

# Front line treatment of elderly multiple myeloma in the era of novel agents

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**Abstract:** Melphalan combined with prednisone (MP) has long been the historical treatment of reference for a large proportion of elderly myeloma (MM) patients ineligible for autologous stem cell transplantation, and is still the backbone of new regimens that include the new era of novel agents. Melphalan–prednisone–thalidomide (MPT) and melphalan–prednisone–bortezomib (Velcade®, MPV), proved superior to MP, currently appear to be the treatments of choice for this population. In the near future melphalan–prednisone–lenalidomide (Revlimid®, MPR) will also provide a third therapeutic option (MPT, MPV, and MPR), in elderly multiple myeloma, eventually. These options could lead to more personalized treatment approaches, based on patient comorbidities, as the three novel agents have somewhat different toxicity profiles. Dexamethasone-based regimen is another option and questions regarding the relative efficacy of melphalan-based versus low-dose dexamethasone-based regimens will require randomized phase III trials. More intensive approaches with new drug combinations or with the incorporation of polyethylene glycolated (PEGylated) liposomal doxorubicin will also require additional studies. Additionally, the important issue of maintenance treatment needs to be further investigated. These new and emerging therapies offer multiple effective treatment options for MM patients and greatly enhanced treatment strategies for clinicians.

**Keywords:** multiple myeloma, elderly, bortezomib, thalidomide, revlimid, IMiDs, supportive care

## Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and a disease of the elderly.<sup>1</sup> The annual age-specific incidence of MM increased considerably with age, up to >40/100,000 for persons >80 years of age in some series. The median age at diagnosis for multiple myeloma is 71 and around 65% of all new cases of MM will be older than 65 years. The number of older patients with this disease is expected to rise over time as a consequence of the increased life expectancy of the normal population.<sup>2</sup> Myeloma is the cause of death in 75% of patients older than 65 years with MM.

The recent report from the Surveillance, Epidemiology, and End Results (SEER) Program in patients with myeloma pointed out the gap between young and elderly patients.<sup>3</sup> From 1990–1992 to 2002–2004, a major improvement of long-term survival had been achieved in younger patients. In contrast, no improvement in survival was observed in patients over 70 years of age and only a modest improvement in patients between 60 and 69 years of age.

Diverse factors including comorbidity, lower performance status, decreased physiologic reserve, and potential undertreatment contribute to this poor outcome, although supportive care of these patients has improved in recent years.<sup>4,5</sup> However, the concerted action of specific myeloma therapeutics, including most recent progresses in novel agents, and supportive therapies can significantly improve the quality of life

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of myeloma patients.<sup>6</sup> At the time of diagnosis, patients with MM can be divided into those who either are asymptomatic (approximately 25% of patients) or symptomatic, these latter requiring a prompt chemotherapy-based intervention. High-dose melphalan with autologous stem cell transplantation (ASCT) is considered the standard of care for patients younger than 65 years of age. Recent studies have suggested that ASCT is safe in some patients over the age of 65, including some rare patients over the age of 70, but it does not represent routine practice.<sup>7–9</sup> Combination chemotherapy with melphalan and prednisone (MP) has been used since the 1960s and, as recently as two years ago, remained the most widely accepted treatment option for elderly patients ineligible for high-dose therapy.<sup>10–12</sup> More complex combinations with alkylating agents have been substituted but often with added toxicity and inconvenience and no survival advantage over MP.<sup>13</sup> Dexamethasone (Dex)-based regimens have provided other options.<sup>12,14,15</sup> Overall, two different backbones have been used for the development of new combinations; MP, mainly in Europe, and Dex, more frequently in North America.

## Melphalan–prednisone-based combinations

### MP + thalidomide

In the wake of the activity of thalidomide noted in the late 1990s against relapsed/refractory myeloma,<sup>16</sup> the drug was then rapidly moved up to the first line, in combination with MP. Following promising results achieved in a phase II study,<sup>17</sup> the MPT combination was evaluated against MP in several phase III randomized studies as a front-line therapeutic in elderly myeloma patients. The results of two studies, one from the GIMEMA (Groupe Italiano Malattie Ematologiche dell'Adulto, 255 patients) and one from the Intergroupe Francophone du Myélome (IFM; IFM 99-06, 447 patients) are now available.<sup>18–20</sup> Two additional trials have recently reported results from phase III placebo-controlled studies comparing MPT with MP-placebo: one from the IFM (IFM 01-01, 232 patients) and the other from the Nordic Myeloma Study Group (NMSG; 362 patients).<sup>21,22</sup> Other studies are ongoing from the HOVON and GIMEMA study groups.<sup>23,24</sup>

### Trial designs

In the IFM99-06 trial, all patients were between 65 and 75 years of age.<sup>19</sup> The MP regimen consisted of twelve 6-week cycles with melphalan 0.25 mg/kg and prednisone 2 mg/kg/day, days 1–4. In the MPT arm, the same MP regimen

was delivered plus thalidomide at the maximum tolerated dose not exceeding 400 mg daily. The thalidomide was stopped at the end of MP (no maintenance phase). The IFM 99-06 trial also incorporated a third arm with standard induction : 2 cycles of vincristine–doxorubicine–dexamethasone (VAD), cyclophosphamide 3 g/m<sup>2</sup> and stem cell mobilization and intermediate dose melphalan 100 mg/m<sup>2</sup> (MEL100) with stem cell transplantation (2 consecutive cycles of MEL100). The study was therefore the first and only study to evaluate thalidomide in combination with standard MP against both standard MP alone and stem cell transplantation with a reduced intensity conditioning regimen.

In the GIMEMA trial comparing MP with MPT, patients were between 60 and 85 years of age.<sup>18,25</sup> The MP regimen consisted of six 4-week cycles with melphalan 4 mg/m<sup>2</sup> days 1–7. The MPT regimen consisted of the same MP regimen plus thalidomide 100 mg daily until progression. The primary endpoint was response rate and event-free survival.

The IFM 01-01 double-blind trial, comparing MP plus placebo with MPT, was remarkable in that it was exclusively devoted to patients over the age of 75 (median age 78.5 years, one third of patients over 80).<sup>21</sup> Even though these patients represent more than 20% of MM patients, there are rarely considered for enrolment in clinical trials. As in the IFM 99-06, twelve 6-week cycles of MP were given but with a lower dose of melphalan (0.2 mg/kg days 1–4). Thalidomide was given at 100 mg daily until the end of MP (no maintenance).

In the NMSG trial, mean age was 75 years (49–92) the MP regimen consisted of 6-week cycles until plateau phase with melphalan 0.25 mg/kg. Thalidomide was started at 200 mg daily and escalated to 400 mg daily. Patients also received thalidomide maintenance treatment in plateau phase at 200 mg daily.<sup>22</sup> In this study, as well as in IFM studies, the primary endpoint was overall survival.

### Study results

In the first two published phase III studies (GIMEMA and IFM 99–06), the superiority of MPT over MP was clearly demonstrated on the basis of response, including complete response (CR), and progression-free survival (Table 1).<sup>18–20</sup> MPT response results were concordant with 13% and 15.5% CR rates in the GIMEMA and IFM 99-06 studies, respectively, and an identical 76% overall response rate. In the IFM 01-01 study, response results of MPT arm were slightly inferior but still significantly superior to those of MP, with a 61% response rate and a 7% CR rate.<sup>21</sup>

**Table 1** Comparative response and survival across trials of MPT compared with MP

Trial	Regimen	N	CR (%)	≥PR (%)	PFS (mo)	OS (mo)
IFM 99-06 <sup>19</sup>	MPT	125	13	76	27.5	51.6
	MP	196	2	35	17.8	33.2
	MEL 100	126	18	65	19.4	38.3
GIMEMA <sup>20</sup>	MPT	129	15.6	76	21.8	45
	MP	126	3.7	48	15.5	47.6
IFM 01-01 <sup>21</sup>	MPT	113	7	61	24.1	45.3
	MP	116	1	31	19.0	27.7
NMSG Study <sup>22</sup>	MPT	182	13	57	16	29
	MP	175	4	40	14	33
HOVON Study <sup>*23</sup>	MPT	152	1	63	–	–
	MP	149	1	47	–	–

**Notes:** For PFS and OS, results are presented in median (months). \*Results from interim analysis. MEL100: High-dose melphalan 100 mg/m<sup>2</sup>.

**Abbreviations:** N, number of patients; CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival.

Median progression-free survival times with MPT were similar in all three studies, ranging from 24 to 27.5 months. Concerning overall survival, only a nonsignificant survival advantage was noted with MP arm in the GIMEMA study. In both IFM studies, the progression-free survival advantage observed with MPT translated into a significant overall survival advantage. In the Nordic Study, the addition of thalidomide to MP resulted in a significant advantage in terms of response rate and time to progression compared with MP.<sup>22</sup> However, these favorable results did not translate into an overall survival advantage. The study was hampered by use of higher doses of melphalan and thalidomide in a population with a high proportion of patients over 75 years of age (mean age 74.5 years) and approximately one third of patients with poor performance status (World Health Organization [WHO] performance status of 3 or 4 in 30% of patients). These characteristics likely contributed to more frequent early deaths in the MPT group, especially in the oldest patients. Of note effective median or mean durations of thalidomide treatment have been somewhat different across trials; 8, 11, and 13.5 months (median) in GIMEMA, IFM 99-06, and IFM 01-01, respectively, and only 6 months (mean) in the NMSG Study.

In the IFM 99-06 study, MPT was also found to be superior to the MEL100 strategy with stem cell transplantation, a strategy with reduced intensity conditioning regimen. This result opens the debate on the role of stem cell transplantation in elderly patients in the era of novel agents. In patients over the age of 65 years (n = 136), the intensive Total Therapy program from the University of Arkansas achieved a median overall survival of 60 months with a 13% treatment-related mortality rate.<sup>26</sup> In patients between 65 and 75 years

of age, the oral MPT from the IFM achieved a median overall survival of 52 months with no toxic deaths.

### Toxicity

Thalidomide induces a certain amount of hematopoietic and nonhematopoietic side effects, and MPT was associated with a significantly increased risk of complications in phase III trials comparing MP with MPT (Table 2).<sup>18,19</sup> Certain complications are short-term side effects which are frequent, reversible, and manageable with appropriate dose reduction such as skin rash, sedation, constipation, sinus bradycardia, hypotension, and fatigue. Although teratogenicity should remain in everybody's mind as contraindicating thalidomide administration in pregnant women, it is not an issue in elderly women. Special recommendations were proposed for men and women of childbearing potential.<sup>27</sup> Others are time- and dose-dependent.<sup>28</sup> However, much has been learned in the past 8 years about the management of thalidomide-related toxicities that are no longer a limitation in myeloma therapeutics for the majority of patients.<sup>29</sup>

In either studies from the IFM, a higher incidence of grade 3/4 neutropenia was noted but without an increase in severe infections.<sup>19,21</sup> In contrast, no difference between MP and MPT was observed in the GIMEMA study for neutropenia, but severe infections were more frequent.<sup>18</sup>

Deep vein thrombosis (DVT) is a major adverse effect of thalidomide therapy, breakdown peripheral deep venous thrombosis and pulmonary embolism, the latter being of greater risk of morbidity. Its pathogenic mechanism has not been clearly established. When associated to dexamethasone or chemotherapy, an increased

**Table 2** Grade 3 and greater hematologic side effects, and incidence of deep venous thromboembolism and peripheral neuropathy of thalidomide in MM

Trial	Trial	N	Thrombocytopenia (%)	Neutropenia (%)	Infection (%)	DVT (%)	Peripheral neuropathy (%)
GIMEMA <sup>18</sup>	MPT	129	3	16	10	12	8
IFM 99-06 <sup>19</sup>	MPT	125	14	48	13	12	6
IFM 01-01 <sup>21</sup>	MPT	113	ND	0	ND	7	2

**Notes:** <sup>†</sup>Grades 2 to 4; <sup>‡</sup>Leukopenia.

**Abbreviations:** N, number of patients; ND, not determined.

risk is described. The outcome of DVT when treated only by thalidomide is estimated at 5% and increases up to 15% when thalidomide is associated to either anthracycline or dexamethasone, in absence of any prophylactic anticoagulation.<sup>30–32</sup> DVT have mainly been reported in the first 6 months of treatment with a large majority in the first 3 months when the burden of the tumor is the highest.<sup>33</sup> Following such high incidence of DVT in the initial phases of studies, prophylactic anticoagulation was added. Clear thromboprophylaxis guidelines have been established for patients receiving a monotherapy by thalidomide or a combination including this drug when suffering of MM.<sup>25</sup> Aspirin, low molecular weight heparin (LMWH), or oral warfarin should be initiated in all patients starting therapy with thalidomide plus dexamethasone and/or chemotherapy.

Peripheral neuropathy is the most common cause of thalidomide discontinuation or dose reduction and effects 15% to 20% of the patients. Moreover elderly patients suffer more frequently of this adverse side. Clinic manifestations are initially sensory symptoms but can evolve towards motor symptoms and autonomic dysfunction. Neuropathy is closely related to duration of treatment and cumulative dose.<sup>34–36</sup> The probability of recovery increases if thalidomide is quickly discontinued. Otherwise neuropathic symptoms may progress and become irreversible. Practical rules were suggested recently by Palumbo in a review on thalidomide: no dose modification if neuropathy is grade I, 50% reduction dose if neuropathy is grade II, and interruption thalidomide if neuropathy is grade III or above.<sup>24</sup>

## MP + bortezomib (Velcade, MPV)

The introduction of proteasome inhibition with bortezomib has expanded treatment options in MM and has significantly improved outcomes for patients with relapsed/refractory MM.<sup>37,38</sup> The drug was also shown to be synergistic in vitro with a wide range of cytotoxic agents, including melphalan.<sup>39</sup> In addition, the combination of bortezomib and melphalan was effective in a phase I/II trial.<sup>40</sup> Based on these promising

results, bortezomib was incorporated into the MP regimen (MPV) for the treatment of elderly untreated MM patients by the spanish group PETHEMA (Programa para el Tratamiento de Hemopatias Malignas).<sup>41</sup> In total, 60 patients were enrolled in this phase I/II study, of whom 53 completed at least one cycle of treatment. The median age of patients was 75 years (range 65–85 years); 47% of patients were older than 75 years and 17% were aged over 80. Patients received four 6-week induction cycles (bortezomib 1.0 or 1.3 mg/m<sup>2</sup> on days 1, 4, 8, 11, 22, 25, 29, 32) followed by five 5-week maintenance cycles (bortezomib 1.0 or 1.3 mg/m<sup>2</sup> on days 1, 8, 15, 22) in combination with oral melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup>/day. The overall response rate was 89%, including 32% of patients with immunofixation-negative CR and an additional 11% with near-CR. The response rate after 1 cycle of MPV was higher than in historical controls after 6 cycles of MP (70 versus 42%). After a median follow-up of 26 months, median time to progression was 27.2 months, median overall survival had not been reached and projected 3-year overall survival was 85%.<sup>42</sup> Time-to-event data in the MPV group compared favourably with MP historical controls: time to progression, event-free survival and overall survival (at 26 months: 27.2 versus 20 months, 23 versus 16 months, and median not reached versus 26.9 months, respectively). MPV was generally well tolerated and the majority of adverse events occurred during the first 2 cycles of treatment. The most common grade-3/4 adverse events were thrombocytopenia and neutropenia (40%–50%) but the frequency of infections was low (16%). Peripheral neuropathy and diarrhea were noted in 17% and 16% of patients, respectively.

These promising results formed the basis from the international VISTA (Velcade as Initial Standard Therapy) trial (682 patients; the median age was 71 years with 30% of patients aged 75 years), which is so far the largest MP-based phase III study (Table 3).<sup>43</sup> Patients received four 6-week induction cycles (bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8, 11, 22, 25, 29, 32) followed by five 6-week maintenance cycles

**Table 3** Comparative response and survival in MPV compared with MP

Trial	Regimen	N	CR (%)	≥PR (%)	TTP (mo)	OS (mo)
VISTA <sup>43</sup>	MPV	344	30	82	24	82.6% (2 yr)
	MP	338	5	50	16.6	69.5% (2 yr)

**Abbreviations:** N, number of patients; CR, complete response; PR, partial response; OS, overall survival; TTP, time to progression.

(bortezomib 1.3 mg/m<sup>2</sup> on days 1, 8, 22, 29) in combination with oral melphalan 9 mg/m<sup>2</sup> and prednisone 60 mg/m<sup>2</sup>/day. The primary endpoint was time to progression. MPV was found significantly superior to MP for all efficacy endpoints: time to progression, progression-free survival, overall survival, time to next treatment, CR rate. An unprecedented 30% CR rate was noted in patients receiving MPV. Time to progression was 24 months in the MPV group. After a median follow-up of 16.3 months, median survival was significantly superior in the MPV group. The survival advantage was demonstrated in patients younger and older than 75 years of age. Serious adverse events were noted in 46% and 36% of patients in MPV and MP, respectively. Most divergent grade 3/4 toxicities between MPV and MP were gastrointestinal (20% in MPV versus 6% in MP), fatigue and asthenia (15% versus 5%), and peripheral neuropathy (14% versus 0%). Peripheral neuropathy resolved or improved in 75% of cases in a median of approximately 60 days. Thrombosis/embolism was very low and the same on both arms (1%). Overall, these results clearly established MPV as a new standard of care for MM patients not eligible for ASCT.

### MP + lenalidomide (Revlimid®)

Another successfully applied strategy has been the development of thalidomide derivatives potentially more potent compared to the parent compound and have fewer side-effects. Lenalidomide (Revlimid®) is a novel immunomodulatory agent that has shown activity both preclinically and clinically,<sup>44</sup> alone or in combination with dexamethasone.<sup>45–47</sup> Results from a phase I/II dose-escalating study of MP with lenalidomide (MPR) have been recently reported.<sup>48</sup> Fifty-four patients were enrolled in the study. The median age of patients was 71 years (range 57–77 years). Patients received 9 cycles of lenalidomide (5–10 mg/daily, days 1–21) plus melphalan (0.18–0.25 mg/kg/day, days 1–4) and prednisone 2 mg/kg/day every 4–6 weeks, followed by maintenance therapy with lenalidomide alone (10 mg/daily, days 1–21, every month). The maximum tolerated dose was lenalidomide 10 mg/daily for 21 days and melphalan 0.18 mg/kg for 4 days every 4–6 weeks. At this dose level, the overall response rate was 81% including

48% of patients with at least a very good partial remission (VGPR; > 90% response rate) and 24% of patients with immunofixation-negative CR. The 1-year event-free survival and overall survival rates were 92% and 100%, respectively. The most common grade 3/4 adverse events were neutropenia and thrombocytopenia (52% and 24%, respectively at the maximum tolerated dose), febrile neutropenia (9%), vasculitis (9%), and thrombosis/embolism (5%). More than 40% of patients required growth factor support. Overall, MPR was considered a promising first-line treatment for elderly patients with an acceptable and manageable toxicity. These results formed the basis for the ongoing European Myeloma Network phase III study comparing MP with MPR, with or without lenalidomide maintenance.

### Dexamethasone-based combinations

Glucocorticoids have significant activity in MM, in relapsed/refractory disease and in newly diagnosed disease. In a study of 112 patients with untreated MM, the response rate with dexamethasone alone was 43%.<sup>14</sup> In the 1990s, dexamethasone was considered a simple, effective, and safe primary treatment for a large fraction of patients, mainly in North America. In the course of time, high-dose dexamethasone was recognized as a major source of concern and disability for patients, especially in the elderly. An important contribution in that field was the IFM study IFM 95 for newly diagnosed myeloma patients aged 65–75 years. In this study, 488 patients were randomly allocated to receive MP, melphalan with dexamethasone (M-Dex), dexamethasone alone, or dexamethasone with interferon alpha (Dex-IFN) (12). Patients receiving melphalan experienced a longer progression-free survival than those receiving dexamethasone-based regimens, but without any survival benefit. In addition, all high-dose dexamethasone-based regimens were associated with a greater risk of severe toxicities, including severe pyogenic infections in the M-Dex arm, and gastrointestinal, diabetic and psychiatric complications in all dexamethasone-based regimens. When combining all severe nonhematological complications, the incidence was significantly lower in

the MP group (16%) than in the dexamethasone-containing groups (28%). Other study has demonstrated the higher incidence of adverse events in the MD arm.<sup>15</sup>

In a recent study from ECOG (Eastern Cooperative Oncology Group) comparing thalidomide plus dexamethasone (Thal/Dex) with dexamethasone alone in newly diagnosed patients, and even though the treatment duration was short and the study population included some young patients (median age 65 years, range 38–82), grade 3 or higher nonhematological toxicities were seen with 43% of patients with dexamethasone alone, and grade 3 or higher hyperglycemia, fatigue, insomnia, and muscle weakness were noted in 15%, 10%, 5%, and 9% of patients, respectively.<sup>49</sup> Toxicity of any type grade 4 or 5 was observed in 18% of patients including 4% treatment-related deaths. In addition, many other patients suffered from grade I/II dexamethasone-related toxicities which were also a source of disability. The toxicity of the Thal/Dex combination was higher than that observed with dexamethasone alone. Grade 3 or higher nonhematological toxicities were seen with 67% of patients within four cycles. Grade 4 or higher nonhematologic toxicities were seen with 35% of patients and treatment-related deaths in 5%.

A confirmation of this significant toxicity was recently provided by the Central European Myeloma Study Group phase III study in elderly patients (289 patients; median age: 72 years) comparing Thal/Dex with MP. The study reported higher complete and near CR rates (30% vs 14%) for patients receiving Thal/Dex.<sup>50</sup> Progression-free survival was similar in both groups (median 20.7 and 16.7 months for MP and Thal/Dex, respectively) but significantly shorter overall survival was observed in the Thal/Dex group (median 49.4 and 41.5 months for MP and Thal/Dex, respectively). The population was very elderly; especially in the Thal/Dex group with 60% of patients between the ages 70 and 79 and 10%  $\geq 80$  years. Patients received a high-dose dexamethasone regimen and thalidomide dosing was, up to 400 mg/daily. Thus, the very elderly patient population and the higher doses of thalidomide and dexamethasone used likely contributed to a higher mortality rate in Thal/Dex-treated patients during the first year of study, especially in patients with a poorer performance status. When taken together with the MPT results from the Nordic Myeloma Study Group trial, these findings suggest that treatment with new drug combinations should be very carefully monitored in elderly patients, especially those over 75 years of age. Anthracyclins or alkylating agents have also been incorporated into the Thal/Dex regimen.<sup>51</sup>

The cyclophosphamide – thalidomide – dexamethasone (CTD) combination has proved to be effective in relapsed patients.<sup>52</sup> These promising results prompted the Medical Research Council to proceed with a large phase III randomized study (MRC IX) comparing, in patients ineligible for transplantation, MP to CTD with an attenuated dexamethasone dose. Results from that study are eagerly anticipated.

Overall, when considering all these Thal/Dex experiences in terms of both efficacy and toxicity, there is evidence that this combination is inferior to MPT and may not be optimal for elderly patients.

Along with the frequent and serious dexamethasone side-effects, there were also data suggesting that high-doses of dexamethasone were possibly not necessary in combination with novel agents, such as thalidomide or lenalidomide.<sup>53,54</sup> The ECOG group proceeded recently with a study (ECOG E4A03) comparing lenalidomide plus high-dose dexamethasone (40 mg daily, days 1–4, 9–12, 17–20) with lenalidomide plus low-dose dexamethasone (40 mg daily, days 1, 8, 15, 22).<sup>55</sup> 445 patients, median age 66 years (up to 88 years), were treated, including 233 over the age of 65 years. The significant toxicity of the high-dose dexamethasone regimen was fully confirmed but the good news was the modest toxicity of the low-dose dexamethasone regimen. Infection/pneumonia, fatigue, hyperglycemia, deep venous thrombosis, and cardiac ischemia were significantly less frequent with the low-dose dexamethasone schedule. Overall, nonhematologic toxicity of any type grade  $\geq 3$  or higher was found in 52% of patients receiving lenalidomide plus high-dose dexamethasone compared to 34% of patients receiving lenalidomide plus low-dose dexamethasone. Early deaths were also significantly less frequent in the low-dose dexamethasone arm; 1.4%, versus 4.5%. The two-year survival was superior in the group of patients receiving the low-dose dexamethasone regimen (87% versus 75%), including in the subgroup of patients aged over 65 years (82% versus 67%). Of note, the excess mortality in the high-dose dexamethasone arm was due to both disease progressive as well as increased toxicity. Overall, and even though the study was not designed to test efficacy of long-term lenalidomide plus dexamethasone (median durations on treatment were only 4 months in the high-dose dexamethasone arm and 6 months in the low-dose dexamethasone arm), lenalidomide and low-dose dexamethasone was found highly active in newly diagnosed elderly patients. There is no doubt that these results will be of major importance in the future and will influence the fate of all dexamethasone-based combinations.

## Maintenance therapy in MM (Table 4)

In the pre-thalidomide era, maintenance therapy<sup>56</sup> with alkylating agents had failed to demonstrate any benefit<sup>57,58</sup> as well as interferon which showed a modest increase in progression free survival and a minimal benefit in overall survival.<sup>59,60</sup> Corticosteroid maintenance was found to prolong the duration of response but the effect on survival was controversial.<sup>61,62</sup> Four randomized phase III trials evaluated the benefit of thalidomide maintenance after ASCT,<sup>63–66</sup> and found thalidomide maintenance an effective approach following autologous stem cell transplantation in young patients (Table 4). Two ongoing studies are furthermore evaluating maintenance by thalidomide, the SouthWest Oncology Group, SWOG 0204 study<sup>67</sup> and the HOVON-50/GMM-HD3 large trial,<sup>68</sup> with only preliminary data available. Unfortunately, no large randomized study has looked so far specifically at older patients. In the near future, results from the MRC IX trial, which has included maintenance study comparing thalidomide versus observation-only, will be available. Several trials are also ongoing with lenalidomide maintenance.

## Supportive care therapy

In symptomatic multiple myeloma, especially in elderly patients, most commonly experienced complications are asthenia, anorexia, and severe bone pain. Focal or diffuse bone involvement represents a common and disabling event in multiple myeloma. At diagnosis, bone pain in the skeleton, and particularly in the lumbar spine, represents the predominant symptom, 70% of patients, and is also a common indicator of relapse or progressive disease. In addition bone involvement contributes, along with immobility, dehydration and impaired renal calcium excretion, to the development of hypercalcemia. Anemia occurs in 30% to 62% of patients with multiple myeloma, particularly in those with advanced disease or delayed diagnosis, where it also has prognostic relevance.<sup>69</sup>

Infections are frequent complications of multiple myeloma and the most common causes of death due to suppression of production of polyclonal immunoglobulins, of decreased T-cell function and neutropenia. Such complications are a major cause of morbidity and mortality in myeloma patients, especially in elderly patients. Supportive care is therefore of critical importance in the treatment of elderly myeloma, in parallel with the specific treatment of myeloma.

## Skeletal-related complications

Bone destruction in multiple myeloma (pathologic fractures, spinal cord compression, hypercalcemia) is a major cause of morbidity and significantly decrease quality of life, cause severe pain from bone lesions and neurological impairments. Although microfractures and pathologic fractures are common clinical manifestations in patients with multiple myeloma, they are rather infrequent. Pathologic fractures are usually site skeletal-related, with the majority involving vertebrae (55% to 70%), lumbar and thoracic predominantly.<sup>4</sup> Although bone destruction in elderly myeloma is not different from younger patients, the diagnosis of bone lesions related to myeloma might be difficult in elderly patients in the context of osteoporosis.<sup>6</sup>

The bone lesions-related pain described by patients with myeloma required specific treatment with effective analgesia. An effective analgesia is recommended using the WHO pain ladder to scale pain description from patients. Sufficient dosing and adequate scheduling of pain treatment are essential in order to ascertain sufficient and continuous pain control. Radiotherapy is also indicated for painful lesions: most patients significantly achieve pain relief with local radiotherapy at a dose of 30 grays in 10 to 15 fractions. Other indications include the treatment of impending or actual pathologic fractures, spinal cord compression, tumor causing local neurological problems, and large soft tissue plasma cell tumors. Radiotherapy has also been shown to prevent the development of new vertebral fractures.<sup>70</sup>

**Table 4** Maintenance treatment with thalidomide

Authors	N. of patients	Duration of treatment	N. of ASCT	CR rate (%)	PFS (%)	OS (%)
Barlogie et al <sup>63</sup>	668	Onset until relapse or toxicity	double	65 vs 43	56 vs 44 (5-year)	65 vs 65 (5-year)
IFM 99-02 <sup>64</sup>	597	Until relapse or toxicity	double	67 vs 57	52 vs 36 or 37(3-year)	87 vs 74 or 77 (4-year)
Australian Study <sup>65</sup>	243	12 months	single	24 vs 15	63 vs 36 (2-year)	51 vs 80 (2-year)
Tunisian Study <sup>66</sup>	140	6 months	single	67 vs 51	85 vs 57	85 vs 65

**Abbreviations:** N., number; CR, complete response; PFS, progression-free survival; OS, overall survival; VS, versus.

Surgical intervention may be required in patients with an impending or actual fracture or a spinal compression.<sup>71</sup> Most patients also require radiotherapy in conjunction with surgery. Recent development of minimally invasive surgical procedures, such as vertebroplasty and kyphoplasty, allows myeloma patients with vertebral compression fractures to have immediate improvement in quality of life and shorter inpatient duration.<sup>72</sup>

Novel therapeutic approach for bone disease in multiple myeloma is represented by bisphosphonates which are derived from pyrophosphates by substitution of an oxygen atom with a carbon atom which confers a resistance to the activity of phosphatases *in vivo*, thus allowing prolonged inhibition of bone resorption.<sup>73,74</sup> Bisphosphonates inhibit the recruitment of osteoclasts from their precursor cells and suppress their subsequent cellular proliferation and differentiation. They also bind to bone surfaces, thus protecting them from destruction, inhibit production of IL6, the most important growth hormone for myeloma cells, and stimulate apoptosis of osteoclasts and myeloma cells. The efficacy of the bisphosphonates clodronate, pamidronate, and zoledronate in preventing bone lesions has been investigated in several randomized trials: bisphosphonates decrease episodes of hypercalcemia, height loss, vertebral fractures, the development of new lytic lesions and pain.<sup>75,76</sup> The addition of high potency intravenous bisphosphonates to myeloma therapy has provided major symptomatic benefits to patients with multiple myeloma.<sup>77</sup> They also decrease the need for palliative radiation and recently presented data suggested that they may prolong time to disease progression.<sup>78</sup>

Osteonecrosis of the jaw (ONJ) is a major oral complication in patients with multiple myeloma secondary to intravenous bisphosphonates use.<sup>79–81</sup> Intravenous bisphosphonates that contain an amino terminal group (pamidronate) or a nitrogen-containing side group (zoledronic acid) seem to present the highest risk for development of this phenomenon. Bisphosphonate-induced ONJ has been documented in both the maxilla and mandible, although there is a higher rate of incidence reported in the mandible. The median time to onset of ONJ among patients receiving zoledronic acid was 18 months and 3 to 6 years for patients receiving pamidronate. It is recommended that patients with multiple myeloma, who are being considered for IV bisphosphonates therapy, undergo a dental examination that includes clinical and radiographic evaluations. Any tooth or periodontal diseases should be appropriately controlled before initiation of IV bisphosphonates therapy. Dental extractions and other procedures that expose or manipulate bone should be avoided in these patients.

Due to the increasing risk of ONJ with duration of therapy, bisphosphonates should be discontinued after a maximum of 2 years of therapy in patients who have achieved CR and/or plateau phase. For patients whose disease is active, who have not achieved response, or who have a threatening bone disease beyond 2 years, therapy can be used to a dose every 3 months.<sup>82,83</sup>

## Anemia

In general, anemia of multiple myeloma is normochromic, normo-macrocytic and especially at the disease onset, is often moderate and well-tolerated. In about 5% of the patients anemia may be the sole sign of the disease. The pathogenesis of anemia in multiple myeloma is multifactorial and causes vary with the phase of the disease. Plasma cell bone marrow infiltration represents the most important cause at diagnosis. However, other causes are hemodilution due to hypervolemia, reduced survival of erythrocytes, poor utilization of circulating iron, and renal failure. In addition, myeloma therapy, either chemotherapy or radiotherapy, may induce or worsen anemia. The role of a blunted production of endogenous erythropoietin (EPO) in anemia of MM patients has been demonstrated.<sup>69</sup> In particular, reduced synthesis of EPO has been documented not only in MM subjects with renal failure (25%), but also in patients with normal renal function. Cytokines such as IL-1 $\beta$  and tumor necrosis factor, produced by normal and neoplastic cells in MM, could inhibit the renal production of EPO while the role of the IL-6 is not clear in this context.

Several clinical trials have investigated the effects of recombinant EPO(r-EPO) in myeloma patients suffering from anemia.<sup>69</sup> These studies indicate that r-EPO is an effective and safe drug for treating anemia of multiple myeloma. Quality of life in responding patients significantly improves with hemoglobin increment and transfusion independency. A functional or relative iron deficiency might occur in some patients during r-EPO treatment, and iron supplementation might be required to respond to r-EPO therapy.<sup>84,85</sup> Thromboembolic complications are the most important adverse event of EPO treatment. The risk is higher in patients with multiple myeloma treated with thalidomide or lenalidomide.<sup>86</sup> Prophylactic anticoagulation with low-molecular-weight heparin or aspirin is recommended in these treatments.<sup>87</sup>

## Infections

In early-stage myeloma, the most common infections are bronchitis and pneumonia, predominantly caused by



*Haemophilus influenzae* and *Streptococcus pneumoniae*. In patients with advanced myeloma and during the neutropenic phases of chemotherapy, *S. aureus* and Gram-negative bacteria are more common. Treatment is based on antibiotics.<sup>6</sup> Vaccination against *H. influenzae* and *S. pneumoniae* is recommended, with 61% of patients producing protective antibodies against pneumococci and 75% against *H. influenzae*. A randomized trial showed that prophylaxis of infection with monthly immunoglobulin infusions (0.4 g/kg) for a period of one year significantly reduced the frequency and severity of infections with patients who responded poorly to pneumococcal immunization.

## Conclusion

Large randomized phase III studies have now established MPT and MPV as new standards of care for a large proportion of elderly MM patients ineligible for ASCT. MPR may also provide a survival advantage over MP. This potentially may lead to the availability of three therapeutic options for the treatment of newly diagnosed elderly patients with MM. These options could lead to more personalized treatment approaches, based on patient comorbidities, as the three novel agents have somewhat different toxicity profiles. Physicians should also keep in mind that an adequate symptomatic treatment remains essential as well as a very careful treatment monitoring. The dexamethasone history, and also some recent experiences with new drugs have shown that the highest doses of drugs are not always optimal in elderly patients. All efforts should be made to avoid excessive toxicity, particularly in patients with initial bad performance status, and early phases of treatment are critical. Outpatient administration of drugs and patient quality of life should also be favored.

## Disclosure

The authors report no conflicts of interest in this work.

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