REVIEW

Optimizing outcomes for patients with newly diagnosed multiple myeloma eligible for transplantation

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High-dose therapy with autologous stem cell transplantation (HDT–ASCT) has been considered to be the standard frontline treatment for younger, fit patients with multiple myeloma (MM) since the 1990s. Efforts continue to optimize the use of HDT–ASCT with the aim of improving outcomes. One strategy has been the incorporation of novel agents (thalidomide, lenalidomide and bortezomib) in the pre-transplantation setting as an induction therapy or in the post-transplantation setting as a consolidation or maintenance therapy. Given their high response rates, three-drug induction therapy regimens (for example, bortezomib–thalidomide–dexamethasone, lenalidomide–bortezomib–dexamethasone and cyclophosphamide–bortezomib–dexamethasone) are now the standard of care. Thalidomide and bortezomib are well suited for consolidation therapy, and regimens using these agents can improve the depth of response following HDT–ASCT. Lenalidomide is particularly well suited for long-term maintenance therapy following HDT–ASCT, and initial results are promising and have shown improvements in disease outcomes such as progression-free survival and overall survival in some cases, although a low incidence of second primary malignancies have been observed. Further studies are needed to determine the optimal regimen and duration of induction therapy, the impact of maintenance on overall survival and the safety of long-term treatment. Many of the studies currently underway in MM will help address these aspects.

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INTRODUCTION

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) for multiple myeloma (MM) was developed in the 1980s, and has been considered the standard frontline treatment for younger patients with normal renal function since the mid 1990s.¹ The recent introduction of the novel agents, thalidomide, bortezomib and lenalidomide is now changing the transplantation scenario in several ways. Indeed, these agents are being incorporated into the pre-transplantation setting as part of induction regimens, with the objective of increasing the response rate before ASCT as well as following the transplantation as consolidation treatments. Induction therapy is aimed at increasing the quantity and depth of the response achieved with high-dose melphalan, whereas maintenance therapy has the goal of prolonging duration of the first response and delaying relapse. The overarching goal of applying treatments in the post-ASCT setting is undoubtedly the extension of progression-free survival (PFS) and hopefully, overall survival (OS). Incorporation of these highly active novel agents is, therefore, attractive in this setting. This review will provide a summary of currently available data on induction, consolidation and maintenance strategies following ASCT in the era of novel therapies.

NOVEL AGENTS INCORPORATED INTO INDUCTION TREATMENTS BEFORE ASCT

Until recently, the combination of vincristine, doxorubicin and dexamethasone (VAD) was the induction regimen most widely used before ASCT and was considered the standard of care. The primary objective of incorporating novel agents in this setting is to increase the complete remission (CR) rate not only before, but also

after ASCT. An additional objective is to reduce the proportion of patients requiring a second ASCT because of a suboptimal response (less than very good partial response (VGPR)) to the first ASCT step.²

Thalidomide was the first novel agent to be compared with VAD either in combination with dexamethasone (TD)³ or with doxorubicin plus dexamethasone.^{4,5} Overall, the benefit of TD or thalidomide and doxorubicin plus dexamethasone compared with VAD remained modest, and other thalidomide combinations have also been evaluated (Table 1). The cyclophosphamide, thalidomide and dexamethasone combination regimen is currently being investigated in a large randomized study in the United Kingdom, and preliminary results showed high CR rates both before and after ASCT.⁶

Bortezomib, the second novel agent to become available in Europe and the United States, was investigated in combination with dexamethasone in a large trial by the Intergroupe Francophone du Myélome (IFM; IFM 2005-01) and was prospectively compared with VAD.⁷ Post-induction CR or near CR (15% versus 6%), at least VGPR (38% versus 15%) and overall response rates (79% versus 63%) were significantly higher with bortezomib plus dexamethasone (VD) versus VAD (Table 1). These superior response rates in the bortezomib plus dexamethasone induction arms of the trial translated into better response rates after HDT (CR/near CR: 35% versus 18%; at least VGPR: 54% versus 37%). This improvement also had an impact on the outcome of the disease (median PFS 36 versus 30 months with VD versus VAD, respectively; $P = 0.064$). Survival was not superior in the VD arms of the study, possibly because of effective salvage regimens at the time of relapse. The level of response achieved with VD post induction in the IFM 2005-01 trial is now considered the goal of

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Table 1. Response rates to novel-agent containing induction therapy and clinical outcomes after high-dose therapy–ASCT in phase III trials

Study by induction regimen	N	Post induction, %		Post transplantation, %		Long-term outcomes
		ORR	CR/nCR/VGPR	ORR	CR/nCR/VGPR	
MAG ³						
TD	100	NR	25 ≥VGPR	NR	44 ≥VGPR	NR
VAD	104	NR	7 ≥VGPR	NR	42 ≥VGPR	NR
HOVON-50 ^{4,5}						
TAD	268	71	3 CR 37 ≥VGPR	88	31 CR 66 ≥VGPR	Median EFS: 34 months Median PFS: 34 months Median OS: 73 months
VAD	268	57	2 CR 18 ≥VGPR	79	23 CR 54 ≥VGPR	Median EFS: 22 months Median PFS: 25 months Median OS: 60 months
IFM 2005-01 ⁷						
Bort/Dex	240	79	6 CR 15 CR/nCR 38 ≥VGPR	84	16 CR 35 CR/nCR 54 ≥VGPR	Median PFS: 36 months 3-year OS: 81%
VAD	242	63	1 CR 6 CR/nCR 15 ≥VGPR	79	9 CR 18 CR/nCR 37 ≥VGPR	Median PFS: 30 months 3-year OS: 77%
GIMEMA MMY-3006 ¹²						
VTD	236	94	19 CR 62 ≥VGPR	NR	49 CR 85 ≥VGPR	
TD	238	79	5 CR 28 ≥VGPR	NR	34 CR 68 ≥VGPR	
PETHEMA/GEM05MEN0565 ¹³						
TD	127		14 CR		24 CR	Median PFS: 28 months 4-year OS: 65%
VTD	130		35 CR		46 CR	Median PFS: 56 months 4-year OS: 74%
VBMCP/VBAD/Bort	129		21 CR		38 CR	Median PFS: 35 months 4-year OS: 70%
IFM 2007-02 ¹⁴						
Bort/Dex	99	81	12 CR 36 ≥VGPR	84	58 ≥VGPR	NR
VTD	100	90	13 CR 49 ≥VGPR	90	74 ≥VGPR	NR
HOVON-65/GMMG-HD4 ¹⁵						
VAD	414	54	7 CR/nCR 17 ≥VGPR	75	24 CR/nCR 36 ≥VGPR	Median PFS: 28 months:
PAD	413	78	18 CR/nCR 42 ≥VGPR	88	31 CR/nCR 62 ≥VGPR	Median PFS: 35 months:

Abbreviations: ASCT, autologous stem cell transplantation; CALGB, Cancer and Leukemia Group B; CR, complete response; Dex, dexamethasone; EFS, event-free survival; GEM, Grupo Español de Mieloma; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON, Hemato-Oncologie voor Volwassenen Nederland; IFM, Intergroupe Francophone du Myélome; nCR, near CR; NR, not reported; ORR, overall response rate; OS, overall survival; PAD, bortezomib, doxorubicin and dexamethasone; PETHEMA, Programa para el Estudio de la Terapéutica en Hemopatía Maligna; PFS, progression-free survival; TAD, thalidomide, doxorubicin and dexamethasone; TD, thalidomide plus dexamethasone; VAD, vincristine, doxorubicin and dexamethasone; VBMCP/VBAD, vincristine, carmustine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin and dexamethasone; Bort, bortezomib; VGPR, very good partial response; VTD, bortezomib, thalidomide and dexamethasone.

current therapies and, as a result, VD has become the backbone of induction therapy before ASCT with which other more complex regimens should be compared.⁷

The addition of a third agent to the bortezomib plus dexamethasone regimen, such as thalidomide (VTD),⁸ doxorubicin (PAD),⁹ lenalidomide (RVD)¹⁰ or cyclophosphamide,¹¹ has been tested in several small phase II studies with improved outcomes, showing response rates of around 90% and CR rates up to 24%. In all of these studies, the frequent, rapid and deep responses consistently translated into improved outcomes. The RVD regimen, for example, was associated with estimated 1.5-year PFS and

OS rates of 75% and 97%, respectively, in a phase I/II trial with a median follow-up of 21 months.¹⁰

Three prospective studies have already shown that VTD is superior to TD or VD (Table 1).^{12–14} An Italian group prospectively compared TD with VTD in 474 patients with newly diagnosed MM before tandem ASCT. They found that VTD resulted in higher CR/near CR rates compared with TD (31% versus 11%; $P < 0.0001$), which translated into better 3-year PFS rates after HDT (68% versus 56%; hazard ratio (HR) = 0.63; $P = 0.0061$).¹² The addition of bortezomib to the TD regimen, however, was associated with a significant increase in the incidence of grade 3–4 adverse events

(56% versus 33%), including peripheral neuropathy (PN; 10% versus 2%). A Spanish group also compared TD with VTD versus a more complex chemotherapy regimen, including bortezomib, before ASCT in 386 patients. They confirmed that compared with TD, VTD was associated with a higher CR rate before ASCT (35% versus 14%; $P=0.001$) and after ASCT (46% versus 24%; $P=0.004$).^{1,13} In the IFM 2007-02 trial, four cycles of VD induction regimen were prospectively compared with four cycles of VTD with lower doses of bortezomib (1 mg/m² instead of 1.3 mg/m²) and thalidomide (100 mg/day instead of 200 mg/day, as in the Italian and Spanish trials) in order to reduce the neuropathy rate.¹⁴ VTD was again found to result in superior response rates (VGPR or better) both before (49% versus 36%; $P=0.05$) and after ASCT (74% versus 58%; $P=0.02$). The reduction in the doses of both bortezomib and thalidomide was associated with a reduction in the incidence of neurotoxicity, with grade ≥ 2 PN occurring in 14% of the patients in the VTD arm. The IFM 2007-02 study confirmed the superiority of a three-drug combination over a two-drug regimen as induction therapy before ASCT. The results of a phase III randomized prospective trial comparing VAD with PAD as induction before HDT have also been reported.¹⁵ This study confirmed the superiority of the bortezomib-based three-drug induction regimen over VAD; OS was also superior in the bortezomib arm of the trial.

No data are available to compare the relative safety and efficacy of VTD, RVD, cyclophosphamide–bortezomib–dexamethasone or PAD. Although response rates are clearly improved with novel agents, the demonstration of a significant OS advantage is often difficult given the large number of patients, low number of events and the need for a long duration of follow-up, as well as the impact of salvage therapies. On the basis of the available data from phase II and III studies as described above, three-drug combination regimens are considered the standard of care for use as induction therapy before ASCT.^{3–5,7,12–15}

NOVEL AGENTS INCORPORATED INTO CONSOLIDATION TREATMENTS FOLLOWING ASCT

Before the availability of novel agents, the main approach to consolidating a response achieved following the initial ASCT procedure was the use of a second ASCT, in a tandem fashion. This was found to be beneficial in patients not achieving at least a VGPR from the first transplantation.² Currently, novel agents are being assessed as consolidation treatment following ASCT to further improve the quantity and quality of the responses.

The first report involving novel agents in this setting was provided by an Italian group. Ladetto *et al.*¹⁶ recruited 39 patients who had achieved at least a VGPR after ASCT, and who had an available molecular marker based on the immunoglobulin heavy-chain rearrangement. These patients were treated with four courses of VTD comprising four infusions per month of bortezomib 1.6 mg/m², thalidomide 200 mg/day and dexamethasone 20 mg/day on days 1–4, 8–11 and 15–18, respectively, of each 28-day cycle.¹⁶ Response was assessed by qualitative nested polymerase chain reaction (PCR) and real-time quantitative PCR using tumor-clone-specific primers. Immunofixation CRs increased from 15% after ASCT to 49% after VTD. Molecular remissions were observed in 3% of patients after ASCT and in 18% after VTD. At a median follow-up of 42 months after consolidation therapy, no patient in molecular remission had relapsed. Treatment with VTD was associated with additional reduction in disease burden (median estimated depletion of tumor burden as evaluated by real-time quantitative PCR: 4.14 natural logarithms; $P<0.001$), thereby increasing the quality of clinical response. Patients with a tumor load lower than the median value were found to have a superior outcome, compared with those who had tumor loads above the median value following VTD treatment; the PFS at 42 months for patients with a low tumor load was 100% versus 57%

for patients with a higher tumor load after VTD ($P<0.001$). This study was the first to document the occurrence of persistent molecular remission in a proportion of MM patients treated with ASCT followed by a novel agent-based consolidation therapy. Such remarkable results had only been reported with myeloablative allogeneic stem cell transplantation previously.

Results of another prospective randomized Italian trial of TD or VTD during induction and as consolidation therapy after a tandem ASCT procedure confirmed these findings.¹² Two 5-week cycles of consolidation therapy were started 3 months after the second transplantation procedure and comprised 100 mg/day thalidomide plus 40 mg dexamethasone on days 1–4 and 20–23 (TD arm) or 1.3 mg/m² bortezomib on days 1, 8, 15 and 22 plus 100 mg/day thalidomide, and 40 mg dexamethasone on days 1, 2, 8, 9, 15, 16, 22 and 23 (VTD arm). Of the 214 patients allocated to receive VTD induction therapy and 239 allocated to receive TD induction therapy, 160 patients in the VTD arm and 161 in the TD arm completed two cycles of consolidation therapy. In the TD arm, consolidation improved the CR rate from 40% to 47% ($P=0.052$). In the VTD arm, the CR rate was increased from 49% to 61% ($P=0.0009$).¹⁷ Samples were available from a subgroup of patients for real-time quantitative PCR analysis and this demonstrated that patients who received VTD consolidation had a greater reduction in residual tumor burden compared with TD (5 log versus 1 log reduction, respectively).¹⁸ This partly explains the PFS benefit observed for the VTD arm of the trial.^{12,17}

Another three-drug combination, comprising lenalidomide (25 mg/day on days 1–14 of each 21-day cycle) with bortezomib and dexamethasone (RVD), has been examined as consolidation treatment following ASCT in a pilot study conducted by the IFM (IFM 2008).¹⁹ Two 21-day cycles, administered after high-dose melphalan to 31 patients, were found to increase the CR plus stringent CR rate from 35% after HDT to 52% after consolidation. Grade 3–4 adverse events included neutropenia (26%) and thrombocytopenia (6%), and grade 1–2 PN was reported in 45% of patients.

Lenalidomide and bortezomib have also been investigated as single-agent consolidation treatments. In the IFM 2005-02 study, two cycles of lenalidomide (25 mg/day on days 1–21 of each 28-day cycle) were administered, and then 614 patients were randomized to lenalidomide or placebo maintenance.²⁰ Following lenalidomide consolidation, which was well tolerated, the rate of VGPR or better increased significantly from 58% to 69% ($P<0.001$).

Single-agent bortezomib as consolidation treatment following ASCT was investigated in a phase III trial conducted by the Nordic Myeloma Group.²¹ Patients ($N=370$) were randomized 3 months post ASCT to receive no treatment or bortezomib 1.3 mg/m² on days 1, 4, 8 and 11 for two 3-week cycles and then on days 1, 8 and 15 for four 4-week cycles, for a total of 20 injections over 21 weeks. Preliminary results indicated that this consolidation treatment was feasible with a median number of bortezomib infusions of 19. The proportions of patients achieving at least a VGPR were 70% in the bortezomib group versus 58% in the control group ($P=0.01$). Importantly, this improvement in response translated to a better outcome with a 7-month gain in PFS following ASCT (median 27 months in the bortezomib arm versus 20 months in the control arm; $P=0.02$).

Overall, several studies are now supporting the use of novel agent-based consolidation therapy following ASCT, either as single agents or in combination. Nevertheless, the optimal consolidation treatment remains to be determined and a number of important trials examining this question are ongoing. In one key trial in the United States, the BMT CTN 0702 study (ClinicalTrials.gov: NCT01109004), patients will be randomized after a single ASCT step to either no consolidation, four cycles of RVD or a second ASCT procedure. Another important international prospective trial has been designed to assess the RVD regimen

with or without ASCT (the IFM/DFCI2009 trial). This trial will examine the impact of two cycles of RVD given as consolidation after ASCT (ClinicalTrials.gov: NCT01191060). The effect of these two cycles of RVD versus no consolidation will also be examined in the prospective European EMN02 study (ClinicalTrials.gov: NCT01208766).

An important consequence of the high-quality deep responses obtained with novel agents is the need for a modification of the established response criteria. The current criteria were validated during the International Myeloma Workshop in 2009,²² when the following response categories were added: stringent CR, which, in addition to the parameters required for CR, also requires the absence of phenotypically aberrant plasma cells in the bone marrow analyzed by multiparametric flow cytometry or immunohistochemistry, and normal free light-chain ratio. In addition, the definition of molecular CR was added, which requires the parameters for stringent CR to be met, plus a negative allele-specific oligonucleotide PCR with a sensitivity of 10^{-5} .

NOVEL AGENTS INCORPORATED INTO MAINTENANCE STRATEGIES

Maintenance treatment with the objective of prolonging response duration and PFS is an attractive concept that has been investigated in MM for some time. Before the introduction of the novel agents, several trials examined conventional chemotherapy treatments in the maintenance setting; however, results were negative and preliminary findings of the efficacy of α -interferon in this indication could not be confirmed.¹

In most countries, thalidomide was the first novel agent to become available. Soon after its potent anti-myeloma activity was recognized, this oral drug was examined post ASCT in the maintenance setting, with the objective of prolonging the duration of response. Several phase II studies demonstrated the feasibility of thalidomide maintenance therapy and five randomized phase III studies, described below, have since been published (Table 2).^{5,23–26}

The Arkansas group performed a large randomized trial to assess the impact of thalidomide within a complex protocol consisting of induction treatment, double ASCT, consolidation therapy and α -interferon plus dexamethasone maintenance (Total Therapy 2).²⁷ In this trial, thalidomide was administered from the outset until disease progression or undue adverse effects. After an initial median follow-up of 42 months, thalidomide therapy was associated with superior response rate (62% versus 43%; $P < 0.001$) and 5-year event-free survival (EFS; 56% versus 44%; $P = 0.001$) compared with the control arm, although no difference in 5-year OS rates was observed (65% in both treatment groups; $P = 0.90$). After a longer follow-up of 72 months, a trend of increased 5-year OS with thalidomide emerged (68% versus 65%; $P = 0.04$).²⁴ A similar phase III trial, the HOVON-50 study, was designed to evaluate the effect of thalidomide during induction treatment, and as maintenance treatment in transplantation-eligible patients.⁵ A total of 556 patients were randomly assigned to VAD or thalidomide and doxorubicin plus dexamethasone induction, followed by high-dose melphalan, 200 mg/m², and ASCT. This was followed by maintenance therapy with α -interferon (VAD patients) or thalidomide 50 mg/day (thalidomide and doxorubicin plus dexamethasone patients). Thalidomide therapy significantly improved the overall response rate (88% versus 79%; $P = 0.005$) and median EFS (34 versus 22 months; HR = 0.60; $P < 0.001$), but median OS did not differ significantly between the two treatment groups (73 versus 60 months; HR = 0.96, $P = 0.77$).

In the IFM 1999-02 trial, 597 patients with standard-risk MM (β_2 -microglobulin ≤ 3 mg/l and/or no deletion 13 by fluorescence *in situ* hybridization were randomly assigned to receive no further treatment (Arm A), pamidronate alone (Arm B) or thalidomide plus pamidronate (Arm C) 2 months after undergoing tandem ASCT.²³

A CR or VGPR was achieved in 55% of patients in Arm A, 57% in Arm B and 67% in Arm C ($P = 0.03$). The 3-year post-randomization probability of EFS was 36% in Arm A, 37% in Arm B and 52% in Arm C ($P < 0.009$). The effect of thalidomide on EFS differed according to the response achieved after tandem ASCT. Patients who had at least a VGPR did not benefit from thalidomide, whereas those who failed to achieve at least a VGPR had significantly longer EFS on the thalidomide arm, indicating that thalidomide may act to further reduce the tumor mass after HDT. This is consistent with a consolidation rather than a purely maintenance effect. The 4-year post-diagnosis probability of survival was 77% in Arm A, 74% in Arm B and 87% in Arm C ($P < 0.04$); recently updated results did not confirm the survival advantage of the thalidomide-containing arm.²⁸ In the Australian trial, 269 patients were randomized post ASCT to receive prednisone maintenance therapy indefinitely and 114 patients were randomized to receive prednisolone treatment with the addition of 12 months of thalidomide consolidation therapy.²⁵ After a median follow-up of 3 years, the post-randomization 3-year PFS rates were 42% and 23% (HR = 0.50, $P < 0.001$) and the OS rates were 86% and 75% (HR = 0.41, $P = 0.004$) in the thalidomide and control groups, respectively.

The most recent trial reported by the Medical Research Council in the UK also confirmed that low-dose thalidomide maintenance (50 mg/day) significantly prolongs PFS compared with no maintenance therapy (median 23 versus 15 months; HR = 1.45; $P < 0.001$), although no significant difference in OS was observed (HR = 0.91; $P = 0.40$). There was evidence of a late OS benefit in the subgroup of patients with favorable interphase fluorescence *in situ* hybridization characteristics.²⁶ In contrast, patients with adverse cytogenetics receiving thalidomide showed no PFS benefit (9 versus 12 months; $P = 0.48$) and significantly worse OS ($P = 0.009$).

Taken together, five separate phase III studies have shown a significant benefit for thalidomide in terms of response and PFS, whereas OS was improved in two of these trials. Interestingly, the improvement in response is indicative of a consolidation rather than a maintenance effect of the agent. The safety profile of thalidomide may hinder its use as long-term maintenance therapy. Notably, PN observed with thalidomide is cumulative and related to treatment duration. The Arkansas study administered treatment over a prolonged period and experienced a 27% incidence rate of grade 3–4 PN.²⁷ In the IFM 1999-02 trial, patients received thalidomide for a median duration of 15 months. PN was observed in 68% of the cases (7% grade 3–4) and was the main reason for treatment discontinuation.²³ In the Australian trial, 58% of patients remained on a median dose of 100 mg/day thalidomide for the planned 12-month consolidation phase. Again, the most common reason for thalidomide withdrawal was PN, which occurred in 52% of the patients (10% grade 3–4).²⁵ Similarly, thalidomide maintenance was discontinued in 33% of patients enrolled in the HOVON-50 trial because of toxicity.⁵ In the Medical Research Council IX trial, the median duration of thalidomide therapy was only 9 months, and neuropathy was the first cause of discontinuation.²⁶ The possible emergence of tumor-resistant clones in patients with prolonged exposure to thalidomide has also led to concerns about its lack of efficacy in patients with adverse cytogenetic abnormalities.²⁶

Lenalidomide is the first available oral immunomodulatory drug (IMiD); it has a favorable toxicity profile and is currently considered the best candidate for use as maintenance therapy. Results from two randomized trials evaluating lenalidomide maintenance following ASCT have recently been published (Table 2).^{20,29} In the IFM 2005-02 study, 614 patients aged ≤ 65 years with non-progressive disease after ASCT (performed within the previous 6 months) received lenalidomide consolidation treatment (25 mg/day for 21 days/month, for 2 months) and were then randomized to receive either placebo (Arm A) or lenalidomide maintenance

Table 2. Phase III trials of maintenance therapy with immunomodulatory drugs

Reference	N	Initial dose, mg	Response vs comparator	EFS or PFS vs comparator	OS vs comparator
Thalidomide					
Attal <i>et al.</i> ²³	597	400	CR or VGPR: 67% vs 55%	3-year EFS: 52% vs 36%	4-year OS: 87% vs 77%
Barlogie <i>et al.</i> ²⁴	668	400	64% vs 43%	5-year EFS: 56% vs 44%	8-year OS: 57% vs 44%
Spencer <i>et al.</i> ²⁵	269	200	CR+VGPR: 63% vs 40%	3-year PFS: 42% vs 23%	3-year OS: 86% vs 75%
Lokhorst <i>et al.</i> ⁵	556	50	CR: 31% vs 23%	Median PFS: 34 vs 25 months	Median OS: 73 vs 60 months
Morgan <i>et al.</i> ²⁶	493	50	—	Median PFS: 30 vs 23 months	3-year OS: 75% vs 80%
Lenalidomide					
IFM 2005-02 ²⁰	614	10	—	—	—
			CR+VGPR: 84% vs 76% ($P=0.009$)	Median PFS ^a : 41 vs 23 months	NR
				Median EFS ^b : 40 vs 23 months	
CALGB 100104 ²⁹	460	10	—	Median TTP ^a : 46 vs 27 months	OS not reached

Abbreviations: CR, complete response; EFS, event-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival; TTP, time-to-progression; VGPR, very good partial response.

^aPost-randomization.

^bWith events that included second primary cancers.

(10–15 mg/day until relapse; Arm B).²⁰ After a median follow-up of 30 months, patients who received lenalidomide maintenance had improved median PFS (primary endpoint of the study) by 18 months (median 23 months in Arm A versus 41 months in Arm B; HR=0.50, $P<0.001$). This benefit was observed among all subgroups of patients identified by predefined stratification criteria. A benefit in terms of OS has not yet been demonstrated. Adverse events more common in the lenalidomide group compared with the placebo group included grade 3–4 hematologic events (58% versus 23%; $P<0.001$) and thromboembolic events (6% versus 2%; $P=0.01$); thrombocytopenia was not used. Second primary malignancies (SPMs) were observed in 26 patients treated with lenalidomide and 11 treated with placebo; the incidence of SPMs was 3.1 per 100 patient-years with lenalidomide and 1.2 per 100 patient-years with placebo ($P=0.002$).

The Cancer and Leukemia Group B group reported the results of a similar phase III randomized trial of lenalidomide or placebo following HDT and ASCT (CALGB 100104 study).²⁹ Patients ($N=460$) aged <70 years with non-progressive MM were randomized 2–3 months post ASCT to receive placebo ($n=229$) or lenalidomide 10 mg/day ($n=231$) until progression, with stratification based on β_2 -microglobulin level at diagnosis and lenalidomide use during induction. The study was stopped prematurely because of the significant superiority observed with lenalidomide maintenance, which resulted in a 63% reduction in the risk of progression compared with placebo ($P<0.001$). The median time-to-progression (primary endpoint) was 46 months for the lenalidomide arm versus 27 months for the placebo arm ($P<0.001$) at a median follow-up of 34 months. Interestingly, despite a crossover of patients with disease progression from the placebo arm to the lenalidomide arm, an improvement in OS was observed favoring the lenalidomide arm (3-year OS rate: 88% versus 80%; HR=0.62; $P=0.03$). Hematologic adverse events were more common in patients who received lenalidomide maintenance therapy compared with placebo, including grade 3–4 neutropenia (19% versus 7%; $P<0.001$), thrombocytopenia (6% versus 2%; $P=0.001$) and anemia (2% versus <1%; $P=0.006$). Eighteen of the 231 patients treated with lenalidomide developed SPMs (7.8%), whereas 6 of the 229 patients (2.6%) treated with placebo developed SPMs.

The benefits observed with lenalidomide maintenance therapy in terms of delaying disease progression and prolonging survival have to be balanced with an increased incidence of SPMs, including acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, Hodgkin disease or solid tumors. Overall, the risk of SPMs was increased fourfold in newly diagnosed MM patients treated with lenalidomide therapy (7.0%),

compared with controls (1.8%). This finding highlights the importance of defining the optimal duration of therapy, elucidating the underlying mechanisms and identifying risk factors for this complication. Other adverse events reported during lenalidomide maintenance therapy are consistent with the known safety profile of lenalidomide and primarily include myelosuppression, rash and fatigue, which are generally manageable with standard interventions and dose modifications.

Bortezomib has also been investigated as maintenance treatment after HDT in a large phase III trial (HOVON-65/GMMG-HD4) comparing VAD with PAD before ASCT, and as maintenance including thalidomide (50 mg/day) on the VAD arm or bortezomib (1.3 mg/m² twice a month) on the PAD arm, for 2 years.¹⁵ Overall results favor the PAD plus HDT–ASCT–bortezomib maintenance arm in terms of response (VGPR or better: 56% versus 76%; $P<0.001$), PFS (median 28 versus 35 months; HR=0.75; $P=0.002$) and OS (5-year: 55% versus 61%; HR in multivariate analysis = 0.77; $P=0.49$). This phase III study was the first to demonstrate a survival advantage with the use of a novel agent-containing treatment. In the PAD arm, 174 patients of 308 started maintenance compared with 204 of 305 patients in the VAD arm. In the bortezomib arm, maintenance was discontinued because of toxicity in 9% of cases (versus 31% in the thalidomide arm), progression in 29% (versus 31%) or other causes in 9% (versus 2%). Maintenance was continued for the entire 2-year period in 47% of the patients in the bortezomib arm compared with 27% of patients in the thalidomide maintenance arm.

SUMMARY

Recent studies examining novel agents as induction treatment before ASCT have shown that three-drug combinations are the standard of care.^{3–5,7,12–15} Consolidation treatments following ASCT have clearly shown improvements in the depth of response, with the achievement of molecular CRs previously seen only with myeloablative stem cell transplantation. However, the optimal consolidation therapy, if any, is still to be defined, as well as the duration of such treatment. The results of ongoing studies are eagerly awaited.

Although maintenance trials have demonstrated a PFS advantage for prolonged treatment, the OS benefit of such a strategy is less clear and longer follow-up of ongoing trials is needed. Evidently, several open questions remain, such as the optimal duration of treatment, and, in addition, the observed PFS benefit has to be balanced with the potential risk of toxicities associated with long-term treatment, together with cost.

Efforts to define the role and impact of consolidation and maintenance treatments following HDT, as well as the role of HDT

itself,^{30,31} will certainly continue with the aim of arriving at an optimal treatment strategy in the transplantation setting, which will provide the best outcome for patients in terms of maximizing efficacy while minimizing the risk of toxicity.

CONFLICT OF INTEREST

PM has participated in the Advisory Boards for Celgene Corporation, Millennium, Janssen and Onyx Pharmaceuticals, and has received honoraria from Celgene Corporation, Millennium and Janssen. CT declares no conflicts of interest.

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REFERENCES

- Moreau P, Avet-Loiseau H, Harousseau JL, Attal M. Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies. *J Clin Oncol* 2011; **29**: 1898–1906.
- Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG *et al*. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **349**: 2495–2502.
- Macro M, Divine M, Uzunhan Y, Jaccard A, Bouscary D, Leblond V *et al*. Dexamethasone + thalidomide (Dex/Thal) compared to VAD as pre-transplant treatment in newly diagnosed multiple myeloma (MM): a randomized trial. *Blood* 2006; **108**: (abstract 57).
- Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R *et al*. Thalidomide in induction treatment increases the very good partial remission rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica* 2008; **93**: 124–127.
- Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH *et al*. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood* 2010; **115**: 1113–1120.
- Morgan GJ, Davies FE, Owen RG, Rawstron AC, Bell S, Cocks K *et al*. Thalidomide combinations improve response rates; results from the MRC IX study. *Blood* 2007; **110**: (abstract 3593).
- Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M *et al*. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol* 2010; **28**: 4621–4629.
- Wang M, Giral S, Delasalle K, Handy B, Alexanian R. Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. *Hematology* 2007; **12**: 235–239.
- Popat R, Oakervue HE, Hallam S, Curry N, Odeh L, Foot N *et al*. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. *Br J Haematol* 2008; **141**: 512–516.
- Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS *et al*. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010; **116**: 679–686.
- Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J *et al*. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia* 2009; **23**: 1337–1341.
- Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M *et al*. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010; **376**: 2075–2085.
- Rosiñol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J *et al*. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood* 2012; **120**: 1589–1596.
- Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C *et al*. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood* 2011; **118**: 5752–5758.
- Sonneveld P, Schmidt-Wolf I, van der Holt B, el Jarari L, Bertsch U, Salwender H *et al*. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 2012; **30**: 2946–2955.
- Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L *et al*. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol* 2010; **28**: 2077–2084.
- Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D *et al*. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy following hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood* 2012; **120**: 9–19.
- Terragna C, Zamagni E, Petrucci MT, Durante S, Patriarca F, Narni F *et al*. Molecular remission after bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as consolidation therapy following double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. *Blood* 2010; **116**: (abstract 861).
- Roussel M, Avet-Loiseau H, Moreau P, Huynh A, Benboubker L, Hulin C *et al*. Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: primary results of the IFM 2008 phase II study. *Blood* 2010; **116**: (abstract 624).
- Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T *et al*. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1782–1791.
- Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K *et al*. Improved progression free survival with bortezomib consolidation after high dose melphalan; results of a randomized phase III trial. *Haematologica* 2011; **96** (Suppl 1): (abstract O-11).
- Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R *et al*. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117**: 4691–4695.
- Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L *et al*. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
- Barlogie B, Pineda-Roman M, van Rhee F, Haessler J, Anaissie E, Hollmig K *et al*. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood* 2008; **112**: 3115–3121.
- Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L *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**: 1788–1793.
- Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM *et al*. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood* 2012; **119**: 7–15.
- Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F *et al*. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **354**: 1021–1030.
- Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P *et al*. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical Sciences. *J Clin Oncol* 2010; **28**: 1209–1214.
- McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG *et al*. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1770–1781.
- Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orłowski R, Bladé J *et al*. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood* 2011; **117**: 6063–6073.
- Boccardo M, Cavallo F, Nagler A, Ben Yehuda D, Omedè P, Cavalli M *et al*. Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) in newly diagnosed multiple myeloma (MM) patients: a phase III trial. *J Clin Oncol* 2011; **29** (Suppl 15): (abstract 8020).