

Shifts in the Therapeutic Paradigm for Patients Newly Diagnosed with Multiple Myeloma: Maintenance Therapy and Overall Survival

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Abstract

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard of care for eligible newly diagnosed multiple myeloma (MM) patients. Several randomized studies showed a survival advantage for patients undergoing transplantation, compared with conventional chemotherapy. Introduction of new drugs in this setting has markedly increased survival rates within the last 10 years. Efforts to further improve response rates and survival in those patients are still needed, mainly by increasing the depth of tumor reduction and the duration of response through more effective induction, consolidation, and maintenance therapies. Nevertheless, this approach is currently challenged by the promising results of long-term treatment with novel agents. Recent data suggest that the upfront combination of a proteasome inhibitor plus 1 immunomodulatory compound (IMiD) is highly effective. The combination of bortezomib, thalidomide, and dexamethasone (VTD) has proven to be highly effective as a frontline treatment and is significantly superior to vincristine, doxorubicin, and dexamethasone (VAD) or thalidomide and dexamethasone (Thal-Dex) before and after ASCT with a very manageable toxicity pattern. The most promising 3-drug association might be bortezomib, lenalidomide, and dexamethasone (VRD). Adjunction of a 4th drug has not proven to be more efficient. In patients not eligible for ASCT, the introduction of novel agents has changed the management of multiple myeloma. The combinations of melphalan, prednisone, and thalidomide and of bortezomib, melphalan, and prednisone have shown improved progression-free survival and overall survival in comparison with melphalan and prednisone alone. Melphalan, prednisone, and thalidomide and bortezomib, melphalan, and prednisone are now the new standards of care for elderly patients. Preliminary results also support the role of the combination of melphalan, prednisone, and lenalidomide followed by maintenance therapy with lenalidomide in the treatment of elderly patients. Physicians now have a wider variety of treatment options to tailor the most appropriate and efficacious treatment according to their patients' characteristics. *Clin Cancer Res*; 17(6); 1253–63. ©2011 AACR.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy that makes up 1% of all cancers and 10% of hematologic neoplasms. Approximately 20,580 new cases were diagnosed in the United States in 2009, including 11,680 cases in men, 8,900 cases in women, and 10,580 deaths overall (1). 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 (2, 3). The number of geriatric patients is expected to increase over time because of the increasing life expectancy of the normal population. Although the disease remains incurable, great advances

have been made with the introduction of novel agents, such as bortezomib, thalidomide, and lenalidomide.

The diagnosis of myeloma is based on the presence of at least 10% clonal bone marrow plasma cells and serum and/or urinary monoclonal protein (4). MM is classified as symptomatic or asymptomatic disease (Fig. 1). Symptomatic MM is characterized by evidence of end-organ damage caused by plasma cell proliferation, or "CRAB" features: C, hypercalcemia [>11.5 mg/dL (2.65 mmol/L)]; R, renal failure [serum creatinine > 2 mg/dL (1.73 mmol/L)]; A, anemia [hemoglobin < 10 g/dL (1.25 mmol/L) or > 2 g/dL (1.25 mmol/L) below the lower limit of normal]; and B, bone disease (lytic lesions, severe osteopenia, or pathologic fractures; refs. 4, 5). Patients with symptomatic MM should be treated immediately; early intervention on asymptomatic patients showed no benefits, and observation alone is the standard (6–8). Patients with MM may be further classified as high- or low-risk subjects according to different parameters, such as the International Staging System (ISS; Fig. 2; ref. 9), and the presence of chromosomal abnormalities like 17p deletion [del (17)], t(4;14), or t(14;16) detected by cytogenetics and FISH (10, 11). Munshi and Avet-Loiseau

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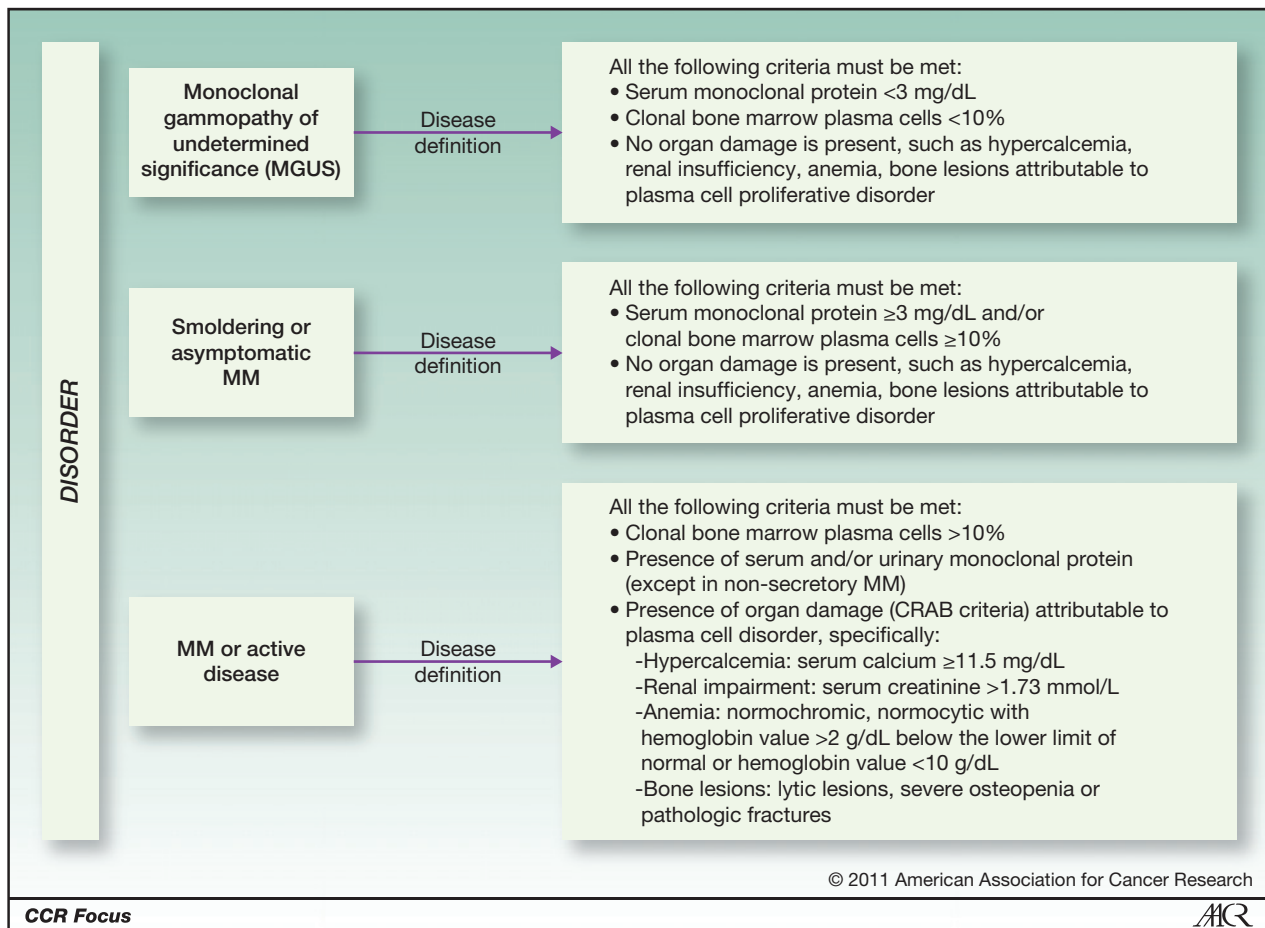


Figure 1. Diagnostic criteria. CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions.

discuss this detection elsewhere in this CCR Focus series (12).

Frontline Treatment in Multiple Myeloma Patients Eligible for High-Dose Therapy

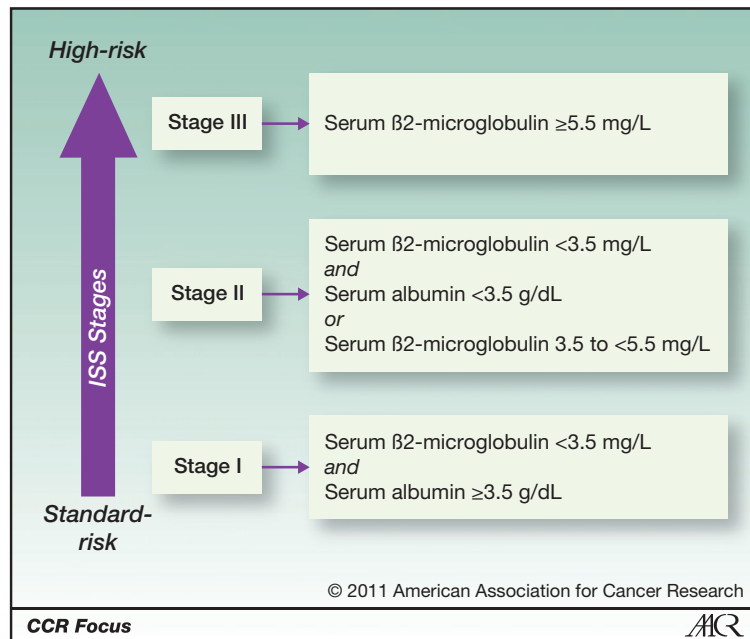
Induction treatment: what combination of new drugs?

For many years, the combination of vincristine, doxorubicin, and dexamethasone (VAD) was the standard induction therapy in upfront patients who were candidates for high-dose therapy (HDT) with autologous stem cell transplantation (ASCT; refs. 13, 14). In the last 10 years, induction regimens dramatically changed following the introduction of thalidomide, bortezomib, and lenalidomide (15, 16). Therefore, various combinations of drugs are now available with high response rates. New drug-based induction regimens decrease the tumor burden before HDT but also offer high response rates after HDT. All of these agents showed significant superiority over VAD, and, as a result, VAD is no longer recommended as initial therapy.

As thalidomide (Thal), bortezomib (Vel), and lenalidomide (Rev) have individually shown excellent feasibility and efficacy when combined with dexamethasone (Dex) as

induction therapy before intensification (17–22), several investigators postulated that this high response rate could be further increased with adjunction of a third or a fourth drug without a burden of toxicities. Several phase II and III studies have explored the combination of bortezomib with thalidomide in untreated MM patients. The Italian group (Cavo et al, 2010), compared bortezomib plus Thal-Dex (VTD) with Thal-Dex (24). VTD was significantly superior after induction [very good partial response (VGPR) or better: 62% versus 28%, $P < 0.0001$] and after consolidation (VGPR or better: 85% versus 68%, $P < 0.001$). The superiority of VTD was confirmed in patients with high-risk cytogenetics [t(4;14) and/or del(17p)]. Progression-free survival (PFS) was also significantly longer (68% versus 56% at 3 years for VTD versus Thal-Dex, respectively). The Spanish group, (Rosinol et al, 2009), did a similar comparison (VTD versus Thal-Dex), with, in addition, a third arm, based on chemotherapy [vincristine, bischloronitrosourea (BCNU), melphalan, cyclophosphamide, and prednisone (VBMCP)–vincristine, BCNU, adriamycin, and dexamethasone (VBAD) plus bortezomib; ref. 25]. The VTD arm was superior in terms of response rate (VGPR or better = 59% before and 78% after ASCT),

Figure 2. International Staging System (ISS) stratification.



time to progression, and PFS. The Intergroupe Franco-phonie du Myélome (IFM) also recently reported on a phase III trial (IFM 2007–02) comparing Vel-Dex to vTD (with low doses of bortezomib = 1 mg/m² and thalidomide = 100 mg/d; ref. 26). vTD induced significantly higher VGPR rates (50% versus 36%, *P* = 0.047) but identical complete response (CR) rates (14% versus 12%). This superiority was persistent after HDT (VGPR or better: 66% versus 54%, *P* = 0.044). All of these regimens resulted in PFS improvement with time (Fig. 3).

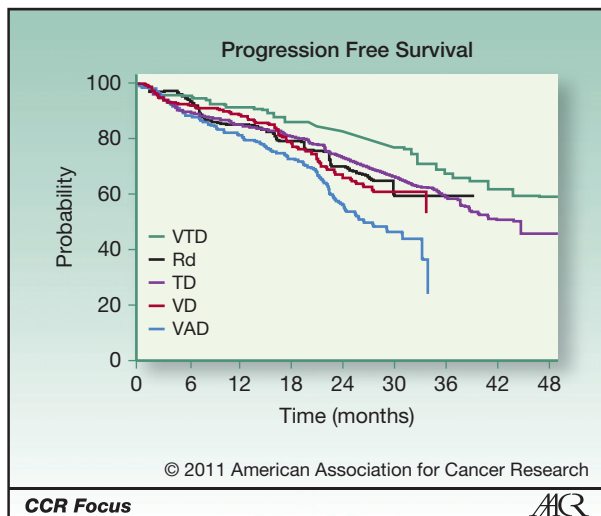


Figure 3. Impact of upfront new drug-containing regimens in the setting of HDT. PFS curves issue from IFM 2005–01 trial (VD, bortezomib, and dexamethasone; ref. 22); Eastern Cooperative Oncology Group (ECOG) E4A03 trial, ref. 23; and GIMEMA phase 3 trial (TD, thalidomide and dexamethasone; ref. 24).

The most promising 3-drug induction regimen may be the combination of bortezomib with Rev/Dex (RVD; ref. 27). RVD has been investigated in a phase I-II trial in which 66 patients were enrolled. All patients responded, including 67% ≥ VGPR and 39% CR-near CR (nCR). Moreover, responses were independent of cytogenetics. With a median follow-up of 21 months, estimated 18-month PFS and overall survival (OS) with or without transplant was 75% and 97%, respectively.

During the last American Society of Hematology (ASH) annual meeting in Orlando the IFM reported the primary results of a phase II study investigating 3 RVD cycles before HDT followed by ASCT and 2 RVD cycles for consolidation, same regimen as induction. All patients except one received the whole planned treatment. After induction and HDT, 91% of patients were responders including 68% VGPR or better and 36% CR + stringent CR (28).

The EVOLUTION trial explored the combination of cyclophosphamide with RVD (VDCR) in 43 patients (29). Overall response rate (ORR) was 94%, with 57% of ≥ VGPR in the VDCR arm, but higher rates of serious adverse events, including possible treatment-related mortality, were reported. The HOVON group (30) has investigated, for its part, the cyclophosphamide + VTD (VTDC) regimen. Response rates were of great value, but toxicities were also increased.

Autologous stem cell transplantation: upfront or at the time of relapse?

In the 1990s, several randomized trials showed the superiority of HDT with ASCT compared with conventional chemotherapy in terms of prolonged PFS, OS, and time without symptoms or treatment toxicities

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(TwiSTT; refs. 31–36). HDT (usually based on melphalan 200 mg/m² = HDM) is currently considered to be the standard care for younger patients with MM. However, HDT is not curative, and most patients relapse. Several approaches have been tested to enhance the efficacy of transplantation (37). These approaches have included the use of a higher dose of melphalan (38), the use of total body irradiation (TBI; refs. 39, 40), and the incorporation of other drugs into the conditioning regimen (41–43). These approaches usually resulted in higher morbidity and mortality, and HDM is the recommended preparative regimen. Recently, promising results have been reported with intravenous busulfan (44) and arsenic trioxide (45).

In the past few years, several novel and highly effective agents, the immunomodulatory compounds (IMiD) and proteasome inhibitors, have improved response rates and patient outcomes, both in the setting of relapse and frontline therapies. These novel agents may also increase the efficacy of HDM and transplant outcomes with deeper and long-lasting responses. The IFM conducted a phase II clinical trial to determine whether combining bortezomib and HDM (Bor-HDM) could provide high CR and VGPR rates after transplantation without the burden of increased toxicity (46). In the setting of new-drug-containing regimens, it is important to assess whether ASCT enhances the quality and depth of response. Several randomized trials already reported a higher CR rate with an improved PFS. These data imply that induction with novel agents and ASCT are complementary, rather than alternative treatment approaches. Nevertheless, the favorable results obtained with long-term treatment with these novel combinations, in patients who are not candidates for HDT, are challenging the role of upfront ASCT. A number of arguments could favor HDT in frontline patients. HDT is no more toxic and expensive (as opposed to novel agents) than ASCT. Quality of life is impaired for only a short period of time after HDT. Furthermore, the strategy of delayed HDT is reasonable only if the feasibility of ASCT at time of relapse is good. It could be a major concern for older patients at time of diagnosis. The IFM and the Dana Farber Cancer Institute (DFCI) will soon assess this issue in a large joint phase III trial. Patients will be randomly assigned to receive HDT upfront or at time of relapse. Induction and consolidation therapies will be based on the DFCI RVD regimen. The Italian GIMEMA group is currently conducting a similar trial. Preliminary data were presented at the last American Society of Clinical Oncology (ASCO) annual meeting. Patients, in a 2 × 2 factorial plan, randomly received, after 4 induction cycles of lenalidomide and low-dose dexamethasone (Rd), either a tandem ASCT with HDM or 6 cycles of melphalan, prednisone, and lenalidomide (MPR; ref. 47). To date, 239 patients (more than 402) are analysable for response: 122 patients after a first course of HDM and 117 after 3 cycles of MPR. There is currently no difference between the 2 arms (VGPR or better: 53% versus 55%, *P* = 0.63).

Maintenance and/or consolidation treatment in young patients

Although HDT with ASCT improves CR rates and PFS, almost all patients ultimately relapse. An optimal maintenance treatment should prolong PFS with acceptable toxicity, not compromise treatment at the time of relapse, and, furthermore, prolong OS. The impact of maintenance therapy with chemotherapy after HDT has always failed to prolong PFS and OS.

In the 1980s, maintenance treatment with corticosteroids (48) and/or interferon was the first choice. Following the initial randomized study showing prolonged remissions with α -interferon maintenance in patients responding to conventional induction therapy (49), a number of randomized trials were carried out, but their results were controversial. Two meta-analyses of randomized trials showed that with interferon maintenance, time to PFS and OS was increased by 4 to 7 months (50, 51). However, most investigators considered that the benefit was small and needed balancing against cost and potential toxicity of prolonged treatment with α -interferon.

The availability of novel agents (particularly oral thalidomide and lenalidomide) has renewed the concept of maintenance. Five randomized studies with thalidomide have been completed (52–56). The IFM group, in the IFM 9902 trial, was the first to show that thalidomide as maintenance after tandem ASCT was superior to no maintenance or pamidronate alone. Thalidomide increased the CR + VGPR rate (67% versus 55% and 57%, respectively), the 3-year PFS (52% versus 36% and 37%, respectively), and the 4-year OS (87% versus 77% and 74%, respectively). The Australian group obtained similar results. Within the Total Therapy 2 program, the Arkansas group also tested the impact of thalidomide as maintenance. In the initial report, CR rate and 5-year PFS were significantly better in the thalidomide arm (62% versus 43% and 56% versus 44%, respectively), but there was no OS improvement. However, in an updated analysis, with a median follow-up of 72 months, prolonged OS was confirmed in a subgroup of patients with poor-risk cytogenetics. In total, 4 of 5 randomized trials showed a benefit in PFS and OS with thalidomide maintenance. But, what group of patients will really benefit from thalidomide? In the IFM trial, only patients who failed to achieve at least VGPR had significantly longer PFS in the thalidomide arm. The shorter OS duration observed in several studies appears to be a result of a shorter survival time after relapse, which may be caused by different factors (duration of maintenance treatment, possible selection of more resistant clones, and the availability of salvage treatments). Future studies should be aimed at identifying patients who may benefit from maintenance and establishing the appropriate dose and optimal duration of therapy. The more favorable toxicity profile of lenalidomide makes it an ideal agent for maintenance therapy. Two large randomized phase III trials, one conducted by the IFM (57), the other by the CALGB (58), were presented in the last ASCO and ASH annual meetings. Lenalidomide was given orally after HDT at low dose up

to progression. Results were similar in both studies, with an improvement of PFS (around 24 months in the placebo arm versus not reached in the lenalidomide arm). The safety profile was good, and subgroup analysis showed that the benefit of maintenance therapy was seen irrespective of response after HDT and initial prognostic factors. With a median follow-up of 24 months for the IFM trial, there is no difference in the OS.

Elderly Patients

Induction therapies in the era of novel agents

Patients older than 65 years are usually considered ineligible for ASCT. However, biological age and chronological age do not always correspond, and a greater emphasis is placed on the former definition.

For more than 40 years, the combination of melphalan and prednisone (MP) was considered the standard approach for transplant-ineligible patients until novel agents were introduced. A meta-analysis including 27 randomized studies compared MP with other chemotherapy-containing regimens. Although favorable results were reported with chemotherapy (60% versus 53%, $P < 0.0001$), MP was, in fact, better tolerated, and no significant survival difference was detected between the 2 approaches ($P = 0.6$; ref. 59).

The introduction of novel agents has increased response rates and improved survival in this subset of patients. Six randomized studies have compared the benefits of the combination of melphalan, prednisone, and thalidomide (MPT) with MP (60–65). MPT led to higher responses, with at least VGPR or nCR of 15 to 47% with MPT versus 6 to 8% with MP. Median PFS was also increased with MPT: 14 to 28 months versus 10 to 19 months. In the 2 French studies, the PFS advantage was also associated with an OS advantage (61, 64). A meta-analysis on 1,685 individual patients enrolled in these 6 trials was done and confirmed the superiority of MPT over MP. MPT led to an increase in median PFS and OS of 5.4 months and 6.6 months, respectively (66). Thalidomide therapy was generally well tolerated, even in patients aged 75 years and older (64), although the MPT regimen was associated with a significantly higher incidence of grade 3

to 4 nonhematologic adverse events, including neurologic adverse events, infections, cardiac toxicity, and deep-venous thrombosis. After the introduction of prophylactic enoxaparin, the incidence of thrombosis was substantially lowered from 20% to 3% (60). Antithrombotic prophylaxis is recommended when MPT is used. Considering its efficacy and safety, MPT is confirmed as a new standard of care for elderly patients.

Another large randomized study assessed the efficacy of the combination of bortezomib, melphalan, and prednisone (VMP; refs. 67, 68). This study showed the superiority of VMP over MP for all efficacy endpoints: CR rate was 30% versus 4% ($P < 0.001$), median time to progression was 24 months versus 17 months ($P < 0.001$), and the 3-year OS was 69% versus 54% ($P = 0.0008$). The incidence of peripheral neuropathy (13% versus 0%), gastrointestinal complications (20% versus 5%), and fatigue (8% versus < 1%) was higher with VMP than with MP. The number of patients with herpes zoster infection was also higher in patients receiving VMP (14% versus 4%), but the frequency dropped to 3% with acyclovir prophylaxis. Considering the positive results achieved, VMP is now considered a standard of care in the nontransplant setting.

In a combination including corticosteroids plus thalidomide or bortezomib, melphalan has been replaced by cyclophosphamide to reduce hematologic toxicity, response rates were unchanged, but no data on outcome are available (69, 70).

In a phase III study, the combination of melphalan, prednisone, and lenalidomide followed by maintenance with lenalidomide (MPR-R) was compared with MP alone. CR rates were significantly higher with the 3-drug combination (16% versus 4%, $P < 0.001$). Two-year PFS was improved in the MPR-R arm as well (55% versus 16%, $P < 0.001$), but no survival differences were seen (92% in both arms; ref. 71). The major serious adverse events associated with the MPR-R regimen were neutropenia (70%), thrombocytopenia (37%), and anemia (23%). No serious cases of peripheral neuropathy were detected. Another trial investigated the role of lenalidomide in combination with high-dose dexamethasone (RD), in comparison with Rd: Rd improved survival and reduced the frequency of serious adverse events

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Table 1. Recommended Dose Reductions

Drug	65 to 75 Years	>75 Years	Further dose reduction
Dexamethasone	40 mg weekly	20 mg weekly	10 mg weekly
Melphalan	0.25 mg/kg daily days 1 to 4	0.18 mg/kg daily days 1 to 4	0.13 mg/kg daily days 1 to 4
Thalidomide	200 mg daily	100 mg daily	50 mg daily
Lenalidomide (plus dexamethasone)	25 mg daily days 1 to 21	15 mg daily days 1 to 21	10 mg daily days 1 to 21
Lenalidomide (plus melphalan-prednisone)	10 mg daily days 1 to 21	5 mg daily days 1 to 21	5 mg every other day days 1 to 21
Bortezomib	1.3 mg/m ² twice weekly	1.3 mg/m ² once weekly	1.0 mg/m ² once weekly

Table 2. Management of Adverse Events in Myeloma Patients Treated with Novel Agents

Adverse event	Suspected novel agent	Management	Dose modification
Neutropenia	Lenalidomide, bortezomib, and combinations	GCSF until neutrophil recovery in case of uncomplicated grade 4 AE or grade 2 to 3 AEs complicated by fever or infection.	25 to 50% drug reduction
Thrombocytopenia	Bortezomib and combinations, lenalidomide and combinations	Platelet transfusion in case of grade 4 AE.	25 to 50% drug reduction
Anemia	Bortezomib and combinations, lenalidomide and combinations	Epoetin or darbepoetin in case of hemoglobin level ≤ 10 g/dL.	25 to 50% drug reduction
Infection	All the agents	Trimethoprim-sulfamethoxazole for <i>Pneumocystis carinii</i> prophylaxis during high-dose dexamethasone. Acyclovir or valacyclovir for herpes zoster virus (HZV) prophylaxis during bortezomib-based therapy.	25 to 50% drug reduction
Neurotoxicity	Bortezomib and combinations, thalidomide and combinations	Neurologic assessment before and during treatment. Prompt dose reduction of the suspected drug is recommended,	Bortezomib: 25 to 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 to 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 to 4 AEs. 50% reduction in case of grade 2 AEs.
Thrombosis	Thalidomide and combinations, lenalidomide and combinations	Aspirin 100 to 325 mg if no or 1 individual/myeloma thrombotic risk factor is present; LMWH or full-dose warfarin if 2 or more individual/myeloma risk factors are present and in all patients with thalidomide-related risk factors.	temporary drug interruption and full anticoagulation, then resume treatment.

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Table 2. Management of Adverse Events in Myeloma Patients Treated with Novel Agents (Cont'd)

Adverse event	Suspected novel agent	Management	Dose modification
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 to 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 nonopioid analgesics. If no benefit is detected, continue with weak opioids (for example, 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 to 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 (74)	None	Vertebroplasty (percutaneous injection of polymethacrylate or equivalent material into the vertebral body). The use of balloon kyphoplasty improves vertebral height. Long-term bisphosphonate treatment helps prevent bone disease. Other: options are i.v. pamidronate, i.v. zoledronic acid as well as oral clodronate (used, for example, in the United Kingdom).	NA

Abbreviations: AE, adverse event; GCSF, granulocyte colony-stimulating factor; LMWH, low-molecular-weight heparin; NA, not available.

(21). Rd thus proved to be a valid alternative option to previous regimens. Future studies comparing Rd with MPT will assess the efficacy and safety of both options.

A more intense approach, that is, the 4-drug combination bortezomib, melphalan, prednisone, and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT), has shown unprecedented results in elderly subjects, with a 3-year PFS of 56% (72). Bortezomib was initially administered twice weekly and was subsequently reduced to a once-weekly schedule to reduce the incidence of peripheral neuropathy from 16% to 4% (73).

Patients older than 75 years and with comorbidities are considered frail patients. They need particular attention and may benefit more from a gentler approach with proper dose reductions (Table 1). The improvement achieved with novel agents should always be balanced against the toxicity profile of the regimen used. The toxicity associated with a regimen may, in fact, jeopardize the efficacy of the treatment itself. Generally, at the occurrence of any grade 4 or higher hematologic or grade 3 or higher nonhematologic toxicity, treatment should be immediately withheld until

the toxicity resolves to grade 1, and restarted at lower doses to avoid subsequent severe adverse events and treatment discontinuation. In these conditions, prompt action is essential to reduce the treatment-associated toxicity (Table 2).

Consolidation and maintenance approaches for elderly patients

Although consolidation/maintenance therapy has the potential to improve patient outcome, no specific guidelines are currently available. However, the idea of increasing responses with consolidation or prolonging remission duration with maintenance is widely accepted.

To date, only some data on the role of maintenance therapy in elderly patients are available. Maintenance with bortezomib plus thalidomide (VT) has been tested in the Italian study, (Brinchen et al, 2010), comparing VMPT-VT versus VMP. An exploratory analysis done on the 82 VMPT-VT patients who received at least 6 months of VT maintenance showed an improvement in CR rate from 58% after 9 cycles of VMPT to 62% after 6 months of VT maintenance (73). Mateos and colleagues investigated the role of main-

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tenance therapy with bortezomib and prednisone (VP) versus VT in elderly patients respectively assigned to induction with VMP and VTP. Overall, CR improved with maintenance treatment from 25% up to 42%, and no significant differences in response rates between the 2 arms were seen. After a median duration of maintenance of 13 months, there was a trend toward a shorter time to progression with VP compared with VT (1-year time to progression, 71% versus 84%; $P = 0.05$), although OS was similar (74).

In the international MM-015 study, after induction with MPR, patients were randomized to receive lenalidomide or placebo maintenance until progression: landmark analysis showed that the addition of lenalidomide maintenance to MPR decreased the risk of progression by 69%. The survival advantage was also confirmed in the elderly patient population older than 75 years (71).

Conclusion

For patients eligible for high-dose therapy, the association of a proteasome inhibitor and an immunomodulatory compound is likely to become the new standard for induction therapy. High-dose melphalan is still the con-

ditioning regimen of choice; new drugs can be safely incorporated. Consolidation and maintenance therapies have shown highly promising results that have to be confirmed in terms of OS. Nevertheless, the favorable results obtained with long-term treatment with these novel combinations are challenging the role of upfront ASCT. The on-going IFM/DFCI phase III joint trial will assess this issue. We cannot speculate on results, but the goal is ultimately to cure patients with more active and less toxic combinations preserving the quality of life of MM patients. In the nontransplant setting, MPT and VMP now represent the latest standards of care. MPR-R proved to be beneficial as well. The 4-drug combination VMPT-VT recently proved to be a more effective regimen than VMP and represents another valuable option for elderly patients. 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 patients with renal insufficiency. Patients with risk factors for thrombosis can be safely treated with bortezomib, whereas IMiDs can be administered with appropriate antithrombotic prophylaxis. The use of novel

Table 3. Current Recommended Therapies for Newly Diagnosed Multiple Myeloma Patients

Study	Regimen	Response Rates	PFS	OS
For patients eligible for high-dose therapy:				
Cavo et al. (24)	VTD + HDT × 2, n = 236	CR 38%, ≥ VGPR 79% ORR 93%	3-year PFS 68%	3-year OS 86%
Moreau et al. (26)	vTD + HDT, n = 100	CR 30%, ≥ VGPR 73% ORR 90%		
Richardson et al. (27)	RVD ± HDT, n = 66	CR 29%, ≥ VGPR 67% ORR 100%	18-month PFS 75%	18-month OS 97%
Roussel et al. (28)	VRD + HDT, n = 31	CR 36%, ≥ VGPR 68% ORR 91%		
Jakubowiak et al. (76)	CRd ± HDT (carfilzomib, lenalidomide, and low-dose dexamethasone), n = 27	CR + nCR 67% ≥ VGPR 83% ORR 100%		
For elderly patients or patients not eligible for high-dose therapy:				
Facon et al. (61), Hulin et al. (64)	MPT, n = 125/113	CR 13%/7% ≥ VGPR 47%/21% ORR 76%/61%	Median PFS 27.5 months (24 months for older patients)	Median OS 51.5 months (45 months for older patients)
Palumbo et al. (60)	MPT, n = 129	CR 15.6%, ≥ VGPR 45% ORR 46%	Median PFS 22 months	Median OS 45 months
San Miguel et al. (67)	VMP, n = 344	CR 33%, ≥ VGPR 41% ORR 74%	Median PFS 24 months	Not reached with a median follow-up of 37 months
Likely to be replaced by: Rd (FIRST trial), CMP (carfilzomib, melphalan, and prednisone)				

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agents has significantly improved both the quality of life and outcome, for the patient. Current recommended therapies for newly diagnosed MM patients are resumed in Table 3.

Disclosure of Potential Conflicts of Interest

Antonio Palumbo has received honoraria from Celgene, Janssen-Cilag, Merck, Amgen, and the advisory committee from Celgene, Janssen-Cilag;

Michel Attal has received honoraria from Celgene, Janssen-Cilag and the advisory committee from Celgene, Janssen-Cilag; Murielle Roussel has received honoraria from Celgene, Janssen-Cilag.

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