Current treatment options for elderly patients with multiple myeloma: clinical impact of novel agents

Multiple myeloma is a plasma cell malignancy that typically affects older individuals, with a median age of presentation being 67–70 years. The treatment paradigms for myeloma have changed dramatically in the past decade as a result of the introduction of several new drugs, as well as more widespread use of high-dose chemotherapy and stem cell transplantation. However, transplant is not an option for a significant proportion of the older patients, owing to either age or comorbidities. In recent years, judicious combination of the new drugs with existing therapies has led to improved outcomes in this group of patients. This article serves to highlight the modern treatment strategies incorporating novel agents, role of maintenance therapy and feasibility of stem cell transplantation in elderly patients with multiple myeloma.

Sumit Madan[1] & Shaji Kumar[†1]

[1]Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
[†]Author for correspondence:
Tel.: +1 507 266 0523
Fax: +1 507 266 4972
kumar.shaji@mayo.edu

Monoclonal gammopathies comprise a group of disorders characterized by the neoplastic proliferation of a single clone of plasma cells. Multiple myeloma (MM; plasma-cell myeloma, myelomatosis, Kahler's disease) is the prototype of monoclonal plasma cell disorders, accounting for 1% of all newly diagnosed cancers and 10% of all hematologic malignancies. It is the second most frequent hematologic malignancy after lymphoma, with an annual incidence of approximately four to five per 100,000 individuals. It afflicts more than 20,000 new people per year, and results in an estimated 10,000 deaths per year in the USA [1].

Diagnosis & indications for therapy in myeloma

Monoclonal gammopathies are characterized by the presence of an M protein, which appears as a dense band on agarose gel serum protein electrophoresis, and as a tall, narrow spike in the γ, β or β–γ region when converted to a densitometer tracing (M spike). The size of the M spike provides a useful measure of the clonal plasma cell burden; it is typically smaller in monoclonal gammopathy of undetermined significance (MGUS) and higher in smoldering MM (SMM) and symptomatic MM. The diagnostic criteria for MGUS, SMM and MM are listed in Table 1 [2]. Both MGUS and SMM are asymptomatic conditions, but assume significant clinical importance owing to their risk of progression to MM, an incurable malignancy.

The common tetrad used to define the end organ damage in MM is hypercalcemia, renal failure, anemia and lytic bone lesions (CRAB).

Although MGUS, SMM and MM represent a progressive continuum of the same disease process, each disease stage should be differentiated and identified in order to ascertain the need for therapy. Thus, while patients with symptomatic MM need active therapy, MGUS and SMM patients do not require any form of therapy at present, and only regular lifelong follow-up is required to ascertain the need for therapy before end-organ damage develops [3].

Special considerations in management of myeloma in the elderly

The incidence rates of MM increases with advancing age. The aging general population, constantly improving investigational techniques for ascertainment of MM and increased disease awareness among the healthcare providers has contributed to MM being more commonly diagnosed in the general population, especially in the elderly. MM is usually diagnosed in the middle-aged or elderly (median age at diagnosis ~70 years), with a quarter of patients older than 80 years and only a small minority (approximately 2%) under the age of 40 years at diagnosis [4,5]. Given the strong correlation of MM with advancing age, a considerable proportion of MM patients are elderly with decreased performance status and coexisting medical conditions (e.g., hypertension, diabetes mellitus, heart disease, other malignancy or chronic obstructive pulmonary disease), which alters their capacity to tolerate treatment. In addition, they are likely to suffer reduced organ function (renal and/or hepatic insufficiency), which

Table 1. Diagnostic criteria for monoclonal gammopathy of undetermined significance, smoldering multiple myeloma and multiple myeloma.

Disease stage	Diagnostic criteria
Monoclonal gammopathy of undetermined significance	Serum M protein <3 g/dl BMPC <10% Very low or no monoclonal light chains (Bence–Jones proteins) in urine Absence of CRAB features
Smoldering multiple myeloma	Serum M protein (IgG or IgA) ≥3 g/dl and/or BMPC ≥10% Absence of CRAB features 0
Multiple myeloma	Presence of a serum and/or urine M protein BMPC ≥10% Presence of CRAB features directly attributable to the monoclonal plasma cell disorder

BMPC: Bone marrow plasma cell; CRAB: Hypercalcemia, renal failure, anemia and lytic bone lesion.

can remarkably modify the pharmacokinetics of chemotherapy drugs, further increasing the risk of toxic side effects requiring dose reduction or discontinuation.

High-dose therapy with autologous peripheral blood stem-cell transplantation (ASCT) remains an effective treatment for MM resulting in high rates of complete response and prolonged overall survival, and is usually incorporated in the therapeutic paradigm (either upfront or at disease relapse) in patients under the age of 65 years and in selected patients older than 65 years [6–8]. Unfortunately, a sizeable number of older patients and/or those with coexisting illnesses are either unable to tolerate the toxicity or fail to adequately mobilize progenitor stem cells, and are thus rendered ineligible to undergo this procedure. Therefore, nontransplant chemotherapy options have become particularly important in this group of patients.

Treatment approaches

Until recently, despite poor efficacy and low complete response rates that rendered a modest median time to progression of 18 months and an overall survival of 2–3 years [9–12], the combination of melphalan + prednisone (MP) was still the most widely accepted treatment option of elderly MM patients, mainly because of its relatively safe toxicity profile. Furthermore, in a meta-analysis of 27 randomized trials, no difference was seen in the overall survival of MM patients treated with combination of cytotoxic drugs or MP, although response rates were higher with combination chemotherapy [10]. On the contrary, more complex combinations with alkylating agents and dexamethasone-based regimens often increased toxicity compared with MP in elderly MM patients [10,11]. However, the emergence of novel chemotherapeutic agents (i.e., thalidomide, lenalidomide and bortezomib) has altered the treatment of

MM, resulting in substantial improvement in response rate, time to progression and overall survival (TABLE 2) [13].

Thalidomide

Thalidomide was used as a sedative and as an antiemetic agent during pregnancy in the late 1950s, but was withdrawn from the markets in a few years, after its association with catastrophic teratogenic effects that left approximately 10,000 children affected worldwide. Several years later in 1999, the unique anti-angiogenic and anti-inflammatory properties of thalidomide were recognized, and Singhal and colleagues first reported disease responses in almost a third of the patients with relapsed or refractory MM [14]. Since then, several studies have reported on the efficacy of thalidomide, administered either as a single agent, or in combination with corticosteroids or conventional chemotherapy for treatment of all disease phases in MM.

Palumbo *et al.* reported on the synergistic antimyeloma effect of the combination of MP + thalidomide (MPT) in a small study of 49 patients with a median age of 71 years. This study showed encouraging results, with an overall response rate of 73%, including complete response rates similar to that seen post-ASCT [15], and paved the path for future Phase III randomized controlled studies with this combination. Subsequently, the Italian investigators (Gruppo Italiano Malattie Ematologiche dell'Adulto [GIMEMA]) conducted a multicenter prospective randomized trial to compare the efficacy of MP with MPT in patients who were older than 65 years, or younger than 65 years but ineligible to undergo ASCT [16]. In total, 255 patients (median age 72 years) who had at least 6 months of follow-up were included in the final analysis. The MP regimen consisted of six 4-week cycles of melphalan 4 mg/m², days 1–7 and prednisone 40 mg/m², days 1–7.

Thalidomide at 100 mg/day for six cycles was added to the same MP regimen (MPT); maintenance with thalidomide continued after the six cycles until relapse. At 6 months of therapy, MP resulted in a response rate of 48% and a 2-year event-free survival of 27%; however, MPT improved the response rate to 76%, and doubled event-free survival to 54% at 2 years. There was also a trend for a better survival in the MPT arm with 3-year overall survival rate of 80% with MPT and 64% with MP (p = 0.19). Grade 3 and 4 adverse events with MPT (48%) were nearly twice as high compared with MP (25%). Hematological side effects (e.g., neutropenia, anemia and thrombocytopenia) and venous thromboembolic disease (VTE) were the most common grade 3 or 4 adverse event associated with MPT. Prophylactic therapy with enoxaparin reduced the rate of thromboembolism from 20 to 3% (p = 0.005). Adverse event-related deaths in the MPT and MP groups were observed in 8 and 5% of patients, respectively. Thus, although the follow-up of this trial was only 16 months, these results suggested that oral MPT regimen can improve long-term outcome in elderly MM patients.

In another randomized trial, the investigators of the Intergroupe Francophone du Myélome (IFM) went a step further by comparing three different treatment modalities (MPT [n = 125], MP [n = 196] or reduced-intensity ASCT with melphalan 100 mg/m² [MEL100; n = 126])

in previously untreated MM patients aged between 65 and 75 years [17]. The standard MP regimen consisted of 12 6-week cycles of melphalan (0.25 mg/kg) and prednisone (2 mg/kg) administered orally for 4 days per cycle. MPT regimen comprised of thalidomide (200 mg/day, <400 mg/day) along with the same dose of MP administered continuously for the same duration; thalidomide was stopped at end of the last MP cycle. Patients in the reduced intensity transplant arm were treated with two cycles of vincristine + doxorubicin + dexamethasone (VAD) followed by stem cell mobilization with cyclophosphamide 3 g/m² and two courses of MEL100 with stem cell support. The IFM 99–06 study recorded a response rate of 76% with MPT (identical to the response rate in GIMEMA study) [16], which was significantly higher than the response rate observed with MP (35%) but comparable to response with MEL100 (65%). Similarly, very good partial response or better was seen in 47 and 43% patients in the MPT and MEL100 groups, respectively, whereas only 7% patients obtained a similar response with MP. After a median follow-up of 51.5 months, the median overall survival was 33.2 months for MP, 51.6 months for MPT and 38.3 months for MEL100. The addition of thalidomide to MP resulted in a significantly better overall survival compared with MP (p = 0.0006) and MEL100 (p = 0.027). The results of this trial clearly demonstrated the superiority of MPT

Table 2. Comparative Phase III trials assessing efficacy of modern regimens including novel agents against melphalan prednisone in elderly patients with multiple myeloma.

Trial	Regimen	Patients (n)	Overall response rate (≥ partial response)	Complete response	Progression-free survival	Overall survival	Ref.
GIMEMA	MPT	129	76	15.6	21.8	45	[16]
	MP	126	48	3.7	15.5	47.6	
IFM 99–06	MPT	125	76	13	27.5	51.6	[17]
	MP	196	35	2	17.8	33.2	
	MEL100	126	65	18	19.4	38.3	
IFM 01–01	MPT	113	62	7	24.1	44	[18]
	MP	116	31	1	18.5	29.1	
Nordic study	MPT	182	57	13	15	29	[20]
	MP	175	40	4	14	32	
HOVON	MPT	165	66	2	13	40	[19]
	MP	168	45	2	10	31	
TD versus MP	TD	145	68	2	16.7	41.5	[25]
	MP	144	50	2	20.7	49.4	
VISTA	MPV	344	71	30	24†	NR	[47,48]
	MP	338	35	4	16.6†	43	

†Time to progression.
GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON: Hemato–Oncology Cooperative Group; IFM: Intergroupe Francophone du Myélome; MEL100: Melphalan 100 mg/m²; MP: Melphalan + prednisone; MPT: Melphalan + prednisone + thalidomide; MPV: Melphalan + prednisone + bortezomib; NR: Not reached; TD: Thalidomide and dexamethasone; VISTA: Velcade as Initial Standard Therapy in Multiple Myeloma.

(over MP), thereby establishing it as a front line regimen for elderly and/or transplant ineligible patients with MM.

However, these trials mostly included patients up to 75 years of age. Another French trial (IFM 01–01) confirmed the superiority of MPT over MP in terms of response rate (including complete response), progression-free survival and overall survival in an older patient's population. This study included 229 previously untreated MM patients (≥75 years) to receive 12 6-week cycles of MP (melphalan at 0.2 mg/kg on days 1–4; prednisone 2 mg/kg on days 1–4) along with either 100 mg/day of oral thalidomide (MPT [n = 113]) or placebo (MP [n = 116]) continuously for 18 months [18]. The response rate with MPT (62%) was twice that obtained with MP (31% [p < 0.001]); very good partial response was observed in 28 and 8% patients, respectively (p < 0.001). The significant differences in the response rate translated to an overall survival advantage with MPT compared with MP (44 vs 29.1 months, respectively; p = 0.028), thus confirming the impressive survival benefit reported with MPT in the IFM 99–06 trial [17]. In addition, the median progression-free survival in the MPT arm was also significantly more prolonged than the in MP arm (24.1 vs 18.5 months; p = 0.001). After a median follow-up of 4 years, half the patients in the MPT arm and two-thirds in the MP arm had died. The disease progression occurred in 64% patients in MPT group and 72% in the MP group, although survival after progression was similar in both groups (11.5 vs 9.9 months, respectively; p = 0.89) [18]. However, a significant increase in neutropenia and peripheral neuropathy were observed with MPT.

Two recently published trials have also evaluated the efficacy of MPT versus MP. The Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON) recruited 333 elderly MM patients (median age 72 years; ~ 33% ≥75 years) who were randomly assigned treatment with either MP (n = 168) or MPT (n = 165) [19]. In the MP arm, melphalan 0.25 mg/kg and prednisone 1 mg/kg daily were administered for 5 days every 4 weeks. In the MPT arm, thalidomide 200 mg/day was given continuously until 4 weeks after the last MPT cycle. In case of an ongoing response, MP or MPT cycles were continued until a plateau phase was reached. Overall, eight cycles of therapy were planned in both groups. The MPT group received thalidomide 50 mg daily as maintenance until progression; no maintenance treatment was offered to the MP group. MPT resulted in a significantly better response rate compared with MP (at least partial response: 66 vs 45%, respectively; p < 0.001; and very good partial response 27 vs 10%, respectively; p < 0.001), and even within the group of very elderly patients (≥75 years), similar results were observed. The median overall survival was higher with MPT compared with MP (40 vs 31 months, respectively; p = 0.05); event-free survival was 13 months with MPT versus 9 months with MP (p = 0.001). As expected, overall toxicity, including at least grade 2 neuropathy and thrombosis were more frequent with MPT. In another series, when MP was compared with MP + higher dose thalidomide in a study from the Nordic countries, low efficacy rates and a lack of improvement in the overall survival was reported with the addition of thalidomide [20]. In total, 363 patients (median age: 74 years) with untreated MM were randomized to receive either MPT (n = 184) or MP and placebo (n = 179). Almost one third of the patients in the study had WHO performance status of 3 or 4. Melphalan (0.25 mg/kg) and prednisone (100 mg) were administered daily for 4 days every 6 weeks until plateau phase. The daily dose of thalidomide/placebo was 400 mg before plateau phase and 200 mg after plateau phase. Although at least very good partial response rates were higher with MPT (23%) than MP (7%), the antimyeloma activity did not translate into improvement in progression-free survival (15 months with MPT and 14 months with MP) or overall survival (29 months with MPT and 32 months with MP) at a median follow-up of 42 months. On the contrary, more patients treated with MPT discontinued therapy owing to adverse effects, such as polyneuropathy, constipation and cutaneous reactions associated with thalidomide [20].

Overall, in elderly patients with newly diagnosed MM, five randomized studies (an Italian study [16], two French studies [17,18], a Dutch study [19] and a Nordic study [20]) have compared MPT with MP. Unlike the improvement in response rate observed with MPT across all the aforementioned studies, considerable differences on survival (progression-free survival and overall survival) have emerged. MPT resulted in improved overall survival and progression-free survival in the two French and the Dutch studies, but not in the Nordic study. In the Italian study, only the progression-free survival improved significantly with MPT. However, two meta-analyses [21,22] that included Phase III trials comparing MP with MPT have essentially confirmed the

benefits of addition of thalidomide to MP, firmly establishing MPT as an important front-line regimen in previously untreated elderly and/or transplant ineligible MM patients. In a study presented at the Annual Society of Hematology meeting in 2009, Kapoor *et al.* reported superior response rate, improvement in progression-free survival and overall survival with MPT, but at the cost of being more toxic than MP [21]. This finding has been corroborated by another study as well [22].

In a trial conducted by the Eastern Cooperative Oncology Group (ECOG), the combination of thalidomide and dexamethasone (TD) was compared with dexamethasone alone in newly diagnosed MM patients in a study group, which included some younger patients (median age: 65 years, range: 38–83 years). Overall, the response rate with TD (63%) was significantly superior than dexamethasone alone (41%) after 4 months of therapy, although the rate of grade 3 and 4 adverse effects were higher in patients treated with TD [23]. In a follow-up study to measure long-term outcome, TD was compared with dexamethasone alone in a double-blind placebo-controlled trial including 470 patients [24]. Patients in TD arm received thalidomide 50 mg/day, escalated to 200 mg/day from cycle two, and dexamethasone 40 mg (days 1–4, 9–12 and 17–20 during cycles one to four and on days 1–4 beginning with cycle five). The overall response rate with TD and placebo/dexamethasone was 63 versus 46%, respectively (p < 0.001). The time to progression was significantly longer with TD compared with placebo/dexamethasone (median: 22.6 vs 6.5 months; p < 0.001).

A recent multi-institutional European Phase III study, for the first time, evaluated the efficacy of TD against MP [25]. A total of 289 elderly patients (median age: 72 years) were randomly assigned to receive TD (n = 145) or MP (n = 144). Patients received either thalidomide 200 mg + dexamethasone 40 mg, on days 1–4 and 15–18 on even cycles, and days 1–4 on odd cycles, during a 28-day cycle, or to melphalan 0.25 mg/kg and prednisone 2 mg/kg orally on days 1–4 during a 28- to 42-day cycle. Although treatment with TD resulted in a higher rate of complete response and very good partial response (26 vs 13%; p = 0.006) and overall response (68 vs 50%; p = 0.002) compared with MP, the overall survival was shorter in the TD group (41.5 vs 49.4 months; p = 0.024) primarily owing to increased toxicity in patients aged at least 75 years. Toxic adverse effects such

as neuropathy, constipation and psychological disturbances were higher with TD, particularly in those older than 75 years with poor performance status. In another small study of 50 patients older than 65 years with newly diagnosed MM, low-dose thalidomide (100 mg/day), high-dose pulsed dexamethasone (40 mg orally on days 1–4 and 9–12), and PEGylated liposomal doxorubicin (40 mg/m^2 intravenously on day 1 over the 28-day cycle [ThaDD]) produced an overall response rate of 98% [26]. In a recent case-match study, 34 very elderly patients (≥75 years) with MM treated with the aforementioned regimen comprising thalidomide, dexamethasone and PEGylated liposomal doxorubicin (ThaDD) were matched with respect to age, International Staging System (ISS) staging, and serum creatinine level with an equal number of patients treated with MPT in the GIMEMA 01 study [27]. ThaDD resulted in a significantly higher response: at least partial response (87.5 vs 61.5%, p = 0.009) and at least very good partial response (55.5 vs 29.5%; p = 0.03), but no statistical differences were detected in terms of progression-free survival and overall survival between the two groups. Neutropenia, neuropathy and heart toxicity were more common with MPT, whereas thromboembolism occurred more frequently with ThaDD. The Medical Research Council Myeloma IX Trial investigated the efficacy of cyclophosphamide, thalidomide plus attenuated dexamethasone (CTDa) against standard MP. In the nonintensive pathway of this trial, which included 900 older or less-fit patients (median age: 73 years), CTDa was superior to MP in achieving higher overall response rate (83 vs 46%) and complete response (21 vs 4%), respectively, but the higher response rate with CTDa did not translate into improved survival [28].

■ Adverse effects

Fatigue, sedation, nausea and vomiting, constipation and skin rash are common side effects associated with thalidomide that can be treated symptomatically and usually do not require cessation of the drug [29,30]. Subclinical hypothyroidism should be considered in patients with fatigue, constipation and bradycardia. In one report, elevation of thyroid-stimulating hormone was observed in 20% MM patients who received thalidomide therapy [31]. Less common side effects include neutropenia and hyperkalemia.

Peripheral neuropathy and VTE are the most significant adverse effects of thalidomide. A dose- and duration-dependent peripheral

neuropathy [32] (initially sensory then motor) is the most common cause of thalidomide discontinuation or dose reduction, and occurs more commonly in the elderly, and in those with pre-existing neuropathic conditions and history of exposure to neurotoxic chemotherapy. Although, neuropathic symptoms usually improve after cessation of thalidomide, in some cases they can become progressive and irreversible. Therefore, patients on thalidomide should be regularly examined to assess for features of peripheral neuropathy.

The incidence of VTE with single-agent thalidomide is low [30,33]. However, the combination of thalidomide with steroids (dexamethasone) or alkylators (MP) is associated with a substantially higher risk (10–25%) of VTE, especially in the absence of any prophylactic anticoagulation [23,34–36]. The risk of VTE is particularly high during the induction phase of treatment when tumor burden is high. Several studies have observed a reduction in VTE after addition of prophylactic anticoagulation therapy [16,37,38]. Current thromboprophylaxis guidelines recommend the use of aspirin for patients with no risk factor or one individual/myeloma-related risk factor, low-molecular-weight heparin (LMWH) for those with at least two individual/myeloma-related risk factors, and LMWH or warfarin for patients on high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independent of the presence of additional risk factors [34]. Other cardiovascular adverse effects of thalidomide include sinus bradycardia, orthostatic hypotension and peripheral edema.

Teratogenicity is the most serious toxicity of thalidomide, although it is less concerning in postmenopausal elderly women. In the USA, thalidomide is marketed under the System for Thalidomide Education and Prescribing Safety (STEPS®) program, which requires women in the childbearing age group to undergo pregnancy testing before starting therapy, and every 2–4 weeks during treatment. In addition, they are required to abstain from sexual intercourse, or use two effective contraceptive methods during treatment. Males must abstain from sexual intercourse or use a condom while on treatment even if they have had a successful vasectomy.

Bortezomib

Bortezomib is the first-in-class proteasome inhibitor approved for treatment of MM. Two Phase II studies [39,40] and a Phase III study [41] had earlier reported significantly improved outcomes with bortezomib in patients with relapsed or refractory MM, compared with dexamethasone. Thereafter, *in vitro* studies demonstrated increased sensitivity of chemoresistant myeloma cells to conventional chemotherapeutic agents (including melphalan) when combined with bortezomib [42,43]. In fact, the synergistic effects of bortezomib and melphalan seen in preclinical studies, translated into promising results with manageable toxicity in patients with relapsed/refractory disease [44]. Based upon these encouraging results, a Phase I/II study was conducted by the Spanish group Programa para el Tratamiento de Hemopatias Malignas (PETHEMA) in 60 elderly MM patients (median age: 75 years, range: 65–85 years). The study aimed to identify the most appropriate dose of bortezomib in combination with a standard MP regimen (Phase I) and to determine the response rate obtained with this combination (Phase II) [45]. Patients received bortezomib 10.0 mg/m^2 (n = 6) or 1.3 mg/m^2 (n = 54) on days 1, 4, 8, 11, 22, 25, 29 and 32 for four 6-week induction cycles, and then on days 1, 8, 15, and 22 for five 5-week maintenance cycles. They also received oral melphalan 9 mg/m^2 and prednisone 60 mg/m^2 on days 1–4 of all nine cycles. The addition of bortezomib (velcade) to MP (VMP) produced a response in 89% patients, including 32% immunofixation-negative complete response after a median of five cycles of bortezomib therapy, and 11% near-complete response. Notably, the response rate and complete response after one cycle of VMP (70%, including 6% complete response, 2% near-complete response, 62% partial response) was higher than that obtained after six cycles of MP (42%, including 3% near-complete response, 39% partial response). After a median follow-up of 26 months, the median time to progression with VMP was higher compared with MP (27.2 vs 20.0 months, respectively; p = 0.001) [46]. The median overall survival was not reached with VMP, compared with 26 months with MP (p < 0.0001). Interestingly, the survival rate with VMP at 3 years was the highest reported with MP-based regimens (85% with VMP versus 38% with MP at 38 months (p < 0.0001), despite half the patients being over 75 years and 17% being 80 years or older. Adverse events with VMP occurred more commonly in the initial treatment cycles; grade 3/4 adverse events such as thrombocytopenia and neutropenia (40–50%); peripheral neuropathy, infections, diarrhea and anemia were reported in 17, 16, 16 and 10% patients, respectively.

These encouraging preliminary results formed the basis of the prospective randomized Phase III Velcade as Initial Standard Therapy for MM

(VISTA) trial comparing MP to VMP [47]. In total, 682 patients with untreated MM at least 65 years of age (median: 71 years) who were ineligible to undergo ASCT were randomized to receive MP (n = 338; melphalan 9 mg/m² and prednisone 60 mg/m²) for nine 6-week cycles or the VMP (n = 344; bortezomib 1.3 mg/m²) combination previously described [47]. The overall response rates were higher in the VMP arm compared with the MP arm (71 vs 35%, respectively), including the rates of complete response (30 vs 4%, respectively; p < 0.001). The median duration of response was 19.9 months in the bortezomib group and 13.1 months in the control group; corresponding values among those with complete response was 240.0 months in the bortezomib group and 12.8 months in the control group. In addition, the time to progression (24 vs 16.6 months; p < 0.001) was higher with VMP than MP, respectively. In a recent updated report that included a prolonged median follow-up of 36.7 months, the median overall survival was not reached versus 43.1 months in the VMP and MP arms, respectively; the 3-year overall survival rates were 68.5 versus 540.0%, respectively [48]. Interestingly, the overall survival advantage with VMP was also seen versus the subgroup of patients treated with MP who received bortezomib as second-line therapy (i.e., retreatment with bortezomib in patients previously treated with upfront bortezomib showed a survival advantage over those treated with bortezomib after receiving first-line therapy with MP) [48]. Therefore, the addition of bortezomib to MP was superior in terms of response rate (overall and complete response rates), time to progression, progression-free survival and overall survival compared with standard MP regimen [47]. In addition, the median time to progression, rate of complete response and median overall survival were identical with VMP in groups with high risk cytogenetic profiles (t[4;14], t[14;16] translocation or a 17p deletion) versus standard-risk cytogenetics and impaired versus normal renal function [47]. Treatment with VMP resulted in no difference in the time to progression between patients aged at least 75 years versus younger patients; however, the rate of complete response and overall survival were slightly inferior within the older age group. The bortezomib group and the control group did not differ significantly with respect to rates of death during treatment (5 and 4%, respectively) or treatment-related death (1 and 2%, respectively), but at least grade 2 peripheral neuropathy (30%), at least grade 3 gastrointestinal symptoms, herpes zoster infections and fatigue were more commonly seen in patients treated with VMP. The hematologic toxic effects were similar in the two groups. Thus, the VISTA trial conferred a survival advantage with VMP over MP in newly diagnosed elderly MM patients who are ineligible for ASCT, although VMP was associated with a higher rate of adverse events [47,48].

In order to reduce toxicity while maintaining the efficacy, a reduced intensity induction with a bortezomib-based regimen was studied, it compared the effect of VMP with VTP in a two-stage trial of 260 patients (>65 years) with untreated newly diagnosed MM [49]. In the first stage, patients were randomly assigned to induction therapy with bortezomib, in combination with prednisone plus either melphalan (VMP; n = 130) or thalidomide (VTP; n = 130). Bortezomib-induction therapy in both arms consisted of six cycles: first cycle was administered twice per week for 6 weeks (1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29 and 32) and the next five cycles of once per week for 5 weeks (1.3 mg/m²), plus either melphalan (9 mg/m² on days 1–4) or daily thalidomide (100 mg) and prednisone (60 mg/m² on days 1–4). This stage was followed by a second randomization to maintenance therapy with bortezomib plus either thalidomide or prednisone. Maintenance consisted of one conventional cycle of intravenous bortezomib for 3 weeks (1.3 mg/m² on days 1, 4, 8 and 11) every 3 months, plus either oral prednisone 50 mg every other day or oral thalidomide 50 mg/day, for up to 3 years. The induction phase yielded similar response rates in the VTP and VMP groups with 81 and 80% of patients achieving at least partial response, respectively (p = 0.9); corresponding rates for complete response were 28 and 20%, respectively (p = 0.2). The median time to achieve first response was 1.6 months in both groups, whereas the time to achieve complete response with VMP and VTP was 4.4 and 4.9 months, respectively. No significant differences were found between the groups for progression-free survival and 3-year overall survival. Patients treated with VMP had higher rates of neutropenia (39 vs 22%; p = 0.008), thrombocytopenia (27 vs 12%; p < 0.001) and infections (7 vs 1%; p = 0.01). However, cardiac events were more commonly seen in patients treated with VTP (8 vs 0%; p < 0.001). Overall, treatment with VTP produced more serious adverse events than treatment with VMP (31 vs 15%, respectively; p = 0.01) resulting in a higher rate of treatment discontinuations (17 vs 12%,

respectively; p = 0.03). Two important results were drawn from this study. First, low-dose bortezomib induction therapy was able to considerably reduce at least grade 3 peripheral neuropathy and gastrointestinal symptoms compared with the conventional dosage schedule of VMP administered in the VISTA trial. Second, primarily owing to poor toxicity profile, bortezomib + thalidomide is a less preferred option than bortezomib + melphalan in elderly patients with MM.

In another randomized trial, Palumbo *et al.* evaluated the efficacy of VMP against thalidomide added to the same combination (VMPT). Newly diagnosed MM patients (median age: 71 years) were randomly assigned to receive VMPT (n = 193) or VMP (n = 200) [50]. The VMP treatment schedule consisted of bortezomib (1.3 mg/m^2, days 1, 8, 15 and 22) plus oral prednisone (60 mg/m^2, days 1–4) and melphalan (9 mg/m^2, days 1–4). In addition to the aforementioned, thalidomide 50 mg/day was administered in the VMPT group. Although very good partial response rates (59 vs 37%; p = 0.004) and complete response rates (28 vs 10%, p = 0.004) were in favor of VMPT than than VMP, respectively, the 3-year overall survival was similar and almost reached 90% in both the groups. However, for patients who achieved complete response after induction therapy, the 2 year progression-free survival was 100% for VMPT and 79% for VMP (p = 0.02). The incidence of grade 3–4 side effects were similar in both the groups.

■ Adverse effects

Bortezomib is relatively well tolerated; most side effects are only mild to moderate and are manageable. The most frequently reported adverse events (incidence >30%) associated with the use of bortezomib are asthenia (fatigue, weakness and malaise), gastrointestinal effects (nausea, vomiting, diarrhea and constipation), thrombocytopenia (transient and cyclical), cutaneous reactions and peripheral neuropathy. Bortezomib-induced peripheral neuropathy (BIPN) should be differentiated from the peripheral neuropathy that can occur secondary to the plasma cell dyscrasia in MM. BIPN is predominantly sensory, characterized by pain, paresthesia and numbness and affects the lower extremities more commonly. Signs and symptoms of BIPN should be monitored at each patient visit. The incidence of BIPN is increased in elderly MM patients with pre-existing neuropathy and a history of diabetes mellitus [51], and is overall related to the cumulative

toxic effects of bortezomib therapy. Therefore, bortezomib (1.3 mg/m^2) once a week reduced the grade 3 or worse BIPN to 4–5 from 13% reported in the VISTA trial with the bortezomib (1.3 mg/m^2) twice weekly [47–49]. The analyses of gene-expression profiles of myeloma plasma cells and single-nucleotide polymorphisms of peripheral blood suggest a strong interaction of myeloma-related factors and the patients genetic make-up in the development of BIPN; while genes associated with apoptosis are involved in early-onset BIPN, those associated with inflammatory pathways and DNA repair are involved in late-onset BIPN [52]. The thrombocytopenia associated with bortezomib is reversible, cyclical and transient that rarely requires dosage modifications. Platelet counts can decrease by approximately 60% during treatment but quickly recover in between cycles [53]. Bortezomib-induced thrombocytopenia is believed to occur via a reversible effect on megakaryocytic platelet production rather than a direct cytotoxic effect on megakaryocytes. There is currently no evidence to suggest cumulative thrombocytopenia associated with bortezomib. Platelet count should be monitored prior to each cycle.

Bortezomib can lead to orthostatic hypotension and should be used cautiously in patients with a history of syncope. Prophylactic therapy with acyclovir or valacyclovir is recommended for patients on bortezomib therapy owing to the heightened risk of herpes zoster infection or a reactivation of varicella zoster [47,49,54]. However, bortezomib does not appear to have an adverse effect on stem cell collection. Furthermore, patients with renal impairment can be safely and effectively treated with bortezomib [55], while patients with hepatic impairment should receive reduced doses while being monitored carefully during treatment.

Lenalidomide

Lenalidomide is a structural analog of thalidomide. It was developed to enhance the antineoplastic and anti-inflammatory properties of thalidomide, in order to improve the efficacy and toxicity profile of thalidomide. It has demonstrated significant activity in both preclinical and clinical studies [56], both alone and in combination with dexamethasone [57,58], for treatment of MM.

The Italian GIMEMA group has reported on the efficacy, dosing and safety of MP in combination with lenalidomide (Revlimid®; MPR) in a Phase I/II dose-escalation study [59]. In total, 54 patients, at least 65 years of age (median age:

71 years, range: 57–77 years) were enrolled across ten treatment centers. Treatment schedule consisted of melphalan (0.18–0.25 mg/kg) on days 1–4, prednisone (2 mg/kg) on days 1–4, and lenalidomide 5–10 mg on days 1–21 for nine monthly cycles, followed by maintenance therapy with 10 mg lenalidomide (days 1–21 every month) until any sign of relapse or progression. Patients given the maximum tolerated dose (melphalan 0.18 mg/kg for 4 days and lenalidomide 10 mg/day for 21 days) achieved partial response or better, at least very good partial response and immunofixation-negative complete response in 81, 48 and 24% patients, respectively, with all patients achieving at least a minimal response. In all patients, the median time to best response was 4 months, and the 1-year event-free survival and overall survival rates were 92 and 100%, respectively. Grade 3 or 4 neutropenia, thrombocytopenia and VTD were seen in 52, 24 and 5% patients, respectively. The promising initial results observed with MPR have prompted follow-up studies in a larger group of patients; and clinical trials comparing the efficacy of MPR with MP, and MPR with MPT have been initiated [60].

In a recent multicenter Phase III study (MM-015), Palumbo *et al.* have evaluated the safety and efficacy of continuous lenalidomide treatment after MPR (MPR-R; n = 152) versus MP (n = 154) or MPR (n = 153) in 459 newly diagnosed transplant ineligible MM patients who were at least 65 years of age [61]. The treatment schema consisted of melphalan 0.18 mg/kg on days 1–4, prednisone 2 mg/kg on days 1–4, with (MPR or MPR-R) or without (MP) lenalidomide 10 mg/day on days 1–21 for nine 28-day cycles. Following nine cycles of MPR, patients received maintenance lenalidomide (10 mg/day on days 1–21) (MPR-R) or placebo (MPR) until progression; MP patients also received placebo until progression. After a median follow-up of 21 months, MPR-R compared with MP resulted in a higher overall response rate (77 vs 50%; p < 0.001) and higher rates of complete response (16 vs 4%; p < 0.001). In addition, MPR-R reduced the risk of disease progression by 58% compared with MP (hazard ratio = 0.423; p < 0.001) and resulted in a higher 2-year progression-free survival rate (55 vs 16%). Adverse events associated with MPR-R and MP resulted in treatment discontinuation in 20% and 8% patients, respectively.

In a Phase II clinical trial, Rajkumar *et al.* demonstrated impressive response rates in previously untreated MM patients treated with lenalidomide (days 1–21 of a 28-day cycle)

plus high-dose dexamethasone 40 mg daily (days 1–4, 9–12 and 17–20 of each cycle) [58]. In a recent Phase III study conducted by the ECOG, 445 patients (52% more than 65 years) with untreated symptomatic MM were randomly assigned to receive RD (lenalidomide day 1–21 of a 28-day cycle + dexamethasone 40 mg, schedule as mentioned previously) or Rd (lenalidomide day 1–21 of a 28-day cycle + dexamethasone 40 mg on days 1, 8, 15 and 22 of a 28-day cycle) [62]. After four cycles of therapy, patients were allowed to pursue ASCT or continue treatment until disease progression [62]. The median duration of therapy in RD and Rd group was 4 and 6 months, respectively. The overall response rate after four cycles of treatment was higher with RD than Rd (79 vs 68%, respectively; p = 0.008); however, the overall survival at 2 years was 87% for patients on Rd compared with 75% with RD (p = 0.006). In addition, the progression-free survival was also in favor of Rd (25.3 months with Rd vs 19.1 months with RD; p = 0.026). Only 2% of the patients who opted for ASCT were unsuccessful at stem cell harvest following initial therapy with lenalidomide and dexamethasone, suggesting its usefulness as a pretransplant induction agent. Importantly, the common grade 3 or 4 toxicities were higher with RD than Rd: deep vein thrombosis (26 vs 12%; p = 0.0003); infections (16 vs 9%; p = 0.04), and fatigue (15 vs 9%; p = 0.08), respectively. Fewer patients (14%) in the RD group remained on treatment for more than 1 year compared with Rd group (30%). Thus, RD produced higher response rates only, while Rd produced superior time to progression, progression-free survival and overall survival, along with a better toxicity profile. More recently, in a study presented at the American Society of Hematology meeting in 2010, Vesole *et al.* reported on 445 MM patients who were randomly assigned to receive either RD (n = 223) or Rd (n = 222). The study population included patients who were younger than 65 and older than 65 years of age in both the groups; those over 65 years were further subdivided into older than 70 and older than 75 years [63]. The results indicate that overall survival was not superior with RD compared with Rd in any age group despite a higher response rate, hence validating the use of low-dose dexamethasone for all newly diagnosed MM patients of all age groups.

■ Adverse effects
The most common grade 3 or 4 adverse effects seen with lenalidomide-dexamethasone is myelosuppression (neutropenia, anemia and

thrombocytopenia). Pulmonary hypertension, skin rash, fatigue, light-headedness and leg cramps are other less common side effects. Unlike thalidomide, lenalidomide does not trigger dose-limiting somnolence, neuropathy and constipation [64]. An increased risk of VTE is observed in patients treated with lenalidomide + dexamethasone compared with dexamethasone alone (11.4 vs 4.6%, respectively) [65]. The risk of developing a VTE is related to steroid dose, and is even higher with concomitant use of erythropoietin and chemotherapy such as melphalan and doxorubicin [34]. In one study, the concomitant administration of erythropoietin significantly increased the risk of VTE (23 vs 5%) in patients who received lenalidomide and dexamethasone at relapse of MM [66]. Therefore, the thromboprophylaxis regimen should be tailored based upon individual- and MM-related risk factors and appropriate anticoagulation therapy (i.e., aspirin, LMWH or warfarin) is indicated for all patients receiving lenalidomide in combination with dexamethasone or melphalan. A trend towards increased risk of secondary malignancy (lymphoma) has also been reported with lenalidomide use post-ASCT or when used in combination with melphalan. Some reports have suggested a suppressive effect of treatment with lenalidomide therapy resulting in inadequate peripheral blood stem cell collection [67,68]. However, a few cycles of lenalidomide + dexamethasone does not negatively impact the process of stem cell collection [68], and current guidelines suggest completing stem cell collection within four cycles of lenalidomide therapy. Patients receiving induction therapy with lenalidomide are able to obtain adequate stem cell collection when treated with a combination of cyclophosphamide and growth factor [69]. In addition, Plerixafor (AMD3100), an inhibitor of CXCR4, is a safe and predictable mobilization agent that can be used to ensure a successful stem cell harvest [70].

Role of transplant

Multiple myeloma is the most common indication to undergo a ASCT in the USA. Due to treatment side effects, it is largely employed in the treatment paradigm of younger MM patients (<65 years). However, not all elderly MM patients are ineligible to undergo this procedure. The eligibility to undergo a high-dose therapy with ASCT varies across medical institutions. In order to assess the feasibility of this procedure, judicious selection of MM patients based not solely upon their chronological age,

but also physical condition, coexisting medical disorders, and aggressiveness of the disease is essential. In general, the standard preparative regimen of melphalan 200 mg/m^2 is usually considered too toxic for most elderly patients (especially those >70 years) [7,71] who are highly susceptible to develop infections, anemia and end-organ damage. By contrast, two or three courses of MEL100 mg/m^2 followed by ASCT have been safely given to patients up to 75 years of age [72,73]. In a randomized trial from the Italian MM group, 194 patients (50–70 years) were included to receive, at diagnosis, either conventional chemotherapy (six courses of oral MP) or two courses of MEL100 with ASCT. In a subgroup analysis of 80 patients aged between 65 and 70 years, MEL100 administerd twice was better than MP in terms of response rate, event-free survival and overall survival (37.2 months with MP vs 58 months with MEL100) [74]. However, the larger three-arm IFM 99–06 study, which included patients between 65–75 years, was not able to confirm this finding. In a direct comparison between reduced intensity ASCT (MEL100) and MP, partial response and complete response rates were significantly higher with MEL100 (65% at least partial response and 18% complete response) than with MP (35% at least partial response and 2% complete response), but progression-free survival and overall survival were not statistically different among the two groups. In patients considered eligible for ASCT, alkylator-based therapy should be avoided in the induction phase to enable an adequate stem cell harvest early in the disease course.

Maintenance options

Clinical trials utilizing thalidomide for maintenance therapy post-ASCT in young patients have shown an improvement in progression-free survival, but the impact on overall survival is less clear [37,75–77]. It is not clear how much of the maintenance effect is the result of a additional cytoreduction or 'consolidation' effect and deepening of response rather than a true prolonged maintenance effect. The GIMEMA group administered thalidomide 100 mg/day for maintenance until the time of relapse or progression, after initial therapy with either MP or MPT [16]. Similarly, maintenance with lenalidomide 10 mg/day was given in the Phase I/II MPR study, where elderly MM patients had received scheduled MPR regimen [59]. Mateos and colleagues used maintenance therapy with one cycle of intravenous bortezomib for 3 weeks (1.3 mg/m² on days 1, 4, 8 and 11) every

3 months, plus either prednisone (50 mg every other day) or thalidomide (50 mg/day) for up to 3 years, in their study comparing VMP with VTP in elderly myeloma patients [49].

Recently, the efficacy of maintenance therapy with thalidomide plus interferon compared with interferon alone was reported in elderly MM patients. Among 289 patients (median age: 71 years) randomized to pretreatment with TD or MP, 137 patients completed nine cycles of induction therapy with resultant stable disease or better, and were eligible to receive maintenance therapy [78]. Of these, 128 were randomized to either thalidomide + interferon or interferon alone. Patients treated with maintenance with thalidomide + interferon compared with interferon alone had an increased progression-free survival (27.7 vs 13.2 months, respectively; p = 0.0068) without any advantage in the overall survival (52.6 vs 51.4 months, respectively; p = 0.81) [78]; in addition, treatment adverse effects (i.e., neuropathy, constipation and skin toxicity) were more common in the former group. From the limited data available owing to an insufficient follow-up period of these trials, maintenance therapy is currently not recommended in elderly MM patients who receive initial therapy with MPT or VMP [79].

Treatment strategy: special considerations in the elderly

Several different therapies with well defined toxicity profiles are now available to ensure a personalized treatment approach for the elderly MM patient. Nevertheless, MM remains a challenging disease to treat in this age group. The choice of the best treatment strategy for every elderly MM patient should be accurately based on the biologic age, comorbid conditions, performance status and the treatment toxicity profile; for example, MPR or Rd may be preferred to bortezomib- and thalidomide-based regimens in patients with pre-existing neuropathy. Similarly, VMP is preferred to IMiD-based combination therapy in patients with high risk of VTE; VMP and MPT can be safely administered in those with renal failure/insufficiency whereas lenalidomide needs dose reduction [55,80,81]. In addition, patient education regarding expected toxicity profile, institution of appropriate prophylactic therapy (acyclovir with bortezomib, aspirin or anticoagulation with IMiDs), and providing adequate supportive treatment (bisphosphonates, growth factor) helps improve compliance. Other issues that can influence a decision are based upon

ease of administration (oral MPT, MPR, Rd preferred over intravenous bortezomib-based regimens) and cost (thalidomide being cheaper than lenalidomide).

Once the therapeutic regimen is chosen, the appropriate dosage should be determined to balance toxicity and efficacy since the standard or high drug dosages are not always optimal for the elderly 'frail' population. In the Nordic study, where the median age of patients was 74.1 years and almost a third had WHO performance status of 3 or 4, the addition of high-dose thalidomide (400 mg/day in treatment phase and 200 mg/day in maintenance) to MP regimen led to greater toxicity, high rate (56%) of treatment discontinuation within the first year, increased number of deaths within the first 6 months of therapy (especially in those over 75 years of age) and no improvement in the progression-free survival and/or overall survival [20]. Similarly, in the study comparing TD with MP, the number of deaths within the first year with high-dose thalidomide (up to 400 mg/day) and dexamethasone was significantly higher compared with MP (28 vs 16%, respectively; p = 0.014) [25]. The high-dose thalidomide proved too toxic for this very elderly population (60% patients were 70–79 years and 10% were ≥80 years) resulting in a significantly shorter median overall survival in the TD arm compared with MP arm (41.5 vs 49.4 months, respectively; p = 0.024). Interestingly, a similar increase of early deaths among those older than 75 years of age has been reported in the Italian and Dutch studies as well [16,19]. The results of these studies indicate increased toxicity associated with thalidomide (especially with higher dosages) in patients over the age of 75 years and/or poor performance status.

Hence, in order to balance toxicity and efficacy of treatment regimens in elderly patients (>75 years) or younger patients with decreased performance status or significant comorbidities, dose adjustment (thalidomide: 50–100 mg/day, bortezomib: 1–1.3 mg/m² once per week and lenalidomide: 10–15 mg/day or 5 mg/day) may be required. The Mayo Clinic proposed a cytogenetic based risk stratification of MM, wherein patients with t(11;14), t(6;14) translocation or hyperdiploidy by karyotype have standard-risk disease; while those with deletion 17p, t(14;16), t(4;14), cytogenetic deletion 13, hypodiploidy by karyotype, or a high plasma cell labeling index (>3%) have high-risk disease [79]. On the basis of this algorithm, the Mayo Clinic MM Group recommends MPT for those with standard-risk disease who are ineligible for ASCT [79].

Conversely, front-line VMP [60,79] is preferred in the high-risk group, as bortezomib appears to overcome the negative effects of chromosomal abnormalities as demonstrated in the VISTA trial [47]. However, similar beneficial effects with bortezomib therapy in MM patients with high-risk cytogenetics have not been homogeneously demonstrated in other trials.

Conclusion & future perspective

Despite better understanding of disease biology, recent therapeutic advances and improvement in supportive care, MM remains an incurable disease. The need for more active and less toxic drugs for the elderly MM patients has been supported by combination treatment including novel agents (MPT and VMP). MPR and Rd have also shown promising results in initial trials and are likely to provide a survival advantage over MP. Although newer regimens have demonstrated striking improvements in response rate and overall survival for elderly MM patients, efforts are being made to develop drugs that can surpass the efficacy of current treatment regimens, exhibit safer toxicity profile, and improve the quality of life. Newer IMiDs (pomalidomide) and proteasome inhibitors (carfilzomib) are currently undergoing investigational trials and preliminary results appear promising.

Executive summary

- Melphalan and prednisone combination is no longer the reference treatment for initial therapy in elderly multiple myeloma (MM) patients who are ineligible to undergo autologous stem cell transplantation.
- Large studies have shown that both melphalan + prednisone + thalidomide (MPT) and bortezomib + melphalan + prednisone (VMP) are better than melphalan + prednisone (MP) in terms of progression-free survival and overall survival, and are now regarded as the standard of care for elderly MM patients. The choice of treatment depends upon individual patient factors. In general, MPT is preferred in standard-/low-risk MM patients; VMP is recommended in high-risk disease, although no randomized trials have been conducted to validate its efficacy within this group.
- MPR, Rd, VTP and CTD provide alternative treatment options and may also provide a survival benefit over MP. The eligibility to undergo a reduced-intensity autologous stem cell transplantation (MEL100) is based upon the risk–benefit assessment; taking into account the performance status, comorbid conditions and patients wishes.
- The choice for the ideal agent or its combination should be based upon the scientific evidence gathered from randomized controlled trials. Specifically, factors such as the biologic age of the patient, drug toxicity profile, ease of administration and expense should be considered prior to making the decision.
- The appropriate dosage must be carefully assessed to avoid excessive toxicity, prevent early discontinuation and reduce treatment-related mortality.
- Prescription of prophylactic therapy based upon expected toxicity profile and/or prompt dose-reduction upon emergence of side effects helps reduce rate of treatment discontinuation and improves compliance.

Bibliography

1   Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J. Clin.* 60(5), 277–300 (2010).

2   Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br. J. Haematol.* 121(5), 749–757 (2003).

3   Kyle RA, Durie BG, Rajkumar SV *et al.* Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia* 24(6), 1121–1127 (2010).

4   Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo Clin. Proc.* 85(3), 225–230 (2010).

5   Kyle RA, Gertz MA, Witzig TE *et al.* Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin. Proc.* 78(1), 21–33 (2003).

6   Attal M, Harousseau JL, Stoppa AM *et al.* A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N. Engl. J. Med.* 335(2), 91–97 (1996).

7   Child JA, Morgan GJ, Davies FE *et al.* High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N. Engl. J. Med.* 348(19), 1875–1883 (2003).

8   Barlogie B, Jagannath S, Vesole DH *et al.* Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 89(3), 789–793 (1997).

9   Boccadoro M, Marmont F, Tribalto M *et al.* Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. *J. Clin. Oncol.* 9(3), 444–448 (1991).

10 Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. *J. Clin. Oncol.* 16(12), 3832–3842 (1998).

11 Facon T, Mary JY, Pegourie B *et al.* Dexamethasone-based regimens versus melphalan–prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. *Blood* 107(4), 1292–1298 (2006).

12 Blade J, San Miguel JF, Fontanillas M *et al.* Increased conventional chemotherapy does not improve survival in multiple myeloma: long-term results of two PETHEMA trials including 914 patients. *Hematol. J.* 2(4), 272–278 (2001).

13 Kumar SK, Rajkumar SV, Dispenzieri A *et al.*: Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111(5), 2516–2520 (2008).

14 Singhal S, Mehta J, Desikan R *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N. Engl. J. Med.* 341(21), 1565–1571 (1999).

15 Palumbo A, Bertola A, Musto P *et al.* Oral melphalan, prednisone, and thalidomide for newly diagnosed patients with myeloma. *Cancer* 104(7), 1428–1433 (2005).

16 Palumbo A, Bringhen S, Caravita T *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 367(9513), 825–831 (2006).

17 Facon T, Mary JY, Hulin C *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial. *Lancet* 370(9594), 1209–1218 (2007).

18 Hulin C, Facon T, Rodon P *et al.* Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J. Clin. Oncol.* 27(22), 3664–3670 (2009).

19 Wijermans P, Schaafsma M, Termorshuizen F *et al.* Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J. Clin. Oncol.* 28(19), 3160–3166 (2010).

20 Waage A, Gimsing P, Fayers P *et al.* Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. *Blood* 116(9), 1405–1412 (2010).

21 Kapoor P. Melphalan and prednisone (MP) versus melphalan, prednisone and thalidomide (MPT) as initial therapy for previously untreated elderly and/or transplant ineligible patients with multiple myeloma: a meta analysis of five randomized controlled trials. *Blood* 114 (2009).

22 Waage A. MP versus MPT for previously untreated elderly patients with multiple myeloma: a meta-analysis of 1,682 individual patient data from six randomized clinical trials. *J. Clin. Oncol.* (2010) (In Press).

23 Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 24(3), 431–436 (2006).

24 Rajkumar SV, Rosinol L, Hussein M *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J. Clin. Oncol.* 26(13), 2171–2177 (2008).

25 Ludwig H, Hajek R, Tothova E *et al.* Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood* 113(15), 3435–3442 (2009).

26 Offidani M, Corvatta L, Piersantelli MN *et al.*: Thalidomide, dexamethasone, and PEGylated liposomal doxorubicin (ThaDD) for patients older than 65 years with newly diagnosed multiple myeloma. *Blood* 108(7), 2159–2164 (2006).

27 Offidani M, Leoni P, Bringhen S *et al.* Melphalan, prednisone, and thalidomide versus thalidomide, dexamethasone, and PEGylated liposomal doxorubicin regimen in very elderly patients with multiple myeloma: a case-match study. *Leuk. Lymphoma* 51(8), 1444–1449 (2010).

28 Morgan J, Davies F, Gregory W *et al.* The addition of thalidomide to the induction treatment of newly presenting myeloma patients increases the CR rate which is likely to translate into improved PFS and OS (Abstract 352). *Blood* 114((2009).

29 Rajkumar SV, Dispenzieri A, Fonseca R *et al.* Thalidomide for previously untreated indolent or smoldering multiple myeloma. *Leukemia* 15(8), 1274–1276 (2001).

30 Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J. Clin. Oncol.* 21(1), 16–19 (2003).

31 Badros AZ, Siegel E, Bodenner D *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am. J. Med.* 112(5), 412–413 (2002).

32 Kumar S, Gertz MA, Dispenzieri A *et al.* Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. *Mayo Clin. Proc.* 78(1), 34–39 (2003).

33 Barlogie B, Desikan R, Eddlemon P *et al.* Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a Phase 2 study of 169 patients. *Blood* 98(2), 492–494 (2001).

34 Palumbo A, Rajkumar SV, Dimopoulos MA *et al.* Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 22(2), 414–423 (2008).

35 Rajkumar SV, Hayman S, Gertz MA *et al.* Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J. Clin. Oncol.* 20(21), 4319–4323 (2002).

36 Zangari M, Barlogie B, Anaissie E *et al.* Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br. J. Haematol.* 126(5), 715–721 (2004).

37 Barlogie B, Tricot G, Anaissie E *et al.* Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N. Engl. J. Med.* 354(10), 1021–1030 (2006).

38 Dimopoulos MA, Anagnostopoulos A, Terpos E *et al.* Primary treatment with pulsed melphalan, dexamethasone and thalidomide for elderly symptomatic patients with multiple myeloma. *Haematologica* 91(2), 252–254 (2006).

39 Richardson PG, Barlogie B, Berenson J *et al.* A Phase 2 study of bortezomib in relapsed, refractory myeloma. *N. Engl. J. Med.* 348(26), 2609–2617 (2003).

40 Jagannath S, Barlogie B, Berenson J *et al.* A Phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *Br. J. Haematol.* 127(2), 165–172 (2004).

41 Richardson PG, Sonneveld P, Schuster MW *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N. Engl. J. Med.* 352(24), 2487–2498 (2005).

42 Ma MH, Yang HH, Parker K *et al.* The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clin. Cancer Res.* 9(3), 1136–1144 (2003).

43 Mitsiades N, Mitsiades CS, Richardson PG *et al.*: The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. *Blood* 101(6), 2377–2380 (2003).

44 Berenson JR, Yang HH, Sadler K *et al.* Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. *J. Clin. Oncol.* 24(6), 937–944 (2006).

45 Mateos MV, Hernandez JM, Hernandez MT *et al.* Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter Phase 1/2 study. *Blood* 108(7), 2165–2172 (2006).

46 Mateos MV, Hernandez JM, Hernandez MT *et al.* Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. *Haematologica* 93(4), 560–565 (2008).

47 San Miguel JF, Schlag R, Khuageva NK *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N. Engl. J. Med.* 359(9), 906–917 (2008).

48 Mateos MV, Richardson PG, Schlag R *et al.* Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the Phase III VISTA trial. *J. Clin. Oncol.* 28(13), 2259–2266 (2010).

49 Mateos MV, Oriol A, Martinez-Lopez J *et al.* Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol.* 11, 934–941 (2010).

50 Palumbo A, Bringhen S, Rossi D *et al.* Bortezomib–melphalan–prednisone–thalidomide followed by maintenance with bortezomib–thalidomide compared with bortezomib–melphalan–prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J. Clin. Oncol.* 28(34), 5101–5109 (2010).

51 Badros A, Goloubeva O, Dalal JS *et al.* Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. *Cancer* 110(5), 1042–1049 (2007).

52 Broyl A, Corthals SL, Jongen JL *et al.* Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *Lancet Oncol.* 11(11), 1057–1065 (2010).

53 Lonial S, Waller EK, Richardson PG *et al.* Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. *Blood* 106(12), 3777–3784 (2005).

54 Chanan-Khan A, Sonneveld P, Schuster MW *et al.* Analysis of herpes zoster events among bortezomib-treated patients in the Phase III APEX study. *J. Clin. Oncol.* 26(29), 4784–4790 (2008).

55 Chanan-Khan AA, Kaufman JL, Mehta J *et al.*: Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. *Blood* 109(6), 2604–2606 (2007).

56 Richardson P, Anderson K. Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma. *J. Clin. Oncol.* 22(16), 3212–3214 (2004).

57 Richardson PG, Schlossman RL, Weller E *et al.*: Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 100(9), 3063–3067 (2002).

58 Rajkumar SV, Hayman SR, Lacy MQ *et al.* Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood* 106(13), 4050–4053 (2005).

59 Palumbo A, Falco P, Corradini P *et al.* Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA – Italian Multiple Myeloma Network. *J. Clin. Oncol.* 25(28), 4459–4465 (2007).

60 Dingli D, Rajkumar SV. How best to use new therapies in multiple myeloma. *Blood Rev.* 24(3), 91–100 (2010).

61 Palumbo A, Delforge M, Catalano J *et al.* A Phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients 65 years with newly diagnosed multiple myeloma (NDMM): continuous use of lenalidomide vs fixed-duration regimens. *Blood (ASH Annu. Meeting Abstr.)* 116, Abstract 622 (2010).

62 Rajkumar SV, Jacobus S, Callander NS *et al.* Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 11(1), 29–37 (2010).

63 Vesole D, Jacobus S, Rajkumar S *et al.* Lenalidomide plus low-dose dexamethasone (Ld): superior one and two year survival regardless of age compared to lenalidomide plus high-dose dexamethasone (LD) (Abstract 308). *Blood* 116 (2010).

64 Kumar S, Rajkumar SV. Thalidomide and lenalidomide in the treatment of multiple myeloma. *Eur. J. Cancer* 42(11), 1612–1622 (2006).

65 Dimopoulos M, Spencer A, Attal M *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* 357(21), 2123–2132 (2007).

66 Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. *N. Engl. J. Med.* 354(19), 2079–2080 (2006).

67 Paripati H, Stewart AK, Cabou S *et al.* Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. *Leukemia* 22(6), 1282–1284 (2008).

68 Kumar S, Dispenzieri A, Lacy MQ *et al.* Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia* 21(9), 2035–2042 (2007).

69 Mark T, Stern J, Furst JR *et al.* Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma. *Biol. Blood Marrow Transplant.* 14(7), 795–798 (2008).

70 Giralt S, Stadtmauer EA, Harousseau JL *et al.*: International Myeloma Working Group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia* 23(10), 1904–1912 (2009).

71 Badros A, Barlogie B, Siegel E *et al.* Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *Br. J. Haematol.* 114(3), 600–607 (2001).

72 Palumbo A, Triolo S, Baldini L *et al.* Dose-intensive melphalan with stem cell support (CM regimen) is effective and well tolerated in elderly myeloma patients. *Haematologica* 85(5), 508–513 (2000).

73 Palumbo A, Triolo S, Argentino C *et al.* Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood* 94(4), 1248–1253 (1999).

74 Palumbo A, Bringhen S, Petrucci MT *et al.* Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood* 104(10), 3052–3057 (2004).

75 Attal M, Harousseau JL, Leyvraz S *et al.* Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 108(10), 3289–3294 (2006).

76   Spencer A PH, Roberts A. Thalidomide improves survivals when used following ASCT. *Hematologica* 92(Suppl.), 7b (2007).

77   Abdelkefi A, Ladeb S, Torjman L *et al.* Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood* 111(4), 1805–1810 (2008).

78   Ludwig H, Adam Z, Tothova E *et al.* Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma. *Haematologica* 95(9), 1548–1554 (2010).

79   Kumar SK, Mikhael JR, Buadi FK *et al.* Management of newly diagnosed symptomatic multiple myeloma: updated Mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines. *Mayo Clin. Proc.* 84(12), 1095–1110 (2009).

80   Jagannath S, Barlogie B, Berenson JR *et al.* Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. *Cancer* 103(6), 1195–1200 (2005).

81   Chen N, Lau H, Kong L *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J. Clin. Pharmacol.* 47(12), 1466–1475 (2007).