Firstline Treatment and Maintenance in Newly Diagnosed Multiple Myeloma Patients

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Abstract High dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard of care for eligible newly diagnosed MM patients. Several randomized studies demonstrated a survival advantage for patients undergoing transplantation, compared with conventional chemotherapy. Introduction of new drugs in this setting have 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 one immunomodulatory drug (IMiD) is highly effective. The most promising 3-drug association might be Bortezomib, Lenalidomide and dexamethasone (VRD). Adjunction of a 4th drug is not proven to be more efficient. Consolidation and maintenance therapies are emerging in all trials with great results. For elderly patients, or not eligible for ASCT, the introduction of novel agents has also changed the management of the disease. Melphalan-prednisone-thalidomide and bortezomib-melphalan-prednisone are the two standards of care. Current trials are challenging the role

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of alkylators in the frontline setting. Maintenance therapy is also undergoing evaluation.

The treatment of newly diagnosed multiple myeloma (MM) patients has been highly modified during the last decade. The availability of the novel agents like thalidomide, bortezomib, and lenalidomide has expanded treatment options and has improved the outcome of patients with MM. Following the introduction of these agents in the relapsed/refractory setting, they reached the initial treatment of MM. A number of phase II and III trials have demonstrated the efficacy of novel agent combinations both in the transplant and non transplant settings, and based on these results standard frontline regimens are being challenged and modified.

Patients with symptomatic MM require treatment (International Myeloma Working Group 2003). The choice of initial therapy depends on eligibility for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), determined by age, performance status, and coexisting comorbidities. All patients under 65 years of age should be evaluated at diagnosis for transplant eligibility. Melphalan-containing regimens should be avoided as induction therapy in transplant candidates in order to preserve hematopoietic stem cells. For others, melphalan-prednisone-thalidomide (MPT) and melphalan-prednisone-bortezomib (MPV) currently appear to be the treatments of choice, but other combinations without alkylating agents could provide good options.

9.1 Frontline Treatment in MM Patients Eligible for High-Dose Therapy

HDT with ASCT is the standard of care for eligible newly diagnosed MM patients following the results of several randomized studies that demonstrated a survival advantage for patients undergoing transplantation, compared with conventional chemotherapy (Attal et al. 1996; Child et al. 2003; Blade et al. 2005; Fermand et al. 2005; Barlogie et al. 2006a). 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 merely with novel agents.

This chapter will focus on the current issues concerning the treatment of newly diagnosed young MM patients. Three main points will be discussed:

1. What is the best induction regimen: two, three, or four-drug combination?
2. Should HDT be performed upfront or at time of relapse?
3. Can consolidation and/or maintenance therapies increase the depth of responses and prolong duration of responses and survival?

9.1.1 Induction Treatment: What Combination of New Drugs?

For many years, vincristine, doxorubicin, and dexamethasone (VAD) was the standard induction therapy in upfront patients who were candidates for HDT (Alexanian et al. 1990; Lane et al. 2005). However, overall response rate (ORR) was only in the range of 55–60%, and complete responses (CRs) were achieved in only a small number of patients. Moreover, the response to VAD induction had no impact on the outcome after ASCT. In the last 10 years, induction regimens dramatically changed following the onset of thalidomide, bortezomib, and lenalidomide. 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 and deep response rates after HDT. All these agents demonstrated significant superiority over VAD, and, as a result, VAD is no longer recommended as initial therapy.

9.1.1.1 Two-Drug Induction Regimens

Thalidomide-Based Induction Regimens

Thalidomide was the first "novel" agent to be tested in frontline setting. The use of thalidomide plus dexamethasone (Thal-Dex) has been studied in four randomized trials and has emerged as one of the most commonly used induction regimens, at least in United States (Cavo et al. 2005; Macro et al. 2006; Rajkumar et al. 2006, 2008). All studies have demonstrated that Thal-Dex regimen was superior to VAD with good response rates (63–76% ORR). Thal-Dex had the advantage of oral administration but the limitation of high rate of non-hematological toxicities, mainly peripheral neuropathy (PN) and thrombotic events. In the French MAG study (Macro et al. 2006), which compared Thal-Dex to VAD, the initial response rate improvement (35% vs. 13%) was not persistent after ASCT (44% vs. 42%). This Thal-Dex induction regimen might therefore be not good enough and, with the availability of lenalidomide, is less prescribed to newly diagnosed MM patients.

Bortezomib-Based Induction Regimens

In the last 5 years, bortezomib also reached the frontline setting and various phase II and phase III clinical trials were conducted (Harousseau et al. 2006, 2008; Rosinol et al. 2007). The ORR ranges from 60% to 85% with 15% to 20% CRs. In all the studies, the CR markedly increased after transplant (30–40%). The IFM phase III trial 2005-01 compared bortezomib plus dexamethasone (Vel-Dex) to VAD. After four cycles of induction, the ORR with Vel-Dex was significantly higher than that with VAD (82% vs. 65%, including 39% vs. 16% very good partial response (VGPR) or better) and this benefit remained after HDT (≥VGPR 68% vs. 47%). With a median follow-up of 32 months, an improvement of progression-free survival (PFS) had already been observed for Vel-Dex relative to the VAD arm (36 vs. 30 months, respectively; $p=0.057$). Predictive factors for prolonged PFS were: VGPR before and after HDT. Superiority of Vel-Dex over VAD induction therapy was also observed for high-risk patients (ISS 2 or 3 and t(4;14) or del 17p) (Harousseau et al. 2009).

Lenalidomide-Based Induction Regimens

Lenalidomide (Rev) is also undergoing first-line evaluation. Rev-Dex regimen was studied in attempt to improve the Thal-Dex regimen, based on the assumption that lenalidomide is more effective and less neurotoxic than thalidomide. Two large randomized trials, one conducted by ECOG (Rajkumar et al. 2010) and the other by SWOG (Zonder et al. 2007), have shown that the majority of patients respond to induction with Rev/Dex (ORR of 82 and 85% with a CR rate of 4–22%, respectively). In the ECOG trial, 90 of the initial 431 patients went off therapy after the initial four cycles and received HDT followed by ASCT; the 2-year PFS in these patients is 65% and the 3-year OS 92%.

9.1.1.2 Three-Drug Regimens

As all new drugs have shown excellent feasibility and efficacy combined with Dex as induction

therapy before intensification, several investigators postulated that this high response rate could be further increased with adjunction of a third drug without a burden of toxicities.

Anthracyclins or Cyclophosphamide in Combination with Thalidomide, Bortezomib, or Lenalidomide

Two randomized trials, conducted by the HOVON group, showed that the addition of adriamycin to Thal-Dex (TAD) (Lokhorst et al. 2010) or Vel-Dex (PAD) (Sonneveld et al. 2008) resulted in an increase in the ORR (71% and 80%, respectively). The CR plus VGPR was 37% and 41%, respectively, which are twice higher values than those obtained with VAD. In the study of TAD vs. VAD, the benefit in favor of TAD remained after ASCT when considering the VGPR rate (54% vs. 44%; $p=0.03$). This translates into a superior PFS for TAD compared with VAD-treated patients (34 vs. 25 months, respectively; $p < 0.001$) but a similar OS (59 vs. 62 months). In the PAD vs. VAD trial, the bortezomib arm induced a significantly higher VGPR rate (41% vs. 17%) but few CRs (5% vs. 1%); nevertheless, the CR significantly increased after transplant (15% vs. 4% $p < 0.001$).

The British group, in the MRC IX myeloma trial, compared cyclophosphamide + Thal-Dex (CTD) with cyclophosphamide + VAD (CVAD) as induction regimen before transplant, and found the CTD arm to be significantly superior, with ORR of 91% and 82%, including 21% and 14% CR, respectively (Morgan et al. 2009). The CR rate after transplant also remained favorable for the thalidomide arm (65% vs. 48% for CTD vs. CVAD, respectively; $p=0.08$).

In the same way, cyclophosphamide was combined to Vel-Dex (VelCD or Cybor-D) as induction regimen before HDT in two trials conducted by the German group and by the Mayo Clinic, respectively (Knop et al. 2009; Khan et al. 2010; Reeder et al. 2009, Reeder et al. 2010). In the German DSMM XIa Trial, 414 patients were included. Data from the first completed 200 pts were analyzed as intend-to-treat (ITT) population: 84% of patients achieved partial response (PR) or better after three cycles with 12% of CR.

The CyBor-D regimen efficacy was evaluated after four cycles in 63 newly diagnosed MM patients (bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11; cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22; and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 on a 28-day cycle). The ORR was impressive with 67% of VGPR or better and 47% of CR/near CR.

Finally, Khan et al. reported the results from a phase II trial combining lenalidomide and low-dose dexamethasone with cyclophosphamide (RCd) as initial therapy for newly diagnosed MM (Khan et al. 2010). Fifty three patients were enrolled. The median number of cycles was 5 (range: 1–20). The best response based on all enrolled patients on an ITT basis was 83%, including CR: 2%, VGPR: 38%, PR: 43%, and less than PR: 17%. Hematological toxicity was the most common with grade 4 toxicity seen in eight patients. Non-hematological toxicities included neuropathy, diarrhea, cystitis, and thrombosis. Thirteen patients had dose adjustments, most commonly due to hematological toxicity attributed to lenalidomide or cyclophosphamide.

Bortezomib in Combination with Thalidomide or Lenalidomide

Several phase II studies have explored the feasibility and efficacy of the combination of bortezomib with thalidomide in untreated MM patients. The high and rapid ORR (90% = PR, with 20% CR) prompted the design of phase III trials.

Thus, the Italian group compared bortezomib plus Thal-Dex (VTD) with Thal-Dex (Cavo et al. 2009). Four hundred and seventy four

patients were randomized to the VTD ($n=236$) or Thal-Dex ($n=238$) arm. VTD was significantly superior after induction (VGPR or better: 61% vs. 28%) and after consolidation (82% vs. 67%). Superiority of the VTD vs. Thal-Dex arm in terms of CR rate was confirmed in patients with high-risk cytogenetics, as defined by the presence of t(4;14) and/or del(17p) (58% vs. 33%, respectively; $p=0.004$). In addition, this translated into a significantly longer PFS (76% vs. 58% at 30 months for VTD vs. Thal-Dex, respectively), but no significant differences in OS have yet been observed.

The Spanish group has performed a similar comparison (VTD vs. Thal-Dex), with in addition a third arm, based on chemotherapy (VBCMP/VBAD plus bortezomib) (Rosinol et al. 2009). Two hundred and ninety nine patients were evaluable for response and toxicity to induction therapy and 177 to ASCT. Results presented at last ASH meeting indicate that the VTD arm was superior in terms of response rates (VGPR or better = 59% before and 78% after ASCT), time to progression (TTP) and PFS.

The IFM also recently reported on a phase III trial (IFM 2007-02) comparing Vel-Dex to vTD (with low doses of bortezomib = 1 mg/m^2 and = 100 mg/day) (Harousseau et al. 2010). Hundred and ninety one patients were evaluable for response after four cycles. vTD induced significantly higher VGPR rates (50% vs. 36%, $p=0.047$) but identical CR rates (14% vs. 12%). It is important to note that dose reduction of bortezomib significantly decreased grade 2 or more PN incidence in the vTD arm without reduced response rates. This superiority was persistent after HDT (VGPR or better: 66% vs. 54%, $p=0.044$).

The most promising three-drug induction regimen might be the combination of bortezomib with Rev/Dex (VRD) (Richardson et al. 2010). VRD has been investigated in a phase I/II trial in which 66 patients were enrolled. All patients responded, including 67% ≥ VGPR and 39% CR/nCR. Moreover, responses were independent of cytogenetics. Most common toxicities included sensory neuropathy (80%) and fatigue (64%), with only 27%/2% grade 2/3 neuropathy (PN). Additionally, 32% reported neuropathic pain (11%/3% grade 2/3). Thrombosis was rare (6% overall) and no treatment-related mortality was seen. With median follow-up of 21 months, estimated 18-month PFS and OS for the combination treatment with/without transplant was 75% and 97%, respectively.

The IFM finished last year the accrual of a phase II study investigating three cycles of VRD before HDT followed by ASCT. Results will be available at the next ASH meeting.

9.1.1.3 Four-Drug Induction Regimens

The EVOLUTION 2 trial have explored the combination of cyclophosphamide with VRD (VDCR) in 43 patients (Kumar et al. 2009); 33 patients were evaluable for response. ORR was 94% with 57% of VGPR or better. Response rates in the VDCR arm appeared somewhat higher than in the other arms at this early time point, although there also appeared to be higher rates of serious AEs, including possible treatment-related mortality in the VDCR arm.

The HOVON group (Ludwig et al. 2010) has investigated, for its part, the cyclophosphamide + VTD (VTDC) regimen. Response rates were of great value but toxicities were also increased. Forty nine patients were randomized to each arm. One patient (VTDC arm) was not evaluable for response. Response rates following induction were ORR: 100%/96% and CR + nCR: 51%/44%, respectively. At data cutoff, 47 VTD and 35 VTDC patients had undergone ASCT; response rates post ASCT in 38 and 27 evaluable patients were similar within the two arms with ORR: 100% and CR + nCR 39%/33%, respectively. PN was reported in 35% (VTD) and 29% (VTDC) of patients, including 8% grade 3 in each arm and 2% grade

4 in the VTD arm. Both VTD and VTDC are highly active induction regimens; the efficacy profiles were similar between the arms, but there were higher rates of toxicity in the VTDC arm compared with the VTD arm.

Taken together, these data suggest that the upfront combination of a proteasome inhibitor plus one immunomodulatory drug (IMiD) is highly effective. These data lead us to conclude that VAD is no longer the gold-standard induction regimen. Thal-Dex can be an option with the addition of another chemotherapy agent, such as cyclophosphamide or an anthracyclin. A similar possibility may exist for lenalidomide-based induction regimens. VTD has proved to be highly effective as a frontline treatment and is significantly superior to VAD or Thal-Dex before and after ASCT with a very manageable toxic pattern. The most promising three-drug association might be VRD. Adjunction of a fourth drug is not proven to be more efficient but is definitely more toxic.

9.1.2 Autologous Stem Cell Transplantation Upfront or at the Time of Relapse?

In the 1990s, several randomized trials demonstrated the superiority of HDT with ASCT compared to conventional chemotherapy in terms of prolonged PFS, OS, and time without symptoms or treatment toxicities (TwiSTT) (Attal et al. 1996; Fermand et al. 1998; Child et al. 2003; Blade et al. 2005; Fermand et al. 2005; Barlogie et al. 2006). HDT (usually based on melphalan 200 mg/m^2) followed by ASCT prolonged OS as compared with chemotherapy in prospective randomized trials conducted by the French (IFM) and English (MRC) groups and has provided evidence for longer than 10-year survivorship in at least a subset of patients. Nevertheless, the US (SWOG 9,321) and French (MAG91) studies and the Spanish (PETHEMA-94) trial, though confirming the benefit of ASCT in terms of ORR and event-free survival (EFS), found no greater OS than with chemotherapy.

ASCT is currently considered to be the standard care for younger patients with MM, mainly because of its low treatment mortality rate (1–2%), the benefit in response rate, and survival. In the setting of new drug-containing regimen, it is important to assess whether ASCT enhances the quality and depth of response. Several randomized trials indicated an improved CR rate following ASCT, which already translates into prolonged 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 candidate for HDT, are challenging the role of upfront ASCT. Some investigators already stated that HDT should no longer be used in frontline therapy. Stem cell collection should be performed within the first months of therapy with novel agents and reserve the HDT at time of relapse. But a lot of arguments could favor HDT in frontline patients. HDT is no more toxic and expensive (arguments that can be opposed to novel agents). Quality of life is only impaired for a short period of time after HDT and it has been already demonstrated that time without symptoms and treatment toxicity was improve if HDT was preformed upfront. 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 patients aged between 60 and 65 years at time of diagnosis. The IFM in association with 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 cooperative group is currently conducting a similar trial. Preliminary data have been presented in the last ASCO congress. Patients, in a 2 × 2 factorial

plan, will receive either a tandem ASCT with melphalan 200 mg/m^2 or six cycles of melphalan, prednisone, and lenalidomide (MPR). 117 pts received three cycles of MPR and 122 pts underwent their first ASCT. Response rates are similar in the two groups with 13% vs. 16% of CR, and 55% vs. 53% of VGPR or better, respectively (Palumbo et al. 2010b).

9.1.3 Maintenance/Consolidation Treatment

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 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 (Berenson et al. 2002) and/or interferon has been a first choice. Following the initial randomized study showing prolonged remissions with α-interferon maintenance in patients responding to conventional induction therapy (Mandelli et al. 1990), a number of randomized trials were performed but their results were controversial. Two meta-analyses of randomized trials showed that with interferon maintenance, time to PFS and OS was increased by 4–7 months (Fritz and Ludwig 2000; Myeloma Trialists' Collaborative Group 2001). However, most investigators considered that the benefit was small and needed balancing against cost and potential toxicity of prolonged treatment with α-interferon. In addition, α-interferon has been used after ASCT, with the hypothesis that it might be more effective in patients with minimal residual disease. In a retrospective analysis of the European Bone Marrow and Blood Transplant Registry, interferon maintenance was associated with improved PFS and OS in patients responding to high-dose therapy (Bjorkstrand et al. 2001). However, two randomized trials failed to confirm this result (Cunningham et al. 1998; Barlogie et al. 2006).

The availability of novel agents (particularly oral thalidomide and lenalidomide) has renewed the concept of maintenance. Five randomized studies with thalidomide have been completed (Attal et al. 2006; Barlogie et al. 2006; Morgan et al. 2009; Spencer et al. 2009; Lokhorst et al. 2010). The IFM group, in the IFM 9,902 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 vs. 55 and 57%, respectively), the 3-year PFS (52 vs. 36 and 37%, respectively), and the 4-year OS (87 vs. 77 and 74%, respectively). The Australian group obtained similar results upon comparing thalidomide (for 12 months) plus prednisone (until progression) with prednisone alone. Within the Total Therapy 2 program, the Arkansas group tested also the impact of thalidomide as maintenance. In the initial report, CR rate and 5-year PFS were significantly better in the thalidomide arm (62 vs. 43% and 56 vs. 44%, respectively) but there was no OS improvement. However, in an updated analysis, with a median follow-up of 72 months, the prolonged OS was confirmed in a subgroup of patients with poor-risk cytogenetics. In total, four of five randomized trials showed a benefit in PFS and OS with thalidomide maintenance. But what group of patients will really benefit of 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, such as the duration of maintenance treatment, the possible selection of more resistant clones, the age of patients, toxicities from previous treatments, and the availability of salvage treatments. Future studies should be aimed at identifying patients who may benefit from

thalidomide maintenance and establishing the appropriate dose and optimal duration of therapy. The Australian trial showed that maintenance for only 1 year did not adversely affect the outcome after relapse, but two studies (from the MRC and the Arkansas group) suggested that the long-term use of thalidomide may induce more resistant relapses. Finally, the incidence of thalidomide induced PN is cumulative and related to the time of exposure. Long-term treatment with thalidomide is actually impossible.

The more favorable toxicity profile of lenalidomide makes it an ideal maintenance agent and has prompted several ongoing trials designed to compare continuous treatment until relapse with non-maintenance or treatment for only a short period after ASCT. Two large randomized phase III trials, one conducted by the IFM (Attal et al. 2010), the second by the CALGB (McCarthy et al. 2010), were presented in the last ASCO meeting. Lenalidomide was given orally after HDT at 10–15 mg/day up to progression. Results were similar 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 benefice 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.

Bortezomib was investigated in the consolidation setting. Consolidation with VTD may induce molecular remission in a number of patients (Ladetto et al. 2010). Ongoing randomized studies by several European study groups are further investigating bortezomib as consolidation and maintenance therapy. For example, the DSMM is investigating the use of bortezomib as consolidation treatment following induction therapy with VCD plus high-dose therapy. The phase III GIMEMA trial also includes a consolidation randomization. Following induction treatment with VTD or TD and tandem transplantation, patients are randomized to receive VTD or TD consolidation therapy. In the HOVON 65 MM/GMMG-HD four trial, bortezomib versus thalidomide maintenance therapy is being examined following initial randomization between PAD and VAD induction.

9.2 Frontline Treatment in Elderly MM Patients

Treatment with melphalan (or cyclophosphamide) and prednisone (MP) has been used since the 1960s. Despite poor CR rates and 40% overall response rates, MP was the most widely accepted treatment option for elderly patients ineligible for HDT (Alexanian et al. 1969; Bataille and Harousseau 1997). Long-term outcomes were disappointing, with a median PFS duration of about 18 months and a median OS time of about 3 years. More complex combinations with alkylating agents have been substituted but often with added toxicity and no survival advantage (Myeloma Trialists' Collaborative Group 1998).

High-dose dexamethasone (Dex) alone or Dex-based regimens have provided other options. Although Dex gives better response rates, its use among patients over 65 is cautious because of greater toxicities, mainly infectious, and lack of benefit in terms of overall survival (Alexanian et al. 1992; Hernandez et al. 2004; Facon et al. 2006).

Introduction of highly active new drugs in this setting has markedly increased survival rates within the last decade. Overall, two "backbones" have been used for the development of combinations with new agents: MP (or C), in Europe, and Dex, in North America.

This chapter will discuss the current issues concerning the treatment of newly diagnosed elderly MM patients. Four main points will be reviewed:

1. What is the best partner for MP or alkylators: thalidomide, bortezomib, and/or lenalidomide?
2. Can new drugs replace alkylating agents?
3. Can we reduce new drugs toxicities, especially for the elderly patients?
4. Can maintenance therapies prolong duration of responses and survival?

9.2.1 What Is the Best Combination with Alkylating Agents?

Alkylating agents with prednisone, at least in Europe, are the core of treatment for frontline elderly patients. Several trials evaluated the role of new agents combined to melphalan or cyclophosphamide in this setting.

9.2.1.1 Thalidomide

Recently, a number of studies have investigated the addition of novel agents to the traditional MP regimen. The combination of MP plus thalidomide has been investigated in five randomized phase III trials (Palumbo et al. 2005; Facon et al. 2007; Wijermans et al. 2008; Hulin et al. 2009; Waage et al. 2010a). In the three first published trials (GIMEMA, IFM 99-06, and IFM 01-01), the superiority of MPT over MP or MP plus placebo was clearly demonstrated. These results were very concordant within the three studies. The addition of thalidomide to MP resulted in a significantly greater ORR, as well as a longer TTP, PFS time, or EFS time. Of note, 30–50% of the patients achieved at least a VGPR. In the IFM 01-01 study, response results were slightly inferior but still significantly superior to those of MP plus placebo, with a 62% ORR and a 7% CR rate. Median PFS times with MPT were similar in all three studies, ranging from 24 to 29 months. In both IFM studies, but not in the GIMEMA study, the PFS advantage observed with MPT translated into a significant OS advantage. There were some substantial differences in study design, such as the dose of thalidomide and duration of treatment, which included maintenance thalidomide in all except the two IFM studies. In the Nordic Study, the addition of thalidomide to MP resulted in a significant advantage in terms of RR and time to progression compared with MP. However, these favorable results did not translate into an OS advantage. The study was hampered by a high proportion of patients with a poor performance status and used higher doses of melphalan and thalidomide. These characteristics likely contributed to more frequent early deaths in the MPT group, especially in the oldest patients. Regarding toxicities, MPT was associated with a significantly increased risk of complications, especially somnolence or fatigue, constipation, PN, and deep venous thrombosis (DVT). Thrombo-embolic events usually occurred early in therapy (90% within 4 months). Anticoagulation prophylaxis is able to reduce thrombosis/embolism, and recommendations have been recently published by the International Myeloma Working Group. PN occurred after prolonged administration of thalidomide and was a frequent cause of discontinuation. More than 50% of patients treated for 12 months suffered from PN, although in most patients it was of grade 1/2. The incidence of grade 3/4 PN varied from 2% to 9%. Neurotoxicity will probably be reduced by thalidomide treatment of shorter durations and at lower doses. These results led to the approval of thalidomide in 2008 for previously untreated MM patients by the European Medicines Agency (EMEA). In a recent meta-analysis on survival of 1682 individual patients treated with MPT or MP in six different randomized studies, including the trials previously reported, the addition of thalidomide to MP significantly improved progression-free survival and overall survival (Waage et al. 2010). Similar data

have been presented in a meta-analysis of published data (Kapoor et al. 2009)

Other combinations have been examined in an attempt to improve outcomes in the elderly patient group. For example, the combination CTD was investigated in a large phase III randomized study by the MRC (Myeloma IX) comparing, in patients ineligible for transplantation, MP to CTD with an attenuated Dex dose (CTDa: cyclophosphamide 500 mg orally weekly, thalidomide 200 mg daily, Dex 20 mg on days 1–4 and 15–16 of a 28-day cycle) (Morgan et al. 2007). This first randomization was followed by a maintenance randomization comparing thalidomide 100 mg daily to relapse to no thalidomide. In this group of 854 less fit patients (median age, 73 years; range, 57–89 years), CTDa achieved a significantly higher RR (82.5% vs. 49%), including VGPR (47.5% vs. 9.5%) and CR (22.5% vs. 6%) rates. Patients induced with CTDa seem to survive for approximately a year longer than patients induced with MP (Morgan et al. 2009). CTDa survival results seem comparable to those achieved in the IFM MPT studies, and CTDa response rates are comparable to those achieved in IFM 99-06.

9.2.1.2 Bortezomib

In vitro studies have shown a synergistic effect between bortezomib and melphalan plus corticosteroids. Based on these promising findings, bortezomib was added to the standard MP (MPV regimen) in elderly untreated MM patients in a phase I/II trial conducted by the Spanish Myeloma Group (GEM/PETHEMA) (Mateos et al. 2006). Sixty patients were enrolled in this trial and, after a median of seven cycles, the ORR was 89% with a 32% CR rate. MPV was generally well tolerated and the majority of adverse events occurred during the first two cycles of treatment. These results led to a large, randomized, phase III VISTA trial (Velcade as Initial Standard Treatment: Assessment with melphalan and prednisone), in which 682 patients were included and randomized to receive either MP alone or in combination with bortezomib (San Miguel et al. 2008). MPV was found to be significantly superior to MP for all efficacy endpoints: CR rate, ORR, PFS, TTP, time to next therapy (TNT), and OS. 30% of patients in the MPV arm achieved CRs, compared with only 4% in the MP arm. Median time to achieve CR was 4 months. Patients who achieved CR had a median duration of response of 24 months. The primary endpoint of the trial was TTP, and MPV resulted in a 52% reduced risk of progression compared with MP, with a median TTP of 24 months for MPV and 16 months for MP. With an updated median follow-up of 26 months, the OS analysis showed a 36% reduced risk of death for MPV and the 3-year OS is 72% for MPV and 59% for MP, despite 45% of MP patients having received treatment with bortezomib upon progression. The efficacy of bortezomib was also evaluated in subgroups of patients who had a poor prognosis. In 107 patients who were 75 years of age or older, as compared with 237 younger patients, the median TTP was identical, the rate of CR (according to EBMT criteria) was slightly lower (26% vs. 32%), and the median OS was not significantly shorter. The 26 patients with high-risk cytogenetic profiles – including the presence of a t(4;14),t(14;16) translocation or a 17p deletion – and the 142 patients with standard cytogenetic profiles had the same rate of CR(28%), with similar TTP and OS. Fewer patients in the MPV versus MP arm required subsequent therapy (38% vs. 57%, respectively). Re-treatment with bortezomib was effective in the MPV arm (6% of CRs) at the moment of relapse, as were the IMiDs (4% of CRs with thalidomide and lenalidomide-based combinations). Regarding toxicity, the frequency of serious adverse events was higher in the MPV arm (46% vs. 36%). No significant differences were reported in the

incidence of hematologic toxicity and the most divergent grade 3/4 toxicities between MPV and MP were gastrointestinal events (20% vs. 6%) and PN (13% vs. 0%). In addition, 17% and 14% of patients experienced grade 2 and grade 1 PN, respectively, for a total incidence of 44%. However, it was reversible in most patients; 79% of PN events improved (by at least one grade) in a median of 2 months and 60% of PN events completely resolved in a median of 6 months. Herpes zoster was more frequent with MPV (13% vs. 4%), but the rate with MPV decreased to 3% among patients receiving antiviral prophylaxis. Thrombo-embolic events were very low and the same in both arms (1%). Upon analyzing the tolerability by treatment cycle it was found that the major incidence of adverse events in the MPV arm occurred during the first four cycles. These results led to the approval in 2008 of bortezomib for previously untreated MM patients by the US Food Drug Administration (FDA) and the EMEA.

9.2.1.3 Lenalidomide

Lenalidomide has also been examined for the treatment of elderly patients with newly diagnosed MM. In a phase I/II trial, the combination of lenalidomide with MP (MPR) was found to result in an ORR of 81% and a 24% CR rate (Palumbo et al. 2007). With a median follow-up of 29.5 months, the median TTP and PFS times were 28.5 months and the 2-year OS rate was 90.5%. The main AEs included neutropenia, thrombocytopenia, and thromboembolism. Following these promising results, an international phase III study, MM 015, was conducted comparing MP with MPR (with or without lenalidomide maintenance) (Palumbo et al. 2010). Four hundred and fifty nine patients were enrolled in the study. Twenty-five percent of patients were older than 75 years. Patients were randomly assigned to receive either nine cycles of MP or MPR or MPR + R maintenance. The ORR was 50%, 68%, and 77%, respectively. Four percent of patients achieved CR within the MP arm compared to 11% in the MPR arm and 16% in the MPR + R arm. The primary objective was PFS between MP vs. MPR + R. Median follow-up at time of reporting was 21 months. Although median PFS was not reached in the MPR + R, PFS was only 13 months for the MP and 14 months for the MPR patients. The most common grade 3/4 adverse events were neutropenia and thrombocytopenia (70% and 38%, respectively in the MPR arm). More than 60% of patients required growth factor support. This hematological toxic pattern, especially in the older patients, could explain the disappointing results of this regimen. Results of the ongoing ECOG E1A06 study comparing MPT with MPR will be of great interest. The HOVON and the Nordic Myeloma Study Group are also conducting a phase III trial in elderly patients comparing MPT plus maintenance thalidomide with MPR followed by maintenance with lenalidomide. This trial will further clarify the role of lenalidomide in the nontransplant setting.

9.2.1.4 Combinations of New Agents Plus MP

VMPT

In the Italian GIMEMA trial, MPV was compared with bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with VT (Palumbo et al. 2010). Initially, patients received a scheme similar to that previously reported in the VISTA trial (bortezomib administered twice per week), adding thalidomide (50 mg/day) in the VMPT arm. The protocol was subsequently amended: both VMPT and MPV schedules were changed to nine 5-week cycles and the bortezomib schedule was modified to weekly administration. Five

hundred and eleven patients were included. The VGPR rate was significantly higher in the VMPT group (59% vs. 50%), including a CR rate of 38% in the VMPT group and 24% in the MPV group. Maintenance therapy did not further enhance response rates. The incidence of grade 3/4 adverse events was similar in both groups except for neutropenia (37% vs. 28%), noting that the weekly infusion of bortezomib significantly decreased the incidence of grade 3/4 PN (9% for VMPT and 8% for MPV). With a median follow-up of 26.5 months, 3-year PFS is 54% in the VMPT + VT arm vs. 40% in the MPV arm ($p = 0.006$).

9.2.2 Firstline Treatment: Can New Agents Replace Alkylators?

9.2.2.1 Thalidomide

Two studies conducted in the United States were designed to compare thalidomide plus dexamethasone (Thal-Dex) versus Dex as primary therapy for newly diagnosed patients (Rajkumar et al. 2006, 2008). These studies enrolled a total of 677 young and elderly patients but primarily targeted patients unable or unwilling to undergo upfront ASCT. Thal-Dex resulted in significantly higher response rates (63% vs. 41%) and prolonged TTP compared to Dex (22.6 vs. 6.5 months), leading to FDA approval in 2006. However, the toxicity of dexamethasone was significant and the combination had an even greater toxicity (hyperglycemia, fatigue, insomnia and muscle weakness). In the ECOG study, there were 5% treatment-related deaths. Similar toxicities were noted in the other Thal-Dex study. A further confirmation of high level of toxicity was provided by the Central European phase III study in elderly patients ($n = 289$) comparing Thal-Dex with MP (Ludwig et al. 2009). Patients were randomized to either thalidomide 50–400 mg daily plus Dex 40 mg on days 1–4 and days 15–18 on even cycles and on 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 28–42-day cycle. For maintenance, patients achieving stable disease or better were randomized to receive 3 MU interferon-α2b three times per week with or without thalidomide 100 mg daily. The study reported significantly higher CR and VGPR rates (26% vs. 13%) as well as RR (68% vs. 50%) for patients receiving Thal-Dex. PFS was similar in both groups (median, 21 and 17 months for MP and Thal-Dex, respectively), but significantly shorter OS was observed in the Thal-Dex group (median, 49 and 42 months for MP and Thal-Dex, respectively). The population was very elderly, especially in the Thal-Dex group, with 60% of patients between the ages 70 and 79 and 10% ≥80 years. Patients received a high-dose Dex regimen and thalidomide dosing was up to 400 mg/day. Thus, the very elderly patient population and the higher doses of thalidomide and Dex used likely contributed to a higher mortality rate in Thal-Dex-treated patients during the first year of study, especially in patients with a poorer performance status.

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

9.2.2.2 Lenalidomide

A subanalysis of the phase III ECOG trial examined the efficacy of lenalidomide-Dex (RD) versus lenalidomide-low dose Dex (Rd) in patients ≥65 years old (Rajkumar et al. 2010). The 1-year survival rate was found to be significantly better for patients receiving Rd than for those receiving RD (94% vs. 83%, respectively; $p < 0.004$). High-dose Dex in a community-setting seems more toxic than low-dose Dex, with more early deaths in the first 4 months, increased risk of thrombo-embolic complications, and higher overall risk of serious adverse events, particularly in patients older than 65 years.

9.2.2.3 Combinations of New Agents

Bortezomib and Thalidomide

In an attempt to optimize the treatment of elderly untreated MM patients, the Spanish myeloma trial (GEMO5) was designed to compare six cycles of induction therapy with MPV versus bortezomib, thalidomide, and prednisone (VTP) (Mateos et al. 2009). The MPV regimen was based on one intensive "VISTA" 6-week cycle followed by five adapted 5-week cycles (bortezomib was given as a weekly dose on days 1, 8, 15, and 22). The VTP arm was the same as MPV, but substituting the melphalan with thalidomide at 100 mg/day. A total of 260 patients have been recruited so far and preliminary results show no significant differences in efficacy (RR of 81% in both arms, with CR rates of 22% and 27% for MPV and VTP, respectively). The VTP arm was found to be cardiotoxic. After induction therapy, patients were randomized to receive maintenance therapy for 3 years with thalidomide (50 mg daily) plus bortezomib (VT) or prednisone plus bortezomib (VP); bortezomib is given on a conventional schedule (days 1, 4, 8, and 11) every 3 months. Maintenance increased response rates.

9.2.3 Can We Reduce Toxicities of New Drugs-Incorporating Regimens?

9.2.3.1 Bortezomib in a Weekly Schedule

As already mentioned, a reduced frequency of administration of bortezomib in combination with MP was investigated in two European studies in patients ≥65 years old. In the Spanish myeloma group trial, patients were randomized to receive six cycles of MPV or bortezomib plus thalidomide plus prednisone (VTP) (Mateos et al. 2009). During cycle 1 of the induction treatment, bortezomib was administered twice weekly, and in subsequent cycles bortezomib was only administered once weekly. The results indicate that efficacy was similar between the two regimens, whereas differences were observed in toxicities. Notably, the rate of grade 3 or 4 PN was only 5% with the reduced-dose MPV regimen, and only 12% of patients discontinued treatment. The Italian myeloma group also investigated a reduced frequency of administration of bortezomib in a trial designed to compare bortezomib, melphalan, prednisone, and thalidomide (VMPT) with MPV in elderly patients (Palumbo et al. 2009). Bortezomib was initially administered twice weekly in a proportion of patients; however, following a protocol amendment, all patients received bortezomib once weekly at 1.3 mg/m^2. A comparison of efficacy and toxicity in patients receiving twice-weekly or once-weekly bortezomib in the MPV arm revealed that a shift from twice weekly to once-weekly bortezomib dosing reduced the rate of CR from 27% to 20%, but that it also substantially reduced the incidence of sensory neuropathy (14% vs. 2%) and rate of treatment discontinuation (15% vs. 4%).

The results of these two studies suggest that a reduction in bortezomib administration from twice weekly to once weekly leads to a reduction in toxicity of the MPV regimen while retaining significant efficacy, although not at the same level as reported in the original VISTA trial. Longer follow-up is needed to assess the impact on PFS and OS.

9.2.3.2 Low-Dose Dexamethasone

Along with the frequent and serious Dex side effects, there were also data suggesting that high doses of Dex were possibly not necessary in combination with novel agents, such as thalidomide or lenalidomide. The ECOG group proceeded recently with the E4A03 study comparing lenalidomide plus high-dose Dex (40 mg daily on days 1–4, 9–12, and 17–20) with

lenalidomide plus low-dose Dex (40 mg daily on days 1, 8, 15, and 22) (Rajkumar et al. 2010). A total of 445 patients (median age, 66 years; aged up to 88 years) were treated, including 233 over the age of 65 years. The significant toxicity of the high-dose Dex regimen was fully confirmed, but the good news was the modest toxicity of the low-dose Dex regimen. Infection/pneumonia, fatigue, hyperglycemia, deep venous thrombosis, and cardiac ischemia were significantly less frequent with the low-dose Dex schedule. Overall, nonhematologic toxicity grade ≥3 was found in 52% of patients receiving RD compared to 34% of patients receiving Rd. Early deaths were also significantly less frequent in the low-dose Dex arm (1.4% vs. 4.5%). In patients aged over 65 years, the 2-year survival was significantly superior in the group of patients receiving the low-dose Dex regimen (82% vs. 67%). In patients receiving primary therapy beyond four cycles with Rd, the ORR was 89% with a 22% CR rate, and a 56% VGPR rate. Overall, and even though the study was not designed to test efficacy of long-term lenalidomide plus Dex (median durations on treatment were only 4 months in the high-dose Dex arm and 6 months in the low-dose Dex arm), Rd was found to be highly active in newly diagnosed elderly patients. There is no doubt that these results will be of major importance in the future and will influence the fate of other Dex-based combinations.

9.2.3.3 Prevention of IMiDs-Associated Venous Thromboembolism (VTE)

The International Myeloma Working Group has provided in 2008 detailed guidelines on the appropriate thromboprophylaxis for patients in patients treated with thalidomide or lenalidomide (Palumbo et al. 2008). The panel recommended aspirin for patients with low risk factor for VTE. LMWH (equivalent to enoxaparin 40 mg/day) is recommended for those with intermediate or high-risk factors. LMWH is also recommended for all patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin targeting a therapeutic INR of 2–3 is an alternative to LMWH, although there are limited data in the literature with this strategy and it might not be recommended for cancer patients. In the absence of clear data from randomized studies as a foundation for recommendations, many of the following proposed strategies are the results of common sense or derive from the extrapolation of data from many studies not specifically designed to answer these questions.

9.2.4 Maintenance Therapy in Elderly

Results from the MRC Myeloma IX maintenance study indicate that thalidomide maintenance has a non significant effect in improving PFS in non-intensively treated patients (Morgan et al. 2009). Lenalidomide and bortezomib are still under investigation and a longer follow-up is needed for confirming their role as maintenance treatment.

The Spanish myeloma group investigated a 3 years maintenance with VT or VP (bortezomib: 1.3 mg/m^2/day 1, 4, 8, 11/3 months; Thalidomide: 50 mg/day; Prednisone: 50 mg alternating days) (Mateos et al. 2009). This maintenance regimen increased the CR from 25% to 42% with a low toxicity profile. VT was superior in terms of TTEvents. Despite these good results, considering their toxicity profile, first of all peripheral neuropathy, and, in case of thalidomide, the lack of correlation between cumulative dose and outcome, a limited administration is suggested. In contrast, lenalidomide showed a benefit from prolonged treatment, making the drug one of the best choices for long-term maintenance treatment. Several trials are also ongoing with lenalidomide maintenance. In the MM 015, at time of

data cut-off (December 1, 2009) most of patients had continued onto maintenance therapy phase (Palumbo et al. 2010). Only 8% of patients receiving lenalidomide maintenance required dose reduction suggesting continued treatment is well tolerated. Median PFS and OS are not reached in this arm.

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