The Belgian 2010 consensus recommendations for the treatment of multiple myeloma.


For the Multiple Myeloma Study Group of the Belgian Hematological Society

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Running title: Belgian recommendations for multiple myeloma treatment

Abstract
Since the introduction of novel therapeutic agents including thalidomide, lenalidomide and bortezomib, the prognosis of multiple myeloma (MM) has significantly improved. These agents have been incorporated into numerous treatment schedules for newly diagnosed as well as more advanced MM patients. Hence, the therapeutic options for MM have become more complex and subject to rapid changes. The multiple myeloma study group (MMSG) of the Belgian Hematological Society has established recommendations for the treatment of MM as based on an extensive review of the literature which is also summarized in this paper. The recommendations are the result of a consensus opinion between hematologists with experience in the field and representing most hematology centers in Belgium. Where applicable, reimbursement criteria are also taken into account. The consensus recommendations should be a reference for use by clinical hematologists in daily practice.

Key words: multiple myeloma, myeloma treatment, recommendations
1. Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by a clonal proliferation of plasma cells in the bone marrow (1). The clinical course is variable with typical features including osteolytic bone lesions, anemia and the presence of monoclonal protein which can be detected as a M-component and/or free light chain in the serum and/or urine. Renal insufficiency occurs at some time point during the disease course in about 25% of patients (pts) and hypercalcemia may be present at diagnosis or at time of disease progression. In most pts, overt MM is preceded by a premalignant state defined as monoclonal gammopathy of undetermined significance (2). Also, MM can evolve over prolonged periods of time without symptoms or end-organ damage, defined as asymptomatic or smoldering MM and accounting for 15% of all cases (3). The MM incidence is estimated at 600 new cases per year in Belgium with a 2/1 male predominance. The median age at presentation is 65 years and 25% of newly diagnosed pts are older than 75 years. Over the past 5-10 years, the knowledge of the biology of MM has greatly increased, defining the disease as being heterogeneous with a large and variable number of cytogenetic and molecular abnormalities (4-6). Also, the interaction of the malignant plasma cells with their microenvironment is better understood (7). New drugs which interfere with this interaction such as thalidomide, lenalidomide and bortezomib have been introduced into clinical practice and have a dramatic impact on the prognosis of MM pts (8). Today, the life expectancy of an average MM patient is well over 5 years but despite this progress, the disease remains incurable. As the therapeutic options for MM expand rapidly, they become increasingly complicated. Also, reimbursement of new drugs is different in many countries. Therefore, country-specific recommendations may be useful to help clinical hematologists in their daily practice for the management of MM pts.

2. Methods

The members of the MM study group of the Belgian Hematological Society (BHS) are clinical hematologists with experience in the management of MM. Several meetings were organized to discuss the different aspects of diagnosis and treatment of MM. The discussions were based on extended reviews of the literature which were presented and subsequently summarized per item by one or two members of the group. After discussion, a consensus recommendation was agreed upon. Where applicable, comments were added with respect to reimbursement modalities in Belgium as of
December 1st 2009. Also, information regarding new developments in the management of MM was added, especially those related to the novel agents, thalidomide, lenalidomide and bortezomib. In this first part, the consensus recommendations for the treatment of MM were written down in a manuscript which was reviewed for approval by all members of the group. With respect to the treatment of MM, the level of evidence for the recommendations and the grading of the recommendations are summarized in Table 1 and were based on previously used methods (9). In a therapeutic field which is expanding rapidly, the group emphasized the importance of including MM pts into clinical trials as much as possible.

RECOMMENDATION
In view of the ongoing advances in the treatment of myeloma, clinicians should make a maximum effort to include pts in clinical trials (level V, grade D).

3. Management of asymptomatic or smoldering myeloma
The overall risk of progression of asymptomatic or smoldering MM to symptomatic MM is 10% for the first 5 years, 3% per year for the following 5 years and 1% for the 10 years thereafter (3). The percentage of monoclonal plasma cells in the bone marrow (≥ 10%) and the level of the M-component in the serum (≥ 3 g/dL) are major risk factors defining 3 categories for progression to MM at 15 years: 87% (both risk factors present), 70% (M-component < 3 g/dL) and 39% (M-component ≥ 3g/dL). In the subset of pts with ≥ 10% plasma cells in the bone marrow, the median time to progression is 2-3 years.
Two randomised trials failed to show benefit from early treatment compared to therapy at time of symptomatic progression (10;11). Hence it can be recommended that smoldering MM pts should not be treated. The standard of care is observation alone with frequent follow-up, every 3-4 months (mths). In pts with otherwise untreated smoldering myeloma, the administration of pamidronate for up to 1 year had no impact on time to progression but resulted in a significant reduction (82% vs 40%) of skeletal events (12). The use of bisphosphonates in smoldering myeloma, without associated anti-myeloma therapy must be limited to selected pts, also taken into account the possible side effects of the bisphosphonates.
4. First-line treatment for symptomatic myeloma: general comments

The main issue related to initiating treatment in MM is related to whether or not the patient is eligible for autologous stem cell transplantation (ASCT). Melphalan 200 mg/m² followed by ASCT is still considered the most powerful therapy in MM, leading to a median progression-free survival (PFS) of 24 mths and a 5-year overall survival (OS) probability of 52%, in pts younger than 65 years (13). In addition, ASCT has become a relatively safe procedure today, with a low treatment related mortality of < 2% in most series. In general, pts above 65 years are usually less fit, are more likely to suffer multiple comorbidities and have not been included in trials examining the role of ASCT. Hence, there is no evidence that high dose melphalan is of benefit in pts older than 65 years. Besides age, other factors may also play a role including good performance status and absence of comorbidities. Some pts older than 65 may be fit enough to tolerate high-dose chemotherapy. Such pts can be eligible for ASCT, either as first-line treatment or at a more advanced stage of the disease. They should then be informed about the potential risks and benefits of ASCT as well as on the possibility of currently available alternative therapies including the novel agents.

5. First-line treatment in pts not eligible for ASCT

In contrast to the situation in younger pts, the 10-year survival rate in the elderly MM patient has only modestly changed over the past 2 decades: slightly improving to 10% for pts between 60 and 79 years and remaining unchanged to 5% for pts older than 80 years (14). These figures have now definitely improved through the introduction of the novel agents. The first-line approach to MM pts can be based on either the combination of melphalan (M) and prednisone (P) with the addition of a novel agent or combinations including dexamethasone (Table 2).

5.1. Melphalan and prednisone based regimens

5.1.1. Melphalan + prednisone + thalidomide

Oral (PO) melphalan+prednisone+daily thalidomide (MPT) has been compared with standard MP in 5 randomised trials of which 3 have been published to date (15-17). All five trials showed an advantage in overall response (OR) rate and PFS. The 2 trials of the Intergroupe Francophone du Myélome (IFM) also showed a significant prolongation (median of + 18 mths) of OS compared to MP (15;16). In the
IFM 99-06 study, the doses of M (0.25 mg/kg/d for 4 days) and P (2 mg/kg/d for 4 days) are identical to the doses used in MP. In the French MPT trials, the rates for OR, complete remission (CR), CR+ very good partial remission (VGPR) were, for pts between 65 and 75 years: 76%, 13%, and 47% and for those above 75 years 61%, 7%, 23%, respectively. Median PFS and OS for both groups were 24.1/27.5 mths and 51.6/45.3 mths, respectively. MPT can thus be considered as a new standard of care regimen for elderly MM pts. The average dose of thalidomide used in the Facon study was 200 mg per day and this dose can be recommended as a target dose in pts up to 75 years of age. In pts above 75 years, the recommended dose is 100 mg per day. The maximal duration of treatment is 12 x 6-weekly cycles and the median duration of treatment in most of the trials was 9-12 mths. In the Hulin study, using the lower dose of thalidomide, the median duration of treatment was 13.5 mths with dose reduction required in 19% of pts. The major toxicities of the MPT regimen, including the comparison with MP + bortezomib (MPV), are summarized in Table 3. The major problem with MPT is sensory polyneuropathy (PNP) which requires appropriate dose reductions and timely stop of the treatment whenever grade 2-3 neurotoxicity occurs (18). Toxicities are thalidomide dose-dependent and are more likely to occur in elderly pts. After 12 mths, more than 50% of the pts have polyneuropathy but mostly grade 1-2, with grade 3-4 in only 2-9% of cases. In the Hulin study, 53% of pts was withdrawn from the trial due to toxicity, mainly due to PNP, somnolence or other central nervous system-related symptoms (16). With the use of MPT, and thalidomide in general, thromboprophylaxis is recommended. Low-molecular weight heparin (LMWH) in a prophylactic dose is preferred at the start of the anti-myeloma treatment. LMWH can be replaced by low dose aspirin after 3-4 mths in responding pts and in the absence of other major risk factors such as previous thrombosis or prolonged immobilisation (reviewed in (19)). Thusfar, there is no indication that thalidomide maintenance after MPT has a beneficial impact on survival. Thalidomide as part of the MPT regimen is available and reimbursed in Belgium.

5.1.2. Melphalan + prednisone + bortezomib

In the MPV regimen, bortezomib (Velcade®) is administered as an IV bolus in a standard dose of 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, 32 of 6-weeks cycles for the first 4 cycles followed by the same bolus dose on days 1, 8, 22, 29 of 6-weeks cycles for the following 5 cycles. The VISTA study comparing MPV vs MP in pts older than 65 years or not eligible for ASCT showed a statistically
significant advantage for MPV in terms of OR rate (ORR) (71%), CR with negative immunofixation (30%), CR duration (24 mths), median time to progression (TTP) (24 mths) and OS (71% at 3 years) (20). The superiority of MPV was consistent across all prognostic subgroups, including pts above 75 years, those with high beta-2 microglobulin and/or adverse cytogenetics and those having renal impairment (creatinin clearance 30-60 ml/min). The median time to first response was only 6 weeks and the median time to CR was 4.2 mths. The regimen is relatively well tolerated and the toxicities are summarized in Table 3. In comparison to MP, there was an excess of 10% of severe adverse events (SAE) with MPV. Toxicity led to discontinuation of treatment in 10% of cases in both arms and an additional 19% of pts discontinued bortezomib and continued with MP alone. MPV has gastro-intestinal toxicity which is usually mild and manageable with anti-emetics and anti-diarrhea agents. As for MPT, the major problem is neuropathy which is sensorial but also associated with neuropathic pain. Dose reductions must be applied strictly if these complications occur. Upon dose reduction or stop of the bortezomib treatment, the PNP improved or disappeared in 74% of cases after a median of 2 mths. Of particular interest is that bortezomib requires no dose reductions in pts with renal impairment. In a subsequent analysis of the VISTA trial, it was shown that the higher response rates and prolonged time to progression for MPV compared to MP, were maintained in pts with creatinin clearance between 30 and 50 mL/min. Also, reversal of renal impairment (defined as increase of the creatinin clearance to > 60 mL/min ) was observed in 44% of pts treated with MPV (21). Finally, the risk of deep venous thrombosis (DVT) in pts treated with MPV seems to be rather low. MPV is registered and reimbursed as a standard first-line treatment schedule in Belgium, for pts who are not eligible for ASCT.

5.1.3. MPT or MPV

Both MPT and MPV are reimbursed first-line regimens for pts not eligible for ASCT. Since there is no randomised comparison, no definite comments regarding the superiority of either one of the regimens in terms of efficacy can be drawn. Nevertheless, there are major differences in toxicity profile. Patients with pre-existing PNP are more likely to develop severe neurotoxicity which is more reversible after bortezomib. Those with previous thromboembolic events or major risk factors for thrombosis might also be safer with MPV. The activity and tolerability of MPV in pts with moderate renal impairment has been clearly demonstrated. Hence, MPV should be the treatment of choice in pts with renal impairment at diagnosis. Several studies suggest that bortezomib maintains activity in pts with adverse
cytogenetics (20;22;23). However, cytogenetics are rarely available at the start of treatment. On the other hand, bortezomib must be administered intravenously (IV) which requires more visits and more professional care. Hence, thalidomide may be preferred in less mobile pts. Also, pts with major intolerance to either one of the regimens should be offered the alternative one after adequate measures to reduce toxicity have failed, including dose reductions. Regardless of these considerations, it is clear that thalidomide and bortezomib have anti-myeloma activity without cross-resistance and hematologists should realize that premature switch to the alternative drug may withhold the patient from a potential active medication and this may have an adverse impact on his/her survival.

5.1.4. Melphalan and prednisone
The combination of PO melphalan (0.25 mg/kg/d d1-4) and prednisone (2 mg/kg/d d1-4) every 6 weeks, has long been the standard of care for elderly MM patients. A large meta-analysis showed that MP was equally effective compared to IV combinations of cytostatic drugs (24). However, the ORR (40-50%, with virtually no CR) and the OS (median of 30 mths) with MP are poor. Nevertheless, MP with appropriate dose reductions, may be a reasonable option in very old or frail pts, not able to tolerate the newer drug combinations. In patients above age 75 years, the dose of melphalan should be reduced to 0.2 mg/kg/d d1-4. The doses of melphalan in the MP schedule should be adapted to nadir cell count, bearing in mind that doses should be sufficient to cause some degree of fall of counts (9). Treatment with MP should be continued for a maximum of 12 x 6-weekly cycles or until maximum response (including stable disease) plus 3 mths (so called “plateau phase”).

5.1.5. Melphalan + prednisone + lenalidomide
The combination of melphalan+prednisone with lenalidomide (Revlimid®) (MPR) was developed in a phase I-II study where melphalan was used in a dose of 0.18 mg/kg/d for 4 days, prednisone at 2 mg/kg/d for 4 days and lenalidomide at 10 mg per day during 21 days of a 4-weeks cycle (17). An interim analysis of a large phase III trial (MM-015) comparing MP with MPR and MPR followed by lenalidomide maintenance (10 mg per day during 21 days of a 4-weeks cycle) (MPR-R) was recently presented at the annual meeting of the American Society of Hematology (ASH) (25). After a median follow-up of only 9 mths, the MPR-R schedule led to a 50% reduced risk of progression as compared to MP. A landmark analysis after 9 cycles of MPR-R versus MPR showed a 75% improvement of PFS
for MPR-R emphasizing the importance of a continued treatment with lenalidomide as the main factor contributing to the superiority of the MPR-R regimen. Also, MPR-R was very well tolerated with only 5-10% grade 3-4 fatigue, venous thrombosis, skin rash and infections, without occurrence of severe PNP. Only 16% of pts had to discontinue the treatment due to toxicity. A longer follow-up is needed to establish the role of the MPR-R regimen as a new treatment modality in MM pts who are not candidates for ASCT.

5.2. Dexamethasone-based regimens

Dexamethasone in monotherapy and in the standard high-dosing of 40 mg per day on days 1-4, 9-12, 17-21 of a 28 or 35-days cycle, cannot be recommended in elderly pts because of excess toxicity (26). Nevertheless, dexamethasone is used in many combinations together with the novel agents. The combination of thalidomide (generally targeted at a dose of 200 mg/d) and high-dose dexamethasone (Dex) (thal+Dex) is too toxic for elderly pts. In a study including mostly elderly pts (median age 72 years), thal+Dex was inferior to MP in terms of OS (41.5 mths vs 49.4 mths) despite a better ORR (68% vs 50%) and this was related to increased toxicity (27). Cyclophosphamide can be added in the schedule to reduce the dosing of dexamethasone while maintaining a similar or even a superior anti-myeloma effect. The Medical Research Council (MRC) has been conducting a phase III trial comparing MP with CTDa ("a" stands for "attenuated") (cyclophosphamide 500 mg PO weekly, thalidomide 200 mg/d and dexamethasone 20 mg/d on days 1-4, 15-18 of a 28-days cycle). The ORR for CTDa was 82.5% (22.5% CR and 47.5% VGPR) and a survival benefit above MP could be shown (28). These data are promising but not mature enough to support firm recommendation at this time point. CTDa can be recommended as an optional first-line treatment regimen in elderly pts e.g. for those not tolerating melphalan due to hematological toxicity. Thalidomide in a first-line regimen combination is reimbursed in Belgium.

A randomised trial comparing the combination of lenalidomide (25 mg per day for 21 days of a 4-weeks cycle) with either low dose dexamethasone (len+dex) (dexamethasone 40 mg per day d1, 8, 15, 22 of a 28-days cycle) or high dose dexamethasone (len+Dex) (dose see above) showed superiority of the len+dex schedule, mainly because of increased toxicity related to high doses of dexamethasone (infections, deep venous thrombosis, generalized weakness) (29). After 4 courses of induction therapy, the ORR was 68.3% (24% CR/VGPR) and pts (median age 66 years) who continued on len+dex after
4 courses, remained on treatment for a median of 11.2 mths, reaching a 91% ORR (22% CR, 57% CR+VGPR) and a 50% 3-year PFS. The len+dex schedule was well tolerated with mainly hematological toxicity, 12% thrombotic events (no prophylaxis was given) and 9% infections or pneumonia. The survival at 2 years in pts above 65 yrs in the len+dex arm was 82%. Currently, a large scale European-USA phase III trial (MM-020/IFM 2007-01) is ongoing comparing MPT with the combination of len+dex and also assessing the interest of using lenalidomide as maintenance treatment. Newly diagnosed pts with adverse cytogenetics and treated with len+dex show comparable response rates but inferior median PFS (18.5 vs 36.5 mths, p< 0.001) (30). In the USA, len+dex is considered a standard first-line treatment for pts without adverse cytogenetics (31). In Belgium, lenalidomide is not reimbursed in first-line therapy for MM.

5.3. Maintenance therapy
Since complete remissions after conventional treatment are obtained in only a minority of pts, the meaning of “maintenance therapy” is most often “continued treatment” after a fixed number of primary treatment cycles. Evidence emerges from several phase III trials that continued treatment with lower doses of bortezomib or thalidomide, either alone or in combination (32;33) further improves response rate and response quality. Maintenance therapy with lenalidomide, which is most suitable for maintenance because of its low toxicity profile, showed promising results in the MM-015 trial (see above). However, for the time being, these data are not mature enough to allow recommendations for maintenance therapy after conventional primary treatment for MM.

RECOMMENDATION
Outside the context of a clinical trial, pts not eligible for ASCT should receive either MPT (level Ia, grade A) or MPV (level Ib, grade A) as standard first-line therapy. The choice between these 2 regimens must be made on an individualized basis and determined by anticipated (as based on risk factors) and observed toxicities. High doses of dexamethasone either in monotherapy or in combination are not recommended for elderly pts. Alternatives to MPT or MPV can be the combination of lenalidomide and low-dose dexamethasone (level II, grade B) or the CTDa schedule (level III, grade B).
6. First-line treatment for pts eligible for autologous stem cell transplantation

6.1. Autologous stem cell transplantation

Several randomised trials have established the role of high-dose melphalan (200 mg/m²) followed by ASCT as standard first-line treatment in pts with MM below the age of 60-65 years (13;34-36). ASCT results in a ORR of around 80%, a median time to progression (TTP) of 24 mths and an estimated 5-years OS rate of +/- 50%. The survival probability after ASCT is correlated with the quality of response obtained after ASCT and significantly better for pts achieving either CR or VGPR, in approximately 40% of cases. The addition of a second high-dose melphalan + ASCT improves survival furthermore but this advantage is significant only for pts not achieving CR/VGPR after the first transplantation (37). In pts with renal failure or severe comorbidities, the dose of melphalan before ASCT must be reduced to 100-140 mg/m².

6.2. Induction treatment before ASCT

Actual treatment in pts eligible for ASCT includes an induction phase of 3-4 mths in order to achieve a maximum degree of tumor reduction before stem cell harvest and transplantation. Before the introduction of the novel agents, the standard induction treatment before high dose melphalan was the combination of vincristine, adriamycin and dexamethasone (VAD) which resulted in a 50-60% response rate after 3-4 courses (38). The toxicities of VAD are mainly myelosuppression, alopecia and cardiac adverse events. Dexamethasone is inferior to VAD in terms of response rate, only around 40% (39). In terms of efficacy, the combination of thalidomide and high-dose dexamethasone (thal+Dex) is superior to dexamethasone alone and comparable to VAD with an ORR of around 70% but at the cost of more toxicity, especially DVT (+/- 15%) and PNP (5-10%). Mobilization eligibility and efficacy are similar after thal+Dex and VAD. Thusfar, there is no clear indication that the quality of response to either thal+Dex, VAD or dexamethasone alone has any impact on the outcome after ASCT. The importance of the response to induction treatment before ASCT was first demonstrated in a recently published Spanish trial, pts achieving PR or near CR after the same induction treatment including polychemotherapy had a 36% vs 52% probability of achieving CR after transplant (40). This study also confirms previous observations that CR after transplant translates into a significantly prolonged event-free survial (EFS) and OS. Today, at least 3 phase III prospective randomised trials investigate
the role of induction treatment including novel agents to improve response quality before and after transplant and subsequent transplant outcome. The combinations used in these trials are: bortezomib+dexamethasone (41;42), bortezomib+thalidomide+dexamethasone (VTD) (43), bortezomib+adriamycine +dexamethasone (PAD) (44;45). These combinations have led to high quality responses (≥ VGPR 42-62%, CR 5-31%) before and after ASCT (≥ VGPR 72-88%, CR 23-57%). At the most recent updates during the 2009 ASH meeting, significant prolonged PFS was noted in the French and the Italian studies. In the IFM 2005-01 trial, the median PFS was 36 mths for bortezomib + dexamethasone vs 30 mths for VAD (p= 0.057). The advantage in PFS was even more pronounced (41 mths vs 30 mths (p< 0.001)) for pts reaching at least VGPR after induction (42). In the GIMEMA study, the PFS at 30 mths was 76% for VTD versus 58% for TD (p= 0.008) (43). Of note is that in these studies, responses as well as benefit in terms of PFS were maintained in pts with adverse prognostic cytogenetic abnormalities including the t(4;14) and del 17p. The use of bortezomib has been studied in pts with impaired renal function at diagnosis. In a small study including 46 newly diagnosed pts with renal impairment, the first-line combination of bortezomib and dexamethasone led to complete and partial renal responses in 30% and 59% of cases, respectively, after a median of already 11 days (range 8-41 days) (46). Some pts could even be rescued from hemodialysis. On the other hand, there was no apparent increase in drug-related toxicity. Bortezomib is not reimbursed in Belgium in first-line in pts eligible for ASCT. In the US, len+dex was shown to be a good option prior to ASCT resulting in a 2-year PFS of 65% and a 3-year OS of 92% after transplant (29). These data support this combination as an option for induction treatment prior to ASCT, in pts without adverse cytogenetics (31). Lenalidomide is not reimbursed in first-line treatment of MM in Belgium.

6.3. Stem cell mobilization

Guidelines for stem cell mobilization in MM pts have been published recently (47). Stem cell mobilization can be done using G-CSF (5-10 mcg/kg SC) either alone or after chemotherapy (cyclophosphamid 2-4 g/m²) following induction treatment. There is a general consensus that a minimum target of 4 million CD34+ cells/kg and, if feasible, an average of 8-10 million CD34+ cells/kg should be collected. These targets would allow to perform at least 2 autografts in most pts. Risk factors for poor stem cell mobilization are advanced age, previous melphalan exposure, extensive prior therapy or prolonged disease duration and extensive radiotherapy to marrow bearing tissue. For
previously untreated patients receiving primary treatment, there is generally no problem for stem cell
collection with G-CSF alone after VAD or thalidomide or bortezomib containing induction therapy.
Prolonged treatment with lenalidomide may reduce mobilization efficiency (48;49) so that
cyclophosphamide may be required for stem cell mobilization (50). Hence, stem cell collection is
recommended early after the start of lenalidomide-based treatment regimens (after 3-4 courses).
When stem cell mobilization appears difficult, the combined use of G-CSF with plerixafor may
considerably improve mobilization efficiency (51;52). Plerixafor in combination with G-CSF is
reimbursed in Belgium for MM pts with poor stem cell mobilization.

6.4. Maintenance or consolidation treatment after ASCT
There are at least 2 prospective trials evaluating the role of maintenance treatment after ASCT. In the
French IFM trial, the use of thalidomide 200 mg per day, given after a single ASCT for a period of 12
mths, led to an increase of +/- 10% in the probability of OS at 4 years. The effect was mainly observed
in pts with suboptimal response (< VGPR) after transplant (53). In a similar approach, Spencer et al.
randomised post-ASCT pts between prednisone 50 mg every 2 days with or without thalidomide 100-
200 mg per day for 12 mths (54). Thalidomide maintenance did improve the response quality for up to
8 mths after transplant and also led to a significant OS advantage. However, considerable toxicity was
observed with 52% of pts developing PNP (10% grade 3-4), leading to premature discontinuation in
40% of cases. Both studies favor the use of thalidomide maintenance after ASCT which is more like a
consolidation treatment with the major advantage of further improving response quality, which
translates into a better survival.

RECOMMENDATION
Outside the context of a clinical trial, high-dose melphalan (200 mg/m²) followed by ASCT is
standard as part of first-line therapy in pts below age 65 years without contraindications for
this procedure (level Ia, grade A). Before ASCT, induction regimens including bortezomib and
dexamethasone are recommended in all pts and most recommended in pts with adverse
cytogenetics (level III, grade B) or severe renal failure (level II, grade B). Induction with
lenalidomide + low-dose dexamethasone is an alternative option in pts without adverse
cytogenetics (level II, grade B). After ASCT, in pts not reaching CR/VGPR within 2-3 mths,
consolidation treatment with thalidomide can be used in an attempt to improve response quality, until stable response or unacceptable toxicity or disease progression occurs (level Ia, grade A). Alternatively, or in case of contraindication for treatment with thalidomide, these pts can be offered a second ASCT, provided the first ASCT was well tolerated (level Ib, grade A). At present, either VAD or thalidomide in combination with dexamethasone-based regimens are available in Belgium and the preference for either one of these schedules should be made on an individual basis, taken into account their practicability and specific toxicities.

7. Treatment of relapsed and refractory myeloma

The new drugs thalidomide, bortezomib and lenalidomide have activity as single agents in relapsed and refractory MM. They have been incorporated in numerous combination regimens which can be used as salvage treatment in MM pts. Some salvage regimens which can be recommended at level I-II are summarized in Table 4 and are described into more detail in the text below, with emphasis on efficacy. Optimal salvage treatment is dependent on several factors. First, there is the patient’s age, physical condition and comorbidity. For example, less mobile pts would prefer to have an oral treatment and those with cardiac disease must not be exposed to anthracyclins. Prior toxicities may have an impact on the possibility to use novel agents. For example, severe polyneuropathy limits the use of thalidomide or bortezomib and a history of prior thromboembolic events may impose caution for the use of immunomodulatory agents. For patients with diabetes, a non-steroid containing regimen may be preferable. Response to previous treatment is also important. A prolonged response duration may justify retreatment with the same schedule, e.g. a second course of bortezomib or a second ASCT (see below). Cytogenetics may have an impact, e.g. the occurrence of a del 17p may increase patient’s eligibility for experimental treatment. Finally, the presence of a HLA-identical donor, reimbursement criteria and patient’s preferences may all interfere with the choice of an optimal salvage regimen.

7.1. High-dose dexamethasone

High-dose dexamethasone (40 mg/d for 4 days on d1, 9, 17 in a 28-days cycle) is effective in advanced MM with response rates of 18 to 27% and a median of 4-6 mths response duration (55-57). However, combination schedules are more efficace and the use of dexamethasone as a single drug
should be limited to specific situations such as severe cytopenias, spinal cord compression, severe hypercalcemia and renal impairment.

7.2. Thalidomide-based salvage regimens

Thalidomide as a single agent in pts with relapsed disease has been shown to produce an ORR of 29% and a 1-year OS rate of 60% (58;59). The response rate is dose-related: 15% and 28% for 100 and 400 mg per day, respectively and when combined with dexamethasone in case of insufficient response. If combined upfront with dexamethasone, the ORR increases to 46%, responses are more rapid (within about a month) but the risk of thrombosis may increase to around 10% (60). Using lower doses of thalidomide (100 mg/d) and of dexamethasone (40 mg 4 days each month) is also relatively effective with a median PFS of 11 mths and more acceptable toxicity (61). Thalidomide is less active in pts with adverse cytogenetic abnormalities (62;63). Currently, no randomised study of thalidomide in pts with relapsed MM has been published. The combination in 3-weekly schedules of cyclophosphamide (50 mg PO qd or 300 mg/m² PO weekly or 2 x 150 mg/m² d1-5), thalidomide (200-800 mg daily, increasing doses or intermittent administration 400 mg d1-5 and d14-18) and dexamethasone (40 mg per day for 4 days) (CTD) results in a ORR of around 60%, a median TTP of 10-12 mths and a 2-years PFS of 57% (64-66). In Belgium, thalidomide is reimbursed in the salvage setting.

7.3. Bortezomib-based salvage regimens

In the APEX trial, bortezomib (1.3 mg/m² qd IV bolus d1, 4, 8, 11 every 3 weeks) was shown to be superior to dexamethasone in a large-scale randomised phase III trial in relapsed/refractory MM with a 38% ORR (6% CR) and a 6 mths median PFS (56). Patients treated in second-line had a superior response rate as compared to those treated at a later stage of the disease (44% vs 34%) (67). The addition of dexamethasone (20 mg on the day and on the day after the administration of bortezomib) improves the ORR with 20-30% (68). Further improvement of ORR can be achieved by combining bortezomib and dexamethasone with cyclophosphamide, either daily (50 mg) or intermittently, hyperfractionated (300 mg/m² q 12 hrs times 6, d1-3) (69;70) or weekly (71). In relapsing pts with previous response (response duration > 6 mths) to bortezomib, a subsequent bortezomib-containing regimen can still be used, provided that no major intolerance had occurred during the first bortezomib
treatment, with an expected ORR of around 40% (72;73). In a phase III trial, the combination of bortezomib with liposomal pegylated doxorubicin proved to be superior to bortezomib alone in terms of response duration (+ 3 mths) and 15-mths survival rate (76 vs 65%) at the cost however of an increased toxicity (80 vs 64% grade 3/4 events) (74). This combination is a reasonable option for pts, in particular for situations where a steroid-free regimen is preferred and is reimbursed in Belgium as of second-line treatment up to a maximum of 8 cycles. Bortezomib has been incorporated in more complex schedules for the treatment of advanced pts such as the combination with thalidomide and dexamethasone (VTD) (75) or with melphalan, prednisone and cyclophosphamide (76). Finally, bortezomib is active in relapsed/refractory MM independently of the presence of adverse cytogenetics including del13 and t(4;14), known to be associated with bad prognosis with more conventional chemotherapy schedules, including high-dose melphalan (22;23). Bortezomib is generally given for 6-8 cycles, often with a dose reduction (e.g. once weekly) after 4 cycles. Several studies have confirmed the efficacy and absence of excess toxicity of bortezomib in MM pts with relapsed/refractory disease and with renal impairment (77-79). Bortezomib is reimbursed in Belgium, for a maximum of 8 cycles, as of second-line in the salvage setting.

7.4. Lenalidomide-based salvage regimens

In a multicenter, randomised phase II study in relapsed/refractory MM, lenalidomide as a single agent, showed activity in 25% of pts (14% CR/PR). In pts who did not respond to lenalidomide alone, an additional 29% responded when dexamethasone was added (80). Two randomised phase III studies have compared lenalidomide and high-dose dexamethasone to placebo and high-dose dexamethasone in pts with relapsed or refractory disease (55;57). Lenalidomide was administered at a dose of 25 mg/d for 21 days every 4 weeks and high-dose dexamethasone 40 mg on days 1-4, 9-12 and 17-20 for the first four cycles, and then on days 1-4 in subsequent cycles. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects. In both studies, the combination of lenalidomide and high-dose dexamethasone was superior to high-dose dexamethasone alone in terms of ORR (60 vs 20%), median TTP (11 vs 5 mths) and median OS (30 vs 20 mths). Previous treatment with thalidomide or bortezomib or ASCT did not affect the response to lenalidomide. In a recent sub-analysis, patients with adverse cytogenetics showed comparable response rates and durations to pts without these abnormalities, with the exception of pts with deletion...
of 17p (81). In another sub-analysis it appeared that pts treated in second-line had superior outcome (67 vs 57% ORR, 40 vs 28% CR+VGPR, median OS + 6 mths) as opposed to those treated at a later stage of their disease (82). Lenalidomide has been successfully combined with cyclophosphamide and dexamethasone (83) and with adriamycin and dexamethasone (84), but the data are not mature enough to make recommendations. In Belgium, lenalidomide is reimbursed as of second-line in the salvage setting, until progression of the disease.

7.5. Autologous stem cell transplantation

For pts with adequate stem cell reserve or cryopreserved hematopoietic stem cells, ASCT can also be a reasonable rescue treatment. High-dose melphalan is less active in case of adverse cytogenetics so that in the absence of t(4;14), t(14;16) or del17p, a first ASCT as a rescue treatment in pts with poor response to a first-line regimen is defendable, especially if the patient was not exposed yet to novel agents. After failure to VAD, ASCT led to a 92% ORR (20% CR) and a 1-year PFS of 70% (85). A second transplant can be envisaged, provided that the response to the first ASCT was of sufficient duration (e.g. more than 12-18 mths) (86).

RECOMMENDATION

Recommended salvage regimens which can be used as of second-line, are bortezomib with or without dexamethasone (up to 8 courses) (level Ib, grade A), lenalidomide+dexamethasone (until progression or unacceptable toxicity) (level Ia, grade A), thalidomide+dexamethasone (level II, grade B) and bortezomib+pegylated liposomal doxorubicin (up to 8 courses) (level Ib, grade A). The preference for one or the other regimen should be determined by previous treatment, comorbidities or risk factors for developing toxicities such as previous thromboembolism (bortezomib preferred over thalidomide or lenalidomide) or neuropathy (lenalidomide preferred over bortezomib or thalidomide) or adverse cytogenetics (bortezomib-including regimen preferred). As of third or beyond lines of treatment, combinations of these novel agents with or without chemotherapy which are published in highly-ranked peer-reviewed journals can be recommended (level II, grade B). It is preferrable that such therapies be administered within specialized centers and under the supervision of recognized clinical hematologists (level V, grade D). The indication for a (first or second) ASCT as rescue
treatment must be based on cytogenetics, patient’s comorbidities and previous response
duration after first ASCT (level II, grade B).

8. Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (alloSCT) with a standard myeloablative conditioning regimen is
capable of inducing durable remissions in pts with myeloma (87). However, because of the very high
treatment-related mortality (TRM) of 25-50%, this approach cannot be generally recommended as a
first-line treatment option in myeloma pts. The use of reduced-intensity conditioning (RIC) regimens for
allografting has reduced TRM but is still limited by a high relapse rate, particularly in MM pts (88).
Several studies have shown that results of alloSCT in MM are poor after failure to previous ASCT or in
case of chemoresistant disease (89). The combination of a first ASCT followed by a nonmyeloablative
or reduced intensity alloSCT from an HLA-identical donor as a first-line treatment option has been the
subject of several prospective trials. Some of these trials were aimed at comparing ASCT+alloSCT vs
double autograft procedure. In the French trial, there was no benefit for alloSCT, but pts included had
bad prognostic characteristics (90). In the Italian trial, alloSCT was superior, mostly due to a marked
reduction in relapse rate (91). In this particular study, the CR rate after alloSCT was 55% and 66% of
these CR's were durable after a median of 38 mths. In the Spanish trial, again there was no benefit of
the auto+allo approach (92). Overall, these trials, including also the recently published GITMO update
(93) show that the CR rate after auto+allo transplantation is high but not impressive (40-62%) and that
graft-versus-host disease (24-43% >grade 1 acute, 36-74% extensive chronic) and relapse (39-56%)
remain major challenges. On the other hand, TRM is remarkably low (11-18%) (Table 5).
Developments in designing better types of RIC regimens should improve results of alloSCT in the
future (94).

RECOMMENDATION

ASCT followed by RIC alloSCT is an acceptable treatment modality for selected MM pts but
cannot be recommended as a first-line option, unless within the context of a clinical trial.
9. Role of radiotherapy

Local radiotherapy with a dose of 40 Grays (20 fractions) including 2 cm margins is the standard treatment for solitary plasmocytoma of the bone or extramedullary plasmocytoma. For lesion greater than 5 cm, the dose may be increased to 50 Grays. The use of helical tomotherapy may significantly reduce the dose to critical organs (95). Local radiotherapy, in association with systemic treatment including bisphosphonates, with a dose of 8-10 Grays as a single fraction is indicated in case of pathological bone fractures and to irradiate painful sites due to vertebral or other lesions (89).
Table 1. Levels of evidence and grading of recommendations

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level Ia</td>
<td>Meta-analysis of multiple, well-designed randomised controlled trials, published in a highly-ranked peer-reviewed journal or at least 2 well-designed controlled randomised trials, published in highly-ranked peer-reviewed journals.</td>
</tr>
<tr>
<td>Level Ib</td>
<td>One well-designed controlled randomised trial, published in a highly-ranked peer-reviewed journal.</td>
</tr>
<tr>
<td>Level II</td>
<td>At least one well-designed non-randomised study, including phase II trials and case-control studies</td>
</tr>
<tr>
<td>Level III</td>
<td>At least one well-designed quasi-experimental study, such as retrospective analysis, descriptive studies or obtained from meta-analysis or randomised controlled trials published in abstract form</td>
</tr>
<tr>
<td>Level IV</td>
<td>Expert committee reports, previously published guidelines</td>
</tr>
<tr>
<td>Level V</td>
<td>Expert consensus opinion from the authors</td>
</tr>
</tbody>
</table>

Grade of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence level Ia and Ib</td>
</tr>
<tr>
<td>B</td>
<td>Evidence level II and III</td>
</tr>
<tr>
<td>C</td>
<td>Evidence level IV</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level V</td>
</tr>
</tbody>
</table>
Table 2. First-line schedules for pts not eligible for autologous stem cell transplantation

<table>
<thead>
<tr>
<th>Schedule (reference)</th>
<th>Dosing</th>
<th>Response rate</th>
<th>Response duration</th>
<th>Level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPT (15)</td>
<td>Melphalan (PO) 0.25 mg/kg/d d1-4 Prednisone (PO) 2 mg/kg/d d1-4 Thalidomide (PO) 100-200 mg/d 12x 6-weekly cycles</td>
<td>ORR 61-76% (7-13% CR)</td>
<td>24-27.5 mths median PFS</td>
<td>Ia, grade A</td>
</tr>
<tr>
<td>MPV (20)</td>
<td>Melphalan (PO) 0.25 mg/kg/d d1-4 Prednisone (PO) 2 mg/kg/d d1-4 Bortezomib (IV) 1.3 mg/m² d1, 4, 8, 11, 22, 25, 29, 32 (d1, 8, 22, 29 after 4 cycles) 12x 6-weekly cycles</td>
<td>ORR 71% (30% CR)</td>
<td>24 mths median TTP</td>
<td>Ib, grade A</td>
</tr>
<tr>
<td>Len+dex (29)</td>
<td>Lenalidomide (PO) 25 mg/d d1-21 dexamethasone (PO) 40 mg/d d1, 8, 15, 22 Until progression or unacceptable toxicity</td>
<td>57% CR+VGPR*</td>
<td>50% 3-year PFS*</td>
<td>Level II, grade B</td>
</tr>
<tr>
<td>CTDa (28)</td>
<td>Cyclophosphamide (PO) 500 mg weekly Thalidomide (PO) 200 mg/d Dexamethasone 20 mg (PO) d1-4 and d15-18</td>
<td>ORR 82.5% (22.5% CR)</td>
<td>NR</td>
<td>Level III, grade B</td>
</tr>
</tbody>
</table>

*PFS in pts continuing lenalidomide (Len) + low dose dexamethasone (len+dex) after initial response to a 4-course induction phase; the ORR after 4 courses of len+dex was 68.3%

Abbreviations: ORR = overall response rate; PFS = progression-free survival; CR = complete remission; VGPR = very good partial remission; NR = not reported
Table 3. Percentage of most relevant grade 3-4 toxicities of MPT and MPV regimens in pts 65-75 years.

<table>
<thead>
<tr>
<th></th>
<th>MPT</th>
<th>MPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2.5</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>12</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea-diarrhea</td>
<td>1.0</td>
<td>4-8 (48-46)</td>
</tr>
<tr>
<td>Sensory polyneuropathy</td>
<td>6</td>
<td>13 (44)</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>0</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>1 (37)</td>
</tr>
<tr>
<td>Somnolence/fatigue</td>
<td>8</td>
<td>8 (29)</td>
</tr>
</tbody>
</table>

Between ( ) = overall toxicity (also including grade 1 and 2) (in %)
References: MPT (15) ; MPV (20)
Table 4. Salvage regimens for myeloma

<table>
<thead>
<tr>
<th>Regimen (reference)</th>
<th>Response rate</th>
<th>Response duration (median)</th>
<th>Level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide + thalidomide + dexamethasone (CTD) (64-66)</td>
<td>55-60% (10-15% CR)</td>
<td>10-12 mths TTP</td>
<td>Level II, grade B</td>
</tr>
<tr>
<td>Bortezomib (56)</td>
<td>30% (4% CR)</td>
<td>6 mths PFS</td>
<td>Level Ib, grade A</td>
</tr>
<tr>
<td>Bortezomib+dexamethasone (68)</td>
<td>47% (5% CR)</td>
<td>6 mths PFS</td>
<td>Level II, grade B</td>
</tr>
<tr>
<td>Bortezomib + cyclophosphamide + dexamethasone (69-71)</td>
<td>75% (31% CR)</td>
<td>7 mths PFS</td>
<td>Level II, grade B</td>
</tr>
<tr>
<td>Bortezomib+pegylated liposomal doxorubicin (74)</td>
<td>52% (4% CR)</td>
<td>9.3 mths TTP</td>
<td>Level Ib, grade A</td>
</tr>
<tr>
<td>Lenalidomide+ dexamethasone (55;57)</td>
<td>60% (15% CR)</td>
<td>11 mths TTP</td>
<td>Level Ib, grade A</td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete remission; TTP = time to progression; PFS = progression-free survival
### Table 5. Results of autologous followed by non-myeloablative or reduced intensity allogeneic stem cell transplantation

<table>
<thead>
<tr>
<th>Center or group (reference)</th>
<th>n</th>
<th>CR%</th>
<th>Fol up (med)</th>
<th>AGVHD ≥II</th>
<th>CGVHD extensive</th>
<th>TRM</th>
<th>Relapse rate</th>
<th>OS (5 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM (90)</td>
<td>46</td>
<td>33</td>
<td>28 mths</td>
<td>24%</td>
<td>36%</td>
<td>11%</td>
<td>56.5%</td>
<td>44%*</td>
</tr>
<tr>
<td>Seattle (96)</td>
<td>102</td>
<td>62</td>
<td>6.3 yrs</td>
<td>42%</td>
<td>74%</td>
<td>18%</td>
<td>55%</td>
<td>64%</td>
</tr>
<tr>
<td>GITMO (93)</td>
<td>100</td>
<td>53</td>
<td>5 yrs</td>
<td>38%</td>
<td>50%</td>
<td>11%</td>
<td>44%</td>
<td>65%</td>
</tr>
<tr>
<td>PETHEMA (92)</td>
<td>25</td>
<td>40</td>
<td>5.2 yrs</td>
<td>32%</td>
<td>66%</td>
<td>16%</td>
<td>39%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Donors were HLA-identical siblings in all studies. Conditioning regimens were: busulfan+fludarabine+ATG (IFM), low-dose TBI (Seattle, GITMO) and fludarabine+melphalan (PETHEMA)

*30% after med fol up of 56 mths; in the IFM study, only pts with bad prognostic features were included (high beta-2 microglobulin and del 13)

Abbreviations: AGVHD/CGVHD = acute/chronic graft-versus-host disease; CR = complete remission; TRM = treatment-related mortality; OS = overall survival
10. References


(33) Mateos MV, Oriol A, Martinez J, Cibeira MT, Gutierrez NC, Terol MJ et al. A Prospective, Multicenter, Randomized, Trial of Bortezomib/Melphalan/Prednisone (VMP) Versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) Versus Bortezomib/Prednisone (VP) in Elderly Untreated Patients with Multiple Myeloma Older Than 65 Years. ASH Annual Meeting Abstracts 2009; 114(22):3.


(43) Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M et al. A Phase III Study of Double Autotransplantation Incorporating Bortezomib-Thalidomide-Dexamethasone (VTD) or
27

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