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(Article begins on next page)



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# Management of older adults with multiple myeloma

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## Abstract

Two-thirds of patients with multiple myeloma are aged 65 years or more and the prevalence of multiple myeloma in elderly patients is expected to rise in the next future. Patients older than 65 years are usually considered ineligible for transplantation. The introduction of novel agents, such as the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib, combined with conventional chemotherapy, has radically changed the treatment paradigm of elderly patients and improved outcome. A sequential approach, consisting of an induction regimen associated with a high rate of complete response, followed by consolidation/maintenance therapy, induces a profound cytoreduction and delays relapse, thus improving survival. Novel agents associated with reduced-intensity autologous transplant showed to be safe and effective in fit elderly patients. Patients older than 75 years or vulnerable ones are more susceptible to adverse events that negatively affect treatment adherence and outcome. In this setting, less toxic regimens and appropriate dose reductions should be adopted. Here we provide an overview of novel agent-based treatment strategies for elderly patients with multiple myeloma.

## Keywords

- Multiple myeloma;
- Thalidomide;
- Lenalidomide;
- Bortezomib;
- Fit;
- Unfit;
- Elderly patients

## 1. Introduction

Multiple myeloma (MM) is a neoplastic plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction (Table 1).<sup>1</sup> Treatment should be immediately started in presence of a symptomatic disease, typically characterized by the occurrence of at least one of the CRAB symptoms (C: hypercalcemia ( $> 11.5$  mg/dL); R: renal failure (serum creatinine  $> 1.73$  mmol/L); A: anemia (hemoglobin  $< 10$  g/dL or  $> 2$  g/dL below the lower limit of normal); and B: bone disease (lytic lesions, severe osteopenia or pathologic fractures). In case of asymptomatic disease, only close monitoring is recommended.

**Table 1.** Diagnostic criteria.

Diagnosis	Diagnostic criteria
Monoclonal gammopathy of undetermined significance (MGUS)	<ul style="list-style-type: none"> <li>• Serum monoclonal protein (IgG or IgA) &lt;3 g/dL</li> <li>• Clonal bone marrow plasma cells &lt;10%</li> <li>• Absence of myeloma-related organ impairment: hyperCalcemia, Renal insufficiency, Anemia and lytic Bone lesions (CRAB) and symptoms.</li> </ul>
Smoldering multiple myeloma (asymptomatic multiple myeloma)	<ul style="list-style-type: none"> <li>• Serum monoclonal protein (IgG or IgA) <math>\geq</math> 3 g/dL and/or clonal bone marrow plasma cells <math>\geq</math> 10%</li> <li>• Absence of myeloma-related organ impairment: hyperCalcemia, Renal insufficiency, Anemia and lytic Bone lesions (CRAB) and symptoms.</li> </ul>
Symptomatic Multiple Myeloma	<ul style="list-style-type: none"> <li>• Clonal bone marrow plasma cells <math>\geq</math> 10%</li> <li>• Monoclonal protein in serum and/or urine <sup>a</sup></li> <li>• Presence of myeloma-related organ impairment and symptoms: <ul style="list-style-type: none"> <li>[C] Hypercalcemia: (serum calcium &gt; 10.5 mg/L or upper limit of normal)</li> <li>[R] Renal insufficiency: (serum creatinine &gt; 2 mg/dL)</li> <li>[A] Anemia (hemoglobin &lt; 10 g/dL or 2 g &lt; normal)</li> <li>[B] Bone disease: lytic lesions, severe osteopenia or pathological fracture</li> </ul> </li> </ul>
Solitary plasmacytoma	<ul style="list-style-type: none"> <li>• Biopsy-proven plasmacytoma of bone or soft tissue in one site only with negative radiographs or MRI outside the primary site.</li> <li>• Absence of clonal plasma cells in bone marrow.</li> <li>• Absence of myeloma-related organ impairment: hyperCalcemia, Renal insufficiency, Anemia and lytic Bone lesions (CRAB) and symptoms.</li> </ul>

<sup>a</sup> Except in patients with true non-secretory multiple myeloma; MRI, magnetic resonance imaging.

In the last decades the introduction of autologous stem-cell transplantation (ASCT) and novel agents, such as the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, radically changed the treatment paradigm of MM, extending overall survival (OS).<sup>1</sup> The estimates of 5-year relative survival of patients with MM in the United States from 1990–1992 to 2002–2004 showed that this benefit was evident in patients aged less than 50 years (5-year relative survival: 45–57%) and in those aged 50–59 years (5-year relative survival: 39–48%), it was less pronounced in those aged 60–69 years (5-year relative survival: 31–36%), and it was absent in those older than 70 years of age (5-year relative survival: 27–29%).<sup>2</sup> The use of more sophisticated imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) may help to better define osteolytic lesions and identify the disease early.

Clonal heterogeneity and genomic instability typical of myeloma cells are responsible for clinical relapse and refractory disease.<sup>3</sup> The clinical heterogeneity of MM is due to the coexistence of different myeloma clones with various mutation patterns and subsequent biological and clinical behaviors. According to a Darwinian evolutionary model, the sequence in which therapies are

performed may induce different biological responses in the different clones, with the eradication of an indolent clone and the growth of a more aggressive one.<sup>4</sup> This will negatively affect post-relapse survival. In the future, a deeper knowledge of the biology of MM cells in the clinical setting should guide the choice of therapy to improve outcome and prevent the occurrence of refractory disease.<sup>5</sup>

At diagnosis, induction therapy has a greater impact on survival duration, in comparison with salvage treatment performed at relapse. Novel agents can be combined with conventional chemotherapy to create multi-drug regimens that may better overcome clonal heterogeneity of myeloma. At diagnosis, the presence of sensitive tumor may increase the chance of deep responses of a longer duration and decrease the risk of adverse events with better quality of life and lower related health care cost<sup>6</sup>; by contrast, in later phases, the presence of resistant disease significantly decreases the proportion of responses and increases the risk of adverse events, negatively affecting both quality of life of patients and health care costs.<sup>7</sup>

The depth of response and its duration are important prognostic factors in MM: the achievement of a complete response (CR), with either negative immunofixation or negative minimal residual disease (MRD), induces longer progression-free survival (PFS) and overall survival (OS), both in young and elderly patients. An analysis performed on 4990 MM patients treated with conventional chemotherapy and ASCT showed that patients achieving CR after induction had significantly longer PFS and OS compared to those who obtained a partial response (PR) only (59–89 vs. 39–68 months).<sup>8</sup> Similarly, attaining a CR proved to be an independent predictor of longer survival in elderly patients treated with both conventional chemotherapy and novel agents.<sup>9</sup> Therefore, combination regimens and treatment strategies with high probability of CR should be adopted, unless a high risk of serious adverse events suggests a more gentle approach.

Continuous treatment with novel agents until disease progression or intolerability increased the depth of response and extended both PFS and recently OS.<sup>[10], [11], [12], [13] and [14]</sup> Lenalidomide maintenance after melphalan–prednisone–lenalidomide (MPR) induction reduced the risk of progression by 66% compared with no maintenance, with no significant increase in toxicity.<sup>14</sup> This advantage was observed regardless of age. Maintenance with bortezomib plus thalidomide (VT) after bortezomib-based induction proved to be effective and well tolerated, and extended median PFS to 36–39 months.<sup>[10], [12], [13], [15], [16] and [17]</sup> In a landmark analysis at start of maintenance, in patients 65 to 75 years of age, VT maintenance after bortezomib–melphalan–prednisone–thalidomide induction reduced the risk of death by 37% compared with standard VMP without maintenance.<sup>10</sup>

Treatment discontinuation due to therapy-related adverse events is another important factor that negatively impacts outcome. Indeed, discontinuations translate into dose-reduction and reduced cumulative dose-intensity, affecting efficacy of therapies. This is particularly evident in patients older than 75 years, in whom adverse events are a major cause of treatment discontinuation, especially with multi-drug regimens.<sup>14</sup> In this subset of patients, the evaluation of frailty and disability is essential to propose tailored therapy in order to reduce treatment discontinuation rate and to deliver the highest cumulative dose-intensity.<sup>18</sup> Three-drug regimens with an acceptable toxicity profile are more suitable for fit patients, while 2-drug regimens with a more tolerable toxicity profile should be adopted for vulnerable patients to decrease discontinuation, thus allowing patients to stay on therapy for a longer period.<sup>19</sup>

In conclusion, major therapeutic efforts should be concentrated at diagnosis, when the disease is sensitive. Regimens associated with high CR rate and continuous therapy should be adopted. Treatment toxicity and discontinuation rate should be reduced in order to decrease the frequency of

adverse events, maximize treatment efficacy and improve outcomes. In unfit patients, a gentler approach to minimize adverse events and preserve patient's quality of life is suggested.

## **2. Epidemiology**

MM comprises 1% of all cancers and 13% of hematologic malignancies. Median age at diagnosis is 70 years; 35% of patients are younger than 65 years, 28% aged between 65 and 74 years and 37% are older than 75 years.<sup>[20] and [21]</sup> The incidence and prevalence of MM increase with age: the annual age-adjusted incidence rises from < 1/100,000 for subjects younger than 40 years, to > 40/100,000 for those older than 80 years; the annual prevalence of MM in patients aged 65–74 is approximately 31/100,000 and rises to 46/100,000 in patients aged older than 75 years. Both the incidence and prevalence of MM in elderly patients are expected to grow in the next future due to the increase in the life expectancy of the general population and the improved survival times achieved with the introduction of novel agents. Although MM is typical of the elderly, these patients are underrepresented in clinical trials because comorbidities and frailty often prevent them from being enrolled in experimental protocols.<sup>22</sup>

## **3. Definition of fit and unfit patients**

The standard age cut-off of 65 years used to evaluate patient's eligibility to ASCT is no longer valid, as chronological age and biological age may greatly differ, especially in the geriatric population. Aging is associated with modifications in the organ functions that may reduce the tolerability of therapy. The presence of comorbidities, frailty and disability should be considered when planning treatment as they may negatively impact the outcome of elderly patients. Comorbidity is defined by the presence of  $\geq 2$  concomitant medically diagnosed diseases. Frailty is a clinical entity characterized by the presence of  $\geq 3$  core elements of frailty: weakness, weight loss, low physical activity, poor endurance and slow gait speed. Disability is defined by limitations in carrying out common daily activities typical of independent living, due to physical or mental impairment.<sup>[23] and [24]</sup> All these factors are associated with an increased risk of therapy-related adverse events and consequently a high frequency of treatment discontinuation, affecting efficacy and long-term outcomes. Therefore, a careful clinical assessment of a patient's physical condition and clinical condition, including the evaluation of organ functions (cardiac, pulmonary, hepatic, gastrointestinal and renal) and the presence of frailty (poor endurance, weakness, low physical activity) and disability (need for help for household activities and personal care), should be routinely performed; this will enable to identify vulnerable elderly patients in whom reduced intensity regimens would increase treatment tolerability, reducing early discontinuation and optimizing efficacy. Patients without risk factors should receive full-dose treatment, whereas for patients with at least one risk factor (age  $\geq 75$  years, comorbidities, frailty or disability) a reduced intensity strategy is recommended.<sup>18</sup>

## **4. The grey zone and the role of reduced-intensity transplantation**

Patients older than 65 years of age, or younger with serious comorbidities, are generally considered unable to receive high-dose melphalan (200 mg/m<sup>2</sup>; Mel200) followed by ASCT. However, since chronological age does not always correspond to biological age, patients older than 65 years in excellent clinical condition may be able to tolerate ASCT. For very fit patients, reduced-dose of melphalan (100 mg/m<sup>2</sup>; Mel100) followed by ASCT can be an option. Two randomized studies comparing reduced-dose of melphalan with the standard MP reported conflicting results. In the first study, conducted in patients aged 65 to 70 years, Mel100 followed by ASCT led to longer median event-free survival (EFS) (28 months vs. 16.4 months;  $p < 0.001$ ) and OS (58 months vs.

37.2 months;  $p < 0.001$ ) compared with melphalan–prednisone (MP).<sup>25</sup> The second study compared MP, MP plus thalidomide (MPT) and Mel100 followed by ASCT in patients aged 65–75 years. MPT induced longer PFS and OS in comparison with both MP and Mel100, while no differences were observed between MP and Mel100.<sup>26</sup>

A German ongoing trial is assessing the role of lenalidomide and low-dose dexamethasone (Rd) as induction therapy followed by ASCT in patients 60–75 years of age considered eligible for transplantation. An intermediate dose of melphalan ( $140 \text{ mg/m}^2$ ) before ASCT has been adopted. Preliminary results confirmed that Rd is a feasible option in elderly patients, and stem cell mobilization was successful in 97% of patients.<sup>27</sup>

Bortezomib administered as induction before transplantation was associated with a high CR rate<sup>28</sup>; lenalidomide has shown a great efficacy and lacks neurotoxicity typical of its predecessor thalidomide.<sup>29</sup> These considerations provided the rationale for a phase II study that evaluated safety and efficacy of these novel agents in combination with a tandem reduced-intensity ASCT (Mel100), in patients aged 65–75 years.<sup>30</sup> Induction therapy consisted of bortezomib–doxorubicin–dexamethasone (PAD) for four 21-day cycles, lenalidomide–prednisone (RP) was administered as consolidation for four 28-day cycles, followed by lenalidomide maintenance (R), until progression. This sequential approach led to a progressive improvement of response, CR rate increased from 13% after PAD induction, to 38% after Mel100 and ASCT, to 71% during RP–R consolidation/maintenance. After a median follow-up of 36 months, the 3-year time to progression (TTP), PFS and OS were 73%, 66% and 85%, respectively. PFS was not significantly different in patients younger or older than 70 years ( $p = 0.16$ ), although it was slightly longer in younger patients. The most common grade 3–4 adverse events were thrombocytopenia (17%), neutropenia (10%), peripheral neuropathy (16%) and pneumonia (10%); lenalidomide given as consolidation/maintenance was well tolerated as it did not cause cumulative or persistent grade 3–4 neutropenia and thrombocytopenia. Different studies showed that the rate of responses induced by bortezomib and lenalidomide rise over the course of treatment, earlier with bortezomib and later with lenalidomide.<sup>[10] and [31]</sup>

The data above suggest that a sequential approach consisting of induction with effective drug combinations followed by reduced-dose ASCT and subsequent consolidation/maintenance therapy is a valuable therapeutic strategy for very fit elderly patients, or patients younger but not eligible for a high-dose melphalan and ASCT.

## 5. Active regimens

### 5.1. IMiDs-based regimens

In a randomized, phase III trial including newly diagnosed MM patients ineligible for transplantation, thalidomide combined with high-dose dexamethasone (TD) was compared with MP.<sup>32</sup> Although TD yielded to a higher overall response rate (ORR) (68% vs. 50%;  $p = 0.002$ ) than MP, no differences in terms of median 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 noted. In patients younger than 75 years, median OS was shorter with TD (44.6 vs. 57.9 months;  $p = 0.14$ ), and this difference was statistically significant in patients older than 75 years receiving TD (19.8 vs. 41.3 months;  $p = 0.071$ ). The incidence of early death, occurred within the first year, with TD twice as high as the one reported with MP (28% vs. 16%;  $p = 0.014$ ); in addition, non-myeloma related deaths were higher in the TD arm, and infection and cardiovascular events were the main causes. These data show that, despite the efficacy benefits observed with TD, this combination is too toxic for elderly patients and the lack of clinical benefit was mainly due to high dose dexamethasone. The choice of different steroids

(e.g. prednisone) and reduced-dose schedules (e.g. low-dose dexamethasone), may increase treatment tolerability and efficacy.

The combination MP had long been the standard of care for patients unsuitable for high-dose therapy and transplantation. Six randomized trials explored the efficacy of the addition of thalidomide (at different doses, 100–400 mg) to MP in newly diagnosed, transplant ineligible MM patients. In two French studies, IFM 99/06 and IFM 01/01, MPT regimen led not only to a higher ORR but also to longer PFS and OS than did MP.<sup>[26] and [33]</sup> Conversely, the Italian trial reported a higher ORR and a prolonged PFS in patients treated with thalidomide, but no OS differences were noted between MPT and MP.<sup>34</sup> Similar data were obtained in the Dutch/Belgian study: MPT prolonged PFS compared with MP, but no OS advantage was seen.<sup>35</sup> In two other trials performed by the Nordic and Turkish groups, ORR was higher in patients who were given thalidomide, but this advantage did not translate into longer PFS and OS in comparison with those who did not receive thalidomide.<sup>[36] and [37]</sup>

An efficacy meta-analysis of the six MPT trials including 1685 patients was conducted (Table 2).<sup>15</sup> Despite the heterogeneity of the trials, both for patient characteristics and thalidomide schedules (dose and duration of treatment), the addition of thalidomide to MP significantly prolonged both PFS and extended OS by 20% (6.6 months) compared to MP. A safety meta-analysis based on the same trials showed that 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 (Table 3).<sup>38</sup> Grade 3–4 non-hematologic adverse events occurred more frequently with MPT than MP (39% vs. 17%), in particular peripheral neuropathy (6–23%) and deep-vein-thrombosis (3–12%), and they were significantly increased in patients with poor performance status. These results showed the superiority of MPT over the old standard of care MP, and MPT is therefore regarded as new standard of care in transplant ineligible patients.

**Table 2.** Efficacy of selected treatments.

Regimen	Number	Schedule	CR (%)	PFS/EFS/TTP (%)	OS (%)
<i>IMiD-based</i>					
MPT <sup>15</sup>	815	M: 0.18 or 0.25 mg/kg day 1–7 or 1–4; P: 2 mg/kg day 1–4; T: 100–200 mg/day; M (0.18 mg) T (100 mg) for six 28-day cycles; M (0.25 mg) T (200 mg) for twelve 42-day cycles	14	43 at 24 months	50 at 39 months
CTDa <sup>39</sup>	426	C: 500 mg/week; T: 50 mg for 4 week increased every 4 weeks in 50-mg increments to maximum 200 mg/day; D: 20 mg/day days 1–4, 15–18 for six to nine 28-day cycles	13	50 at 13 months	50 at 33 months
RD <sup>42</sup>	223	R: 25 mg days 1–21; D: 40 mg days 1–4, 9–12, 17–20; for four 28-day cycles	5	50 at 19 months	75 at 24 months
Rd <sup>42</sup>	222	R: 25 mg days 1–21; d: 40 mg days 1, 8, 15, 22; for four 28-day cycles	4	50 at 25 months	76 at 24 months
MPR induction	152	M: 0.18 mg/kg days 1–4; P: 2 mg/kg days 1–4; R: 10 mg days 1–21 for nine 4-week cycles	10	50 at 31 months	70 at 36 months
R maintenance <sup>14</sup>		R: 10 mg days 1–21 until disease progression	33 ≥ VGPR		
<i>Bortezomib-based</i>					
VMP <sup>43</sup>	344	V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4), days 1, 8, 22, 29 (cycles 5–9); M: 9 mg/m <sup>2</sup> days 1–4; P: 60 mg/m <sup>2</sup> days 1–4 for nine 42-day cycles <sup>†</sup>	30	50 at 24 months	68 at 36 months
VCD <sup>49</sup>	33	V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11; C: 500 mg/m <sup>2</sup> days 1, 8; D: 40 mg days 1, 8, 15 for eight 21-day cycles	22	93 at 12 months	100 at 12 months
VD <sup>45</sup>	168	V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11; D: 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 (cycle 1–4), days 1, 2, 4, 5 (cycle 5–8) for 8 21-day cycles	33 CR/nCR	50 at 14 months	87 at 12 months
<i>IMiD plus bortezomib</i>					
VMPT induction	254	V: 1.3 mg/m <sup>2</sup> days 1, 8, 15, 22; M: 9 mg/m <sup>2</sup> days 1–4; P: 60 mg/m <sup>2</sup> days 1–4; T: 50 mg/day for nine 35-day cycles	38	56 at 36 months	89 at 36 months
VT maintenance <sup>10</sup>		V: 1.3 mg/m <sup>2</sup> every 14 days; T: 50 mg/day for 2 years	42		
VRD <sup>48</sup>	35	V: 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11; R: 25 mg days 1–14; D: 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 (or days 1, 8, 15) for eight 28-day cycles	37	75 at 18 months	97 at 18 months

MPT, melphalan–prednisone–thalidomide; CTDa, 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; VD, bortezomib–dexamethasone; VMPT, bortezomib–melphalan–prednisone–thalidomide; VT, bortezomib–thalidomide; VRD, bortezomib–lenalidomide–dexamethasone; CR, complete response; nCR, near complete response; VGPR, very good partial response; PFS, progression-free survival; EFS, event-free survival; TTP, time to progression; OS, overall survival.

<sup>†</sup> Alternative VMP schedule: V 1.3 mg/m<sup>2</sup> days 1, 8, 15, 22; M 9 mg/m<sup>2</sup> d 1–4; P 50 mg/m<sup>2</sup> d 1–4.



**Table 3.** Safety of selected treatments.

Regimen	Discontinuation due to AEs (%)	Grade 3–4 hematologic AEs		Grade 3–4 non-hematologic AEs		
		Neutropenia (%)	Thrombocytopenia (%)	PN (%)	VTE (%)	Infection (%)
<i>IMiD-based</i>						
MPT <sup>15</sup>	16–45	16–48	3–14	1–6	2–6	4–20
CTDa <sup>39</sup>	NA	15	NA	2.6/4 <sup>b</sup>	0	13
Rd <sup>42</sup>	19	20	5	2	12	9
MPR induction	16 <sup>a</sup>	35 <sup>a</sup>	11 <sup>a</sup>	0 <sup>a</sup>	3 <sup>a</sup>	11 <sup>a</sup>
R maintenance <sup>14</sup>	9 <sup>a</sup>	7 <sup>a</sup>	6 <sup>a</sup>	0 <sup>a</sup>	2	3 <sup>a</sup>
<i>Bortezomib-based</i>						
VMP <sup>43</sup>	15	40	37	13	1	10
VCD <sup>49</sup>	9	13	25	7	7	NA
VD <sup>45</sup>	24	NA	NA	23	8	10
<i>IMiD plus bortezomib</i>						
VMPT induction	23	38	22	8	5	13
VT maintenance <sup>10</sup>		3	<1	5	2	1
VRD <sup>48</sup>	19	9	6	7.5	4.5	2

MPT, melphalan–prednisone–thalidomide; CTDa, 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; VD, bortezomib–dexamethasone; VMPT, bortezomib–melphalan–prednisone–thalidomide; VT, bortezomib–thalidomide; VRD, bortezomib–lenalidomide–dexamethasone; AEs, adverse events; PN, peripheral neuropathy; VTE, venous thromboembolism; NA, not available.

<sup>a</sup> Grade 4 adverse event.

<sup>b</sup> Sensory neuropathy/motor neuropathy.

A phase III trial assessed the role of thalidomide in combination with different alkylating agent and steroid than those commonly used, respectively cyclophosphamide and dexamethasone, with an attenuated schedule (CTDa).<sup>39</sup> In this trial, 849 newly diagnosed MM elderly patients were randomly allocated to CTDa or MP. Of note, 75% of patients had an advanced stage disease (ISS II/III). CTDa resulted in higher ORR (63.8% vs. 32.6 p < 0.0001%), very good partial response (VGPR; 16.9% vs. 1.7%) and CR (13.1% vs. 2.4%) than MP. Despite a deeper response, no differences were noted in median PFS (13 months vs. 12.4 months, p = 0.1) and OS (33.2 months vs. 30.6 months, p = 0.24) between patients treated with CTDa or MP. CTDa induced a higher rate of grade 3–4 adverse events, especially peripheral neuropathy, constipation and DVT. However, patients with favorable FISH benefited more from CTDa and showed an improved OS.

Lenalidomide is a potent IMiD derived from thalidomide; this compound showed to be safe and effective in relapsed/refractory MM patients, as well as in newly diagnose MM patients.<sup>[40] and [41]</sup> In a phase III trial, lenalidomide plus high-dose dexamethasone (RD) was compared with lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed MM patients, both eligible and ineligible for ASCT.<sup>42</sup> Despite a higher ORR with RD (79% vs. 68.3%, p = 0.008), patients treated with Rd had a significantly longer 1-year OS (87% vs. 96%, p < 0.001). The survival benefit associated with Rd was particularly evident in patients older than 65 years of age (1-year OS: 83% with RD vs. 94% with Rd). In a landmark analysis, 3-year OS for patients who continued treatment until progression or intolerance was 79%. RD was associated with a worse toxicity profile, with a higher incidence of grade 3–4 adverse events, particularly DVT (26% vs. 12%) and infections (16% vs. 9%). Early deaths were also significantly higher with the high-dose dexamethasone (5% vs. 0.4%, p < 0.003). Consequently, discontinuation rate was higher with RD than with Rd (27 % vs. 19%). In a subgroup analysis including patients older than 70 years of age, the 3-year OS was 61% with RD and 73% with Rd, and the incidence of grade 3–4 non-hematologic adverse events was 78% and 59%, respectively. Based on these results, Rd regimen can be considered a valid therapeutic option for elderly newly diagnosed MM, and low-dose dexamethasone (40 mg weekly) should be preferred in this setting.

## 5.2. Bortezomib-based regimens

The international phase III VISTA trial assessed the role of bortezomib in combination with melphalan and prednisone (VMP), with the standard MP.<sup>43</sup> VMP led to higher ORR and CR rate, which translated into longer TTP (24 months vs. 16.6 months;  $p < 0.001$ ) and OS (56.4 vs. 43.1;  $p = 0.0004$ ), with a 31% reduced risk of death. These results were confirmed in different subgroups of patients, included patients older than 75 years, but not in those with high-risk cytogenetic profile. VMP was more toxic than MP, with grade 3–4 adverse event rate of 91% and a discontinuation rate of 34%; the most frequent grade 3–4 toxicities were neutropenia (40%), thrombocytopenia (37%), peripheral neuropathy (17%) and infections (10%). When bortezomib schedule was changed from twice-weekly (cycles 1 to 4) to once-weekly (cycles 5 to 8), the rate of adverse events decreased in the VMP group, with no negative impact on outcome. Therefore, VMP today is considered one of the standard approaches for elderly MM patients, and the once-weekly bortezomib schedule is a valid alternative strategy.<sup>[10] and [44]</sup>

In another phase III trial including newly-diagnosed elderly MM patients, VMP was compared with bortezomib–dexamethasone (VD) and bortezomib–thalidomide–dexamethasone (VTD).<sup>45</sup> In this study median age was 72–74.5 years, more than 2/3 of patients had an advanced disease (ISS stage II/III) and approximately 50% of them presented with a Charlson comorbidity index  $\geq 1$ . 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 noted. Grade 3–4 adverse events and discontinuation rate were higher in patients treated with VTD. These data support the use of lower doses of standard regimens or a 2-drug combination, rather than a more intense treatment, in very elderly patients, or in younger patients with heart, lung, liver, or renal dysfunctions, or in those needing help for household care and personal care.

Promising results came from a phase II study combining bortezomib with cyclophosphamide and dexamethasone (VCD) in newly diagnosed MM patients, both eligible and not eligible for ASCT.<sup>[46] and [47]</sup> In the first cohort including 33 patients, twice-weekly bortezomib was administered; in the second cohort including other 30 patients, once-weekly bortezomib was given. After 4 cycles of induction, the ORR was 90% and the CR/near Cr (nCr) rate was 41%, with no differences between the once-weekly and the twice-weekly schedule in terms of response. However, the rate of grade 3–4 adverse events was lower with the once-weekly group.

## 5.3. Bortezomib plus IMiDs-based regimens

The proteasome inhibitor bortezomib has been combined with IMiDs, thalidomide and lenalidomide, as induction therapy for newly diagnosed MM patients. In the Spanish PETHEMA trial, 260 patients older than 65 years or otherwise ineligible for ASCT, were randomized to receive 6 cycles of either bortezomib–thalidomide–prednisone (VTP) or VMP induction; a gentler approach with once-weekly bortezomib was used from cycle 2 of both regimens.<sup>44</sup> Both VTP and VMP led to high ORR rate (81% and 80%, respectively) and CR rate (28% and 20%, respectively). VTP regimen was more toxic than VMP, inducing a higher rate of serious adverse events, particularly cardiac events, (31% vs. 15%;  $p = 0.01$ ) and discontinuation rate (17% vs. 12%;  $p = 0.03$ ). VMP was associated with a higher rate of grade 3–4 hematologic adverse events compared to VTP, in particular neutropenia (39% vs. 22%;  $p = 0.008$ ) and thrombocytopenia (27% vs. 12%;  $p < 0.001$ ). The once-weekly schedule of bortezomib adopted after the first cycle, reduced the rate of grade 3–4 peripheral neuropathy and gastrointestinal symptoms compared with the twice-weekly schedule, without affecting efficacy.<sup>43</sup> Therefore, VMP with a once-weekly schedule of bortezomib should be preferred to VTP as induction for elderly MM patients.

A phase I/II trial evaluated the safety and efficacy of the combination of bortezomib–lenalidomide–dexamethasone (VRD) in both young and elderly newly diagnosed MM patients.<sup>48</sup> The first phase of this trial established the maximum planned dose of bortezomib (1.3 mg/m<sup>2</sup>), lenalidomide (25 mg) and dexamethasone (20 mg cycle 1–4; 10 mg cycle 5–8). Patients who did not proceed to ASCT, received eight 3-week cycles of VRD. This regimen proved to be highly effective, leading to a PR rate of 100% and a CR/nCR rate of 37%. VRD was also well tolerated: the most frequent grade 3–4 adverse events were neutropenia (9%) and thrombocytopenia (6%); in addition, no grade 4 peripheral neuropathy was reported. After 18 months from start of treatment, PFS was 75% and OS was 97%.

A subsequent phase II trial explored the role of bortezomib–cyclophosphamide–dexamethasone (VCD), compared to VRD and VRD plus cyclophosphamide (VDCR) in both transplant eligible and ineligible newly diagnosed MM patients.<sup>49</sup> All regimens were effective: ORR and CR rate were 75% and 22% with VCD, 85% and 24% with VRD, and 88% and 25% with VDCR. These responses translated into similar 1-year PFS (97%, 68%, 83%, respectively) and 1-year OS (100%, 100%, 92%, respectively). The 4-drug regimen led to higher rate of grade 3–4 adverse events, particularly neutropenia, and discontinuation rate, and its efficacy is thus comparable to the 3-drug regimens.

## 6. Continuous treatment

Despite the improvement reported with novel agents containing therapies, residual disease is always present. Therefore, a continuous treatment to keep residual disease under control is an effective strategy. Recently, the international MM015 phase III study assessed the role of lenalidomide given as maintenance.<sup>14</sup> Four-hundred and fifty-nine patients were randomized to receive induction therapy consisting of nine 4-week cycles of MPR, followed by either lenalidomide maintenance or placebo, or standard MP. Lenalidomide was administered at the dose of 10 mg daily, both at induction and during maintenance. The median age at enrollment was 71 years and half of patients had advanced disease (ISS III). The ORR was higher with MPR-R and MPR compared with MP (77%, 68%, 50%, respectively). MPR-R significantly improved median PFS in comparison with MPR and MP (31 months vs. 14 months vs. 13 months;  $p < 0.001$ ). Of note, MPR-R reduced the risk of progression by 51% and 60% compared with MPR and MP, respectively. This advantage was more evident in patients younger than 75 years, in whom MPR-R significantly improved PFS compared to MPR and MP. In a landmark analysis from start of maintenance, lenalidomide maintenance significantly prolonged PFS as compared to placebo, regardless of age (26 months with MPR-R vs. 7 months with MPR-placebo,  $p < 0.001$ ), with a 66% reduced risk of progression. The most frequent hematologic grade 4 adverse events were neutropenia (35% with MPR-R, 32% with MPR, 8% with MP), and thrombocytopenia (11%, 12%, and 4%, respectively). Infections were the most frequent non-hematologic grade 3 adverse events (9% with MPR-R, 13% with MPR, 7% with MP), while the rate of deep vein thrombosis (DVT) was low (1%, 4%, and 1%, respectively) because thromboprophylaxis with aspirin was used. Maintenance therapy was well tolerated, as the rate of new or worsened grade 3–4 adverse events lowered (0 to 6%).

The role of continuous treatment with bortezomib has been assessed in two different trials. In the Spanish PETHEMA trial, patients were randomized to receive bortezomib maintenance (standard schedule day 1, 4, 8, 11 administered every 3 months) with either thalidomide (VT) or prednisone (VP), after VTP or VMP induction.<sup>17</sup> After 38 months from the initiation of maintenance, both VT and VP increased the CR rate achieved after induction (up to 46% with VT and up to 39% with VP) without significantly adding to toxicity (grade 3–4 neutropenia: 1% in the VT arm vs. 0% in the VP arm; grade 3–4 peripheral neuropathy: 9% vs. 3%, respectively). PFS was longer with VT

compared with VP (39 months vs. 32 months,  $p = 0.1$ ), 5-years OS was slightly prolonged with VT (69% vs. 50%,  $p = 0.1$ ).

In the Italian study, bortezomib was tested as maintenance in combination with thalidomide (VT), after nine 6-week cycles of VMPT induction, and compared with nine 6-week cycles of VMP induction followed by placebo. During maintenance, bortezomib was given at the dose of  $1.3 \text{ mg/m}^2$ , every 14 days for up to two years or until disease progression.<sup>[10] and [13]</sup> After 47 months of follow-up, 5-year OS was 59.3% for VMPT–VT and 45.9% for VMP, with a 26% reduced risk of death in favor of VMPT–VT. The survival benefit associated with VMPT–VT was more evident in patients younger than 75 years (67.8% vs. 49.4%;  $p = 0.001$ ) and in patients who achieved CR after induction (81.4% vs. 48.2%;  $p = 0.006$ ). On the contrary, no advantage with VMPT–VT was observed in patients older than 75 years in comparison with VMP. In a pre-specified landmark analysis at the start of maintenance, 4-year OS was 64.6% in the VMPT–VT arm and 49.7% in the VMP arm, with a 33% reduced risk of death in favor of VMPT–VT. VT maintenance was well tolerated: the incidence of grade 3–4 adverse events was low, with peripheral neuropathy rate of 7%. No OS differences were noted at relapse, showing that VMPT–VT did not negatively impact on efficacy of salvage therapy. When bortezomib schedule was changed from twice- to once-weekly administration, the incidence of non-hematologic grade 3–4 adverse events decreased from 51% to 36% ( $p = 0.003$ ), particularly peripheral neuropathy (from 16% to 3%,  $p < 0.001$ ).<sup>[10] and [50]</sup> This modification did not affect efficacy, as the cumulative delivered dose of bortezomib was similar.<sup>50</sup> Therefore, VMPT–VT with once-weekly bortezomib seems a valid alternative for elderly patients, especially for those 65–75 years of age.

Beside the weekly schedule, the recent use of subcutaneous administration rather than the intravenous administration showed to be a feasible and equally effective option.<sup>51</sup> Therefore, subcutaneous bortezomib may be considered for prolonged treatment.

These data confirm that a sequential approach including maintenance with either lenalidomide alone or bortezomib in combination with thalidomide is safe and effective in elderly patients. This strategy prolongs PFS with an acceptable toxicity rate, and also extends OS.

## **7. Treatment options for fit and unfit patients**

As previously reported, in presence of  $\geq 1$  risk factor (age  $\geq 75$  years, presence of comorbidities, frailty or disability), dose reductions are recommended (Table 4). In case of grade 3–4 adverse events occurring during treatment, therapy should be withheld until the toxicity resolves; therapy could then be restarted at the beginning of the next cycle at a lower dose level.<sup>1</sup> Thalidomide may be reduced from 200 mg to 100 mg or even 50 mg per day; lenalidomide from 25 mg to 15–10 mg on days 1–21; once weekly administration of bortezomib at the dose of  $1.3 \text{ mg/m}^2$ , or even  $1.0 \text{ mg/m}^2$ , instead of the standard twice-weekly, should be considered; the dose of melphalan may be decreased from 0.25 mg to 0.18 mg or even 0.13 mg per kilogram of body weight on days 1–4; low-dose schedule dexamethasone (40 mg daily on days 1,8,15,22) should be preferred to the high-dose schedule, and may be further decreased to 20 mg weekly.

**Table 4.** Suggested dose adjustments.

Drug	Initial/standard dose	Reduced dose	Further reduction if needed
Dexamethasone	40 mg/d days 1,8,15,22 every 4 weeks	20 mg/d days 1,8,15,22 every 4 weeks	10 mg/d days 1,8,15,22 every 4 weeks
Melphalan	0.25 mg/kg or 9 mg/m <sup>2</sup> d 1–4 every 4–6 wks	0.18 mg/kg or 7.5 mg/m <sup>2</sup> d 1–4 every 4–6 wks	0.13 mg/kg or 5 mg/m <sup>2</sup> d 1–4 every 4–6 wks
Thalidomide	100 mg/d	50 mg/d	50 mg qod
Lenalidomide (plus dexamethasone)	25 mg/d days 1–21 every 4 weeks	15 mg/d days 1–21 every 4 weeks	10 mg/d days 1–21 every 4 weeks
Lenalidomide (plus melphalan–prednisone)	10 mg/d days 1–21 every 4 weeks	5 mg/d days 1–21 every 4 wks	5 mg qod days 1–21 every 4 weeks
Bortezomib	1.3 mg/m <sup>2</sup> twice weekly days 1,4,8,11 every 3 wks	1.3 mg/m <sup>2</sup> once weekly days 1,8,15,22 every 5 weeks	1.0 mg/m <sup>2</sup> once weekly days 1,8,15,22 every 5 weeks

The standard of care for elderly patients consists of a 3-drug regimen (VMP, VCD or VRD). In patients aged 65–75 years, the 4-drug regimen VMPT can be adopted, as it significantly increased the CR rate compared with VMP (38% vs. 24%;  $p < 0.001$ ).<sup>10</sup> If an oral treatment is required, IMiD-containing regimens are recommended, such as the standard MPT or Rd. Recently, maintenance therapy with lenalidomide or VT improved PFS, but longer follow-up is needed to detect an OS advantage. Lenalidomide maintenance proved to be highly effective, regardless of age, and is a feasible option, especially for its oral administration.<sup>14</sup> VT maintenance, after bortezomib-based induction, is a valuable option for elderly patients, and the once-weekly administration has improved its tolerability.<sup>10</sup>

Unfit patients should receive a gentler approach associated with a low rate of adverse events and treatment discontinuation. In this setting, 2-drug combinations such as VD and Rd are recommended. VD proved to be less toxic and equally effective as VMP and VTD in an elderly and frail population.<sup>45</sup> Similarly, Rd was better tolerated than RD and proved to be even more effective, owing to the low-dose schedule of dexamethasone, both in young and elderly patients.<sup>42</sup>

A phase II trial tested the role of lenalidomide–prednisone (RP) induction, followed by consolidation with MPR and subsequent RP maintenance therapy in elderly patients. Median age was 75 years and 60% had at least 1 comorbidity.<sup>52</sup> This strategy led to a significant reduction in the rate of grade 4 hematologic adverse events associated with MPR. These results suggest that an initial gentler approach with a 2-drug regimen as induction, when toxicity rate is higher, followed by a more intense treatment with a 3-drug combination is an effective option for vulnerable elderly patients.

## 8. Treatment strategy at relapse

Patients with relapsed MM experience disease progression after achieving maximal response to induction treatment, whereas refractory patients either do not respond to therapy or progress within 60 days from last treatment.<sup>53</sup> The choice of therapy at relapse should be based on quality and duration of response obtained with the previous therapy. A profound cytoreduction followed by a sustained response (longer than 24 months at diagnosis and 6–12 months at relapse) suggests to retreat with the same combination previously administered; in presence of short-term remission duration (less than 6 months) or progression during initial therapy, a different treatment regimen should be adopted.<sup>54</sup> In presence of a biochemical relapse, that is  $\geq 25\%$  increase in the serum or urine protein and  $\geq 0.5$  mg/dL without symptoms, early treatment may keep the recurrence of the disease under control and delay clinical relapse.

Two-drug regimens consisting of dexamethasone plus bortezomib<sup>[55] and [56]</sup> or lenalidomide<sup>[40] and [57]</sup> are the treatments of choice for relapsed patients. In the phase III APEX trial conducted in patients relapsed after at least 1 prior therapy, bortezomib alone showed to be superior to dexamethasone in terms of ORR (38% vs. 18%;  $p < 0.001$ ), TTP (6.2 vs. 3.5 months;  $p < 0.001$ ) and 1-year OS (80% vs. 60%;  $p = 0.003$ ).<sup>58</sup> An updated analysis showed an increase in ORR with bortezomib (43%) and confirmed the survival advantage with bortezomib over dexamethasone (29.8 vs. 23.2 months;  $p = 0.27$ ), although 60% of patients in the dexamethasone arm were allowed to receive bortezomib.<sup>59</sup>

Two phase III randomized trials, MM09 and MM010, enrolled relapsed/refractory patients after 1 to 3 lines of prior therapy, and showed the superiority of RD over dexamethasone alone.<sup>[29] and [40]</sup> RD resulted in higher ORR (60% vs. 20–24%) and longer median TTP (11 vs. 4.7 months) and median OS (29.6 vs. 20.6 months) compared with dexamethasone. These results led to the approval of lenalidomide for relapsed/refractory MM patients both in USA and Europe.

When the treatment proves to be ineffective, a third drug (melphalan, cyclophosphamide or doxorubicin) may be added to enhance efficacy. In addition, bortezomib-based regimens should be preferred in relapsed patients with renal failure or previous deep-vein thrombosis.<sup>60</sup> Patients previously treated with a thalidomide-containing regimen benefit from treatment with lenalidomide, although efficacy and survival may be lower.<sup>61</sup> Because of the lack of neurotoxicity, lenalidomide is suggested in case of concomitant peripheral neuropathy.<sup>60</sup>

The second generation proteasome inhibitor carfilzomib has shown a remarkable activity in relapsed/refractory MM patients, with a low rate of hematological AEs and the absence of neurotoxicity.<sup>62</sup> The pivotal PX-171-003-A0 and PX-171-003-A1 studies tested single-agent carfilzomib in MM patients previously exposed to bortezomib and at least one IMiD.<sup>[63] and [64]</sup> The ORR was 24% and the duration of therapy was 7.4 months. These data led to the FDA approval of carfilzomib as a single agent in relapsed/refractory MM patients after  $\geq 2$  lines of previous therapy, including bortezomib and one IMiDs. Carfilzomib was also tested in less heavily pre-treated and bortezomib-naïve relapsed/refractory MM, showing ORR of 42–52%.<sup>65</sup> Recently, different doses of carfilzomib, lenalidomide and low-dose dexamethasone (CRd) were investigated in the relapse setting, resulting in an ORR of 75% at the highest dosage.<sup>66</sup> The ongoing, phase III, randomized ASPIRE trial, is assessing the role of CRd in comparison with Rd in relapse/refractory MM patients.

Pomalidomide, a new immunomodulatory drug, has recently shown high efficacy in patient's refractory to bortezomib and IMiDs. Clinical trials evaluating the efficacy of the dexamethasone and pomalidomide (dose, 2–4 mg) in patients relapsed and/or refractory to lenalidomide, bortezomib or both, reported a PR rate of 32–35% and a median PFS of 4.6–6.3 months. The addition of a third drug (cyclophosphamide) to the combination of prednisone and pomalidomide (PCP) increased at least PR rate (54%) and prolonged PFS (52% at 1 year).<sup>67</sup> In a heavily pre-treated population (median of 5 lines of previous therapy), the addition of clarithromycin to pomalidomide–dexamethasone induced a PR rate of 32% and a median PFS of 8.2 months.<sup>68</sup>

A new generation of novel agents is currently under evaluation in relapsed/refractory MM patients: anti-CS1 monoclonal antibody (elotuzumab plus lenalidomide- or bortezomib–dexamethasone), oral proteasome inhibitor MLN9708, anti-CD138 antibody BT062 and histone deacetylase inhibitors vorinostat and panobinostat. Future trials will validate the role of these agents.

## 9. Management of adverse events

Prompt action with appropriate dose reductions is needed to manage adverse events, more frequent in elderly patients.

## **9.1. Hematologic toxicity**

### **9.1.1. Anemia**

Anemia, typically due to bone marrow infiltration of MM cells, occurs in approximately two-thirds of newly-diagnosed MM patients.<sup>69</sup> Erythropoiesis-stimulating agents (ESAs) are recommended for patients receiving chemotherapy to improve quality of life and reduce the risk of transfusion, particularly in patients with impaired renal function and those with low hemoglobin levels despite responding to therapy. ESAs should be started when hemoglobin level drops below 10 g/dl; in patients with impaired cardiac function or difficulty in performing daily-life activity, treatment can be started earlier. Hemoglobin level should be approximately 11–12 g/dl, as higher levels may increase the risk of cardiac events; when ESAs are administered in patients treated with multi-drug regimens containing thalidomide or lenalidomide, the risk of thromboembolic events may increase.<sup>70</sup>

### **9.1.2. Neutropenia**

Neutropenia increases the risk of severe infection, a major cause of death in MM patients, and is generally related to chemotherapy. The risk of severe neutropenia (grade 3–4) during treatment is related to patient characteristics, baseline absolute neutrophil count (ANC), disease stage and type of chemotherapy administered (3-drug regimens including lenalidomide plus alkylators or doxorubicin are at high risk).<sup>71</sup> Granulocyte-colony stimulating factor (G-CSF) can be used to manage severe neutropenia, both as primary prophylaxis or reactive treatment, thus allowing patients to stay on therapy for a longer period. Patients receiving high-risk therapies (expected grade 3–4 neutropenia rate > 50%) and those receiving intermediate- or low-risk regimens (expected grade 3–4 neutropenia rate < 50%) with additional risk factors, should be given G-CSF as primary prophylaxis. In patients receiving intermediate- or low-risk regimens with no other risk factor, G-CSF should be used only after occurrence of grade 3/4 neutropenia. If ANC rises to > 1000 cells/mL, therapy can be resumed and no dose modifications are needed. In case of persisting severe neutropenia despite G-CSF, therapy should be delayed until ANC recovery (> 1000 cells/mL) and then restarted with appropriate dose reductions.<sup>71</sup>

### **9.1.3. Thrombocytopenia**

Alkylating and novel agents, especially bortezomib and lenalidomide, are frequently associated with thrombocytopenia.<sup>72</sup> When platelet count falls below < 25,000/mm<sup>3</sup> (grade 4 thrombocytopenia) therapy should be withheld until thrombocytopenia resolves to at least grade 2 (platelet count ≥ 50,000/mm<sup>3</sup>). Therapy could be then reintroduced with appropriate dose reductions of myelotoxic drugs.

## **9.2. Non-hematologic toxicity**

### **9.2.1. Peripheral neuropathy**

Peripheral neuropathy (PN) is a common side effect observed in patients receiving thalidomide or bortezomib. It may frequently present as sensory neuropathy, neuropathic pain or, less frequently, as motor or autonomic neuropathy. Since PN is associated with the duration of drug exposure and no effective prophylactic measures are currently available to prevent it, dose reductions and

temporary discontinuation are fundamental.<sup>73</sup> Patients must be advised about signs and symptoms related to PN in order to promptly recognize and report them to physician. Different strategies have been recently assessed to decrease the rate of PN related to bortezomib. Phase III trials reported that the once-weekly schedule of bortezomib significantly decreased the rate of all grade PN and grade 3–4 PN compared to the twice-weekly schedule, without affecting efficacy.<sup>[10], [13] and [44]</sup> Recently, a phase III study showed that the subcutaneous administration of bortezomib significantly reduced the rate of all grades PN and grade  $\geq 3$  PN in comparison with the intravenous administration, without negatively affecting responses and survival.<sup>51</sup> When grade 1 PN without pain occurs, bortezomib dose should be decreased by one dose level or the schedule changed from twice- to once-weekly administration; if PN occurs during once-weekly bortezomib, the dose should be reduced by one dose level. In case of grade 2 PN, bortezomib dose should be decreased or changed to once-weekly administration; for patients receiving once-weekly bortezomib, dose reduction or temporary interruption should be considered. If neuropathy resolves to at least grade 1, bortezomib can be restarted at reduced dose and administered once-weekly. If grade 3–4 PN occurs treatment should be discontinued.<sup>74</sup> For patients receiving thalidomide, when grade 2 PN occurs, halving thalidomide dose is an effective strategy; when grade  $\geq 3$  PN occurs, treatment with thalidomide should be discontinued and may be resumed if PN improves to grade 1 after appropriate dose reduction.<sup>75</sup>

### **9.2.2. Venous thromboembolism**

Patients with MM have an increased risk of venous thromboembolism (VTE). Patient-related risks (age, obesity, inherited thrombophilia, history of VTE, immobilization, surgery, central venous catheter, comorbidity, ESAs treatment), myeloma-related risks (myeloma itself and hyperviscosity) and the type of chemotherapy performed should guide the choice of the most appropriate antithrombotic prophylaxis. Thalidomide<sup>76</sup> and lenalidomide<sup>77</sup> alone do not increase the risk of VTE. However, the addition of high-dose dexamethasone or doxorubicin to thalidomide or lenalidomide, or their administration in multi-drug chemotherapy, significantly increased the VTE risk.<sup>[35], [42] and [78]</sup> In two randomized trials including patients receiving thalidomide- and lenalidomide-based regimens, aspirin and low-molecular weight heparin (LMWH) showed equal efficacy in reducing VTE. In low-risk patients (none or only one risk factor) receiving thalidomide or lenalidomide, prophylaxis with aspirin is recommended; in high-risk patients ( $\geq 2$  risk factors) or in those treated with high-dose dexamethasone, doxorubicin or multi-drug chemotherapy, LMWH or full-dose warfarin should be used.<sup>78</sup>

### **9.2.3. Renal failure**

Renal failure occurs in 20–40% of MM patients at diagnosis, due to damages related to free-light chains and concomitant factors, such as hyperuricaemia, hypercalcemia, dehydration and infections; nephrotoxic drugs may further impair renal function. Early intervention consists of reducing the load of free-light chains, removing precipitating factors. High-dose dexamethasone is able to rapidly reduce the load of light chains and to improve renal function.<sup>79</sup> Pharmacokinetic of bortezomib and thalidomide are not affected by renal dysfunction. Bortezomib is well tolerated and highly active in patients with renal failure, being able to reverse renal impairment.<sup>80</sup> Bortezomib plus dexamethasone is the treatment of choice in this setting.<sup>81</sup> Lenalidomide is primarily excreted by kidneys, hence its dose must be adjusted based on creatinine clearance (CLcr).<sup>82</sup> When CLcr level is between 30–60 mL/min, lenalidomide recommended dose is 10 mg per day; if CLcr level is below 30 mL/min, lenalidomide should be given at the dose of 15 mg every other day in patients not requiring dialysis or at the dose of 5 mg on the day of dialysis in patients under dialysis. Hematologic function should be closely monitored.<sup>83</sup>

### **9.2.4. Infections**



Bone marrow infiltration by MM cells and myelotoxic chemotherapy increase the risk of severe infections (grade 3–4). In patients treated with novel agent-based regimens, the rate of severe infections varies between 7% and 14%.<sup>[10], [16], [38] and [42]</sup> Bortezomib administration may lead to the reactivation of herpes zoster virus<sup>79</sup>; in patients receiving bortezomib, prophylaxis with acyclovir is recommended<sup>84</sup>. For patients treated with corticosteroids or myelotoxic drugs, or those with a higher risk of severe infections, routine antibiotic prophylaxis is suggested during the first cycles. Early recognition of fever or signs and symptoms of infection should lead to prompt administration of broad spectrum antibiotics.

### 9.2.5. Bone disease

Skeletal involvement due to MM cells infiltration occurs in 80% of MM patients, causing pathological fractures and pain, spinal cord compression and hypercalcemia.<sup>1</sup> Biphosphonates, such as oral clodronic acid and intravenous pamidronic and zoledronic acid, are indicated to prevent bone disease. Zoledronic acid reduced skeletal-related events more than clodronic acid, with the advantage of longer PFS and OS.<sup>[85] and [86]</sup> Both zoledronic and pamidronic acid are effective in decreasing skeletal-related events<sup>87</sup>; recently, no efficacy difference was seen with pamidronate administered at either 30 or 90 mg. In patients with mild to moderate renal impairment (30–60 mL/min of creatinine clearance), dose reductions of zoledronic acid are recommended; in case of severe renal impairment (< 30 mL/min of creatinine clearance), pamidronic acid should be preferred.<sup>88</sup> Therapy with bisphosphonates should last approximately 2 years to limit the risk of osteonecrosis of the jaw.<sup>89</sup> Bone pain can be managed both pharmacologically and with local, fractionated radiotherapy. Analgesia should be firstly provided with non-opioid drugs (avoiding non-steroidal antiinflammatory drugs); if pain persists, opioid drugs should be used. Lytic lesions causing bone instability may be treated with preventive orthopedic stabilization, vertebroplasty may be indicated to reduce pain due to vertebral fractures.

## 10. Conclusions

The combination of novel agents, bortezomib and IMiDs, with conventional chemotherapy has deeply improved outcome in elderly patients. The attainment of a profound and sustained cytoreduction proved to be a predictor of longer outcome. An induction regimen associated with a high probability of CR, and a continuous therapy with IMiDS or proteasome inhibitors prolong remission duration and improve outcome. A careful assessment of comorbidities, frailty and disability is essential to optimize treatment efficacy and reduce the frequency of adverse events. For very fit elderly patients, a sequential approach consisting of induction regimens incorporating novel agents, followed by reduced intensity ASCT and consolidation/maintenance is a valid therapeutic option. The standard of care for elderly patients not eligible for transplantation includes regimens with proteasome inhibitors, IMiDs, corticosteroids or alkylating agents in different combinations. In elderly unfit patients, a gentler approach with 2-drug regimen and a lower dose intensity should be adopted to avoid discontinuation and maximize treatment efficacy. In the relapse setting, the new proteasome inhibitor carfilzomib and the third generation IMiD pomalidomide, showed a great efficacy in patients relapsed/refractory to induction treatments. Newer agents, such as new oral proteasome inhibitors, monoclonal antibodies, and histone deacetylase inhibitors are currently under evaluation in clinical trials.

## Conflicts of interest

Dr. Palumbo reports receiving consultancy fees and honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millenium, Onyx. Roberto Mina has no conflicts of interest.

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