relapse setting.

Expert commentary

The introduction of novel agents, combined with conventional chemotherapy, has dramatically changed the outcome of MM patients. In an elderly population, patient's comorbidities and treatment-related toxicities negatively impact on patient's capability of withstanding anti-myeloma therapies; furthermore, combinational regimens not only increase treatment efficacy but also treatment related toxicity. This translates into a higher discontinuation rate and, consequently, into a lower efficacy of therapies. Hence, a careful clinical evaluation, assessing the presence of frailty, comorbidities and disability, is necessary in order to provide patients with appropriate tailored therapy .

Patients older than 65 years of age in excellent condition may undergo a reduced intensity ASCT (Mel 100); in this regard, a continuous approach incorporating novel agents, both at induction and as consolidation/maintenance, and reduced intensity ASCT, may be a valid option.

In elderly patients not eligible for ASCT, full dose treatment should be provided: the standard of care consists of a 3-drug regimen (VMP, VCD and VRD); in patients aged 65-75 years, the 4-drug regimen VMPT-VT may be considered, as it showed to both increase the CR rate and to prolong PFS and OS in comparison with the standard VMP.[40] Maintenance therapy after induction, with either lenalidomide or VT, is a valid option and has recently proved to extend PFS.[34, 40]

In unfit patients, a reduced-dose therapy is recommended: 2-drug regimens including bortezomib or lenalidomide are suggested, though a third drug may be added if necessary.

Vd proved to be safer and as effective as 3-drug bortezomib-based combinations in a frail population;[37] elderly patients treated with Rd had a prolonged OS as compared to those who received RD, owing to the inferior toxicity rate reported with the low-dose schedule of dexamethasone.[11]

Treatment at relapse should be selected based on patient's clinical conditions and quality and duration of response to prior therapies. Dexamethasone, combined with lenalidomide (Rd) or bortezomib (VD) is the standard of care in this setting. In patients relapsed and/or refractory after lenalidomide and bortezomib, newer drugs such as pomalidomide and carfilzomib now represent a valid treatment strategy.

Five-year view:

To date, MPT and VMP are the standards of care for newly diagnosed MM patients ≥65 years of age. However, the regulatory trials did not include vulnerable patients.

Bringhen et al. have recently analyzed data from 1435 elderly patients enrolled in 4 European phase III trials including thalidomide and/or bortezomib. The analysis showed that age and renal failure, occurrence of infections and cardiac or gastrointestinal grade 3-4 adverse events have a significant negative impact on survival in elderly patients.

Future trials should aim to provide tailored, personalized therapy, and to deliver the appropriate dose intensity in all patient subgroups. The optimization of MM treatment schedules will enable to provide the best approach to improve efficacy and tolerability in elderly patients.

Personalized therapy should also take into account patient's quality of life, in orde to meet the physical, psychological and social needs of patients. To achieve this aim, an integrated-care model including the oncologist and the palliative care expert may be suggested.

Key issues:

A) Novel agents such as the IMiDs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib have revolutionized the treatment of elderly patients with MM.

B) Elderly patients with MM are usually not considered eligible for high dose melphalan and transplantation.

C) A careful assessment of patient's conditions and status is needed to chose the best and more appropriate strategy.

D) Very fit patients may undergo reduced-dose intensity ASCT; in these patients a sequential approach with novel agents and transplantation may be of benefit. Fit patients can be safely treated with full-dose regimens. Reduced-dose regimens or two-drug regimens should be preferred for unfit patients

G) Therapy at relapse should be based on type of previous therapy, type and duration of response to previous therapy.

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References

1. Palumbo A, Anderson K: Multiple myeloma. N Engl J Med 364:1046–1060, 2011

2. Howlade N, Noone A, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012

3. Kyle RA, Rajkumar SV: Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leuk Off J Leuk Soc Am Leuk Res Fund UK 23:3–9, 2009

4. Rajkumar SV, Larson D, Kyle RA: Diagnosis of smoldering multiple myeloma. N Engl J Med 365:474–475, 2011

5. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383, 1987

6. Palumbo A, Bringhen S, Ludwig H, et al: Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). Blood 118:4519–4529, 2011

7. Fayers PM, Palumbo A, Hulin C, et al: Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood 118:1239–1247, 2011

8. San Miguel JF, Schlag R, Khuageva NK, et al: Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 359:906–917, 2008

9. Reeder CB, Reece DE, Kukreti V, et al: Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leuk Off J Leuk Soc Am Leuk Res Fund UK 23:1337–1341, 2009

10. Richardson PG, Weller E, Lonial S, et al: Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 116:679–686, 2010

11. Rajkumar SV, Jacobus S, Callander NS, et al: Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 11:29–37, 2010

12. Greipp PR, San Miguel J, Durie BGM, et al: International staging system for multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol 23:3412–3420, 2005

13. Dimopoulos M, Kyle R, Fermand J-P, et al: Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood 117:4701–4705, 2011

14. Avet-Loiseau H, Durie BGM, Cavo M, et al: Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. Leuk Off J Leuk Soc Am Leuk Res Fund UK , 2012

15. Ross FM, Avet-Loiseau H, Ameye G, et al: Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 97:1272–1277, 2012

16. Rajkumar SV: Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. Am J Hematol 87:78–88, 2012

17. Snozek CLH, Katzmann JA, Kyle RA, et al: Prognostic value of the serum free light chain ratio in newly diagnosed myeloma: proposed incorporation into the international staging system. Leuk Off J Leuk Soc Am Leuk Res Fund UK 22:1933–1937, 2008

18. Martinez-Lopez J, Blade J, Mateos M-V, et al: Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. Blood 118:529–534, 2011

19. Gay F, Larocca A, Wijermans P, et al: Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood 117:3025–3031, 2011

20. Usmani SZ, Crowley J, Hoering A, et al: Improvement in long-term outcomes with successive Total Therapy trials for multiple myeloma: are patients now being cured? Leukemia 27:226–232, 2013

21. Kumar SK, Lee JH, Lahuerta JJ, et al: Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leuk Off J Leuk Soc Am Leuk Res Fund UK 26:149–157, 2012

22. Palumbo A, Bringhen S, Petrucci MT, et al: Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 104:3052–3057, 2004

23. Facon T, Mary JY, Hulin C, et al: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation

in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 370:1209–1218, 2007

24. Straka C, Schafer-Eckart K, Bassermann F, et al: Prospective Randomized Trial of Len/Dex Induction Followed by Tandem MEL140 with Autologous Blood Stem Cell Transplantation and Len Maintenance Versus Continued Therapy with Len/Dex in Myeloma Patients Age 60-75 Years: Protocol-Defined Safety Analysis After 100 Patients. ASH Annu Meet Abstr 120:2012, 2012

25. Palumbo A, Gay F, Falco P, et al: Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. J Clin Oncol Off J Am Soc Clin Oncol 28:800–807, 2010

26. Ludwig H, Hajek R, Tóthová E, et al: Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 113:3435–3442, 2009

27. Hulin C, Facon T, Rodon P, et al: Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol Off J Am Soc Clin Oncol 27:3664–3670, 2009

28. Beksac M, Haznedar R, Firatli-Tuglular T, et al: Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol 86:16–22, 2011

29. Wijermans P, Schaafsma M, Termorshuizen F, et al: Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed

multiple myeloma: the HOVON 49 Study. J Clin Oncol Off J Am Soc Clin Oncol 28:3160–3166, 2010

30. Palumbo A, Bringhen S, Caravita T, et al: Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 367:825–831, 2006

31. Palumbo A, Bringhen S, Liberati AM, et al: Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 112:3107–3114, 2008

32. Palumbo A, Waage A, Hulin C, et al: Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica 98:87–94, 2013

33. Morgan GJ, Davies FE, Gregory WM, et al: Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood 118:1231–1238, 2011

34. Palumbo A, Hajek R, Delforge M, et al: Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 366:1759–1769, 2012

35. Kumar SK, Lacy MQ, Hayman SR, et al: Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. Am J Hematol 86:640–645, 2011

36. Mateos M-V, Richardson PG, Schlag R, et al: Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol Off J Am Soc Clin Oncol 28:2259–2266, 2010

37. Niesvizky R, Flinn IW, Rifkin R, et al: Efficacy and Safety of Three Bortezomib-Based Combinations in Elderly, Newly Diagnosed Multiple Myeloma Patients: Results From All Randomized Patients in the Community-Based, Phase 3b UPFRONT Study. ASH Annu Meet Abstr 118:478, 2011

38. Mateos M-V, Oriol A, Martínez-López J, et al: Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol 11:934–941, 2010

39. Mateos M-V, Oriol A, Martínez-López J, et al: Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 120:2581–2588, 2012

40. Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol Off J Am Soc Clin Oncol 28:5101–5109, 2010

41. Palumbo A, Bringhen S, Rossi D, et al: Overall Survival Benefit for Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance with Bortezomib-Thalidomide (VMPT-VT) Versus Bortezomib-Melphalan-Prednisone (VMP) in Newly Diagnosed Multiple Myeloma Patients. ASH Annu Meet Abstr 120:200, 2012

42. Kumar S, Flinn I, Richardson PG, et al: Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 119:4375–4382, 2012

43. Falco P, Cavallo F, Larocca A, et al: Lenalidomide-prednisone induction followed by lenalidomide-melphalan-prednisone consolidation and lenalidomide-prednisone maintenance in newly diagnosed elderly unfit myeloma patients. Leuk Off J Leuk Soc Am Leuk Res Fund UK , 2012

44. Kumar SK, Rajkumar SV, Dispenzieri A, et al: Improved survival in multiple myeloma and the impact of novel therapies. Blood 111:2516–2520, 2008

45. Anderson KC, Kyle RA, Rajkumar SV, et al: Clinically relevant end points and new drug approvals for myeloma. Leuk Off J Leuk Soc Am Leuk Res Fund UK 22:231–239, 2008

46. Kastritis E, Palumbo A, Dimopoulos MA: Treatment of relapsed/refractory multiple myeloma. Semin Hematol 46:143–157, 2009

47. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487–2498, 2005

48. Richardson PG, Sonneveld P, Schuster M, et al: Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 110:3557–3560, 2007

49. Weber DM, Chen C, Niesvizky R, et al: Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 357:2133–2142, 2007

50. Dimopoulos M, Spencer A, Attal M, et al: Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 357:2123–2132, 2007

51. Siegel DS, Martin T, Wang M, et al: A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 120:2817–2825, 2012

52. Jakubowiak AJ, Siegel DS, Martin T, et al: Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. Leukemia , 2013

53. Vij R, Wang M, Kaufman JL, et al: An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood 119:5661–5670, 2012

54. Bensinger W, Wang M, Orlowski RZ, et al. Dose-escalation study of carfilzomib (CFZ) plus lenalidomide (LEN) plus low-dose dexamethasone (Dex) (CRd) in relapsed/refractory multiple myeloma (R/R MM). J Clin Oncol. 2010;28(15):8029.

55. Lacy MQ, Kumar SK, LaPlant BR, et al: Pomalidomide Plus Low-Dose Dexamethasone (Pom/Dex) in Relapsed Myeloma: Long Term Follow up and Factors Predicing Outcome in 345 Patients. ASH Annu Meet Abstr 120:201, 2012

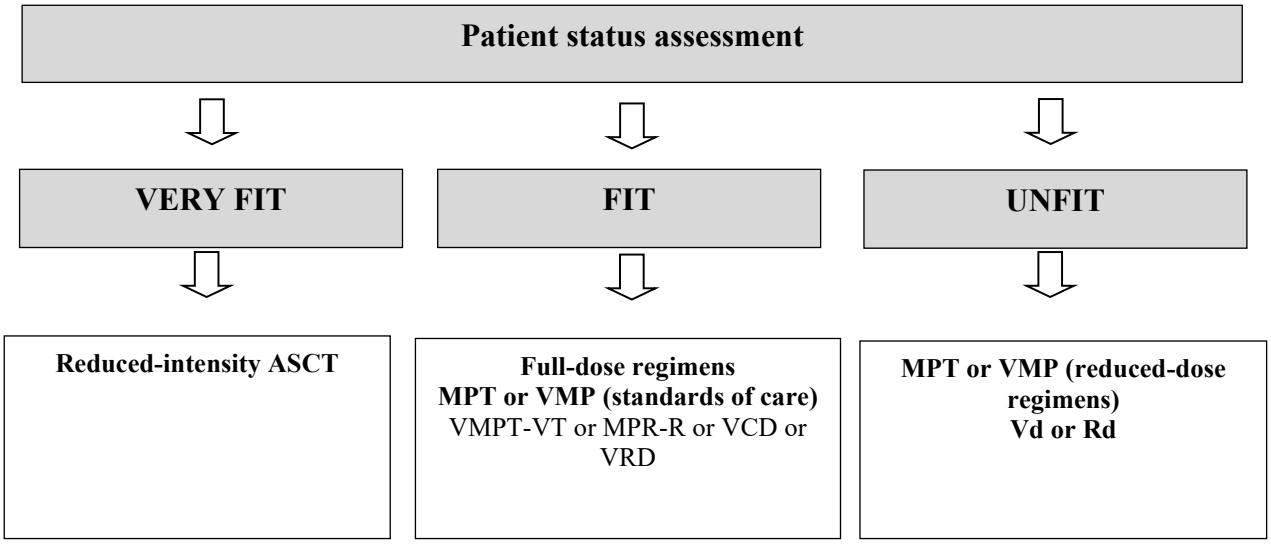
56. Dimopoulos MA, Lacy MQ, Moreau P, et al: Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study. ASH Annu Meet Abstr 120:LBA–6, 2012

57. Larocca A, Montefusco V, Oliva S: . Pomalidomide Cyclophosphamide Prednisone Is Act Lenalidomide RelapsedRefractory Mult Myeloma Abstr No O-5 IMW Clin Lymphoma Myeloma Leuk Meet Abstr 2013

58. Mark TM, Boyer A, Rossi AC, et al: ClaPD (Clarithromycin, Pomalidomide, Dexamethasone) Therapy in Relapsed or Refractory Multiple Myeloma. ASH Annu Meet Abstr 120:77, 2012

Figure 1

Treatment algorithm for newly diagnosed MM patients



ASCT, autologous stem cell transplantation; MPT, melphalan-prednisone-thalidomide; VMP, bortezomib-melphalan-prednisone; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide maintenance; VCD, bortezomib-cyclophosphamide-dexamethasone; VRD, bortezomib-cyclophosphamide-dexamethasone; Vd, bortezomib-dexamethasone; Rd, lenalidomide-dexamethasone.

Table 1

Management of adverse events in multiple myeloma patients treated with novel agents

AE	Suspected agent	Management	Dose-modification
Neutropenia	Bortezomib, Lenalidomide,	G-CSF until neutrophil recovery in case of uncomplicated grade 4 AE or grade 2-3 AEs with fever or infection.	25% to 50% reduction
Thrombocytopenia	Lenalidomide, Bortezomib	Platelet transfusion in case of grade 4 AE.	25% to 50% reduction
Anaemia	Bortezomib, Lenalidomide	Erythropoietin or darbepoietin if hemoglobin level is ≤ 10 g/dL.	25% to 50% reduction
Infection	Bortezomib, Thalidomide, Lenalidomide	Trimetoprin-cotrimoxazole for *Pneumocystis carinii* prophylaxis during high-dose dexamethasone. Acyclovir or valacyclovir for HVZ prophylaxis during bortezomib-containing therapy.	25% to 50% reduction
Neurotoxicity	Bortezomib, Thalidomide	Neurological assessment before and during treatment. Immediate dose reduction is recommended	*Bortezomib*: 25%-50% reduction for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy recovers to at least grade 1 and restart with 50% dose reduction for grade 2 with pain or grade 3 peripheral neuropathy; treatment discontinuation for grade 4 peripheral neuropathy. *Thalidomide*: 50% reduction for grade 2 neuropathy; discontinuation for grade 3; restart with reduced dose if neuropathy improves to grade 1.
Skin toxicity	Thalidomide, Lenalidomide	Steroids and antihistamines.	Interruption in case of grade 3-4 AE. 50% reduction in case of grade 2 AE.
Gastrointestinal toxicity	Bortezomib, Thalidomide, Lenalidomide	Appropriate diet, laxatives, physical exercise, hydration, antidiarrheics.	Interruption in case of grade 3-4 AE, 50% reduction in case of grade 2 AE.
Thrombosis	Thalidomide, Lenalidomide	Aspirin 100-325 mg if ≤1individual/myeloma thrombotic risk factor is present. LMWH or full dose warfarin if there are ≥2 individual/myeloma risk factors and in all patients with thalidomide-related risk factors.	Drug temporary interruption and full anticoagulation. Afterwards, resume treatment

Renal toxicity	Lenalidomide	Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections, and concomitant use of nephrotoxic drugs).	Reduce dose based on creatinine clearance: If 30-60 mL/min: 10 mg/day; If < 30 mL/min without dialysis needing: 15 mg every other day; If < 30 mL/min with dialysis required: 5 mg/day after dialysis on dialysis day.
Bone pain	None	Start with simple non-opioid analgesics. When no improvement is observed, use weak opioids. In case of no relief, use synthetic opioids or strong (natural) opioids. Local radiotherapy is also an effective strategy.	-
Bone disease	None	Vertebroplasty (percutaneous injection of polymethacrylate or equivalent material into the vertebral body). Use balloon kyphoplasty to enhance vertebral height. Long-term bisphosphonates may prevent bone disease. Intravenous pamidronate, intravenous zoledronic acid, oral clodronate are additional strategies.	-

G-CSF, granulocyte-colony stimulating factors; HVZ, herpes-varicella-zoster; LMWH, low-molecular-weight heparin; AE adverse event.

Table 2. Efficacy and safety of selected regimens for newly diagnosed MM

	Number	Schedule	≥PR (%)	PFS/EFS/TTP (%)	OS (%)	TOXICITIES Grade 3/4 (%)
MPT	815	M: 0.18 or 0.25 mg/kg d 1-7 or 1-4; P: 2 mg/kg d 1-4 ; T: 100-200 mg/d; M (0.18 mg) T (100 mg) for six 28-d cycles ; M (0.25 mg) T (200 mg) for twelve 42-d cycles	67	43 at 24 months	50 at 39 months	- Neutropenia: 16-48 - PN: 6-23 - Infections: 4-28
CTD	426	C: 500 mg/wk; T: 50 mg for 4 wk increased every 4 wks in 50-mg increments to maximum 200 mg/d; D: 20 mg/d d 1-4, 15-18 for six to nine 28-d cycles	64	50 at 13 months	50 at 33 months	- Infections: 13 - PN: 7 - VTE: 16
Rd	222	R: 25 mg d 1-21; d: 40 mg d 1, 8, 15, 22; for four 28-d cycles	68	50 at 25 months	76 at 24 months	- Neutropenia: 20 - VTE: 12 - Infections: 9
VRD	35	B: 1.3 mg/m^2 d 1, 4, 8, 11; L: 25 mg d 1-14; D: 20 mg d 1, 2, 4, 5, 8, 9, 11, 12 (or d 1, 8, 15)[36] for eight 28-d cycles	37	75 at 18 months	97 at 18 months	- Neutropenia: 9 - PN: 6 - Infections: 5
CRd	53	C: 36 mg/m^2 d 1, 2, 8, 9, 15, 16; L: 25 mg d 1-21; d: 40-20 mg weekly (cycles 1–4/5–8) for eight 28-d cycles	79 ≥ nCR	-	-	- Neutropenia: 12 - VTE: 10 - Infections: 6
MPR	152	M: 0.18 mg/kg d 1–4; P: 2 mg/kg d 1–4; R: 10 mg d 1–21 for nine 4-week cycles R: 10 mg d 1-21 until disease progression	77	50 at 31 months	70 at 36 months	- Neutropenia: 35* - Thrombocytopenia: 11* - Infections:11
R maintenance		R: 10 mg d 1-21 until disease progression	33 ≥VGPR			- Neutropenia: 7* - Thrombocytopenia: 6* - Infections: 3
VMP	344	V: 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1-4), d 1, 8, 22, 29 (cycles 5-9); M: 9 mg/m^2 d 1-4; P: 60 mg/m^2 d 1-4 for nine 42-d cycles	89	50 at 24 months	68 at 36 months	- Neutropenia: 40 - Thrombocytopenia: 37 - PN: 13 - Infections: 10
VMPT	254	V: 1.3 mg/m^2 d 1, 8, 15, 22; M: 9 mg/m^2 d 1–4; P: 60 mg/m^2 d 1–4; T: 50 mg/d for nine 35-d cycles	89	56 at 36 months	89 at 36 months	- Neutropenia: 38 - Thrombocytopenia: 22 - PN: 8 - Infections: 13
VT maintenance		V: 1.3 mg/m^2 every 14 d; T: 50 mg/d for 2 years				- Neutropenia: 3 - PN: 5

MPT, melphalan-prednisone-thalidomide; CTD, attenuated regimen of cyclophosphamide-thalidomide-dexamethasone; RD, lenalidomide plus high-dose dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; MPR, melphalan-prednisone-lenalidomide; R, lenalidomide; VMP, bortezomib-melphalan-prednisone; VCD, bortezomib-cyclophosphamide-dexamethasone; VMPT, bortezomib-melphalan-prednisone-thalidomide; VT,

bortezomib-thalidomide; VRD, bortezomib-lenalidomide-dexamethasone; CRd, cyclophosphamide-lenalidomide-dexamethasone; PR, partial response; PFS, progression-free survival; EFS, event-free survival; TTP, time to progression; OS, overall survival, NA not available. * grade 4 only.

Table 3. Suggested dose-adjustments

Drug	Full-dose	First reduction	Further reduction
Lenalidomide	25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Thalidomide	100 mg/d	50 mg/d	50 mg/every other day
Bortezomib	1.3 mg/m2 d 1,8,15,22 / 5 wks	1.0 mg/m2 d 1,8,15,22 / 5 wks	1.3 mg/m2 d 1,15 / 4 wks
Melphalan	0.2 mg/kg/d d 1-4 / 5 wks	0.15 mg/kg d 1-4 / 5 wks	0.10 mg/kg d 1-4 / 5 wks
Prednisone	2 mg/kg/d d 1-4 / 5 wks	1.5 mg/kg/d d 1-4 / 5 wks	1 mg/kg/d d 1-4 / 5 wks

d, day; wk, week