Chapter 10
Early Combination Studies in Multiple Myeloma

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10.1 Introduction

Multiple myeloma (MM) is the second most common haematological malignancy. It accounts for 20,580 new cancer cases in the USA in 2009, including 11,680 cases in men, 8,900 cases in women and 10,580 deaths overall [1]. Although the disease remains still incurable, outcomes have improved substantially over recent years, thanks to the use of high-dose therapy and the availability of novel agent-based therapies [2, 3].

Prolongation of both progression-free survival (PFS) and overall survival (OS) remains the main and ultimate goal, but newer and more effective therapies enabled to achieve a complete response (CR) in a larger proportion of patients.

The proteasome inhibitor bortezomib and the immunomodulatory agents thalidomide and lenalidomide are basic components of first-line therapy. Different induction therapies combining novel agents have been introduced for the treatment in both transplant and non-transplant settings. Physicians should choose the best treatment strategy by taking into account patients' baseline comorbidities and the possible regimen-associated toxicities, in particular peripheral neuropathy, thrombotic risk, changes in renal function and bone disease.

Despite recent advances, patients with MM eventually relapse. Efforts to prolong PFS and at least ensure long-term survival with a good quality of life are needed. Several studies have recently focused on the role of achieving a CR. In the transplant setting, CR was found to be closely related to overall survival. Conversely, CR was not associated with a survival advantage in elderly patients, mainly due to the small proportion of subjects achieving a CR. With the introduction of novel agents, a greater number of elderly patients were able to obtain a CR, but only rarely was

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this associated with an enhanced survival. The achievement of a durable CR remains a crucial treatment goal, but it should carefully be balanced with an acceptable toxicity. Longer follow-up is still required to assess the impact of this increased CR on long-term survival [4–6].

10.2 Diagnosis and Treatment Strategy

MM is characterized by malignant plasma cell infiltration in the bone marrow and is associated with an increased level of monoclonal protein in the blood and/or urine. Besides the monoclonal protein, the presence of an abnormal serum-free light-chain ratio is a further sign of MM. Identifying symptomatic MM is the very first step to start treatment. Patients with symptomatic MM should be treated immediately, while asymptomatic patients do not benefit from early intervention.

Symptomatic disease is defined by evidence of end-organ damage caused by plasma cells proliferation according to the CRAB criteria: C, hypercalcemia (>11.5 mg/dL); R, renal failure (serum creatinine >1.73 mmol/L); A, anaemia (haemoglobin <10 g/dL or >2 g/dL below the lower limit of normal); and B, bone disease (lytic lesions, severe osteopenia or pathologic fractures) [7]. Afterwards, physicians should recognize organ damage and its correlation with MM and finally choose the most appropriate treatment approach [8].

A preliminary distinction within MM patient population is needed. The choice of treatment is based on both scientific evidence and patient's characteristics, in particular age. Young patients are subjects younger than 65 years, usually fit enough and without severe comorbidities, who are able to undergo intensive treatments or repetitive therapies. This group of patients is commonly considered eligible for autologous stem cell transplantation (ASCT). On the contrary, elderly patients are older than 65 years or have serious comorbidities. These patients are usually not considered ASCT candidates, and a gentler approach is necessary. However, physiological age and chronological age do not always correspond, and in some countries, like the USA, a greater emphasis is placed on the former rather than the latter. The incidence of MM varies between the two groups: the median age at diagnosis is 70 years, with 36% of patients younger than 65 years, 27% aged 65 to 74 years and 37% older than 75 years [9].

Other factors may determine whether a patient is eligible for ASCT or not, such as performance status, impaired renal failure and comorbidities. Patients with normal cardiac function (normal electrocardiogram [EKG] and echocardiography or multiple-gated acquisition (MUGA) evaluation and New York Heart Association [NYHA] class I/II), normal pulmonary function (normal chest X-ray, normal spirometry and normal diffusion capacity), normal liver function and normal renal function are good candidates for ASCT. Reduced dose-intensity transplantation (melphalan 100 mg/m^2, Mel100) may be a valuable option for patients with a good performance status and a physiological age ranging between 65 and 75 years [10].

The major adverse events associated with novel agents include venous thromboembolism (thalidomide and lenalidomide), myelosuppression (lenalidomide and bortezomib), gastrointestinal discomfort and peripheral neuropathy (thalidomide and bortezomib). These toxicities are easily manageable by using appropriate supportive care, dose reduction and eventually drug interruption. During treatment, a constant monitoring is needed to enable physicians to intervene promptly.

The National Cancer Institute Toxicity Criteria (NCI-CTC) are used to grade adverse events. At the occurrence of any serious adverse event, namely grade 4 or higher haematological or grade 3 or higher non-haematological toxicities, treatment should be immediately withheld. It can be restarted once the event resolves completely or turns into a grade 1, and appropriate dose reductions are necessary [11].

Prognostic factors play a controversial role in determining the best treatment approach for MM. According to the International Staging System (ISS), symptomatic patients may be classified in three different risk groups: stage I (serum β2-microglobulin < 3.5 mg/L and serum albumin ≥ 35 g/L) is associated with a median survival of 62 months, stage II (serum β2-microglobulin > 3.5 mg/L and serum albumin < 35 g/L, or serum β2-microglobulin 3.5–5.5 mg/L) is associated with median survival of 44 months and stage III (β2-microglobulin ≥ 5.5 mg/L) is associated with a median survival of 29 months [12]. Serum-free light-chain incorporated into the ISS may improve the risk stratification [12, 13]. Chromosomal abnormalities can be detected by using cytogenetics and fluorescent in situ hybridization (FISH). In particular, patients with isolated deletion 13 (del13) on FISH analysis do not have a worse outcome, unless this abnormality is associated with 17p deletion (del17) or t(4;14). By FISH, t(4;14) and t(14:16) are associated with poorer outcome, t(11:14) does not have negative impact, and hyperdiploid is associated with more favourable outcome. Although new drugs, such as bortezomib and/or lenalidomide, may overcome poor prognosis, no specific therapy is routinely recommended for patients with chromosome abnormalities. Risk stratification on the basis of cytogenetics or FISH warrants confirmation from further studies with large numbers of patients [14].

This chapter will provide an overview of the latest combinations including novel agents used for the treatment of both young and elderly patients with newly diagnosed MM.

10.3 Therapeutic Options for Young Patients with Newly Diagnosed MM

10.3.1 The Traditional Approach: Vincristine plus Adriamycin and Thalidomide (VAD)

Since its introduction in the 1980s, VAD combination became one of the most commonly used treatments for young patients with MM eligible for ASCT. Patient deemed as candidates for transplant would receive VAD for 4–6 cycles and then proceed to

collection of stem cells and to transplantation. VAD was then adopted as the standard induction regimen for MM in major randomized studies, leading to a partial response (PR) rate ranging from 52 to 63%, with 3 to 13% of CR rate [13].

In recent years, the treatment of myeloma has undergone substantial changes. The use of novel agents, such as the first in-class proteasome inhibitor bortezomib and the immunomodulatory drugs (IMIDs) thalidomide and lenalidomide, in combination with established antimyeloma agents such as dexamethasone, adriamycin and cyclophosphamide, provided physicians with various new and more effective combinations that have replaced VAD regimen. Here follows a description of the main induction treatments for myeloma patients eligible for ASCT.

10.3.2 The Latest Combinations Including Novel Agents

10.3.2.1 Thalidomide-Based Therapies

The use of thalidomide in combination with adriamycin and dexamethasone (TAD) has been investigated in the prospective phase III HOVON-50/GMMG-HDR study. This trial explored the role of TAD in comparison with VAD as induction treatment [15]. One thousand two hundred and forty patients aged 34 to 65 years were enrolled in this study. A first interim analysis was performed on 402 patients, 201 per each treatment group. The at least PR rate after the 3 planned courses of TAD was significantly higher compared with the response after 3 courses of VAD (72% vs. 54%, $P<0.001$). The corresponding figures for the very good PR (VGPR) were 33% vs. 15% ($P<0.001$), with 4% of CR in the TAD group as compared to 2% in the VAD group. Despite the better quality of response induced by TAD, these results should be balanced against the greater proportion of venous thromboembolism (VTE) associated with the use of thalidomide: induction with TAD caused 8% of VTE, while the incidence of VTE in the VAD group was 4% only ($P=0.08$). No other significant difference in terms of serious adverse events was detected between the two groups. It is not yet known whether the higher responses achieved with TAD translate into prolonged event-free survival (EFS) and overall survival (OS). The benefit in favour of TAD remained after ASCT when considering the VGPR rate but not for the CR rate. This also translated into a superior PFS for TAD compared to VAD (33 months vs. 25 months, $P<0.001$), but OS was similar (59 months vs. 62 months) [13].

The British group explored the role of thalidomide in combination with cyclophosphamide and dexamethasone (CTD), compared to cyclophosphamide plus VAD (CVAD) as induction therapy before ASCT [16]. A total of 1,800 patients were enrolled in this large study. Preliminary results were in favour of CTD, which led to better responses than CVAD: at least PR rate was 96% after induction with CTD vs. 83% after CVAD and CR rates were 20% vs. 12%, respectively. Higher responses with CTD were also confirmed after ASCT, thus confirming its superiority over CVAD. A longer follow-up of patients entered into this large study will assess whether these increased and enhanced responses will translate into improved PFS and OS.

10.3.2.2 Bortezomib-Based Therapies

The association bortezomib-dexamethasone (VD) is a valuable induction option before ASCT. The IFM phase III study compared the combination VD with the standard VAD [17]. Patients were randomized to 4 arms: 119 patients received induction with VD followed by consolidation with dexamethasone, cyclophosphamide, etoposide and platinum (DCEP); 121 patients received VD without subsequent consolidation; 121 patients received VAD followed by DCEP and 121 received VAD without subsequent consolidation. After 4 cycles, VD induction resulted in higher response rates than VAD: in the intention to treat analysis, VD resulted in significantly higher CR plus near CR as compared to VAD (21% vs. 8%, $P=0.0023$) and at least VGPR of 47% vs. 19%, respectively ($P<0.0001$). The advantage obtained with VD was also maintained after ASCT, but the subsequent consolidation DCEP did not increase response rates. The incidence of adverse events was similar in the two groups (38% vs. 41%, respectively); serious adverse events were less frequent with VD than with VAD (25% vs. 31%) and caused death in less than 1% of patients who received induction with VD and in 3% of those who received induction treatment with VAD. Despite its higher efficacy, VD was associated with a higher incidence of all grade neuropathy than VAD (35% vs. 23%).

The role of bortezomib induction has been also explored in a recent phase III study conducted by the HOVON group [18]. In this study the combination of bortezomib–adriamycin–dexamethasone (PAD) was compared with VAD regimen. At least PR achieved with PAD was 78% and was significantly higher than 54% achieved after induction with VAD ($P<0.001$). At least VGPR was 42% after induction with PAD and 14% after VAD ($P<0.001$), with few CR (7% vs. 2%, $P<0.001$), which increased after transplantation (21% vs. 9%, $P<0.001$). Despite better responses with PAD, induction with VAD proved to be less toxic: in particular, grade 2 to 4 peripheral neuropathy occurred in 40% of patients in the PAD group and in 18% of patients who received induction with VAD; similarly, deep vein thrombosis occurred in 4% and 3% of patients (P<0.001), respectively.

An open, prospective, multicenter, uncontrolled phase II study conducted in Germany further investigated the role of bortezomib-containing induction regimens in combination with cyclophosphamide and dexamethasone (VCD) [19]. In this study, 200 patients aged up to 60 years with untreated myeloma were enrolled to receive 3 induction cycles with VCD. At least PR rate was 84%, with a CR rate of 12%. Eighty-four patients (24%) experienced a serious adverse event, which was due to bortezomib in 16% of patients, cyclophosphamide in 14% of patients and dexamethasone in 9% of patients. The mortality rate was 1% only. Fifty-three percent of the patients experienced grade 3 to 4 adverse events: grade 3 to 4 infections were reported in 2%, and grade 3 paraesthesia occurred in 2% of patients. These results confirm that VCD is a highly effective induction option for patients younger than 60 years. The benefits of VCD are further supported by another smaller study, where 33 patients were included [20]. By intention to treat, at least PR rate was 88%, with 22% of patients achieving VGPR and 39% of CR/near CR rate. Grade 3 and 4 toxicities included neutropenia (13%), thrombocytopenia (25%), hyperglycemia

(13%), thrombosis (7%) and peripheral neuropathy (7%). Grade 1 to 3 peripheral neuropathy was the main toxicity associated with this regimen; no grade 4 neuropathy was reported.

10.3.2.3 Lenalidomide-Based Combinations

Different studies have been designed to evaluate the feasibility and efficacy of lenalidomide-containing regimens as induction therapy in untreated patients with MM. The randomized ECOG trial compared lenalidomide and high-dose dexamethasone (RD; with dexamethasone given at 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle) vs. lenalidomide plus low-dose dexamethasone (Rd; with dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle) showing a better short-term OS and lower toxicity with Rd [21].

A case-match study proved that the combination lenalidomide–dexamethasone–clarithromycin (BiRD) is superior to Rd [22]. Seventy-two newly diagnosed patients with myeloma received BirD regimen. In both groups patients were allowed to discontinue treatment to pursue transplant. CR was significantly higher with BiRd compared to Rd (46% vs. 14%, respectively, $P<0.001$); similarly, VGPR or better was higher with BiRd (74% vs. 33%, $P<0.001$). Median time to progression (48.3 vs. 27.5 months, $P=0.071$) was higher with BirD, and there was a trend towards better OS no statistically significant (3-year OS –90% vs. 73%, HR 0.48; 95% CI 0.17–1.37; $P=0.170$). Main grade 3–4 toxicities with BiRd were haematological, in particular thrombocytopenia (24% vs. 8%, $P=0.012$), whereas neutropenia was similar between the 2 groups (19% vs. 17%, $P=0.665$). Infections (17% vs. 10%, $P=0.218$) and dermatological toxicity (12% vs. 4%, $P=0.129$) were higher in patients who received Rd. The rate of venous thromboembolism was similar in the two groups (10% vs. 12%, respectively, in Rd and BiRd patients, $P=0.596$). This analysis shows that there may be a significant additive value when clarithromycin is added to Rd as induction treatment; however, these results still need to be confirmed in future prospective, randomized phase III studies.

Kumar and colleagues confirmed the additive positive effect of cyclophosphamide in combination with Rd (RCd) as initial therapy for newly diagnosed MM patients [23]. In this phase II dose finding pilot study of 53 patients, the best response was CR 2%, VGPR 38% and PR 43%. Grade 4 haematological toxicity was detected in 15% of patients, whereas 11% of patients experienced a severe non-haematological adverse event attributed to the drug (thrombosis, confusion, depression and sepsis). Myelosuppression was a significant toxicity and was lower with decreased dose of cyclophosphamide without any apparent loss of responses.

10.3.2.4 Bortezomib and IMID-Based Combinations

Several studies have been designed to assess the activity of bortezomib associated with either thalidomide or lenalidomide. A phase III study by Cavo and colleagues

investigated the efficacy and safety of bortezomib–thalidomide–dexamethasone (VTD) vs. TD as induction and consolidation therapies in a randomized trial of 474 patients [24]. The response rate was significantly higher with VTD induction therapy compared to TD: CR 19% vs. 5% and at least VGPR 62% vs. 31% ($P<0.001$). However, no difference in OS was seen between the two treatment groups, and longer follow-up is required. Grade 3 peripheral neuropathy was reported more frequently with VTD induction therapy than with TD (10% vs. 2%, respectively; $P<0.001$). The once-weekly administration of bortezomib and a reduced dose of thalidomide in VTD as consolidation therapy resulted in a dramatic decrease in the frequency of grade 3 peripheral neuropathy (2%).

Richardson and colleagues performed a phase I/II study to evaluate the role of bortezomib–lenalidomide–dexamethasone (VRD) in front-line treatment [25]. Sixty-six patients received 8 three-week cycles of the study combination. VRD showed to be highly effective, reporting a response rate of 100%, including 74% of at least VGPR. After a median follow-up of 21 months, estimated 18-month PFS and OS for the combination treatment were 75% and 97%, respectively. VRD demonstrated favourable tolerability as well: grade 3 to 4 haematologic toxicities included lymphopenia (14%), neutropenia (9%) and thrombocytopenia (6%). Thrombosis was rare (6% overall) and no treatment-related mortality was seen.

A most powerful combination of bortezomib, lenalidomide, cyclophosphamide and dexamethasone (VRCD) was studied in 25 patients to define the dose [26]. The maximum tolerated dose was not reached, so the recommended phase II 2 cyclophosphamide dose in VDCR is 500 mg/m^2, which was the highest dose tested. The overall response rate was 96%, including 20% stringent CR, 40% CR/near CR and 68% at least VGPR. This regimen showed to be effective and well tolerated.

Efficacy and safety profile of regimens discussed above are summarized in Tables 10.1 and 10.2.

10.4 Therapeutic Options for Elderly Patients with Newly Diagnosed MM

10.4.1 The Old Standard: Melphalan and Prednisone (MP)

Newly diagnosed elderly patients with MM, as well as younger patients ineligible for ASCT, have traditionally been treated with the oral combination MP for more than 40 years. A meta-analysis including 27 randomized studies, including MP and other chemotherapy-containing regimens, showed that higher response rates were reported with chemotherapy compared with MP (60% vs. 53%, $P<0.0001$), and MP was better tolerated; no significant difference in terms of survival was detected ($P=0.6$) [27].

Similar results were seen in a randomized trial comparing MP with melphalan plus dexamethasone (MD), high-dose dexamethasone (HD) and HD plus interferon-α. Response rates and PFS were superior in patients receiving melphalan-containing

Table 10.1 Efficacy of regimens used as front-line treatment in young patients with multiple myeloma

Regimen		*N*	Pre-transplant		Post-transplant		PFS/ EFS/TTP	OS	References
			At least PR	CR + VGPR	At least PR	CR + VGPR			
Thalidomide-based									
TAD vs. VAD	*TAD* Thal: 200–400 mg po days 1–28 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4, 9–12, 17–20 *VAD* Vcr: 0.4 mg IV days 1–4 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4, 9–12, 17–20	402	72% vs. 54%	33% vs. 15%	76% vs. 79%	49% vs. 32%	PFS 33 vs. 25 months	59 vs. 62 months	Lokhorst et al. [15]
CTD vs. CVAD	*CTD* CTX: 500 mg days 1,8,15 Thal:100 mg/day Dexa: 40 mg days 1–4,12–15 *CVAD* CTX: 500 mg days 1–8,15 Vcr: 0,4 mg IV days 1–4 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4, 9–12	254	96% vs. 83%	20% vs. 12% (CR)	99% vs. 96%	58% vs. 41% (CR)	NA	NA	Morgan et al. [16]

Bortezomib-based									
VD vs. VAD	*VD* Vel: 1,3 mg/m^2 days 1,4,8,11 Dexa: 40 mg po days 1–4 9–12 *VAD* Vcr:0,4 mg IV days 1–4 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4 9–12, 17–20	480	NA	47% vs. 19%	NA	72% vs. 51%	NA	NA	Harousseau et al. [17]
PAD vs. VAD	*PAD* Vel: 1.3 mg/m^2 IV days 1, 4, 8, 11 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4, 9–12, 17–20 *VAD* Vcr: 0.4 mg IV days 1–4 Doxo: 9 mg/m^2 IV days 1–4 Dexa: 40 mg po days 1–4, 9–12, 17–20	827	78% vs. 54%	42% vs. 14%	88% vs. 75%	62% vs. 36%	PFS 35 vs. 28 months	NA	Sonneveld et al. [18]
VCD	Vel: 1,3 mg/m^2 days 1,4,8,11 CTX: 900 mg IV days 1 Dexa: 40 mg po days 1–2, 4–5, 8–9, 11–12	200	84%	12% (CR)	NA	NA	NA	NA	Knop et al. [19]
VCD	Vel: 1.3 mg/m^2 IV days 1, 4, 8, 11, CTX: 300 mg/m^2 po days 1, 8, 15, 22 Dexa: 40 mg po days 1–4, 9–12, 17–20	33	88%	61%	NA	NA	NA	NA	Reeder et al. [20]

(continued)

Table 10.1 (continued)

Regimen		*N*	Pre-transplant		Post-transplant		PFS/ EFS/TTP	OS	References
			At least PR	CR + VGPR	At least PR	CR + VGPR			
Lenalidomide-based									
RD vs. Rd	*RD* Len: 25 mg days 1–21 Dexa: 40 mg days 1–4, 9–12, 17–20 *Rd* Len: 25 mg days 1–21 Dexa: 40 mg days 1, 8, 15, 22	445	81% vs. 70%	50% vs. 40%	NA	NA	NA	1-year.OS 87% vs. 96% 2-year OS 75% vs. 87%	Rajkumar et al. [21]
BiRD vs. Rd	*BiRD* Len: 25 mg po days 3–21(cycle1) and days 1–21 of subsequent cycles Dexa: 40 mg po days 1, 2, 3, 8, 15 and 22 (cycle 1) and days 1, 8, 15, 22 of subsequent cycles Cl: 500 mg po twice daily *Rd* Len: 25 mg po days 1–21 Dexa: 40 mg po days 1, 8, 15, 22	144	NA	74% vs. 33%	NA	NA	TTP 48 vs. 27.5 months	3-year OS 90% vs. 73%	Gay et al. [22]
RCd	Len: 15 mg days 1–21 CTX: 300 mg or 300 mg/m^2 days 1, 8, 15 Dexa: 40 mg 1,8,15, 22	53	83%	40%	NA	NA	NA	NA	Kumar et al. [23]

Bortezomib- and IMID-based									
VTD vs. TD	*VTD* Vel:1.3 mg/m^2 IV days 1, 4, 8, 11 Thal: 200 mg/d po days 1–63 Dexa: 320 mg/cycle *TD* Thal: 200 mg/d po days 1–63 Dexa: 320 mg/cycle	474	NA	62% vs. 31%	NA	80% vs. 65%	2-year PFS 85% vs. 75%	OS no differences	Cavo et al. [24]
VRD	Vel: 1.0–1.3 mg/m^2 IV days 1, 4, 8, 11 Len: 15–25 mg po days 1–14 Dexa: 40 or 20 mg po days 1, 2, 4, 5, 8, 9, 11, 12	66	100%	74%	NA	NA	18-month PFS 75%	18-month OS 97%	Richardson et al. [25]
VRCD	Vel:1.3 mg/m^2 IV days 1, 4, 8, 11 CTX: 500 mg/m^2 IV days 1 and 8 (MTD) Dexa:40 mg po days 1, 8, 15 Len: 15 mg po days 1–14	25	96%	68%	NA	NA	NA	NA	Kumar et al. [26]

N indicates number of patients, *CR* complete remission, *PR* partial response, *VGPR* very good partial response, *PFS* progression-free survival, *EFS* event-free survival, *TTP* time to progression, *OS* overall survival, *M* melphalan, *P* prednisone, *T* thalidomide, *Vel* bortezomib, *Len* lenalidomide, *CTX* cyclophosphamide, *Dexa* dexamethasone, *Doxo* doxorubicin, *Vcr* vincristine, *Cl* clarithromycin. *TAD* thalidomide–Adriamycin–dexamethasone, *VAD* vincristine–adriamycin–dexamethasone, *CTD* cyclophosphamide–thalidomide–dexamethasone, *CVAD* cyclophosphamide–bortezomib–thalidomide–dexamethasone, *VD* bortezomib–dexamethasone, *VCD* bortezomib–cyclophosphamide–dexamethasone, *PAD* bortezomib–doxorubicin–dexamethasone, *RD* lenalidomide plus high-dose dexamethasone, *Rd* lenalidomide plus low-dose dexamethasone, *BiRD* clarithromycin–lenalidomide–dexamethasone, *RCd* lenalidomide–cyclophosphamide plus low-dose dexamethasone, *VTD* bortezomib–thalidomide–dexamethasone, *TD* thalidomide–dexamethasone, *VRD* bortezomib–lenalidomide–dexamethasone, *VRCD* bortezomib–lenalidomide–cyclophosphamide–dexamethasone, *NA* not available

Table 10.2 Safety (grade 3–4 adverse events) of regimens used as front-line treatment in young patients with multiple myeloma

Regimen	*N*	Neutropenia	Thrombocytopenia	Infection	Peripheral neuropathy	VTE	References
Thalidomide-based							
TAD	201	NA	NA	NA	12% (neurology)	8%	Lokhorst et al. [15]
TD	238	NA	NA	NA	2%	NA	Cavo et al. [24]
Bortezomib-based							
VD	240	NA	NA	NA	Grade 1-4, 35%	NA	Harousseau et al. [17]
PAD	413	3%	10%	26%	24%	4%	Sonneveld et al. [18]
VCD	200	NA	NA	2%	2%	NA	Knop et al. [19]
VCD	33	13%	25%	NA	7%	7%	Reeder et al. [20]
Lenalidomide-based							
RD	223	12%	6%	16%	2%	26%	Rajkumar et al. [21]
Rd	222	20%	5%	9%	2%	12%	Rajkumar et al. [21]
Rd	72	17%	8%	17%	NA	10%	Gay et al. [22]
BiRD	72	19%	24%	10%	NA	12%	Gay et al. [22]
Bortezomib- and IMID-based							
VTD	236	NA	NA	NA	9.7%	NA	Cavo et al. [24]
VRD	66	9%	6%	NA	NA %	Grade 1-4, 6%	Richardson et al. [25]
VRCD	25	Grade 3, 20% Grade 4, 4%	Grade 4, 12%	NA	48%	0	Kumar et al. [26]

N indicates number of patients, *TAD* thalidomide-adriamycin-dexamethasone, *TD* thalidomide-dexamethasone, *VD* bortezomib-dexamethasone, *PAD* bortezomib-adriamycin-dexamethasone, *VCD* bortezomib-cyclophosphamide-dexamethasone, *RD* lenalidomide-high-dose dexamethasone, *Rd* lenalidomide-low-dose dexamethasone, *BiRD* lenalidomide-dexamethasone-clarithromycin, *VTD* bortezomib-thalidomide-dexamethasone, *VRD* bortezomib-lenalidomide -dexamethasone, *VRCD* bortezomib-lenalidomide-cyclophosphamide-dexamethasone, *NA* not available

regimen, such as MP or MD, but this did not translate into an improved survival. Moreover, dexamethasone-containing regimens proved to be more toxic than MP, thus negatively affecting outcome [28].

In another randomized study comparing MP with TD, a higher response rate and longer PFS were reported with TD. However, patients receiving MP had a significantly longer survival, probably due to the better tolerability of MP compared to TD: extra-haematological toxicities, mainly related to high-dose dexamethasone, were superior in patients treated with TD, thus leading to a higher treatment-discontinuation rate. During the first year of therapy, non-disease-related deaths in the TD group were doubled compared to MP, with infections being the primary cause of death, especially in patients older than 72 years with poor performance status [29].

These findings suggest the benefit of incorporating an alkylating agent in the induction regimens of elderly MM patients and provided the rationale to explore the role of novel agents in combination with the standard MP.

10.4.2 New Treatments Containing Novel Agents

10.4.2.1 Thalidomide-Based Therapies

The role of thalidomide plus MP (MPT) has been extensively explored. Five randomized studies compared the combination MPT with the standard MP: PR rate was 42–76% with MPT and 28–48% with MP, and at least VGPR rate was 15–47% with MPT and 6–8% with MP; longer PFS (14–28 months) was reported in the MPT arms [10, 30–35]. In the two French studies, the PFS advantage observed with MPT also translates into a significant OS improvement (45–52 vs. 28–32 months) [10, 34], but this trend was not confirmed in the three other trials [30–33, 35]. In the Nordic study (NMSG), these results were also affected by the use of higher doses of melphalan (0.25 mg/kg) and thalidomide (200 mg every day) in a patient population older than 75 years and with approximately one-third patients having poor performance status (World Health Organization [WHO] performance status of 3 or 4 in 30% of patients) [31].

A recent meta-analysis pooled the existing data related to the efficacy of MP vs. MPT [36]. A total of 1,682 patients were included, 868 in the MP arm and 814 in the MPT arm. Median PFS was 15 (14, 17) months in the MP arm and 20 (19, 22) months in the MPT arm. Median OS was 33 (95% CI 30.4–36.5) months in the MP arm and 39 (35.6–39.0) months in the MPT arm. Overall hazard ratio of MPT compared to MP was 0.67 (0.55–0.80) for PFS when a random effects model was used and 0.82 (0.66–1.02) for OS. These results confirmed the role of MPT as one of the new standards of care for newly diagnosed elderly patients.

The main toxicities associated with MPT were grade 3–4 neutropenia, ranging from 16 to 48% and mainly linked to melphalan administration; peripheral neuropathy, reported in 6–20% of patients, particularly related to thalidomide; and venous thromboembolism (VTE) that varies from 3% to 12% [10, 30–34].

Another alkylating agent, cyclophosphamide, has been assessed in combination with thalidomide and dexamethasone (CTD). The Medical Research Council (MRC) Myeloma IX trial analysed and compared the combination CTD with the standard MP in 900 patients. Patients treated with CTD had higher responses than MP (at least PR was 83% vs. 46% and CR was 21% vs. 4%, respectively), but this did not translate into a longer survival. CTD showed to be a valuable option for elderly patients and also proved to be well tolerated, despite a slight increase of VTE [37].

An Italian study also reported positive results with thalidomide in association with pegylated liposomal doxorubicin and dexamethasone (ThaDD), followed by maintenance with thalidomide, in 62 patients transplant ineligible [38]. ThaDD resulted in 92% of at least PR, including 59% patients with at least VGPR and 24% of CR. After a median follow-up of 36 months, median TTP and PFS were 31 and 39 months, respectively, and five-year OS was 49%. Treatment was well tolerated; grade 3 or higher infections were reported in 14% of patients, thromboembolism, peripheral neuropathy in 10% and neutropenia in 8% of patients after 6 courses of therapy.

10.4.2.2 Lenalidomide-Based Therapies

A phase III randomized trial showed the superiority of RD vs. high-dose dexamethasone alone. Results with RD are promising: CR rate was 22% and was higher than with dexamethasone alone. A significant improvement in 1-year PFS (77% vs. 55%, $P=0.002$), without difference in OS, was observed with RD. As expected, RD also proved to be more toxic with grade 3–4 neutropenia 14% vs. 3% ($P=0.001$) [39].

In newly diagnosed MM, Rd showed to improve TTP, PFS and OS as compared to RD. In particular, the 1-year OS was 96% vs. 87% ($P<0.001$) and the 2-year OS was 87% vs. 75% ($P<0.001$). Responses were in favour of the high-dose dexamethasone regimen: CR rate was 5% vs. 4% ($P=0.04$), at least PR was 81% vs. 70% ($P=0.009$) with RD and Rd, respectively. However, RD administration was associated with a higher proportion of early deaths and adverse events, particularly thromboembolic events. Because of the safety advantages associated with Rd, patients crossed over to low-dose dexamethasone treatment, thus resulting in the premature interruption of the protocol. As a consequence of the crossover, 3-year OS rates are similar in the two treatment groups. A landmark analysis at 4 months was performed to assess the impact of the two different approaches: 3-year OS for patients who continued on primary therapy with RD beyond 4 months was 79%, whereas in patients who stopped treatment after 4 months, it was only 55% [21]. Considering its good tolerability and efficacy, Rd continued until progression can be considered a valuable option for patients older than 65 years.

The ECOG phase III study analysed the role of RD vs. Rd in a subset of 147 patients older than 70 years. PR was 75% with RD and 74% with Rd, including an at least VGPR of 42% and 48%, respectively. Median PFS was 16 months with RD and 22 months with Rd ($P=0.11$). Survival was significantly superior in the Rd

group, and 3-year OS was 73% compared to 61% with RD ($P=0.03$). Toxicities were again higher with RD (grade 3–4 non-haematologic toxicities with RD 78% and Rd 59%) and included 30% of VTE and 20% of infections, while the corresponding figures for Rd were 20% and 10%. This study further supported the positive role of Rd also in very elderly patients, and future comparison with standard regimen such as VMP is needed [40].

A phase I/II dose escalating study explored the combination of MP in combination with lenalidomide (MPR). At the maximum tolerated dose (lenalidomide 10 mg/daily for 21 days and melphalan 0.18 mg/kg for 4 days every 4–6 weeks, plus prednisone 2 mg/kg days1–4), PR rate or better was 81%, including 48% of at least VGPR and 24% of patients with immunofixation-negative CR [41]. The 2-year EFS and OS rates for all patients were 80% and 91%, respectively [42]. These data provided the basis for the European Myeloma Network phase III study, comparing MP with MPR, with or without lenalidomide maintenance [43]. Responses were significantly higher with MPR followed by lenalidomide maintenance (MPR-R) compared to MP: at least PR rate was 77% vs. 50%, with 23% vs. 9% VGPR and 10% vs. 3% CR, respectively ($P<0.001$). Similarly, the median PFS was higher in patients who received MPR-R than in those who received MP (31 months vs. 14 months). No differences were detected in the median OS (45 months in the MPR-R group vs. not reached in the MP group; $P=0.81$). The main grade 3 toxicities associated with both regimens were neutropenia (67% of patients treated with MPR-R vs. 29% with MP), thrombocytopenia (35% vs. 12%), infections (9% vs. 7%) and fatigue (5% vs. 3%). No grade 3–4 peripheral neuropathy was reported in the two groups. These data suggest that MPR-R may be considered a new and valuable option for myeloma patients in the non-transplant setting.

10.4.2.3 Bortezomib-Based Therapies

The VISTA trial explored the role of the combination bortezomib, melphalan and prednisone (VMP) compared to standard MP. This is the largest MP-based phase III study so far conducted, and a total of 682 patients were evaluated. VMP proved to be superior to the traditional MP for all efficacy endpoints: CR rate was 30% vs. 4% ($P<0.001$), median TTP was 24 months vs. 16.6 months ($P<0.001$) and the 3-year OS was 72% vs. 59% ($P=0.0032$) [44]. Haematologic toxicities were similar in the two groups, with grade 4 thrombocytopenia (17% in the VMP group vs. 14% in the MP group) and grade 4 neutropenia (10% with VMP vs. 15% with MP) being the most serious toxicities. Peripheral neuropathy (13% with VMP vs. 0% with MP), gastrointestinal adverse events (20% vs. 5%) and fatigue (8% vs. <1%) were higher in patients given VMP than in those given MP. Grade 4 peripheral neuropathy was less common (<1% of VMP patients). The positive results achieved with VMP made it a new standard of care for myeloma patients who are not eligible for ASCT. A recent update of the VISTA trial further confirmed the benefits of the VMP regimen on survival. The 3-year OS from diagnosis was 69% with VMP as compared to 54% with MP. The median survival from start of subsequent therapy was longer with VMP than with MP (30 vs. 22 months; HR 0.815, $P=0.219$) [45].

10.4.2.4 Bortezomib- and Thalidomide-Based Therapies

The new standard VMP has been compared to the combination of bortezomib, thalidomide and prednisone (VTP) as induction therapy in a randomized trial. Response rates were similar between the two groups: at least PR was 79% in both groups, with a CR rate of 22% vs. 27% (*P* nonsignificant [NS]), respectively, in the VMP regimen and VTP regimen. After a median follow-up of 22 months, there were no significant differences between the two arms in terms of 2-year TTP (VMP 75% vs. VTP 70%), PFS (VMP 71% vs. VTP 61%) and OS (VMP 81% vs. VTP 84%). Despite similar responses, VTP was more toxic than VMP: grade 3–4 cardiac toxicity rate was 8.5% vs. 0% ($P<0.001$), thromboembolic events were 4% vs. <1% ($P=$NS) and peripheral neuropathy was 9% vs. 5% ($P=$NS) with VTP and VMP, respectively. Thus, a higher proportion of patients in the VTP group discontinued treatment (17% vs. 8%, $P=0.003$). However, patients receiving VMP had a higher rate of neutropenia (37% vs. 21%, $P=0.003$), thrombocytopenia (22% vs. 12%, $P=0.03$) and infections (7% vs. <1%, $P=0.01$). These results lend further support to good tolerability of VMP, thus confirming its role as new standard of care for elderly myeloma patients [46].

Another recent, US community-based, randomized, phase IIIb study investigated the safety and efficacy of three bortezomib-based regimens (bortezomib–dexamethasone [VD], bortezomib–thalidomide–dexamethasone [VTD] and VMP) in previously untreated MM patients ineligible for high-dose therapy and ASCT. At least PR rate was 60%, 70% and 52% in the VD, VTD and VMP arms, respectively; at least VGPR 15%, 23% and 24%, respectively, including CR/near CR rates of 13%, 18% and 15%. VD was better tolerated, with a lower incidence of grade 3–4 AEs (58% compared to 71% seen in both the VTD and VMP arms). The incidence of serious AEs was 39% with VD, 50% with VTD and 36% with VMP. Discontinuation due to AEs was 10% in VD, 18% in VTD and 16% in VMP arm. VTD thus showed to be rather toxic. Consistently, any grade peripheral neuropathy occurred in 29% of patients in the VD group, 48% in the VTD group and 30% in the VMP group, and the rates of serious thromboembolic events was 6% with VD, 8% with VTD and 3% with VMP [47].

A recent phase III trial compared the combination of bortezomib, melphalan, prednisone and thalidomide followed by maintenance with VT (VMPT-VT) and VMP without maintenance. Responses were in favour of the four-drug regimen: at least PR rate was 89% vs. 81% ($P=0.01$), VGPR rate was 59% vs. 50% ($P=0.03$) and CR rate was 38% vs. 24% ($P=0.0008$), respectively. The improvement in response rate translated into prolonged survival: after a median follow-up of 17.8 months, the 2-year PFS was significantly longer in the VMPT-VT group (70% vs. 58%, HR = 0.62, 95% CI 0.44–0.88, $P=0.008$). No differences in OS were detected between the two arms. Grade 3–4 neutropenia (37% vs. 28%, $P=0.02$) and cardiac complications (10% vs. 5%, $P=0.04$) were more common among VMPT-VT patients. The incidence of other grade 3–4 AEs was similar in the two groups: thrombocytopenia (21% vs. 19%), peripheral neuropathy (5% vs. 8%), infections (12% vs. 9%) and gastrointestinal complications (6% vs. 8%) with VMPT-VT and

VMP, respectively [48]. In both arms, bortezomib was initially administered twice weekly and was subsequently reduced to a once-weekly schedule to reduce toxicity, particularly peripheral neuropathy. After the amendment, the incidence of grade 3–4 peripheral neuropathy considerably decreased in both VMPT-VT (from 18% to 4%, $P=0.0002$) and VMP arms (from 13% to 2%, $P=0.0003$, respectively), without negatively affecting efficacy and PFS [49]. This is the first trial demonstrating the superiority of a 4-drug combination followed by maintenance over the latest standard of care VMP. This study also showed the effectiveness and good tolerability of the once-weekly schedule of bortezomib.

The efficacy of the treatments described above has been summarized in Table 10.3. The most frequent grade 3–4 AEs associated with these treatments have been summarized in Table 10.4. Table 10.5 shows the main treatment-related toxicities associated with the use of novel agents and provide some basic management information.

10.5 Role of Transplant in Elderly Patients

Patients older than 65 years, as well as those with significant comorbidities, are generally considered ineligible for standard melphalan 200 mg/m^2 followed by ASCT. A randomized trial exploring the efficacy of high-dose chemotherapy and transplant in patients with newly diagnosed MM showed a significantly higher 5-year OS in patients younger than 65 years undergoing ASCT compared to elderly patients (68% vs. 50%, respectively; $P=0.008$) [50]. Two randomized studies compared intermediate-dose melphalan (melphalan 100 mg/m^2, Mel100) and reduced-intensity ASCT with standard MP. The first study included patients aged 65 to 70 years and showed an improvement in EFS and OS with reduced-intensity ASCT compared with MP [51]. The second study included patients aged 65–75 years and compared reduced-intensity ASCT with MP and MPT. In this trial, PFS and OS were higher with MPT than with MP or Mel100, and no differences between MP and Mel100 were noted [10]. A recent phase II trial evaluated the efficacy of novel agents incorporated in both pre-transplant induction (PAD) and post-transplant consolidation and maintenance with lenalidomide, in patients aged 65–75 years, who received reduced-intensity ASCT: the CR rate was 13% after induction with bortezomib, 43% after Mel100 and 73% after consolidation-maintenance with lenalidomide. These data show that a sequential approach, including bortezomib as induction, followed by reduced-intensity ASCT and lenalidomide as consolidation-maintenance progressively improves responses, by taking advantage of a subsequent exposure to different drugs. Grade 3–4 toxicities during PAD induction included thrombocytopenia (17%), neutropenia (10%), peripheral neuropathy (16%) and pneumonia (10%). Lenalidomide therapy was well tolerated, with no cumulative or persistent neutropenia (grade 3–4 reported in 16%) and/or thrombocytopenia (6%); pneumonia (5%) and cutaneous rash (4%) were the more frequent extra-haematologic AEs [52].

Table 10.3 Efficacy of regimens used as a front-line treatment in elderly patients with multiple myeloma

Regimen		*N*	CR	≥ PR	PFS/EFS/TTP	OS	References
Thalidomide-based							
MPT	M: 4 mg/m^2 d 1–7 P: 40 mg/m^2 d 1–7 for six 4-week cycles T: 100 mg/day until PD	129	16%	76%	50% at 22 mo	50% at 45 mo	Palumbo et al. [32, 33]
MPT	M: 0.25 mg/kg d 1–4 P: 2 mg/kg d 1–4 T: 400 mg/day for 12 6-week cycles	125	13%	76%	50% at 28 mo	50% at 52 mo	Facon et al. [10]
MPT	M: 0.25 mg/kg d 1–4 P: 2 mg/kg d 1–4 T: 100 mg/day for 12 6-week cycles	113	7%	62%	50% at 24 mo	50% at 45 mo	Hulin et al. [34]
MPT	M: 0.25 mg/kg d 1–4 P: 100 mg d 1–4 T: 200–400 mg/day in a 6-week cycle until plateau T: 200 mg/day until disease progression	182	6%	42%	50% at 20 mo	50% at 29 mo	Waage et al. [31][a]
MPT	M: 0.25 mg/kg P: 1 mg/days 1–5 T: 200 mg/day for eight 4-week cycles, followed by T: 50 mg/day until disease progression	165	2%	66%	50% at 14 mo	50% at 37 mo	Wijermans et al. [35][a]
CTD	C: 500 mg d 1, 8, 15 T: 100–200 mg/day D: 40 mg d 1–4, 12–15 in a 3-week cycles	450	21%	83%	NA	NA	Morgan et al. [37]
ThaDD	Dox: 40 mg/m^2 d 1 D: 40 mg d 1–4, 9–12 T: 100 mg/d continuously	62	24%	92%	NA	66% at 36 mo	Offidani et al. [38]
Lenalidomide-based							
RD	R: 25 mg d 1–21 D: 40 mg d 1, 8, 15, 22 in a 4-week cycle	223	5%	81%	NA	96% at 12 mo	Rajkumar et al. [21]
Rd	R: 25 mg d 1–21 d: 40 mg d 1, 8, 15, 22 in a 4-week cycles	222	4%	70%	NA	87% at 12 mo	Rajkumar et al. [21]

MPR	M: 0.18 mg/kg d 1–4 P: 2 mg/kg d 1–4 for nine 4-week cycles R: 10 mg d 1–21 until relapse or progressive disease	152	10%	77%	50% at 31 mo	50% at 45 mo	Palumbo et al. [43]
Bortezomib-based							
VMP	M: 9 mg/m^2 d 1–4 P: 60 mg/m^2 d 1–4 V: 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 for the first four 6-week cycles; d 1, 8, 15, 22 for the subsequent five 6-week cycles	344	30%	71%	50% at 24 mo	72% at 36 mo	San Miguel et al. [44]
VMP	M: 9 mg/m^2 d 1–4 P: 60 mg/m^2 d 1–4 V: 1.3 mg/m^2 d 1, 8, 15, 22	257	24%	81%	70% at 36 mo	87% at 36 mo	Palumbo et al. [48]
VMP	M: 9 mg/m^2 d 1–4 P: 60 mg/m^2 d 1–4 V: 1.3 mg/m^2 twice weekly (d 1, 4, 8, 11; 22, 25, 29 and 32) for one 6-week cycle, followed by once weekly (d 1, 8, 15 and 22) for five 5-week cycles	344	22%	79%	72% at 24 mo	81% at 24 mo	Mateos et al. [46]
Bortezomib- and thalidomide-based							
VTP	T: 100 mg/day P: 60 mg/m^2 d 1–4 V: 1.3 mg/m^2 twice weekly (d 1, 4, 8, 11; 22, 25, 29 and 32) for one 6-week cycle, followed by once weekly (d 1, 8, 15 and 22) for five 5-week cycles	130	27%	79%	61% at 24 mo	84% at 24 mo	Mateos et al. [46]

(continued)

Table 10.3 (continued)

Regimen		*N*	CR	≥ PR	PFS/EFS/TTP	OS	References
VMPT	M: 9 mg/m^2 d 1–4 P: 60 mg/m^2 d 1–4 V: 1.3 mg/m^2 d 1, 8, 15, 22 T: 50 mg d 1–42 for nine 5-week cycles followed by Bor: 1.3 mg/m^2 every 15 days and T: 50 mg/day as maintenance	254	38%	89%	60% at 36 mo	88% at 36 mo	Palumbo et al. [48]

N indicates number of patients, *CR* complete remission, *PR* partial response, *PFS* progression-free survival, *EFS* event-free survival, *TTP* time to progression, *OS* overall survival, *M* melphalan, *P* prednisone, *T* thalidomide, *V* bortezomib, *R* lenalidomide, *C* cyclophosphamide, *D* high-dose dexamethasone, *d* low-dose dexamethasone, *Dox* doxorubicin, *MPT* melphalan-prednisone-thalidomide, *VMP* bortezomib-melphalan-prednisone, *VTP* bortezomib-thalidomide-prednisone, *VMPT* bortezomib-melphalan-prednisone-thalidomide, *CTD* cyclophosphamide-thalidomide-dexamethasone, *ThaDD* thalidomide-doxorubicin-dexamethasone, *MPR* melphalan-prednisone-lenalidomide, *NA* not available, *PD* progressive disease

[a]Updated information was presented at the meeting (American Society of Clinical Oncology, European Haematology Association and American Society of Hematology congress)

Table 10.4 Safety (grade 3–4 adverse events) of regimens used as front-line treatment in elderly patients with multiple myeloma

Regimen	*N*	Neutropenia	Thrombocytopenia	Infection	Peripheral neuropathy	VTE	References
Thalidomide-based							
MPT	129	16%	3%	10%	8%	9%	Palumbo et al. [32, 33]
MPT	125	48%	14%	13%	6%	12%	Facon et al. [10]
MPT	113	23%[a]	NA	NA	Grade 2-4, 20%	6%	Hulin et al. [34]
MPT	165	NA	NA	14%	9%	3%	Wijermans et al. [35][a]
CTD	450	NA	NA	NA	NA	NA	Morgan et al. [37]
ThaDD	62	8%	0%	14%	10%	10%	Offidani et al. [38]
Lenalidomide-based							
MPR[b]	152	67%	35%	9%	0%	1%	Palumbo et al. [43]
Bortezomib-based							
VMP	344	40%	37%	10%	13%	3%	S Miguel et al. [44]
VMP	257	28%	20%	9%	8%	2%	Palumbo et al. [48]
VMP	344	40%	38%	NA	13%	NA	Mateos et al. [45]
Bortezomib- and Thalidomide-based							
VTP	130	21%	12%	<1%	9%	4%	Mateos et al. [46]
VMPT	254	38%	22%	13%	12%	5%	Palumbo et al. [48]

N indicates number of patients, *MPT* melphalan-prednisone-thalidomide, *VMP* bortezomib-melphalan-prednisone, *VTP* bortezomib-thalidomide-prednisone, *VMPT* bortezomib-melphalan-prednisone-thalidomide, *CTD* cyclophosphamide-thalidomide-dexamethasone, *MPR* melphalan-prednisone-lenalidomide, *NA* not available

[a]Updated information was presented at the meeting (American Society of Clinical Oncology, European Haematology Association and American Society of Hematology congress)

[b]Grade 3 only

Table 10.5 Management of adverse events in multiple myeloma patients treated with novel agents

Adverse event	Antimyeloma agents involved	Management	Dose modification
Neutropenia	Lenalidomide, bortezomib and combinations	G-CSF until neutrophil recovery in case of uncomplicated grade 4 AE or grade 2–3 AEs complicated by fever or infection	25–50% drug reduction
Thrombocytopenia	Bortezomib and combinations, lenalidomide and combinations	Platelet transfusion in case of grade 4 AE	25–50% drug reduction
Anaemia	Bortezomib and combinations, lenalidomide and combinations	Erythropoietin or darbepoietin in case of haemoglobin level ≤ 10 g/dL	25–50% drug reduction
Infection	All the agents	Trimethoprim-co-trimoxazole for *Pneumocystis carinii* prophylaxis during high-dose dexamethasone. Acyclovir or valacyclovir for HVZ prophylaxis during bortezomib-based therapy	25–50% drug reduction
Neurotoxicity	Bortezomib and combinations, thalidomide and combinations	Neurological assessment before and during treatment. Prompt dose reduction of the suspected drug is recommended	Bortezomib: 25–50% reduction for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves to grade 1 or better with restart at 50% dose reduction for grade 2 with pain or grade 3 peripheral neuropathy; treatment discontinuation for grade 4 peripheral neuropathy. Thalidomide: 50% reduction for grade 2 neuropathy; discontinuation for grade 3; resume thalidomide at a decreased dose if neuropathy improves to grade 1
Cutaneous toxicity	Thalidomide and combinations, lenalidomide and combinations	Steroids and antihistamines	Interruption in case of grade 3–4 AE 50% reduction in case of grade 2 AE
Gastrointestinal toxicity	All the agents	Appropriate diet, laxatives, exercise, hydration, antidiarrheic drugs	Interruption in case of grade 3–4 AEs 50% reduction in case of grade 2 AEs

Thrombosis	Thalidomide and combinations, lenalidomide and combinations	Aspirin 100–325 mg if no or one individual/myeloma thrombotic risk factor is present. LMWH or full-dose warfarin if two or more individual/myeloma risk factors are present and in all patients with thalidomide-related risk factors	Drug temporary interruption and full anticoagulation, then resume treatment
Renal toxicity	Lenalidomide	Correct precipitant factors (dehydration, hypercalcemia, hyperuricemia, urinary infections and concomitant use of nephrotoxic drugs)	Reduce dose according to creatinine clearance: If 30–60 mL/min: 10 mg/day; If <30 mL/min without dialysis needing: 15 mg every other day; If <30 mL/min with dialysis required: 5 mg/day after dialysis on dialysis day
Bone pain	None	Start with simple non-opioid analgesics. If no benefit is detected continue with weak opioids (e.g. codeine 8 mg/paracetamol 500 mg as co-codamol tablets; usual dosage is 2 tablets 6 hourly). In case of no relief, use strong (natural) opioids (for instance, morphine 5–10 mg orally, given 4 hourly in case of severe pain) or synthetic opioids. Local radiotherapy is also effective for pain relief of bone disease	NA
Bone disease	None	Vertebroplasty (percutaneous injection of polymethacrylate or equivalent material into the vertebral body). The use of balloon kyphoplasty improves vertebral height. Long-term biphosphonate treatment helps prevent bone disease. Other options are intravenous pamidronate, intravenous zoledronic acid as well as oral clodronate (used, e.g. in the UK)	NA

G-CSF granulocyte colony-stimulating factor, *HVZ* herpes-varicella-zoster, *LMWH* low-molecular-weight heparin, *NA* not available, *AE* adverse event

Data from these trials support the use of reduced-intensity ASCT for both elderly and younger patients with pre-existing comorbidities, for whom full-dose chemotherapy and ASCT would be too toxic. However, further validation in randomized trials is needed.

10.6 Conclusion

The availability of new targeted therapies in combination with conventional chemotherapy or low-dose dexamethasone has substantially changed the treatment of MM. The treatment should be initiated only in symptomatic MM patients and should be tailored on the basis of patients' characteristics, comorbidities and expected toxicity profile associated with each regimen.

Full-dose melphalan followed by ASCT is the treatment of choice in patients younger than 65 years, and induction therapy including new drugs seems the most suitable preparatory regimen before transplant. The incorporation of new drugs as induction followed by ASCT appears to lead to VGPR rates slightly superior to those achieved with conventional chemotherapy with new drugs. Randomized trials are needed to directly compare the current best chemotherapeutic approach with the best ASCT strategies and to determine the best induction, consolidation and maintenance therapy.

In elderly patients, the combination of an alkylating drug with a novel agent should be considered as standard approach. Randomized phase III studies have shown that MPT, MPV and MPR proved to be more effective than the traditional treatment with MP; hence, they can now be regarded as new standards of care for patients ineligible for ASCT. The four-drug combination VMPT-VT recently showed to be more effective than VMP, thus it can be considered a new valuable option for elderly patients with MM. Preliminary results on Rd are also encouraging, but they still need to be further validated in comparative studies with confirmed regimen MPT, MPV and MPR.

The wide variety of treatment options now available will support the choice of a more personalized therapy, by balancing efficacy and toxicity of each drug. Patients with renal impairment can be treated with both thalidomide- and bortezomib-based therapies. Lenalidomide should be preferred in patients with pre-existing neuropathy, and appropriate dose reduction is needed in case of renal insufficiency. Patients with risk factors for thrombosis can be safely treated with bortezomib, and IMIDs can be administered with appropriate antithrombotic prophylaxis.

These novel agents and combinations alter the natural history of MM and improve both the quality of life and outcome, with a subsequent great advantage for the patient.

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