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REVIEW

New developments in the treatment of patients with multiple myeloma

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ABSTRACT

Much progress has been made in the treatment of patients with multiple myeloma (MM). The introduction of new drugs such as thalidomide, bortezomib and lenalidomide has created more possibilities for patients than many years before. In addition, autologous peripheral blood stem cell transplantation after high-dose melphalan has become the standard of care for younger patients. Allogeneic stem cell transplantation is an experimental option for those younger patients with a human leucocyte antigen identical donor. Because of these rapid developments and many treatment options we need good quality clinical studies that can guide us in what to do in everyday practice. This review will focus on those studies that have changed the treatment guidelines for patients with MM.

KEYWORDS

Multiple myeloma, bortezomib, thalidomide, lenalinomide, stem cell transplantation

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder which is diagnosed in nearly 700 patients in the Netherlands each year. The disease is characterised by the clonal proliferation of plasma cells in the bone marrow, which produce a monoclonal immunoglobulin (paraprotein or M-protein). This patient-specific M-protein can be detected in the serum or in the urine as free light chains. Typical clinical and laboratory features in patients with MM include bone pain, due to lytic lesions, osteoporosis, anaemia, renal insufficiency, hypercalcaemia and increased susceptibility to infections.

The treatment of MM has been very cumbersome for a long time because the disease is relatively resistant to conventional chemotherapeutic therapy. Since the majority of plasma cells do not divide, cell cycle dependent cytotoxic agents are of limited effectiveness. Alkylating agents such as melphalan and cyclophosphamide and corticosteroids are the most effective *conventional* agents for the treatment of this disease.

In addition, the interaction of myeloma cells with extracellular matrix proteins and bone marrow stromal cells, as well as osteoblasts and osteoclasts, play a crucial role in the drug resistance of the disease, the so-called 'cell adhesion-mediated drug resistance'. Several antiapoptotic factors are secreted by the bone marrow microenvironment, such as interleukin 6 (IL-6) which induces resistance to drug-induced apoptosis. Myeloma cells also secrete several cytokines which further stimulate IL-6 production, neoangiogenesis, osteoclast proliferation and osteoblast inhibition. Additionally, the transcription factor nuclear factor kappa B (NF-κB) is constitutively expressed in MM cells also leading to drug resistance.

Internationally and within the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) clinical studies are performed that should be translated into daily patient care and hopefully will lead to better survival of patients with MM. Indeed, a recent SEER (Surveillance, Epidemiology, and End Results) programme analysis demonstrated a clear survival benefit of three years in younger patients with MM diagnosed in the years 2002-2004 compared with previous calendar periods.[1]

TREATMENT OF YOUNGER PATIENTS (≤65 YEARS)

A way to overcome the above-described drug resistance in MM is to further increase the dosing schedule of a drug. Since melphalan has moderate nonhaematological toxicity, high doses can be used in younger patients.

However, this treatment induces severe and prolonged myelosuppression. This can be overcome by the infusion of autologous haematopoietic stem cells that are collected before the administration of high-dose therapy. This autologous peripheral stem cell transplantation (PBSCT) has no antitumour effect of its own, but is a form of rescue treatment after high-dose therapy. The presence of malignant plasma cells in the infused autologous stem cell product has no influence on the relapse risk after PBSCT, and because CD34+ stem cell selection increases the infection risk post-transplant, unselected stem cell products are used for this procedure.[2]

Autologous peripheral blood stem cell transplantation

Several prospective, randomised studies have been performed comparing conventional chemotherapy with high-dose therapy combined with PBSCT.[3-7] The HOVON 24 study compared single nonmyeloablative intensive treatment with double, intensive treatment consisting of intermediate dose melphalan with additional high-dose cyclophosphamide, total body irradiation (TBI) and autologous PBSCT in previously untreated patients. A significantly higher proportion of patients achieved a complete response (CR) on protocol treatment with the high-dose therapy (32 *vs* 13%, p<0.001) and outcome was also better in terms of progression-free survival (PFS) but not overall survival (OS).

As a result of this and other studies which demonstrated improved response rates (RR), PFS rates and in some studies also improved OS rates, autologous PBSCT after high-dose melphalan (HDM) has become the standard of care for younger patients (≤65 years) and eligible patients should always be referred to hospitals with transplantation facilities for this part of their treatment.

Another important conclusion from these studies was that achievement of a CR (negative immunofixation of serum) and very good partial response (VGPR, reduction of M-protein >90%) are significantly correlated with PFS and OS.

If this relation between remission rate and survival exists, several additional treatment strategies can be developed that increase remission rates, which should lead to better outcome in the first-line treatment of younger MM patients. One strategy is to increase the remission rate before autologous PBSCT and the other is to increase the remission rate after first autologous PBSCT.

Novel drugs and autologous PBSCT

The introduction of thalidomide (Softenon) in 1999, bortezomib (Velcade) in 2005 and lenalidomide (Revlimid) in 2007 for the treatment of relapsed MM created the possibility to investigate these intensification strategies in newly diagnosed patients.

Prospective randomised studies comparing thalidomide-based induction regimens with conventional regimens such as VAD (vincristine, adriamycin and dexamethasone) followed by intensive therapy with HDM and autologous PBSCT have been performed, including the HOVON 50 study. In this study higher responses were achieved with the addition of thalidomide. At least PR was achieved in significantly more patients with thalidomide combined with adriamycin and dexamethasone (TAD) compared with VAD, 71 *vs* 57% respectively, p=0.001.[8] Response after total protocol treatment including HDM and autologous PBSCT and maintenance treatment was also better in the TAD arm compared with VAD, 88 *vs* 79% (p=0.005) with also better VGPR + CR rates, 66 *vs* 54% (p=0.005).

These better RR translated into a significantly better PFS of 34 months compared with 25 months (p<0.001) after a median follow-up of 52 months (*table 1*). However, OS was not significantly different with a median of 60 months in the control arm and 73 months in the thalidomide arm (p=0.77). This is possibly explained by the difference in

Table 1. *Phase III trials comparing different induction regimens and autologous PBSCT ± maintenance therapy*

Author	Conditioning	ORR after PBSCT	Median EFS/PFS (months)	Median OS (months)
Barlogie et al. 2006[6]	VAD + 3 cycles cyclo/ etoposide/ cisplatin/dex ± T 400 mg	Double PBSCT CR rate only 43 *vs* 62%	Est. 50 *vs* 60	Est. 86 *vs* not reached (ns)
Lokhorst et al. 2009[8]	VAD *vs* TAD T 200 mg	79 *vs* 88% CR+VGPR 54 *vs* 66%	25 *vs* 34	60 *vs* 73 (ns)
Sonneveld et al. 2008, abstract[10]	VAD *vs* PAD	84 *vs* 94% CR+VGPR 60 *vs* 73%		
Harousseau et al. 2008, abstract[11]	VAD *vs* Bor/Dex 4 cycles	CR+VGPR 42 *vs* 62%		

ORR=overall response rate; PBSCT=peripheral blood stem cell transplantation; EFS=event-free survival, PFS=progression-free survival; OS=overall survival; CR=complete response; VGPR=very good partial response; est=estimated; ns=not significant; VAD=vincristine-adriamycin-dexamethasone; cyclo=cyclophospahmide; T=thalidomide; TAD=thalidomide-adriamycin-dexamethasone; PAD=bortezomib-adriamycin-dexamethasone; Bor/Dex=bortezomib/dexamethasone.

survival after relapse. Relapsed patients who had received thalidomide had a median OS after relapse of 20 months *vs* 31 months (p=0.009) for the patients in the VAD arm.
Patients in the TAD arm had more neurological toxicity, mainly peripheral neuropathy, 31 *vs* 21% (p=0.008). With the use of low-molecular-weight heparin prophylaxis in patients receiving TAD, the incidence of venous thromboembolism was almost similar in both study arms, 8 *vs* 4%.
Comparable with the HOVON 50 study, also Barlogie *et al*. did not find any survival benefit in patients receiving additional thalidomide at induction, double autologous PBSCT, consolidation and maintenance therapy, despite increased RR and event-free survival (EFS) rates.[9] This was also due to the shorter median survival after relapse of 1.1 years in the thalidomide arm compared with 2.7 years in the control group. Since this Total Therapy II schedule is very different from the treatment regimens applied in the Netherlands, these findings cannot be easily translated into our daily practice. However, the notion that long duration of thalidomide use in the induction regimen and also in maintenance treatment can be detrimental when treating a subsequent relapse in these patients, as was also found in the HOVON 50 study, is important.
In the HOVON 65 phase III study, bortezomib was studied in induction therapy combined with adriamycin and dexamethasone (PAD) compared with VAD induction and followed by autologous PBSCT and maintenance therapy. This seems to be an effective regimen with very high response rates (≥PR) at interim analysis of the first 300 patients after HDM and autologous PBSCT of 92% in the PAD arm and 77% in the VAD arm (p=0.01) and CR rates of 15 *vs* 4% (p=0.05).[10] These results confirm the results of the IFM 2005/01 trial which also demonstrated superiority of bortezomib in the induction regimen compared with VAD for response rates.[11] Data on PFS and survival are therefore eagerly awaited.
Because information on trials using lenalidomide in the induction regimen before autologous PBSCT is scarce, its use will be discussed in the section of patients >65 years.
In conclusion, the introduction on thalidomide into the induction regimen before autologous PBSCT has proven benefit in response rates *and* PFS in randomised controlled trials. Therefore, thalidomide combined with (adriamycin and) dexamethasone is recommended as first-line therapy in the induction regimen of younger patients eligible for autologous PBSCT.

Treatment after autologous PBSCT

Strategies exploring ways to increase remission rates after the first HDM and autologous PBSCT are: second HDM with autologous PBSCT within a few months after the first procedure, allogeneic SCT (see section on allogeneic SCT) or maintenance/consolidation therapy. Randomised trials have shown that double autologous PBSCT may increase PFS, but only in patients not having at least a VGPR after the first stem cell infusion.[12,13] However, these trials were performed with the 'older' induction regimens, questioning its significance nowadays and there is no consensus regarding this strategy.
The goal of maintenance or consolidation therapy after HDM and autologous PBSCT is to improve the quality and duration of response, both of which should lead to a better survival. Interferon-α was used as maintenance therapy but meta-analysis of randomised trials showed a minimal benefit in survival and considering the costs and side effects of interferon treatment this approach has been abandoned.[14]
In 2006, the French IFM group published the 99-02 trial demonstrating that maintenance treatment with thalidomide 400 mg daily and pamidronate started two months after a double autologous PBSCT until disease progression improved overall survival compared with no maintenance or pamidronate therapy only.[15] After relapse, the one-year probability of survival was similar. In a sub-analysis of the study only patients who did not achieve a VGPR or CR benefited from the thalidomide maintenance suggesting an action of mostly tumour reduction, such as consolidation therapy, rather than a maintenance effect. In an Australian study thalidomide consolidation therapy of 200 mg daily for 12 months combined with prednisolone 50 mg on alternate days until disease progression compared with prednisolone therapy alone after single autologous PBSCT improved the PFS and OS rate at three years in the thalidomide arm.[16] Also this effect was more pronounced in the no CR/VGPR group in a sub-analysis. Another study on thalidomide maintenance was recently retracted.[17]
In the HOVON 50 study there was no separate randomisation for maintenance treatment and patients who had induction treatment with VAD continued with interferon-α and patients with TAD induction with thalidomide 50 mg daily for two years. Therefore, a separate conclusion on the value of this maintenance treatment cannot be made.
In conclusion, maintenance therapy after autologous PBSCT may have benefit; however, the optimal duration and the effect once maximal response is achieved is currently unknown. Therefore, thalidomide maintenance therapy should not be given until relapse but possibly for a fixed period.

TREATMENT OF ELDERLY PATIENTS AND PATIENTS NOT ELIGIBLE FOR HIGH-DOSE MELPHALAN

The majority of patients diagnosed with MM will be older than 65 years and therefore ineligible for HDM. Until recently, the mainstay of treatment for these patients

was melphalan combined with prednisone (MP) or dexamethasone-based regimens. In the past few years, several trials showed important improvements in patient outcome by addition of novel agents to these regimens.

Melphalan-prednisone based studies

The IFM and the GIMEMA group published the first phase III studies that showed the superiority of adding thalidomide to MP (*table 2*). The GIMEMA trial compared six 4-weekly cycles of MP with MP-thalidomide (MPT) in patients between 60 and 85 years, using thalidomide continuously (100 mg/day) in the MPT regimen, followed by maintenance thalidomide of 100 mg until relapse.[18] Median follow-up was 38 months. The RR was significantly higher in patients treated with MPT compared with MP (69 *vs* 48%, p<0.001). In addition, CR and VGPR were significantly higher after MPT (29 *vs* 11%, p<0.001). Although after MPT the PFS improved (median 22 *vs* 15 months, p=0.004), no difference was seen in OS (median 48 *vs* 45 months, p=0.79).

The IFM 99-06 trial did show improvement of survival using MPT *vs* MP.[19] In patients aged 65 to 75 years, twelve 6-week cycles of MPT were tested with dosages up to 400 mg thalidomide, *vs* the same MP regimen without thalidomide. There was no maintenance therapy in either arm. Median follow-up was 51.5 months. The RR was superior using MPT (76 *vs* 35%, p<0.0001) and even more importantly, the median OS improved from 33 months to 52 months (p=0.001). A trial also performed by IFM in an even older patient group, aged 75 to 89 years, confirmed the benefit of adding thalidomide in both RR and OS.[20] The Nordic study group and the HOVON 49 study also tested MP *vs* MPT. MP(T) therapy was continued until plateau and thalidomide maintenance was given in the MPT group in both studies. The Nordic group showed improvement in PFS, but not in OS. The HOVON 49 study, however, showed improvement in RR (66 *vs* 45%, p<0.001), median PFS (15 *vs* 11 months, p=0.002) as well as median OS (40 months *vs* 31 months, p=0.05).[21]

In conclusion, addition of thalidomide to the MP regimen leads to clear improvement in responses and PFS. The beneficial effect on OS was demonstrated in three studies. As expected, the MPT regimen is more toxic than MP alone. An increased risk of thromboembolic events, which mainly occurs within the first four months of therapy, necessitates prophylactic anticoagulation with aspirin or low-molecular-weight heparin.[22] Furthermore, over 50% of patients develop peripheral neuropathy after prolonged use of thalidomide, although grade 3/4 neuropathy only arises in 2 to 9%.

Lenalidomide, an analogue of thalidomide, has demonstrated significant activity in relapsed and refractory MM patients in combination with dexamethasone[23,24] (see section on relapsed MM for further details). A phase II study from Italy combined lenalidomide with MP as first-line treatment in elderly patients (median age 71 years, range 57-77). Lenalidomide dosage was 5 or 10 mg per day, yielding a PR or better in 81% of patients, including 24% CR. The EFS and OS were 92 and 100% at one year, respectively.[25] The results of a recently closed phase III trial testing MP *vs* MP with lenalidomide are awaited.

Lenalidomide is not registered for use as first-line treatment in the Netherlands and can only be given to newly diagnosed patients in the context of clinical trials.

After promising results in a phase II study,[26] the Spanish PETHEMA group tested addition of bortezomib to MP (MPV) *vs* MP alone, in previously untreated elderly patients. As with thalidomide, also the addition of bortezomib resulted in a better RR of 71 *vs* 35% (p<0.001), and very good CR rates of 30 *vs* 4% (p<0.001).[27] More importantly, MPV-treated patients had a better OS after a median follow-up of 16.3 months, hazard ratio 0.61 (p=0.008), but there was a higher rate of gastrointestinal symptoms, peripheral neuropathy and herpes zoster infections. It is recommended to use valacyclovir prophylaxis to prevent these herpes zoster reactivations with bortezomib use. This VISTA trial led to registration of MPV in first-line therapy for elderly patients not eligible for high-dose therapy and who cannot be treated with thalidomide due to comorbidity or side effects.

Table 2. *Phase III trials comparing MP vs MPT or MPV ± maintenance*

Author	Treatment	ORR	Median PFS/EFS (months)	Median OS (months)
Palumbo *et al.* 2008[18]	MP *vs* MPT	48 *vs* 69%	15 *vs* 22	45 *vs* 48 (ns)
Facon *et al.* 2007[19]	MP *vs* MPT	35 *vs* 76%	17.8 *vs* 27.5	33 *vs* 52
Hulin *et al.* 2009[20]	MP *vs* MPT	31 *vs* 62%	18.5 *vs* 24.1	29.1 *vs* 44
Wijermans *et al.* 2008, abstract[21]	MP *vs* MPT	45 *vs* 66%	11 *vs* 15	31 *vs* 40
San Miguel *et al.* 2008[27]	MP *vs* MPV	35 *vs* 71%	16.6 *vs* 24	Not reached at 16.3 months follow-up

ORR=overall response rate; EFS=event-free survival, PFS=progression-free survival; OS=overall survival; ns=not significant, MP=melphalan prednisone; T=thalidomide; V=bortezomib.

Dexamethasone-based regimens

Dexamethasone is not commonly used in the treatment of elderly patients due to its high toxicity in this patient group. In a recent study by Ludwig *et al.*, MP was compared with thalidomide 50 to 400 mg daily combined with dexamethasone 40 mg on days 1-4 and 15-18 in even cycles and on days 1-4 in odd cycles.[28] Patients received nine cycles and responding patients underwent a second randomisation to maintenance treatment with thalidomide or interferon-α. The median age of the patients was 72 years (range 54 to 86) and 10% were older than 80 years. Although the TD arm resulted in a better RR of 68 *vs* 50% (p=0.002), the PFS was similar in both groups. However, median OS was significantly shorter in the TD group of 41.5 months compared with 49.4 months in the MP arm (p=0.024) due to more treatment-related deaths. Especially in elderly patients (>75 years) with a poor performance status, this dexamethasone regimen clearly resulted in higher toxicity and should be avoided.

This was also very recently demonstrated by Rajkumar *et al.* who included newly diagnosed patients without age limit in an open-label randomised phase III trial comparing lenalidomide 25 mg on days 1-21 in a 28-day cycle with high-dose dexamethasone or low-dose dexamethasone.[29] High-dose dexamethasone consisted of 40 mg on days 1-4, 9-12 and 17-20 or low-dose dexamethasone of 40 mg only once a week. The primary endpoint of the trial was response rate after four cycles of treatment. More than 50% of patients were ≥65 years, maximum age was 87 years. Comparable with the Ludwig trial, response rates were better in the high-dose group, 81 and 70% respectively (p=0.009), but OS was not. The one-year OS was 96% in the low-dose group compared with 87% in the high-dose group (p=0.0002) and this difference was even more pronounced in the patients >65 years, 94 and 83% respectively. Because of this difference in OS the study was stopped on the recommendation of the independent data monitoring committee and patients in the high-dose group were instructed to cross over.

The most common causes of treatment-related mortality (TRM) were venous thrombotic events despite prophylaxis (9 *vs* 2%), infection (7 *vs* 3%), and cardiac complications (11 *vs* 4%) in the high-dose and the low-dose group, respectively.

Conclusion

After years of absence of improvement in elderly MM patients, addition of novel agents to old regimens finally resulted in better patient outcome in elderly patients, however at the expense of an increase in side effects. Recently the new HOVON 87 elderly study opened, a phase III study comparing MPT *vs* MP-lenalidomide. Patients who cannot participate in this trial should be treated with MPT, or MPV in those patients who cannot be treated with thalidomide.

RELAPSE TREATMENT

The introduction of thalidomide, lenalidomide, and bortezomib, used either as a single agent or in combination with other drugs, has improved the median survival of patients relapsing after autologous stem cell transplantation from one to two years after relapse.[30] No clear superiority of one novel agent over the other has been demonstrated in relapsed/refractory MM in the absence of a randomised study. In addition, because of patient heterogeneity it is difficult to directly compare the results of the different studies. Since thalidomide is recommended for use in first-line treatment, only lenalidomide and bortezomib are discussed.

Lenalidomide

Lenalidomide is an amino-substituted derivative of thalidomide, which has more potent biological activity. Richardson *et al.* showed that lenalidomide monotherapy was effective and well tolerated in relapsed/refractory patients who received a median of three prior regimens. The maximum tolerated dose was 25 mg and 29% of the patients obtained at least PR.[31] Responses were also observed in thalidomide-exposed patients. In contrast to thalidomide, lenalidomide was associated with a low incidence of somnolence, rash, constipation, and peripheral polyneuropathy. Most common adverse events included neutropenia and thrombocytopenia, which were manageable with dose reduction or granulocyte colony stimulating factor (G-CSF) support. Single agent lenalidomide did not significantly increase the risk of venous thromboembolism. Other studies confirmed the effectiveness and good tolerability of single agent lenalidomide.[32]

Lenalidomide-based combinations

Laboratory studies demonstrated that dexamethasone enhances the antimyeloma effects of lenalidomide. Based on these preclinical data and results of single agent lenalidomide, two randomised phase III trials compared lenalidomide (25 mg on days 1-21 of a 28-day cycle) plus dexamethasone (40 mg on days 1-4, 9-12, and 17-20 for the first four cycles and thereafter 40 mg on days 1-4) with placebo plus dexamethasone in relapsed/refractory patients who had received a median of two previous therapies. Dimopoloulos *et al.* demonstrated superior efficacy of the study arm, in terms of higher overall RR (60.2 *vs* 24.0%, p<0.001), CR rate (15.9 *vs* 3.4%, p<0.001), and median OS (not reached and 20.6 months, p=0.03).[24] In the

other study by Weber comparable results were reported.[23] Adverse events associated with lenalidomide therapy were neutropenia, thrombocytopenia, and thromboembolic complications in both studies. The rate of grade 3 and 4 thromboembolic events varied between 11.4 and 14.7%, which is significantly higher when compared with lenalidomide monotherapy. Importantly, the introduction of prophylactic treatment with aspirin significantly reduced the rate of thromboembolic events induced by lenalidomide containing regimens.

To further improve efficacy of lenalidomide-based regimens, various other combinations have been studied. Lenalidomide in conjunction with adriamycin and dexamethasone (RAD) in refractory and relapsed patients resulted in a high response rate of 73% including 15% CR, with mainly haematological toxicity and infections as side effects.[33]

We recently demonstrated that the combination of low-dose oral cyclophosphamide and prednisone with lenalidomide has a remarkably high activity (CR in 14.3% and ≥ minimal response in 64.3%) with good tolerability in relapsed patients who were refractory to lenalidomide-dexamethasone combinations (van de Donk NWCJ *et al.*, BJH in press).

Bortezomib monotherapy

Several phase I and II studies have demonstrated that the potent reversible proteasome inhibitor bortezomib induces clinically significant responses with acceptable toxicity in relapsed/refractory MM.[34,35] In a phase III randomised trial (APEX study) bortezomib was compared with high-dose dexamethasone in patients who relapsed after a median of two treatment regimens.[36] Bortezomib (1.3 mg/m^2) was administered by intravenous bolus on days 1, 4, 8, 11 for 8 three-week cycles followed by treatment on days 1, 8, 15, and 22 for 3 five-week cycles. Dexamethasone (40 mg) was administered on days 1-4, 9-12, 17-20 for 4 five-week cycles, followed by treatment on days 1-4 for 5 four-week cycles. In the bortezomib group the RR was 38% including 6% CR, whereas it was 18% (<1% CR) in the dexamethasone group (p<0.001) One-year survival was 80 and 66% in the bortezomib and dexamethasone groups, respectively. Gastrointestinal events, herpes zoster infection, peripheral polyneuropathy, neutropenia, and thrombocytopenia were more common in the bortezomib-treated patients. Importantly, bortezomib was not associated with an elevated risk of deep venous thrombosis or pulmonary embolism. Bortezomib clearance is independent of renal function and dose adjustments are not required for patients with renal insufficiency. Various studies have shown that bortezomib or bortezomib-based combinations result in rapid responses independent of renal function and improvement of renal function with tolerability comparable with that seen in patients with normal renal function.[37,38]

Bortezomib-based combinations

Addition of dexamethasone to bortezomib treatment, in patients with relapsed/refractory MM who had progressive or stable disease during bortezomib monotherapy, resulted in improved responses without altering the type and incidence of adverse events.[39]

A phase III randomised clinical study tested the combination of bortezomib with or without pegylated liposomal doxorubicin (PLD; 30 mg/m^2 on day 4) in relapsed/refractory MM.[40] A modest improvement in overall RR was observed when PLD was added; however, there was superior efficacy, in terms of longer median TTP (time to progression) (9.3 *vs* 6.5 months, p<0.001) and 15-month survival rate (76 *vs* 65%, p=0.03). The combination arm had higher incidences of neutropenia, thrombocytopenia, and gastrointestinal events.

Conclusion

At the moment, there is no generally accepted standard treatment for relapsed patients. Choice of therapy depends on various factors including age, performance status, prior therapies, response to prior therapies, bone marrow reserve, presence of polyneuropathy, risk for thromboembolism, and renal function. Lenalidomide may be indicated in case of pre-existing peripheral neuropathy, or when a history of thromboembolism may contraindicate its use. On the other hand, bortezomib rapidly reduces tumour load in patients with renal insufficiency and is not associated with increased risk of thromboembolism. It is advised to combine both drugs with dexamethasone for higher efficacy. Prospective randomised studies are needed to determine the best salvage regimens.

ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic stem cell transplantation (allo-SCT) is probably the only treatment for MM with a curative potential due to the graft-*vs*-MM effect (GVM) which was proven by the achievement of sustained complete remissions by donor lymphocyte infusions (DLI) without any other therapy in patients with a relapse after allo-SCT.[41] Clinical responses to DLI after myeloablative and nonmyeloablative conditioning have been reported in up to 50% of patients, including 20% of patients with a CR. In several patients these CR lasted for more than ten years. Chemo-sensitive disease and the occurrence of chronic Graft versus Host Disease (cGvHD) were associated with response to DLI.[42,43]

The role of allo-SCT in MM, however, is debated due to the high mortality and morbidity related with this procedure. Even as part of first-line therapy with myeloablative conditioning the TRM exceeded 30% and survival was

inferior to a matched group of patients receiving HDM with autologous PBSCT.[44]

Reduced intensity conditioning

The initial promising results of transplantations with reduced intensity conditioning (RIC) renewed the interest in allo-SCT as a treatment option. The pioneering studies were performed by the Seattle group who showed that donor engraftment could be achieved with the combination of low-dose TBI only (2 Gy) and high-dose immune suppressive drugs cyclosporine and mycophenolic acid.[45] They introduced the strategy of an autologous PBSCT followed two to four months later by a RIC allograft. In 52 patients treated with this tandem modality, a CR was achieved in 48% of patients and PFS and OS at 48 months were 48 and 69% respectively. A wide variety of conditioning regimens for MM have since been pioneered and in a previous review 26 different conditioning schemes with and without T cell depletion were identified.[46] No definite conclusions could be drawn from these studies but the best outcome after RIC was seen in those patients transplanted in first remission with less than two previous autologous PBSCT. Post transplant factors for prolonged PFS were achievement of CR and the occurrence of chronic GvHD.

Prospective studies of RIC allo-SCT as part of first-line therapy

The definite value of allo-SCT should be determined by prospective phase III studies with newly diagnosed patients that include a donor *vs* no donor comparison. Three such studies have been published. In the French IFM study, patients with an HLA-identical sibling donor and high-risk MM defined by B2 microglobulin >3 mg/l and deletion of chromosome 13 were candidates for autologous PBSCT followed by RIC allo-SCT ('auto-allo') with busulfan, fludarabine and a 5-day course of antithymocyte globulin (ATG).[47] Patients without a sibling donor were treated with double autologous PBSCT ('double auto'). The intention-to-treat analysis showed no significant difference in event-free survival (EFS) and OS. A major drawback of this study was the use of high-dose ATG included in the conditioning which resulted in profound *in vivo* T-cell depletion. The beneficial effects of this *in vivo* T-cell depletion are the low incidence of acute and chronic GvHD, the detrimental effect is the elimination of the desired GvM effect.

Also the Spanish PETHEMA study could not find a difference in EFS and OS between patients receiving a 'double auto' PBSCT compared with patients treated with 'auto-allo' SCT, despite higher response rates in the 'auto-allo'group.[48] A more positive result was published by Bruno *et al.*[49] In this study, 58 patients with an HLA identical sibling donor assigned to be treated with 'auto-allo' (conditioning low-dose TBI only) not only achieved more CR but also significantly prolonged EFS and OS as compared with the 59 patients assigned to be treated with the 'double auto' arm. Limitations of this study were the small number of patients and the relative inferior outcome of the double autologous PBSCT arm. What is encouraging is that the TRM of RIC allo-SCT in the upfront setting was strongly reduced to 11%. However, these studies cannot be compared due to differences in patient selection and conditioning regimens. A more definite conclusion about the role of allo-SCT in MM may come from two other prospective donor *vs* no donor studies with larger groups of patients in both arms that were performed by HOVON and the European Group for Blood & Marrow Transplantation (EBMT). In the HOVON 54 study patients with an HLA identical sibling donor could proceed to RIC allo-SCT between two and six months after HDM and autologous PBSCT. On the basis of an intention-to-treat analysis no difference in PFS and OS was found during an interim analysis that included 126 patients with a donor and 141 patients without a donor. The final analysis of both studies, expected in 2010, has to be awaited for definite conclusion. Until that time, allo-SCT should be offered to patients only in the context of clinical studies, such as the HOVON 76 study.

Treatment with allo-SCT is also possible for relapsed patients with chemo-sensitive disease.[50] However, no good-quality prospective clinical studies exist and therefore HOVON will start a randomised phase II trial in the near future for patients who relapsed after autologous PBSCT.

GENERAL CONCLUSION

After years of relative stagnation in the treatment of MM, much progress is now being made. For younger patients the introduction of autologous PBSCT has been important and all patient groups have benefitted from the introduction of novel drugs.[51] The use of these drugs has moved from the relapsed setting to the front-line setting and also combinations with the older chemotherapeutic drugs can be very active. Developments in the treatment will not stop here and already new drugs are being tested in relapsed MM patients. Therefore it is very important to try to include patients in clinical trials which hopefully will again lead to further improvement in the prognosis for MM patients.

REFERENCES

1. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111:2521-6.

2. Bourhis JH, Bouko Y, Koscielny S, et al. Relapse risk after autologous transplantation in patients with newly diagnosed myeloma is not related with infused tumor cell load and the outcome is not improved by CD34+ cell selection: long term follow-up of an EBMT phase III randomized study. Haematologica. 2007;92:1083-90.

3. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335:91-7.

4. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348:1875-83.

5. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005;106:3755-9.

6. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006;24:929-36.

7. Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. Haematologica. 2007;92:928-35.

8. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, et al. for Dutch-Belgian HOVON. A randomized phase III study on the effect of thalidomide combined with adriamycin, dexamethasone (TAD) and high dose melphalan followed by thalidomide maintenance in patients with multiple myeloma. Online prepublished: 2009, Oct. 30.

9. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354:1021-30.

10. Sonneveld P, van der Holt B, Schmidt-Wolf I, et al. First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycin, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan in patients with newly diagnosed Multiple Myeloma [abstract]. Blood. 2008;112:653.

11. Harousseau JL, Mathiot T, Attal M. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated Multiple Myeloma (MM) [abstract]. J Clin Oncol. 2008;26:15S.

12. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349:2495-502.

13. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007;25:2434-41.

14. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol. 2001;113:1020-34.

15. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289-94.

16. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009;27:1788-93.

17. Abdelkefi A, Ladeb S, Torjman L, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. Blood. 2008;111:1805-10.

18. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008;112:3107-14.

19. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370:1209-18.

20. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol. 2009;27:3664-70.

21. Wijermans P, Schaafsma MR, van Norden Y, et al. Melphalan + prednisone versus melphalan + prednisone + thalidomide in induction therapy for multiple myeloma in elderly patients: final analysis of the Dutch Cooperative Group HOVON 49 Study [abstract]. Blood. 2008;112:649.

22. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22:414-23.

23. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357:2133-42.

24. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357:2123-32.

25. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. J Clin Oncol. 2007;25:4459-65.

26. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. Haematologica. 2008;93:560-5.

27. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906-17.

28. Ludwig H, Hajek R, Tothova E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood. 2009;113:3435-42.

29. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2009; online prepublisehd Oct. 30.

30. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111:2516-20.

31. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood. 2002;100:3063-7.

32. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2006;108:3458-64.

33. Knop S, Gerecke C, Liebisch P, et al. Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom). Blood. 2009;113:4137-43.

34. Orlowski RZ, Stinchcombe TE, Mitchell BS, et al. Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol. 2002;20:4420-7.

35. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348:2609-17.

36. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487-98.

37. Jagannath S, Barlogie B, Berenson JR, et al. Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impaired renal function. Cancer. 2005;103:1195-1200.

38. San-Miguel JF, Richardson PG, Sonneveld P, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. Leukemia. 2008;22:842-9.

39. Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica. 2006;91:929-34.

40. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25:3892-3901.

41. Tricot G, Vesole DH, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. Blood. 1996;87:1196-8.

42. Lokhorst HM, Wu K, Verdonck LF, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. Blood. 2004;103:4362-4.

43. van de Donk NW, Kroger N, Hegenbart U, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marr Transplant. 2006;37:1135-41.

44. Lokhorst HM, Segeren CM, Verdonck LF, et al. Partially T-cell-depleted allogeneic stem-cell transplantation for first-line treatment of multiple myeloma: a prospective evaluation of patients treated in the phase III study HOVON 24 MM. J Clin Oncol. 2003;21:1728-33.

45. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood. 2003;102:3447-54.

46. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood. 2005;105:4532-9.

47. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood. 2006;107:3474-80.

48. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood. 2008;112:3591-3.

49. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med. 2007;356:1110-20.

50. van Dorp S, Meijer E, van de Donk NW, et al. Single-centre experience with nonmyeloablative allogeneic stem cell transplantation in patients with multiple myeloma: prolonged remissions induced. Neth J Med. 2007;65:178-84.

51. Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111:2962-72.