Multiple Myeloma in the Elderly: When to Treat, When to Go to Transplant

By Jean-luc Harousseau, MD [5]

Until recently, standard treatment of multiple myeloma (MM) in elderly patients who were not candidates for autologous stem cell transplantation was with the combination of melphalan plus prednisone (MP). Novel agents (thalidomide, lenalidomide, bortezomib) are dramatically changing frontline therapy of MM. Randomized studies have shown the superiority of adding one novel agent to MP, either thalidomide (MPT) or bortezomib (MPV). The combination of lenalidomide with low doses of dexamethasone is another attractive alternative. Recent results show that maintenance therapy with low-dose lenalidomide may prolong progression-free survival. The objective of these improved treatment regimens should be to achieve complete response, as in younger patients. However, toxicity is a significant concern, and doses of thalidomide and of myelotoxic agents should be reduced in patients who are older than 75 years or who have poor performance status. Weekly bortezomib appears to induce severe peripheral neuropathy less frequently than the same agent administered twice weekly. Autologous stem cell transplantation is feasible in selected fit patients over 65 years of age, and its results are improved by the addition of novel agents before and after high-dose therapy. However, considering the progress in non-intensive therapy, autologous transplantation should not currently be offered to elderly patients outside of a clinical trial.

Multiple Myeloma (MM) is a disease of the elderly: the median age at diagnosis is increasing along with the increase in life expectancy in the general population and is currently more than 70.[1] Age is an important prognostic factor in MM, and overall survival (OS) declines continuously by decade from age 50 to ages greater than 80.[1] This decline in OS may be explained in part by the higher incidence of more severe disease in older patients, but it is mainly explained by patient characteristics (eg, performance status, comorbidities).[1,2] Elderly patients do not tolerate chemotherapy-related adverse events as well as younger patients, and they are rarely candidates for high-dose therapy (HDT) plus autologous stem cell transplantation (ASCT)—which, back in the 1990s, was the first improvement in the treatment of MM.[3] In the context of MM, the definition of “elderly” is generally based on the age limit for treatment with HDT plus ASCT. In most randomized studies that have compared ASCT and conventional-dose chemotherapy as primary treatments for MM, the upper age limit has been 65 years.[3] Thus, the usual definition of an elderly MM patient is one who is over 65 years of age.

While the introduction of HDT supported by ASCT has markedly increased progression-free survival (PFS) and OS in younger patients, for four decades now there has been almost no improvement in the prognosis of elderly patients with MM.[4] Until recently, the standard of care has been the combination of melphalan and prednisone (MP).[5] The introduction of immunomodulatory drugs (the “IMiDs”: thalidomide and lenalidomide) and of proteasome-inhibitors (bortezomib) has dramatically changed the management of MM in both younger and elderly patients. The use of these agents in patients who have relapsed and in patients with refractory disease has already improved outcomes,[6] and they are currently added to frontline treatment in patients with newly diagnosed disease.

Recent Improvements in the Treatment of Elderly Patients With Multiple Myeloma

TABLE 1

Randomized Studies Comparing MP and MPT Regimens: Patient Characteristics in MPT Regimens
Novel agents have been added to the treatment of elderly patients in three ways: the addition of one novel agent to the MP combination, the addition of one novel agent to dexamethasone, and the use of a novel agent as maintenance therapy after induction treatment.

### Table 2

**Randomized Studies Comparing MP and MPT Regimens: Results**

#### MP-Based Combinations

The first novel agent to be combined with MP was thalidomide. To date, five randomized studies have been published comparing MP with MP plus thalidomide (MPT) as primary treatment in elderly patients with MM.[7-12] The design of these studies, inclusion criteria, and doses of chemotherapy and thalidomide have varied (Table 1). However, the results are quite reproducible. These are shown in Table 2 and can be summarized as follows:

- Response rates—of either at least partial response or at least very good partial response (VGPR)—were significantly increased in the MPT arm in all five studies.
- PFS was significantly improved in the MPT arm in four out of five studies.
- OS was significantly improved in the MPT arm in three out of five studies; however, OS is partly dependent on the efficacy of salvage treatment after progression and on the availability of novel agents for relapse management.

As a consequence of these studies, the regimen MPT is now considered a new standard of care and it has been approved by the European Medicines Agency (EMEA) for the treatment of patients older than 65 years with newly diagnosed MM. However, safety may be a concern, especially in very old or frail patients. For example, in the Nordic trial, the median patient age was 78 years, and the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status higher than 2 was 30%.[12] This high incidence of more frail patients resulted in a high rate of toxic death (23 deaths in the first 6 months in patients over 75 years of age in the MPT arm versus a rate of 12 deaths during the first 6 months in the MP arm) and lower compliance with treatment (59 treatment discontinuations in the MPT arm versus 18 in the MP arm). As a consequence, PFS was not improved in the MPT arm. One might speculate that higher doses of melphalan (0.25 mg/kg/d for 4 days every 6 weeks) and thalidomide (200 mg/d for 1 week, and up to 400 mg/d) and inclusion of older and more frail patients were the reason that a better response rate did not translate into a longer PFS in the MPT arm.[12]

Conversely, in the French trial in patients over 75 years of age, doses of melphalan and thalidomide were lower (0.2 mg/kg/d and 100 mg/d, respectively) and both response rate and PFS were significantly superior in the MPT arm compared with the MP arm.[10]

#### Table 3

**MP and MPV Regimens Compared: Results of the VISTA Randomized Trial**

The second agent to be combined with MP is bortezomib. Following encouraging data from a phase I/II trial of the combination MP plus bortezomib (MPV),[13] the large randomized Velcade as Initial Standard Therapy in Multiple Myeloma (VISTA) trial compared MP and MPV.[14] Results were recently updated[15] and are summarized in Table 3. MPV was significantly superior to MP for all parameters that measured response or outcome. An important finding from this trial was that the complete response (CR) rate was 30%; this is quite comparable to the rate achieved with HDT in younger patients. Thus, MPV is also now an EMEA-approved standard of care regimen for use in elderly patients.

However, while results were not significantly diminished in patients in this trial who were older than 75 years, safety was a concern. In the MPV arm, the incidence of grade 3/4 peripheral sensory neuropathy was 14%, and 30% of patients had to discontinue treatment or at least discontinue bortezomib because of treatment-related adverse events.[14] Lenalidomide has also been used with MP (MPR regimen). While a phase I/II study has yielded...
encouraging results,[16] preliminary analysis of a randomized trial comparing MP, MPR, and MPR plus lenalidomide maintenance failed to show a better PFS in the MPR arm than in the MP arm, despite a higher response rate in the former.[17] Again, this might be explained by higher myelotoxicity and lower compliance in patients older than 75 years.

TABLE 4

Dexamethasone-Based Combination Regimens: Results of Randomized Studies

**Dexamethasone-Based Combinations**

The combination of thalidomide and dexamethasone (TD) has been widely used as primary therapy in MM. This combination was compared to MP in a randomized study in elderly patients.[18] While the response rate, including CR rate, was superior in the TD arm, there was no benefit in terms of PFS, and OS was significantly shorter in the TD arm, particularly in patients over 75 years of age (median, 19.8 months—versus 41.3 months in the MP arm) (Table 4). These results were explained by the higher toxicity and lower compliance in the TD arm. In this study, both the thalidomide dosage (50 to 400 mg/d) and the dexamethasone dosage (4-day blocks at 40 mg/d) were probably too high in patients who were older than 75 or who had poor performance status; the elevated dosages might also explain the high incidence of early deaths from infection or cardiac complications.

Determining the optimal dose of dexamethasone to be combined with IMiDs in frontline therapy of MM was the purpose of a randomized study recently published by the ECOG. This study compared lenalidomide plus high-dose dexamethasone (40 mg/d for 4 consecutive days, 3 times a month) with lenalidomide plus low-dose dexamethasone (40 mg weekly).[19] Here, too, while the response rate was superior with high-dose dexamethasone, median PFS and 1-year survival were significantly longer in the low-dose arm (Table 4) because of higher toxicity in the high-dose arm. The incidence of any grade 3/4 adverse events was 52% in the high-dose dexamethasone arm, compared with 35% in the low-dose dexamethasone arm (P=.0001). As a result, there were more early deaths (5% vs 1%; P=.003) and more treatment discontinuations due to adverse events (27% vs 19%) in the high-dose dexamethasone arm. This trend was particularly evident in patients over the age of 70. The fact that the median duration of treatment was 9.7 months in the low-dose dexamethasone arm, compared with only 3.8 months in the high-dose dexamethasone arm, may explain why median PFS and 3-year OS were superior in the low-dose arm.[20] In any event, lenalidomide plus low-dose dexamethasone might be another standard of care in elderly patients and is currently being compared to MPT in an ongoing randomized trial.

**Maintenance Therapy**

The goal of maintenance therapy is to increase the duration of remission by controlling the malignant clone. In the past, interferon produced a moderate increase in PFS,[21] but because of toxicity, long-term treatment could not be justified. The concept of maintenance therapy is currently being revisited in elderly patients using novel agents.

With MPT primary therapy, there is no current evidence that thalidomide maintenance further increases PFS, since in none of the randomized trials evaluating MPT has this question been specifically addressed. However, it should be noted that in the two Intergroupe Francophone du Mylome (IFM) studies, the better PFS translated to an OS benefit despite the absence of maintenance therapy,[9,10] while in the Italian study, MPT induction was followed by thalidomide maintenance therapy but there was no OS benefit in the MPT arm due to a shorter survival after relapse.[8] Three recent studies favor maintenance therapy in elderly patients. The most convincing is the MM015 randomized trial, which compared 9 cycles of MP, 9 cycles of MP plus lenalidomide (MPR), and 9 cycles of MPR followed by low-dose lenalidomide maintenance (MPR-R).[17] PFS in the MPR-R arm was dramatically superior to PFS in the other two arms. However, up to now there has been no OS benefit in the lenalidomide maintenance arm.
Preliminary analysis of an Italian randomized trial showed that, compared with the new standard MPV regimen, four-drug induction therapy (MPT plus bortezomib) followed by maintenance therapy with bortezomib plus thalidomide significantly increased both the response rate (38% CR vs 24%; \(P = .0008\)) and the 3-year PFS (60% vs 42%; \(P = .007\)).[22] A randomized Spanish study also used maintenance therapy with bortezomib plus thalidomide or bortezomib plus dexamethasone and showed a further increase in the CR rate during maintenance (from 25% before maintenance to 42% with maintenance).[23] Although these two studies did not directly assess the role of maintenance, they both show that maintenance therapy may improve results achieved by induction treatment.

**When to Treat Elderly Patients**

**TABLE 5**

Diagnostic Criteria for Plasma Cell Disorders

**Which Plasma Cell Disorders Should Be Treated?**

MM is a late stage in the evolution of monoclonal gammopathies and is always preceded by a phase of monoclonal gammopathy of unknown significance (MGUS)—although this phase is not always recognized. An intermediate stage is smoldering (or asymptomatic) myeloma (SMM). The difference between SMM and MM is that patients with SMM must have no evidence of related organ or tissue impairment (end-organ damage). The criteria for end organ damage are CRAB symptoms (hypercalcemia, renal insufficiency, anemia, lytic bone lesions) or recurrent infection. The diagnostic criteria for MGUS, SMM, and MM are listed in Table 5.[24] TABLE 6

**TABLE 6**

Risk Factors Associated With a Shorter Time to Progression in SMM

The risk of progression to overt symptomatic MM is 25% at 20 years for MGUS[25] and 73% at 15 years for SMM.[26] Therefore, considering the age-adjusted life expectancy of the general population and the potential toxicity of myeloma treatment, currently MGUS should not be treated and SMM is usually not treated before there is evidence of progression. However, although in MGUS the risk of progression is uniform (about 1% per year), in SMM the risk is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and only 1% per year for the last 10 years.[26] Prognostic factors that are associated with a shorter time to progression are listed in Table 6.[26-33] For example, in a group of patients with a high percentage of plasma cells (10% or more) and a high serum M-component level (3g/dL or greater), the probability of progression at 15 years was 87%, compared with a probability of only 39% in patients with less than 10% plasma cells.[26] Thalidomide has been tested in SMM, but toxicity was a serious concern.[34] Clinical studies of novel agents with a good efficacy/toxicity ratio seem justified in patients with SMM at high risk of transformation. Preliminary results of a Spanish randomized trial have showed that induction treatment with lenalidomide-dexamethasone followed by lenalidomide maintenance therapy significantly delays the risk of progression compared with no treatment.[35] However, the real proof of the benefit of this approach will be demonstration of an improved OS. Until there is evidence of such a benefit, outside of a clinical trial, careful observation remains the recommended management strategy in these patients.

**Treatment of Symptomatic MM in Elderly Patients**

As with younger patients, elderly patients with symptomatic MM should be treated. The introduction of novel agents in primary therapy has had two important consequences:

• While there had been no significant improvement in conventional chemotherapy for 4 decades, we...
now have several possibilities that are significantly superior to MP (MPT, MPV, and lenalidomide with low-dose dexamethasone [Rd]).

- While patients over 75 years of age had been treated with reduced-dose alkylating agents or only with palliative approaches, they can now be treated with effective combinations.

As in younger patients treated with HDT plus ASCT, the objective of primary therapy in elderly patients should be to achieve CR.[36] The prognostic impact of achieving CR has been shown in a sub-analysis of the VISTA trial and in a retrospective analysis of recent Italian protocols.[37,38] However, induction therapy should not be too toxic; otherwise, the benefit of more effective treatment may be negated by an excessive toxic death rate or by poor compliance with treatment.[12,18]

Until the results of ongoing randomized trials are available, it is not possible to determine which of the new standard regimens is best. A number of criteria must be considered when deciding on the initial therapy for an elderly patient with symptomatic MM.

Most of these criteria are patient-related. Bortezomib-based regimens are preferred in patients with renal failure or a previous episode of deep vein thrombosis. IMiD-based regimens are preferred when oral administration is more suitable. Lenalidomide-based regimens are preferred in patients with concomitant peripheral neuropathy, since both thalidomide and bortezomib are potentially neurotoxic.

Other criteria are myeloma-related. For instance, bortezomib might be preferred in a patient with translocation (4;14), since it has been shown that even a short treatment may at least partially overcome the poor prognosis associated with this cytogenetic abnormality.[14,39] Data involving lenalidomide are less clear.

The key to treating elderly patients is to actually evaluate the efficacy/toxicity ratio and to reduce the toxicity of the regimens. To this end, the issue of the dose is critical.

**Dexamethasone.** The IFM demonstrated that despite higher response rates, PFS was not better with dexamethasone-based regimens than with MP—and that toxicity was greater (more infections, diabetes, and gastro-intestinal and psychiatric complications).[40] The IFM thus concluded that high-dose dexamethasone should not be routinely recommended as first-line therapy in elderly patients. As suggested by the results of the ECOG randomized trial,[19] dexamethasone is best used weekly (low-dose regimen) in all elderly patients (at a dosage of 40 mg/wk up to the age of 70 years, and at a dosage of 20 mg/wk in patients older than 70 years).

**MP Regimens.** In patients older than 75 years, melphalan should be used at a reduced dosage (0.2 mg/kg on 4 consecutive days every 6 weeks). The dose of thalidomide should not be more than 100 mg/d.[10]

**Bortezomib.** In an attempt to find a way to reduce the risk of peripheral neuropathy, which is the most frequent reason for stopping bortezomib treatment, two groups have evaluated a new MPV regimen that uses weekly instead of twice-weekly administration of bortezomib.[22,23] Both groups found that efficacy was not significantly different with weekly administration but that the incidence of severe peripheral neuropathy was dramatically reduced.

Other measures are also important. These include prophylaxis for herpes-zoster infections in patients treated with bortezomib and prevention of deep vein thrombosis with low-molecular weight heparin or aspirin in patients treated with thalidomide or lenalidomide. Careful monitoring of blood cell counts is mandatory in patients receiving alkylating agents and/or lenalidomide.

Before deciding on treatment, a geriatric evaluation must be performed in all frail patients over the age of 75 and in patients with severe comorbidities. In patients for whom geriatric assessment does not show a positive benefit/risk ratio, attenuated-dose treatment (such as low-dose alkylating agents) should be considered.

**Current Role of HDT Plus ASCT**

The great majority of randomized trials comparing HDT plus ASCT and conventional-dose chemotherapy have recruited patients up to 65 years of age; this explains the age limit for ASCT.[3] However, ASCT is feasible in patients older than 65 years, at least in selected patients with good performance status and no severe comorbidities. The Arkansas group even stated that age was not a biologically adverse parameter and should not constitute an exclusion criterion for ASCT.[41] However, the overall toxicity is higher in patients over 70 and the dose of 200 mg/m² is too toxic for this population.[42] For this reason, the Italian group has proposed 2 to 3 courses of melphalan, 100 mg/m², supported by ASCT[43] and has demonstrated that this semi-intensive approach was superior to conventional chemotherapy with MP in patients aged 50 to 70 years, including in patients...
aged 65 to 70 years.[44] However, using the same regimen, the IFM failed to confirm this finding. In the three-arm randomized IFM trial 99606 for patients aged 65 to 75 years, the above regimen yielded a higher response rate and CR rate than MP, but PFS and OS were not significantly better; moreover, the MPT regimen was significantly superior both to MP and to melphalan plus ASCT.[9] This discrepancy between the results of the Italian and French studies might be explained by the inclusion criteria, since patients aged 70 to 75 years were included in the French study but not in the Italian one. Still, in light of these results, the use of ASCT in patients older than 65 years, even in conjunction with reduced dosages of melphalan, should not be proposed outside of a clinical trial. However, there are two other possible explanations for the poor PFS in the IFM 99-06 study:

• Only 65% of patients received the two planned transplants, and in the majority of patients who dropped out, the reason was either complications of induction treatment with chemotherapy or progression.
• Despite a high percentage of patients with VGPR or better, relapses were rapid in the absence of maintenance treatment.

The use of novel agents in combination with intermediate-dose melphalan might improve results by increasing the efficacy/toxicity ratio of induction treatment and by delaying relapses with post-ASCT consolidation/maintenance. The Italian group recently reported results obtained with such an approach.[45]

**Reference Guide**

**Therapeutic Agents**

- Bortezomib (Velcade)
- Dexamethasone
- Doxorubicin
- Lenalidomide (Revlimid)
- Melphalan (Alkeran)
- Prednisone
- Thalidomide (Thalomid)

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

Four cycles of bortezomib combined with doxorubicin and dexamethasone (PAD regimen) were administered in 102 patients aged 65 to 75 years. The rate of CR plus VGPR was 58%. Because the induction treatment was effective and well tolerated, 90% of patients received the first ASCT and 83% received the second. After ASCT, patients received lenalidomide consolidation/maintenance therapy, and the final rate of CR plus VGPR increased to 78%, with very encouraging 2-year PFS and OS rates of 69% and 86%, respectively.

Patient selection was probably biased, and patients in poor general condition or with severe comorbidities were certainly not included; it is noteworthy that only 12% of patients had International Staging System stage III disease. Nonetheless, these results show that in the elderly,
there is probably a subgroup of patients who may benefit from intermediate-dose melphalan plus ASCT in combination with novel agents. This finding is particularly important at a time when the place of ASCT in frontline therapy is again being debated even for younger patients.[3] Results obtained with novel agents in patients who are not candidates for ASCT are good enough to justify randomized trials comparing novel agents with or without ASCT as frontline therapy in younger patients. This implies that although ASCT should not be abandoned too early in fit older patients, its role remains undetermined in the era of novel therapies and it should not be proposed outside of a clinical trial.

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