

## MULTIPLE MYELOMA: FROM THE BENCH TO BEDSIDE

## Frontline therapy of multiple myeloma

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**In the past decade, one of the major advances in the management of patients with symptomatic newly diagnosed multiple myeloma has been the introduction of novel agents, thalidomide, bortezomib, and lenalidomide, as part of frontline treat-**

**ment in both transplant and nontransplant candidates. These drugs have markedly improved the rate of complete remission, and time to progression, progression-free survival, and overall survival have significantly increased. This article focuses on**

**more recent frontline therapeutic approaches both in older patients, not eligible for high-dose therapy and autologous stem cell transplantation (ASCT), and in younger patients eligible for early ASCT. (*Blood*. 2015; 125(20):3076-3084)**

## Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and ~13% of all hematologic malignancies.<sup>1</sup> Approximately 86 000 new cases of MM occur annually worldwide.<sup>2</sup> This malignant neoplasm primarily affects elderly individuals with a median age at the time of diagnosis of ~70 years.<sup>1</sup> Active MM is consistently preceded by precursor states of monoclonal gammopathy of undetermined significance and smoldering MM,<sup>3</sup> which represent a continuum of progression of the tumor burden in the absence of symptoms or signs of end organ damage. The current standard practice for patients diagnosed with smoldering MM is observation,<sup>4</sup> and therapy is only initiated once the disease progresses to symptomatic active MM.<sup>5,6</sup> Treatment approaches depend on “fitness” with chronological age still being an important discriminator for selecting therapy. The initial evaluation of patients includes an assessment of eligibility for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) based on age, performance status, and comorbidities. In the past decade, one of the major advances in the management of MM has been the introduction of novel agents, thalidomide, bortezomib and lenalidomide, as part of frontline treatment in both transplant and nontransplant candidates.<sup>5-9</sup> These drugs have markedly improved the rate of complete response (CR), without substantially increasing toxicity, and, importantly, time to progression (TTP), progression-free survival (PFS) and overall survival (OS) have significantly increased. This manuscript focuses on more recent frontline therapeutic approaches both in older patients, not eligible for HDT and ASCT, and in younger patients eligible for early ASCT.

### Frontline treatment of younger patients: incorporation of novel agents into the transplant setting

In the 1990s, a number of randomized studies and case-controlled analyses showed that intensive therapy with ASCT improved survival

over conventional chemotherapy in patients with newly diagnosed MM (NDMM) younger than 65 years and resulted in the procedure becoming the standard of care.<sup>10,11</sup> Over the past decade, the novel agents thalidomide, bortezomib, and lenalidomide have been included both before and after ASCT.<sup>6-8</sup>

#### Induction treatment prior to ASCT

The inclusion of novel agents during induction resulted in an improvement in responses. The rate of very good partial responses (VGPRs) increased from 15% following induction with the vincristine-doxorubicin-dexamethasone (VAD) regimen, the standard in the 1990s, up to 70% using triplet combinations based on bortezomib-dexamethasone (VD), which are further upgraded with melphalan 200 mg/m<sup>2</sup> (Mel200) as the conditioning regimen prior to ASCT (Table 1).<sup>6-8</sup> The addition of a third agent to VD<sup>12</sup> (eg, thalidomide [VTD], doxorubicin [PAD], lenalidomide [RVD], or cyclophosphamide) results in improved response rates over the VD combination alone,<sup>6-8,13</sup> and the superiority of VTD over TD or VD has been shown in 3 prospective studies.<sup>14-16</sup> Although no phase 3 trial has as yet been conducted to compare the different regimens, the recent phase 2 EVOLUTION study suggests that RVD and bortezomib-cyclophosphamide-dexamethasonemide yield similar results.<sup>17</sup> Based on response rates, depth of response, and PFS as surrogate markers for outcome, 3-drug combinations including bortezomib and dexamethasone are currently, in 2014, the standard of care prior to ASCT.<sup>6-18</sup> Three to 6 courses of induction may be administered before proceeding to stem cell collection.<sup>6,7,14-16</sup>

#### Conditioning regimen

The current standard conditioning regimen prior to ASCT is Mel200.<sup>19</sup> Several attempts have recently been made to improve this step of the HDT procedure, such as the addition of bortezomib, bendamustine, or IV busulfan to high-dose melphalan.<sup>20</sup> Ongoing phase 3 trials aimed at comparing Mel200 vs other regimens are underway.

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**Table 1. Phase 3 trials incorporating novel agent–based induction prior to ASCT**

Study by induction regimen	Treatment schema	No.	Postinduction (%)			Posttransplant (%)		Long-term outcomes (%)
			ORR	CR	VGPR	ORR	CR VGPR	
<b>IFM 2005-01<sup>12</sup></b>								
VAD	VADx4 ± DCEPx2-ASCT Mel200	242	63	1		77	9	Median PFS: 30 mo
vs								
VD	VDx4 ± DCEPx2- ASCT Mel200	240	78	6		80	16	Median PFS: 36 mo
<b>GIMEMA MM-BO2005<sup>14</sup></b>								
VTD	VTDx3-ASCT Mel200x2-VTDx2-Dm	236	93	19 CR		93	42 CR	3-y PFS: 68
vs				62 ≥ VGPR			82 ≥ VGPR	3-y OS: 86
TD	TDx3-ASCT Mel200x2-TDx2-Dm	238	79	5 CR		84	30 CR	3-y PFS: 56
<b>PETHEMA GEM05MENOS65<sup>16</sup></b>								
TD	TDx6-ASCT Mel200-IFNm/Tm/VTm × 3 y	127	62	14 CR		NR	40 CR	Median PFS: 28 mo
vs				29 ≥ VGPR				4-y OS: 65%
VTD	VTDx6-ASCT Mel200-IFNm/Tm/VTm × 3 y	130	85	35 CR		NR	57 CR	Median PFS: 56 mo
vs				60 ≥ VGPR				4-y OS: 74%
VBMCP/VBAD/Vel	VBMCP/VBADx4-Vx2-ASCT Mel200-IFNm/Tm/VTm × 3 y	129	75	21 CR		NR	48 CR	Median PFS: 35 mo
<b>IFM 2007-02<sup>15</sup></b>								
VD	VDx4-ASCT Mel200	99	81	12 CR		86	31 CR	Median PFS: 30 mo
vs				36 ≥ VGPR			58 ≥ VGPR	
VTD	VTDx4-ASCT Mel200	100	88	13 CR		89	29 CR	Median PFS: 26 mo
<b>HOVON-65/GMMG-HD4<sup>22</sup></b>								
VAD	VADx3-CAD-ASCT Mel200-Tm × 2 y	414	54	2 CR		75	9 CR	Median PFS: 28 mo
vs				14 ≥ VGPR			36 ≥ VGPR	5-y OS: 55%
PAD	PADx3-CAD-ASCT Mel200-Vm × 2 y	413	78	7 CR		88	21 CR	Median PFS: 35 mo
<b>42 ≥ VGPR</b>								
<b>62 ≥ VGPR</b>								
<b>5-y OS: 61%</b>								

CAD, cyclophosphamide-doxorubicin-dexamethasone; DCEP, dexamethasone-cyclophosphamide-etoposide-cisplatin; Dm, dexamethasone maintenance; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; HOVON, Dutch-Belgian Hemato-Oncology Group; IFM, Intergroupe Francophone du Myélome; IFNm, interferon maintenance; NR, not reported; ORR, overall response rate; PAD, bortezomib-doxorubicin-dexamethasone; PETHEMA/GEM, Programa para el Estudio y la Terapéutica de las Hemopatías Malignas/ Grupo Español de Mieloma; PR, partial response; TD, thalidomide-dexamethasone; Tm, thalidomide maintenance; V, bortezomib; VBAD, vincristine-BCNU-doxorubicin-dexamethasone; VBMCP, vincristine-BCNU-melphalan-cyclophosphamide-prednisone; Vm, bortezomib maintenance; VTD, bortezomib-thalidomide-dexamethasone; VTm, bortezomib-thalidomide maintenance.

**Tandem ASCT**

Prior to the era of novel agents, tandem ASCT was often proposed in patients achieving less than VGPR after the first HDT.<sup>7,8,21,22</sup> Recent data indicate that this strategy, in addition with novel agent–based induction could overcome the poor prognosis of high-risk cytogenetics.<sup>23-25</sup> This needs to be confirmed in prospective randomized studies designed to address this issue.

**Consolidation therapy after ASCT**

The use of a short-term consolidation therapy after HDT and ASCT is aimed at improving disease control through deepening responses (Table 2). Consolidation therapy should consist of highly efficient combinations of agents with minimal toxicity, applied for a limited period of time. Initial results of phase 2 and phase 3 trials investigating novel agent–based consolidation therapy<sup>26-33</sup> show that this strategy may result in the achievement of deep molecular–defined or flow cytometry–defined CRs,<sup>26,31</sup> with some patients remaining alive and free of disease, with minimal residual disease (MRD) negativity,<sup>31</sup> and a concomitant improvement in PFS.<sup>27,29,30</sup> A number of trials are ongoing to assess the impact of consolidation on OS, as well as the optimal consolidation regimen.

**Maintenance therapy after ASCT**

Unlike consolidation, maintenance therapy is administered long-term with the objective of prolonging response duration, PFS, and, ultimately, OS, while keeping toxicity minimal (Table 3). Thalidomide was the first novel agent examined in this setting. Six randomized studies have been published, with all of them showing a significant

benefit for thalidomide in terms of response and PFS,<sup>33-38</sup> while OS was improved in 3 of them.<sup>33-35</sup> The safety profile of thalidomide, notably the occurrence of peripheral neuropathy, which is cumulative and which was found to be the main cause of treatment discontinuation, may hinder its use as long-term maintenance therapy. Furthermore, in one study, a negative impact on quality of life was noted with Tm.<sup>38</sup> The possible emergence of tumor-resistant clones in patients with prolonged exposure to thalidomide has led to concerns about its lack of efficacy in patients with adverse cytogenetic abnormalities.<sup>37</sup> Lenalidomide is currently considered the best candidate for use as maintenance therapy. Results from 2 randomized trials evaluating lenalidomide maintenance vs placebo following ASCT have been published, and both have shown that PFS was dramatically increased by almost 2 years, a benefit that was observed across all patient subgroups.<sup>28,39</sup> In one of the studies (CALGB100104), the PFS benefit translated into a significantly longer OS.<sup>39</sup> Despite the higher incidence of grade 3/4 hematologic adverse events (AEs) in the lenalidomide group, lenalidomide maintenance was considered feasible and manageable, with <30% of patients having to discontinue the drug because of AEs. However, in both studies an unexpected finding was the occurrence of more secondary primary malignancies in the lenalidomide group. The pathophysiology of these secondary neoplasms remains to be clarified. A third study from Italy has also evaluated lenalidomide maintenance.<sup>40</sup> Designed to assess the role of transplantation, patients received induction therapy with lenalidomide/dexamethasone (len/dex) followed by a randomization to consolidation with either melphalan-prednisone-lenalidomide (MPR) or tandem ASCT. In a second randomization step, patients were assigned to lenalidomide maintenance or no treatment. Median PFS was significantly longer with lenalidomide maintenance than with no

**Table 2. Phase 2 and 3 trials incorporating novel agent–based consolidation following ASCT**

Reference	Treatment schema (x cycles)	No.	Response after ASCT (%)		Response after consolidation (%)	PFS of TTP
26	VTDx4	39	CR	15	49	NR
			VGPR	85	98	
28	Lenalidomide x2	577	VGPR	58	69	NR
31	RVDx2	30	CR + sCR	47	50	NR
			>VGPR	70	87	
30	No consolidation	96	CR	30	30	4-y TTP 29%
	vs		>VGPR	64	64	
			>PR	91	91	
	VTDx2	121	CR	33	52	4-y TTP 62%
			>VGPR	76	83	
			>PR	96	96	
27	TD	161	CR	40	47	PFS from start of consolidation
	vs		CR + nCR	55	61	48% at 3 y
			>VGPR	81	88	
	VTD	160	CR	49	61	PFS from start of consolidation
			CR + nCR	63	73	60% at 3 y
			>VGPR	86	92	
29	No consolidation	183	>nCR	21	35	PFS from start of randomization
	vs		>VGPR	39	57	20 mo
			>PR	89	96	
	IV weekly bortezomib (20 infusions)	187	>nCR	20	45	PFS from start of randomization
			>VGPR	40	71	27 mo
			>PR	91	96	

nCR, near complete response; sCR, stringent CR.

maintenance (41.9 months vs 21.6 months), but 3-year OS was not significantly prolonged (88.0% vs 79.2%). The important question of the optimal duration of lenalidomide maintenance is being investigated in several ongoing trials. Vm therapy has been investigated in 2 randomized trials.<sup>22,41</sup> In one study, thalidomide daily was compared with intravenous bortezomib administered twice monthly for 2 years following ASCT.<sup>22</sup> Patients who received Vm had received induction therapy consisting of PAD, while patients treated with Tm had received VAD induction. Despite these discrepancies in induction therapy, in a landmark analysis starting 12 months after initial randomization of patients who had received HDT/ASCT and were still without progression, PFS and OS were statistically improved in the bortezomib arm. Bortezomib toxicity during maintenance was manageable, but in 35% of patients the proteasome inhibitor had to be discontinued, dose-reduced, or administration delayed because of AEs, and only 47% of patients could stay on

maintenance for the planned 2 years. The second trial, not yet fully published, prospectively explored 3 different types of maintenance: interferon  $\alpha$ , thalidomide, or the combination of bortezomib and thalidomide (VT) following 3 different induction regimens.<sup>41</sup> PFS was significantly improved with VTm without significant toxicity, whereas there was no difference in OS. Overall, these 2 trials suggest that bortezomib presents also a feasible maintenance strategy,

#### Toward an optimal strategy of induction, HDT plus ASCT, consolidation, and maintenance

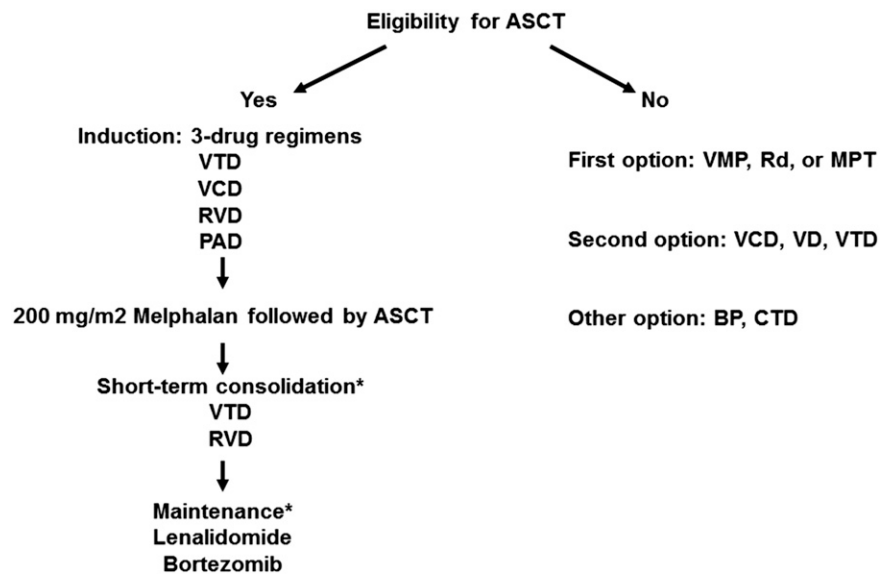
The implementation of an “optimal strategy,” consisting of novel agent–based induction, HDT, and the use of novel agents in consolidation and maintenance, may result in a 5-year survival rate of 80%, which is unprecedented, and cure might be considered in a subset of patients who present with good prognostic features at the time of

**Table 3. Phase 3 trials incorporating novel agent–based maintenance following ASCT**

Reference (by maintenance regimen)	No.	Initial dose	Response vs comparator	Median follow-up	EFS or PFS vs comparator	OS vs comparator
<b>Thalidomide</b>						
34	597	400 mg	CR + VGPR: 67% vs 55%	30 mo	3-y EFS: 52% vs 36%	4-y OS: 87% vs 77%
33	668	400 mg	CR: 64% vs 43%	72 mo	Median EFS: 6.0 vs 4.1 y	8-y OS: 57% vs 44%
35	269	200 mg	CR + VGPR: 63% vs 40%	3 y	3-y PFS: 42% vs 23%	3-y OS: 86% vs 75%
36	556	50 mg	CR: 31% vs 23%	52 mo	Median PFS: 34 vs 25 mo	Median OS: 73 vs 60 mo
37	492	50 mg	NR	38 mo	Median PFS: 30 vs 23 mo	3-y OS: 75% vs 80%
38	332	200 mg	NR	4.1 y	4-y PFS: 32% vs 14%	4-y OS: 68% vs 60%
<b>Lenalidomide</b>						
28	614	10 mg	CR + VGPR: 84% vs 76%	45 mo	Median PFS: 41 vs 23 mo	4-y OS: 73% vs 75%
39	460	10 mg	NR	34 mo	Median TTP: 46 vs 27 mo	3-y OS: 88% vs 80%
<b>Bortezomib</b>						
22	827	1.3 mg/m <sup>2</sup>	CR + VGPR: 76% vs 56%	41 mo	Median PFS: 35 vs 28 mo	5-y OS: 61% vs 55%
41	266	1.3 mg/m <sup>2</sup>	NR	24 mo	2-y PFS: 78% vs 63% vs 49%	NR

EFS, event-free survival.

**Figure 1. Summary of frontline therapy.** Asterisk indicates optional. BP, bendamustine-prednisone; CTD, cyclophosphamide-thalidomide-dexamethasone; MPT, melphalan-prednisone-thalidomide; Rd, lenalidomide and low-dose dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; VMP, bortezomib-melphalan-prednisone.



diagnosis (Figure 1).<sup>31-42</sup> The long-term results of the nonrandomized Total Therapy III study best exemplify what is achievable by combining novel agents with ASCT in a comprehensive treatment program.<sup>42</sup> With a median follow-up of 5.5 years, the 5-year estimates of OS and PFS are 73% and 62%, respectively. Moreover, a reduction in mortality to the level of the general US population was observed, speaking to the efficacy of this treatment approach. Similarly, the recent phase 2 IFM 2008-01 trial combining RVD induction, ASCT prepared by Mel200, RVD consolidation, and lenalidomide maintenance for 1 year yielded impressive PFS and OS results along with a high rate of MRD-negative CRs with no relapse at the time of reporting.<sup>31</sup> This regimen is being further evaluated in the ongoing IFM/DFCI 2009 phase 3 study.

The strategy of optimized induction, HDT and ASCT, followed by novel agent-based consolidation and maintenance is currently restricted to clinical trials.

**Novel agents alone are now questioning the role of frontline ASCT**

The high efficacy of the novel agents has led some groups to investigate these agents up-front without ASCT. In a nonrandomized trial conducted by the ECOG, len/dex as part of frontline therapy without ASCT yielded similar survival rates at 2 years as len/dex followed by ASCT.<sup>43</sup> Furthermore, in another nonrandomized phase 2 trial of RVD in the up-front setting, no difference in outcome was seen for patients undergoing HDT or not.<sup>44</sup> Impressive results, including high rates of MRD-negative responses, have been reported for the combination of carfilzomib and Rd (KRd) without up-front ASCT in phase 1/2 and phase 2 studies in patients with NDMM.<sup>40,45,46</sup> These early results of KRd appear to be superior to what has been achieved with other novel drug combinations in terms of high-quality response rates. In 2 retrospective analyses investigating novel agent-based initial therapy and the application of either frontline/early or delayed ASCT in patients with untreated MM, no difference in outcome was observed for either strategy.<sup>47,48</sup> Based on these results, many colleagues have begun to consider the use of novel agent-based therapies without the up-front application of ASCT as an alternative to early transplantation, and the role of ASCT itself has become a matter of debate: should it be used up-front or as a salvage treatment at the time of progression for patients initially treated with novel

agents? More drastically, some physicians are even floating the idea of the death of ASCT based on the results of the KRd regimen, despite the studies not being randomized.

**Preliminary randomized data favor early ASCT plus novel agents over novel agents alone**

At the end of 2014, only few data from prospective and retrospective trials are available to address the issue of early vs late ASCT. In 2010, Siegel et al<sup>49</sup> reported a post hoc, retrospective analysis of the ECOG E4A03 study in which patients could proceed to ASCT following 4 cycles of treatment with len/dex or continue len/dex therapy. Although the nonrandom assignment to early ASCT vs continued initial therapy makes a direct comparison impossible, the survival with ASCT at 3 years appeared higher, supporting the role of early consolidative ASCT in newly diagnosed patients. The first prospective study comparing conventional chemotherapy plus novel agents to tandem ASCT in NDMM patients is being conducted by the Italian myeloma group and was recently reported by Palumbo et al.<sup>40</sup> As outlined previously, patients received len/dex induction and were then randomized to MPR or tandem ASCT. Both PFS and OS were significantly longer with high-dose melphalan plus ASCT than with MPR (median PFS, 43.0 months vs 22.4 months; and 4-year OS, 81.6% vs 65.3%). These results favor the early, systematic use of frontline HDT. At 2013 meeting of the American Society of Hematology, the Italian group also reported early results of a prospective randomized trial of len/dex induction followed by either cyclophosphamide-lenalidomide-dexamethasone or tandem ASCT.<sup>50</sup> Again, preliminary PFS results favored the intensive arm of the trial. Nevertheless, the 2 Italian trials have to be analyzed cautiously. In both of them, induction therapy was len/dex, which is suboptimal as compared with a triple bortezomib-based combination, currently considered the most effective regimen prior to ASCT.<sup>6,7,13</sup> Two other ongoing trials, 1 conducted by the European Myeloma Network (EMN02 study, NCT01208766) and 1 by the IFM plus a US consortium (IFM/DFCI 2009 study, NCT01208662), are investigating the same question and have enrolled 1500 and 1000 patients, respectively. Although variability in consolidation and maintenance may impact PFS when comparing early vs late transplant approaches, these 2 studies will solve many issues regarding the role of systematic frontline ASCT in the treatment of young patients eligible for HDT; however, results are not expected before the end of 2015.

**Table 4. Phase 3 studies and meta-analysis results in transplant-ineligible patients**

Study	Treatment schema/duration	No. of patients in treatment arm	Median follow-up	Best response	PFS	OS
MPT meta-analysis <sup>56</sup>	MPT for 8 cycles, 12 cycles, or until relapse	1685 (total no. of patients included)	Not available	VGPR: 25%	20.3 mo	39.3 mo
MPT (FIRST trial) <sup>74</sup>	MPT for 12 cycles	547	37 mo	CR: 9.3%	21.2 mo	4-y OS: 51.4%
CTD <sup>64</sup>	CTD for up to 9 cycles (6 cycles minimum)	426	44 mo	CR: 13.1%	13 mo	33.2 mo
VMP (VISTA trial) <sup>66</sup>	VMP for 9 cycles	344	60.1 mo	CR: 30%	21.7 mo	56.4 mo
MPR-R <sup>73</sup>	MPR for 9 cycles, followed by R until disease progression	152	30 mo	CR: 9.9%	31 mo	4-y OS: 59%
VMPT-VT <sup>67,69</sup>	VMPT for 9 cycles, followed by VT for 2 y or until progression or relapse	254	54 mo	CR: 38%	35.3 mo	5-y OS: 61%
VMP/VTP-VT <sup>68,70</sup>	VMP or VTP for 6 cycles, followed by VT for up to 3 y	91	46 mo	CR: 46%	39 mo	5-y OS: 69%
Rd continuous (FIRST trial) <sup>74</sup>	Rd until disease progression	535	37 mo	CR: 15.1%	25.5 mo	4-y OS: 59.4%
BP <sup>76</sup>	BP until maximum remission or disease progression	68	Not available	CR: 32%	TTF: 14 mo	32 mo

MPR-R, melphalan-prednisone-lenalidomide-lenalidomide maintenance; TTF, time to treatment failure; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide-bortezomib, thalidomide maintenance; VMP/VTP-VT, bortezomib-melphalan-prednisone/bortezomib-thalidomide-prednisone-bortezomib-thalidomide maintenance.

\*Meta-analysis based on individual data from 1685 patients included in 6 randomized trials.

### ASCT in real life outside the clinical trial setting

The idea of implementing a tailored approach for patients, based on individual risk factors, is strongly supported by the whole myeloma community. However, in 2014, we have not yet reached the point of being able to offer a risk-adapted strategy in MM that is derived from the results of large phase 3 studies and aimed at adapting strategies to initial clinical and biological features, as well as taking into account the “dynamic” prognostic factor of response to initial therapy.<sup>18,51</sup>

Moreover, the results of the 2 most important prospective clinical trials mentioned previously, which are aimed at comparing frontline vs late ASCT in the context of novel agent-based therapy (EMN02, IFM/DFCI 2009), which also include correlative studies of systematic genomic and cytogenetic analyses with the specific goal of defining subgroups of patients that may benefit from the different therapeutic approaches in order to develop a valuable risk-adapted strategy, are not yet available. Therefore, the optimal approach to the treatment of MM remains the administration of the most effective treatment of all patients, regardless of risk status and including the so-called “good risk” patients, and this most effective treatment should involve the use of ASCT up-front as this procedure is safe, is associated with a mortality rate of <2%, and is cost-effective.<sup>52</sup> Recent numbers from both the European Group for Blood and Marrow Transplantation<sup>53</sup> and Center for International Blood and Marrow Transplant Research (CIBMTR)<sup>54</sup> registries clearly indicate that MM remains by far the principal indication for ASCT in the United States and the European Union, and that an increasing amount of intensive therapy is performed year after year (almost 7000 ASCT for MM in the United States in 2011, and 8500 in the European Union), illustrating the profound importance of the technique for the treatment of young patients.

## Frontline treatment of elderly patients

### What have we learned over the past 10 years?

Since the introduction of thalidomide, bortezomib, and lenalidomide, several regimens that include 1 or 2 of these novel agents have been explored (Figure 1). The combination of MPT is a standard option for NDMM patients who are not candidates for ASCT.<sup>5,55-57</sup> The addition of thalidomide to melphalan-prednisone (MP) was shown to delay disease progression in several randomized trials<sup>55,58-63</sup> and to improve

OS in some of them.<sup>55,58,59</sup> A meta-analysis of published data from 6 randomized trials confirmed an improvement in PFS and OS with MPT compared with MP.<sup>56</sup> The reported median PFS and OS with MPT were 20.3 and 39.3 months, respectively. The combination of CTD has also demonstrated benefit over MP and is commonly used in the United Kingdom.<sup>64</sup>

VMP is another well-established standard of care. It initially involved twice-weekly IV administration of bortezomib, based on the phase 3 VISTA trial.<sup>65,66</sup> Initial results indicated that VMP was superior to MP across all efficacy end points, including response rate, CR rate, median TTP (24 months vs 16.6 months using a stringent definition of disease progression [change from immunofixation negativity to positivity]), and OS. Bortezomib use then evolved from twice-weekly to weekly dosing in 2010 based on new clinical evidence,<sup>67-70</sup> and from IV to subcutaneous administration in 2012.<sup>71</sup> The final analysis of the VISTA trial after a median follow-up of 60 months confirmed the superiority of VMP vs MP in terms of median time to second-line antineoplastic therapy (31 months vs 20.5 months) and median OS (56 months vs 43 months).<sup>66</sup> VD and VTD have yielded similar results.<sup>72</sup>

Lenalidomide has been mainly used in combination with MP (ie, MPR)<sup>73</sup> or with low-dose dexamethasone (ie, Rd).<sup>43,74</sup> The MPR regimen was not always well tolerated in patients >75 years of age and has been associated with an increased incidence of hematologic second primary malignancy.<sup>73</sup> In a recent phase 3 FIRST study involving 1623 transplant-ineligible patients, continuous Rd regimen administered until disease progression or intolerance or for a fixed duration of 18 cycles (Rd18; 72 weeks) was compared with MPT administered for 12 cycles (72 weeks; Table 4). Continuous Rd significantly extended PFS, with an OS benefit, compared with MPT. With a median follow-up of 37 months, the median PFS was 25.5 months for Rd, compared with 20.7 months for Rd18 and 21.2 months for MPT. The 4-year estimated OS was 59% for Rd, 56% for Rd18, and 51% for MPT. In addition, Rd was superior to MPT across all other efficacy end points, including response rate TTP, TTF, time to second-line antineoplastic therapy, and duration of response. Rd was also generally better tolerated than MPT.<sup>74</sup>

Apart from these 3 major drugs, bendamustine has also been studied in NDMM in combination with prednisone<sup>75</sup> or bortezomib and prednisone.<sup>76,77</sup>

Importantly, several studies have recently evaluated maintenance therapy or continuous therapy; approaches include VMPT followed by VT maintenance,<sup>67,69</sup> VMP or VTP followed by VT or bortezomib-prednisone maintenance,<sup>68,70</sup> MPR-R,<sup>73</sup> or

continuous Rd.<sup>74</sup> Taken together, these studies support the role of continuous therapy, at least in terms of PFS and time to second-line antimyeloma therapy.

MPT and VMP are currently the 2 most widely used regimens. Since 2013, bortezomib is usually administered subcutaneously, and weekly dosing seems to be preferred, although some experts still recommend twice-weekly dosing for patients with renal impairment or extensive bone disease.<sup>78</sup>

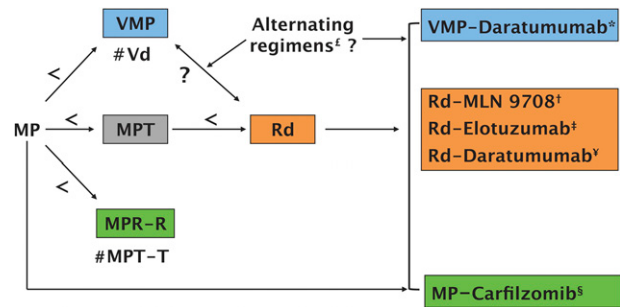
**What are some of the most important challenges?**

Standard prognostic features, such as disease stage, renal function, and cytogenetics, apply to both older and younger NDMM patients. At the time of diagnosis, ~50% of transplant-ineligible patients have creatinine clearance <60 mL/min, and this feature may influence treatment decision.<sup>74</sup> Similarly, 30% to 50% of patients have stage III disease, according to the International Staging System (ISS).<sup>65,73,74</sup> Cytogenetics is a powerful prognostic factor, and some chromosomal abnormalities, such as t(4;14) or del(17), dictate patient outcome. In a recent study, frailty was a better predictor of OS than were cytogenetics and ISS stage.<sup>79</sup>

**Elderly patients with poor cytogenetics.** Most of the cytogenetic data collected in the past few years have come from younger, transplant-eligible NDMM patients. Registrational studies conducted in elderly patients have partly evaluated cytogenetics,<sup>55,65,74</sup> but few countries have implemented routine cytogenetic testing for transplant-ineligible patients. The IFM group recently reported on a series of 1890 elderly patients (median age 72 years; 651 patients >75 years of age), including 1095 patients with updated data on treatment modalities and survival.<sup>80</sup> The incidence of del(13) and t(4;14) was lower in older patients, whereas the incidence of del(17p) was similar across age groups. Regardless of treatment, both t(4;14) and del(17p) were associated with a poorer clinical outcome. The median PFS in patients with t(4;14) and del(17p) was 14 and 11 months, respectively, compared with 24 months for patients lacking both abnormalities. Similarly, the median OS was 32 and 19 months, respectively, compared with 50 months.

**The challenge of frailty.** The age of 65 years is a commonly used cutoff for determining ASCT eligibility in MM patients, even if the feasibility of ASCT is well established in fit patients up to the age of 70.<sup>24</sup> The percentage of Europeans aged ≥65 years is projected to increase from 85 million (17% of the population) in 2008 to 151 million (30% of the population) in 2060.<sup>81</sup> This expanding population represents a heterogeneous group that poses many challenges for clinicians. Elderly and unfit/frail patients have been underrepresented in clinical trials investigating new drugs; few studies have been dedicated to patients over the age of 75 years,<sup>58,82</sup> and currently no studies have been designed based on frailty.

In a retrospective analysis of 4 European phase 3 trials evaluating MP, MPT, VMP, and VMPT (1435 patients), a higher risk of mortality was noted in patients ≥75 years of age; the estimated 3-year OS was 68% in patients aged <75 years vs 57% in those aged ≥75 years. In addition to advanced age, other significant predictors of shorter OS included renal failure, severe cardiac events and infection, and drug discontinuation.<sup>83</sup> In another study from the same group, a frailty score was developed based on age, Charlson Comorbidity Index,<sup>84</sup> Index of Activities of Daily Living (ADL),<sup>85</sup> and Instrumental ADL scores.<sup>86,87</sup> Patients were categorized as fit, unfit, or frail with distinct clinical outcomes. Unfit and frail patients were more likely to experience nonhematologic AEs and treatment discontinuation. The median PFS was significantly lower in frail patients (11 months) than in fit patients (14 months), as was the 1-year OS rate (78% vs 96%, respectively). Importantly, frailty was more significant than ISS stage or cytogenetics



**Figure 2. Ongoing or planned phase 3 trials designed for registration.** <, inferior; #, or; ?, no comparison available.

in the multivariate analysis for OS.<sup>79</sup> There is now consensus that not only chronological age but also comorbidity and frailty must be adequately assessed and taken into consideration when making treatment decisions. One way to achieve this goal is to better define the dose reductions required for elderly/frail patients when using standard treatment regimens. This has been done for dexamethasone (the dose is reduced to 20 mg weekly for patients >75 years of age) and also with reduced doses of thalidomide and weekly and subcutaneous administration of bortezomib. Another way that could be complementary to adequate dose reductions is to implement a simple geriatric assessment, at least for some patients. Apart from the Charlson Comorbidity Index, ADL, and Instrumental ADL questionnaires, the G8 questionnaire, which is a very simple screening tool, also warrants evaluation.<sup>88</sup> Geriatric assessment may help reduce treatment toxicity, avoid early treatment discontinuation, and improve quality of life by delivering a more individualized therapy. However, the approach is time-consuming, and there are no available data showing a correlation between geriatric assessment and clinical outcome.

**What is the next step forward?**

The current standard regimens MPT and VMP are based on melphalan and given for a fixed duration (9 to 12 cycles).<sup>6</sup> Recently, the alkylator-free doublet regimen Rd, delivered as continuous therapy, has demonstrated superiority over MPT,<sup>74</sup> and continuous Rd will likely become a new standard of care for transplant-ineligible patients with NDMM. This represents a dual paradigm change in a disease where alkylating agents and fixed-duration therapy have been standard for decades.

It should be noted that use of combinations based on MP or cyclophosphamide will most likely persist as a new complementary category of Rd-based regimens emerges. Triplet regimens combining an immunomodulatory drug and steroid with either a proteasome inhibitor or a monoclonal antibody are anticipated to become new standards of care in the next 10 years. Alternating regimens considering immunomodulatory drugs, proteasome inhibitors, and potentially other novel agents might also become a treatment option.<sup>89</sup> Figure 2 presents ongoing or planned phase 3 trials designed for registration.

To improve outcomes in elderly NDMM patients, priority should be given to developing more effective strategies for frail patients and those with adverse cytogenetics. Strategies that are beneficial in these populations are also likely to improve outcomes in elderly, fit patients and those with standard-risk cytogenetics.

Since the availability of thalidomide, and the subsequent approval of bortezomib and lenalidomide, the median OS in elderly NDMM patients has increased from roughly 30 to 60 months.<sup>70,74,90,91</sup> Future development of second- and third-generation immunomodulatory drugs and proteasome inhibitors, new drug families such as

monoclonal antibodies and histone deacetylase inhibitors, and better tools for patient management will enable us to further improve outcomes in these patients.

## Authorship

Contribution: P.M., M.A., and T.F. wrote the manuscript.

Conflict-of-interest disclosure: P.M. has received honoraria from and serves on the advisory boards of Janssen, Celgene, Millenium-Takeda, and Onyx. M.A. has received honoraria from and serves on the advisory boards of Janssen and Celgene. T.F. has received honoraria from and serves on the advisory boards of Janssen, Celgene, Millenium-Takeda, and Onyx.

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