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International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation

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The role of high-dose therapy followed by autologous stem cell transplantation (ASCT) in the treatment of multiple myeloma (MM) continues to evolve in the novel agent era. The choice of induction therapy has moved from conventional chemotherapy to newer regimens incorporating the immunomodulatory derivatives thalidomide or lenalidomide and the proteasome inhibitor bortezomib. These drugs combine well with traditional therapies and with one another to form various doublet, triplet, and quadruplet regimens. Up-front use of these induction treatments, in particular 3-drug combinations, has affected unprecedented rates of complete response that rival those previously seen with conventional chemotherapy and subsequent ASCT. Autotransplantation applied after novel-agent-based induction regimens provides further improvement in the depth of response, a gain that translates into extended progression-free survival and, potentially, overall survival. High activity shown by immunomodulatory derivatives and bortezomib before ASCT has recently led to their use as consolidation and maintenance therapies after autotransplantation. Novel agents and ASCT are complementary treatment strategies for MM. This article reviews the current literature and provides important perspectives and guidance on the major issues surrounding the optimal current management of younger, transplantation-eligible MM patients. (*Blood*. 2011; 117(23):6063-6073)

Introduction

Multiple myeloma (MM) is a disease of the elderly. Overall, only 35% of the patients are younger than 65 years at the time of diagnosis, whereas the remaining two-thirds are older.[1] Age is an independent prognostic factor in MM[2] and, importantly, provides a major criterion by which patients can be considered eligible to tolerate high-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (ASCT). Over the last decade, the survival of patients with newly diagnosed MM, particularly those younger than 60 years, has significantly improved.[3] The widespread use of ASCT and the introduction into clinical practice of the novel agents bortezomib and the immunomodulatory derivatives (IMiDs) thalidomide and lenalidomide have significantly contributed to major advances in MM therapy and prognosis.[4,5]

Thalidomide or bortezomib combined with melphalan and prednisone represent new standards of care for elderly, transplantation-ineligible MM patients.[6-8] In this setting, lenalidomide in combination with low-dose dexamethasone is an alternative treatment option.[9] In younger patients, the novel agents have been incorporated into the therapeutic algorithm along with ASCT to improve clinical outcomes.[10-12] In particular, these drugs have been used as part of induction therapy before ASCT and as consolidation/maintenance after autotransplantation. This manuscript from the International Myeloma Working

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Group (IMWG) presents an overview of the most recent studies of novel agents combined with ASCT and focuses on the main areas of current debate, including the choice of induction regimen, the role of post-ASCT consolidation and maintenance therapies, the impact on prognosis of ASCT incorporating the new drugs, and the management and prevention of major toxicities related to the use of novel therapies.

What is younger?

There is no formal definition of a younger patient with MM, although this term is commonly used to identify a person for whom ASCT is planned as part of the treatment program. As many phase 3 studies of ASCT have enrolled patients with an upper age limit not exceeding 65 years,[13-19] younger MM patients are often operatively defined as being 65 years of age and younger. However, this arbitrary cut-off does not exclude patients who are older than 65 years from ASCT. In particular, in selected patients up to the age of 70 to 75 years who are medically fit, ASCT is a treatment option that can be performed safely at most specialized transplantation or myeloma centers.[20] Unlike in younger patients, benefits from ASCT have not been consistently demonstrated in the elderly.

When to start myeloma-specific therapy

When symptomatic, or active, MM is diagnosed based on the presence of organ damage related to the underlying malignant clone (eg, hypercalcemia, renal insufficiency, anemia, and bone disease),[21] therapy is required immediately. By contrast, patients with asymptomatic or smoldering MM are closely observed without specific therapy until the disease progresses to a symptomatic phase. Clinical trials are currently underway to investigate whether novel agents can delay the risk of progression from smoldering to active MM and improve overall survival (OS).[22] At present, the IMWG does not recommend treatment for smoldering MM but considers patients at high risk of progression to symptomatic disease as candidates for investigative clinical trials.

Single ASCT

Over the last decade, ASCT has been considered the standard of care for younger patients with newly diagnosed MM[23-25] based on the increased rate of complete response (CR) and prolonged OS compared with conventional chemotherapy in several randomized studies.[13,14] However, not all the studies published so far have uniformly demonstrated the superiority of ASCT over chemotherapy at standard doses.[16-18] A number of factors may account for these discrepancies, including treatment crossover for patients randomized to conventional treatment, possible bias in patient selection criteria, and differences between studies with respect to the intensity and duration of conventional therapy. A systematic review and meta-analysis of randomized studies has shown a significant benefit with single ASCT in terms of prolonged progression-free survival (PFS), but not of OS.[26] However, these results should be cautiously interpreted because of methodologic limitations of the analysis and significant heterogeneity across different studies. An alternative to autotransplantation up-front is to delay HDT with ASCT at the time of relapse. Although in a pilot study the length of OS for patients receiving early or late ASCT after conventional induction chemotherapy was equivalent, early autotransplantation was associated with a longer event-free survival (EFS) and better quality of life.[27] In the novel agent era, the issue of early versus late ASCT needs to be reevaluated in the context of large randomized clinical trials. Two of these studies are currently ongoing, one of them headed by the European Myeloma Network and the other performed by a consortium of centers in France and the United States. While final results of these studies are awaited, the IMWG recommends that ASCT should be offered at some point in the course of the treatment program for a patient eligible to receive HDT. Although favorable results with ASCT up-front are backed by phase 3 studies, increasing numbers of patients and physicians, particularly in United States, are currently opting to collect stem cells early and deferring transplantation at the time of relapse.

Double ASCT

Five randomized trials directly addressed the question of single versus double, or tandem, ASCT as up-front therapy for MM.[15,19,28-30] Results were conflicting because of differences between studies with respect to their structural and methodologic characteristics. In particular, although extended EFS with double ASCT was observed in most of the trials, an OS benefit was demonstrated in only 2 of them. A meta-analysis of data pooled from controlled clinical trials (one of which has been recently retracted) failed to show superior OS with double ASCT which, by the opposite, was associated with improved response rates and EFS.[31] A number of concerns related to the methodology of the analysis and errors involving data extractions have been raised, suggesting that these caveats might have negatively influenced the conclusion.[32,33] More recently, a report of long-term outcomes of several trials of autotransplantation(s) confirmed superior results offered by double ASCT compared with a single transplantation.[34]

In 2 studies of double ASCT, post-hoc subgroup analyses showed that the second autotransplantation improved clinical outcomes in those patients who failed high-quality responses after the first ASCT.[15,19] However, a major limitation of these studies was their lack of power to demonstrate the equivalence of 1 versus 2 transplants for patients with high-quality responses after the first course of HDT. With the recent availability of highly effective novel agents, the role of single versus double ASCT is being explored in the context of prospective, randomized clinical trials, such as that currently headed by the Bone Marrow Transplant Clinical Trials Network. In the meantime, the IMWG suggests considering timely second ASCT in those patients who fail to achieve a very good partial response (VGPR) or better after the first ASCT.

Prognostic relevance of CR

Attainment of CR after both induction therapy and ASCT is one of the strongest predictors of long-term outcomes[35,36] and represents a major endpoint of current treatment strategies incorporating autotransplantation up-front. To more carefully identify high-quality responses occurring beyond the CR level, the IMWG has recently introduced the category of stringent CR, as defined by negative immunofixation, normal free-light chain ratio, and absence of clonal bone marrow plasma cells by immunohistochemistry.[37] It is probable that incorporation of novel agents into ASCT results in

Table 1. Phase 2 and 3 studies of thalidomide-dexamethasone and triplet thalidomide-based combinations in preparation for ASCT

		After induction		After ASCT				
Regimen	N	CR + PR, %	CR/ ≥ VGPR, %	CR + PR, %	CR/ ≥ VGPR, %	PFS	OS	Reference
TD vs	100	76	10/19	NR	NR	NR	NR	42
VAD (retrospective case-matched study)	100	52	8/14	NR	NR	NR	NR	
TD vs	103	63	4/NR	NR	NR	NR	NR	44
VAD	104	41	0/NR	NR	NR	NR	NR	
TD vs	100	66	NR/35	68	NR/44	NR	NR	43
Descamethasone	104	52	NR/13	62	NR/42	NR	NR	
TAD vs	268	71	3/37	84	14/54	median, 34 mo	median, 73 mo	47
VAD	268	57	2/18	76	12/44	median, 22 mo	median, 60 mo	
						$P < .001$	$P = .77$	
CTD vs	NR	87	19/NR	NR	51/NR	NR	NR	48
CVAD	NR	75	9/NR	NR	40/NR	NR	NR	
TT2 + THAL vs	323	NR	NR	NR	62/NR	5-yr, 56%	5-yr, 65%	46
TT2 without THAL	345	NR	NR	NR	43/NR	5-yr, 44%	5-yr, 65%	
						$P = .01$	$P = .90$	
Double ASCT + THAL vs	135	NR	NR/30	NR	NR/68	4-yr, 51%	5-yr, 69%	45
Double ASCT without THAL (retrospective case-matched study)	135	NR	NR/15	NR	NR/49	4-yr, 31%	5-yr, 53%	
						$P = .001$	$P = .07$	

Studies incorporating thalidomide-dexamethasone throughout double ASCT are also included.

CTD indicates cyclophosphamide, thalidomide, dexamethasone; CVAD, cyclophosphamide added to VAD (vincristine, doxorubicin, dexamethasone); NR, not reported; TAD, thalidomide, doxorubicin, dexamethasone; TD, thalidomide, dexamethasone; THAL, thalidomide; and TT2, Total Therapy 2.

increased rates of immunophenotypic and/or molecular remissions[38] compared with that reported in the recent past.

Other studies have also emphasized the adverse prognostic importance of residual focal lesions detected by magnetic resonance imaging.[39] In contrast, sustained CR is predictive of favorable long-term outcomes.[40] Therefore, not only attainment of CR per se, but maintenance of a durable CR, appears to be a major prognostic variable in MM. Interestingly, achievement of CR does not seem to be of critical prognostic relevance for several subgroups of patients, including those with low-risk disease or in whom active MM reverts to an indolent phase similar to that of monoclonal gammopathy of undetermined significance.[41]

Review of evidence supporting newer induction treatments in preparation for ASCT

Patients who are eligible for early ASCT typically receive a limited number of cycles of induction therapy to reduce tumor cell mass and bone marrow plasma cell infiltration before collection of peripheral blood stem cells. Compared with conventional treatments used in the past, a number of novel agents are now available that affect increased rates of CR. Currently, these novel agents are incorporated into induction regimens to enhance the depth of response before ASCT and further improve post-ASCT outcomes.

Thalidomide and dexamethasone

The activity of thalidomide, especially when combined with dexamethasone (TD), in the relapsed/refractory setting has provided the rationale for the design of phase 2 and 3 trials investigating the role of this regimen in patients with newly diagnosed disease.[42-44] In 2005, a retrospective case-matched study provided the first demonstration of superior rate and depth of response affected by TD compared with VAD as induction therapy in preparation for ASCT,[42] a finding confirmed by a subsequent phase 3 study[43] (Table 1). Based on the results of a randomized study showing a higher response rate with TD compared with high-dose dexamethasone[44] (Table 1), the United States Food and Drug Administration granted accelerated approval for TD in patients with newly diagnosed MM. As a result, over the past years, TD has emerged as one of the most commonly used induction regimens in the United States and European countries (European Union).

In 2 additional studies in which TD was incorporated into double ASCT and given from the outset through the second ASCT[45] or until relapse/progression,[46] superior rates of CR or at least VGPR, EFS, and OS were seen with TD plus double ASCT compared with tandem transplantation not incorporating thalidomide (Table 1). However, the rate of adverse events, in particular peripheral neuropathy and venous thromboembolism, was consistently high with thalidomide maintenance therapy and led to drug discontinuation in 30% and 60% of patients after 2 and 4 years, respectively.[46]

Thalidomide-dexamethasone and a cytotoxic drug

Two phase 3 trials explored the activity of induction regimens combining TD with doxorubicin or cyclophosphamide in transplantation candidates. In one study, TD and doxorubicin provided a significantly higher rate of VGPR or better compared with VAD (37% vs 18%), a gain that was maintained after the first ASCT (54% vs 44%, respectively).[47] Median EFS for patients randomly assigned to TD and doxorubicin followed by post-ASCT thalidomide maintenance was 34 months versus 22 months for those assigned to VAD and subsequent maintenance with interferon.

In another study, superior rates of CR both before and after ASCT were seen with TD and cyclophosphamide compared with cyclophosphamide added to VAD (pre-ASCT, 19% vs 9%; and post-ASCT, 51% vs 40%, respectively).[48]

Table 2. Phase 2 studies of bortezomib-based regimens in preparation for ASCT

		After induction		After transplantation				
Regimen	N	CR + PR, %	CR/ ≥ VGPR, %	CR + PR, %	CR / ≥ VGPR, %	PFS, median	OS, 30 mo	Reference
V (single agent)	64	41	NR (9)*/17	NR	NR	17 mo	30 mo, 79%	49
V ± D	32	87.5	6 (25)*/NR	NR	NR	NR	NR	50
VD	48	66	NR (21)*/31	90	NR (33)*/55	NR	NR	51
V alternated with D	40	65	12.5/22.5	88	33/55	NR	NR	52
PAD-1	21	95	24 (5)*/62	95	43 (14)*/81	median, 29 mo	2-yr, 95%	54
PAD-2	20	89	11 (5)*/42	90	37 (5)*/53	median, 24 mo	2-yr, 73%	54
VDD	50	78	NR (27)*/NR	93	27/NR	NR	NR	56
VDD	40	85	NR (37.5)*/57.5	87	NR (57)*/77	2-yr, 80%	2-yr, 92%	57
CyBorD	33	88	3 (39)*/61	NR	NR (70)*/74	NR	NR	58
VCD	391	85.4	NR (15)*/37	NR	NR	NR	NR	59
VTD vs VTDC	49 vs 48	100 vs 96	(29)/69 vs (31)/69	100 vs 100	(50)/87 vs (44)/85	NR	1-yr, 94.1% vs 94.2%	66
TT3 + VTD-PACE vs TT2 + THAL (retrospective comparison)	303 vs 323	NR vs NR	NR vs NR	NR vs NR	2-yr, 54/NR vs 51/NR	2-yr, 84% vs 77% ($P = .008$)	2-yr, 87% vs 83% ($P = .12$)	67

CyBorD indicates cyclophosphamide, bortezomib, dexamethasone; D, dexamethasone; NR, not reported; PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide; PAD, bortezomib, doxorubicin, dexamethasone; PAD-2, reduced-dose bortezomib; THAL, thalidomide; TT3, Total Therapy 3; V, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; VDD, bortezomib, pegylated liposomal doxorubicin, dexamethasone; and VTD, bortezomib, thalidomide, dexamethasone.

*At least near CR.

Bortezomib and dexamethasone

The role of up-front standard-dose bortezomib (1.3 mg/m^2) given twice weekly either as a single agent or with added dexamethasone in patients with suboptimal response to the first cycles of therapy was initially explored in patients who were either eligible or ineligible for ASCT (Table 2).[49,50] In 2 additional phase 2 studies, bortezomib and high-dose dexamethasone (VD) were given either in combination[51] or on an alternating basis[52] before ASCT. The rate of at least VGPR was 31% with VD and 22.5% with the alternating schedule; the corresponding value after ASCT was 55% in each of the 2 studies. In a phase 3 study, VD was prospectively compared with VAD as induction therapy in preparation for single or double ASCT; in both arms, lenalidomide was given as post-ASCT consolidation and maintenance therapy.[53] After 4 21-day cycles, the rates of at least VGPR, including CR and near CR (nCR), affected by VD were significantly higher than with VAD (≥ VGPR, 38% vs 15%; CR-nCR, 15% vs 6%, respectively), a gain maintained after both the first and second ASCT (≥ VGPR, 68% vs 47%; CR-nCR, 39.5% vs 22.5%, respectively). A borderline, albeit not statistically significant, PFS benefit was seen in the VD arm compared with the VAD arm (median, 36 vs 30 months, respectively).

Bortezomib-dexamethasone and a cytotoxic drug

Cytotoxic drugs added to VD as part of a 3-drug regimen in preparation for ASCT have included doxorubicin or cyclophosphamide (Table 2). A combination of bortezomib, doxorubicin, and dexamethasone, referred to as PAD, was investigated in 2 small cohorts of patients who received either standard-dose or reduced-dose bortezomib (1.0 mg/m^2) on a twice-weekly basis (Table 2).[54] In a phase 3 study, the PAD regimen was compared with VAD as induction therapy before 1 or 2 autotransplantations.[55] Superior CR-nCR rates were seen with PAD compared with VAD after both induction (11% vs 5%, respectively) and autotransplantation(s) (30% vs 15%). PAD induction followed by ASCT and subsequent bortezomib maintenance was associated with significantly longer PFS and OS compared with VAD induction and post-ASCT thalidomide maintenance therapy (Table 2). Two additional phase 2 studies confirmed the activity of a PAD-like induction regimen incorporating pegylated liposomal doxorubicin (Table 2).[56,57]

In addition, cyclophosphamide has also demonstrated substantial activity when combined with VD (CyBorD or VCD) in preparation for ASCT.[58,59] In 2 phase 2 studies, the rate of at least VGPR was between 37% and 61%, a range that reflected heterogeneities between studies with respect to the number of planned treatment cycles and the delivered cyclophosphamide dose.

Bortezomib, dexamethasone, and thalidomide

Preclinical data suggesting that IMiDs increase bortezomib activity, provided the rationale for combining thalidomide with VD (VTD). Promising rates of high-quality responses reported with VTD in small cohorts of relapsed/refractory and newly diagnosed MM patients[60] led to the design of a phase 3 study of VTD versus TD as induction therapy before, and consolidation therapy after, double ASCT.[61] After three 21-day induction cycles, VTD was superior to TD with respect to all response categories, including CR, CR-nCR (31% vs 11%), and at least VGPR (62% vs 28%). Increased frequencies of high-quality responses in the VTD arm compared with the TD arm were also seen after double autotransplantation and subsequent consolidation therapy (CR-nCR, 62% vs 45%; ≥ VGPR, 85% vs 68%, respectively). The estimated 3-year PFS for the VTD group of patients was significantly longer than for those assigned to TD plus double ASCT (68% vs 56%, respectively). In two additional phase 3 studies comparing VTD with either TD[62] or VD[63] as induction therapy in preparation for a single ASCT, superior rates of high-quality responses, both before and after ASCT, and extended PFS[62] were seen with the triplet regimen (Table 3). Remarkable activity of VTD was further confirmed by several phase 2 studies,[64,65] including a prospective comparison of VTD with the same regimen combined with cyclophosphamide[66] (Table 2).

In Total Therapy 3, VTD combined with cisplatin, doxorubicin, cyclophosphamide, and etoposide was given as induction therapy

Table 3. Phase 3 trials of bortezomib-based regimens in preparation for ASCT

		After induction		After ASCT				
Regimen	N	CR + PR, %	CR/ ≥ VGPR, %	CR + PR, %	CR/ ≥ VGPR, %	PFS	OS	Reference
VD vs	223	78.5	6 (15)*/38	80	16 (35)*/54	median, 36 mo	3-yr, 81%	53
VAD	218	63	1 (6)*/15	77	9 (18)*/37	median, 30 mo	3-yr, 77%	
						(*P* = .06)	(*P* = .5)	
VTD vs	236	93	19 (31)*/62	93	42 (55)*/82	3-yr, 68%	3-yr, 86%	61
TD	238	79	5 (11)*/28	84	30 (41)*/64	3-yr, 56%	3-yr, 84%	
						(*P* = .005)	(*P* = .3)	
VBMCP/VBAD + V vs	129	75	21/36	73	38/51	38 mo	NR	62
VTD vs	130	85	35/60	77	46/65	27 mo	NR	
TD	127	62	14/29	58	24/40	Not reached	NR	
						(*P* = .006)		
PAD vs	371	78	NR (11)*/42	88	NR (30)*/61	3-yr, 36%	3-yr, 78%	55
VAD	373	55	NR (5)*/15	77	NR (15)*/36	3-yr, 27%	3-yr, 70%	
						(*P* = .01)	(*P* = .02)	
VD vs	99	81	12 (22)*/35	84	33 (54)*/59	NR	NR	63
vTD	100	90	13 (32)*/51	90	30 (61)*/73	NR	NR	

PAD indicates bortezomib, doxorubicin, dexamethasone; V, bortezomib; TD, thalidomide-dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; VBAD, vincristine, carmustine, doxorubicin, dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VD, bortezomib, dexamethasone; VTD, bortezomib (1.3 mg/m^2), thalidomide, dexamethasone; vTD, bortezomib (1.0 mg/m^2), thalidomide, dexamethasone; and NR, not reported.

*At least near CR.

before, and consolidation after, double ASCT, whereas VTD maintenance therapy was continued for 1 year after ASCT.[67] Compared with Total Therapy 2 incorporating TD into double ASCT, Total Therapy 3 significantly improved 2-year EFS (77% vs 84%) and duration of CR.

Lenalidomide, dexamethasone, and other agents

Lenalidomide plus high-dose dexamethasone (480 mg total in a 28-day cycle; RD) was prospectively compared with lenalidomide and low-dose dexamethasone (160 mg total per cycle; Rd) as frontline therapy for MM.[9] Patient enrollment into the study was not restricted by age or eligibility for ASCT. Despite the overall response rate, including VGPR or better within 4 cycles of therapy was significantly higher with RD compared with Rd (42% vs 24%, respectively), a substantially higher toxicity and early mortality was seen with RD, particularly in patients older than 65 years. On landmark analysis, the 3-year OS of patients who received ASCT after RD or Rd was 92%; the corresponding value for patients who continued on primary therapy and did not receive ASCT was 79%.

Lenalidomide, dexamethasone, and other agents

Lenalidomide and dexamethasone were combined with bortezomib to form a triplet regimen (RVD), which has been investigated in limited series of patients with newly diagnosed MM.[68-70] In a phase 1/2 study, a total of 66 patients who were either transplantation-eligible or ineligible for ASCT received a maximum of 8 RVD cycles; in responders, RVD maintenance was allowed.[69] After 4 cycles, the rate of at least nCR and VGPR was 6% and 11%, respectively. However, in approximately two-thirds of patients, the quality of response improved from cycle 4 through cycle 8, and a further improvement was also seen in the maintenance phase.

In addition to RVD, alternative lenalidomide-containing regimens have included a combination of lenalidomide-cyclophosphamide-dexamethasone and a quadruplet regimen in which cyclophosphamide was added to RVD[71] (Table 4). A prospective comparison of RVD with VCD and cyclophosphamide combined with RVD given for up to 8 cycles has been recently reported; the rate of CR-nCR after 4 cycles was in the 7%, 3%, and

Table 4. Phase 2 and 3 trials of doublet and triplet lenalidomide-based induction treatments for transplant-eligible and transplant-ineligible patients

		After induction		After ASCT				
Regimen	N	CR + PR (best response), %	CR/ ≥ VGPR (best response), %	CR + PR, %	CR + nCR, %	PFS	OS	Reference
RD vs	223	81	5/50	NR	NR	median, 19 mo	median, not reached	9
Rd	222	70	4/40	NR	NR	median, 25 mo	median, not reached	
						(*P* = .02)	(*P* = .4)	
RVD	66	100	29 (39)*/67	NR	NR	18 mo, 75%	18 mo, 97%	69
RVD vs	42	83	24 (40)*/50	NR	NR	NR	NR	72
VCD vs	32	75	22 (31)*/41					
RVCD	42	86	24 (33)*/57	NR	NR	NR	NR	73
RVDD	57	4 cycles, 96	4 cycles, NR (30)*/58	NR	NR	NR	NR	

CRD indicates cyclophosphamide, lenalidomide, dexamethasone; NR, not reported; RD, lenalidomide, high-dose dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; RVCD, lenalidomide, bortezomib, cyclophosphamide, dexamethasone; RVDD, lenalidomide, bortezomib, pegylated liposomal doxorubicin, dexamethasone; and VCD, bortezomib, cyclophosphamide, dexamethasone.

*At least near CR.

10% range, respectively.[72] An additional quadruplet regimen incorporating lenalidomide, bortezomib, dexamethasone, and pegylated liposomal doxorubicin was explored.[73] After a median of 4 cycles, the rates of CR-nCR and VGPR or better were 30% and 58%, respectively.

Special patient populations

Cytogenetic abnormalities

The prognostic value of major cytogenetic abnormalities and the impact of novel agents on clinical outcomes of patients carrying different cytogenetic changes have been recently reviewed by the IMWG.[74] Detection at diagnosis of translocation t(4;14) and t(14;16) or deletion of chromosome 17, del(17p), by fluorescence in situ hybridization, as well as deletion/monosomy of del(13q) or hypodiploidy by metaphase cytogenetics define approximately one-fourth of patients[75] who in the past years did not benefit from ASCT and had shortened remission duration and OS.[76,77]

Recent reports have suggested that incorporation of novel agents into ASCT may overcome, at least in part, the poor prognosis imparted by high-risk cytogenetic profiles. In two phase 3 studies of VD[78] and PAD[55] induction therapy followed by lenalidomide and bortezomib maintenance therapy, respectively, t(4;14)-positive patients had better outcomes than the control groups who carried the same abnormality but received VAD induction followed by maintenance therapy with either lenalidomide[78] or thalidomide.[55] However, in both of these studies, t(4;14) partly retained its adverse influence on PFS and OS, even among patients treated with bortezomib-based induction regimens and subsequent maintenance with novel agents.[55,78] In contrast, in a phase 3 study of VTD induction and consolidation therapy plus double ASCT, PFS curves were almost identical regardless of the presence or absence of t(4;14).[61] In an additional study, incorporation of VTD into double ASCT as part of both induction and consolidation therapy and as post-ASCT maintenance therapy resulted in improved CR duration, PFS, and OS for the gene expression profile-defined high-risk subgroup of patients carrying the *MMSET/FGFR3* hybrid transcript.[67] The role of bortezomib-based regimens and ASCT for the treatment of del(17p)-positive patients needs to be carefully evaluated in larger sample sizes than those explored so far.[78] In particular, areas of major interest include the ability of less or more intense treatments (eg, doublet vs triplet or quadruplet combinations) given for different time periods (eg, short-term vs long-term) to impact on the poor prognosis related to this high-risk cytogenetic profile.

In most studies incorporating thalidomide as part of induction therapy[79] or as post-ASCT maintenance,[80,81] the outcome of patients with del(13q), t(4;14), and/or del(17p) was inferior to that of patients who lacked these abnormalities. Conflicting results concerning the ability of lenalidomide to overcome the poor prognosis associated with del(13q) and t(4;14) were found in 2 retrospective studies of patients with relapsed/refractory MM.[82,83] The adverse prognostic impact of del(17p) was emphasized in one of these studies.[83] In a recent report on newly diagnosed MM patients who were either transplantation-eligible or ineligible for ASCT and received lenalidomide-dexamethasone up-front, both response duration and PFS, but not OS, were significantly worse when high-risk genetic abnormalities were present at baseline.[84]

Renal failure

In patients with MM and renal failure, rapid reduction of myeloma cell mass and recovery of normal renal function are critical goals of both myeloma-specific therapy and supportive care measures.[85] Neither thalidomide[86] nor bortezomib[87] is excreted through the kidneys, and dose adjustments are not required for patients with renal impairment. In contrast, it is mandatory to modify the dose and schedule of lenalidomide according to renal clearance.[85] In general, bortezomib-based regimens are the preferred treatment option in this setting, as recently recommended by the IMWG.[85]

Major toxicities with IMiD- or bortezomib-based induction therapies

Thalidomide and lenalidomide

For patients who receive thalidomide up-front, either as a single agent or in combination therapy, the most common toxicities include constipation, somnolence, and peripheral neuropathy (PN).[88] Thalidomide-induced PN is more frequently sensory or sensorimotor, is dose-dependent (more prevalent with doses higher than 200 mg/day) and duration-dependent (more likely to occur after 6-12 months).[89,90] Reduction of the dose or discontinuation of thalidomide according to the severity of PN are measures commonly used in clinical practice. Unlike thalidomide, lenalidomide induces myelosuppression, mainly neutropenia and thrombocytopenia, which can be managed via dose reductions and/or hematopoietic growth factor support.[91] PN is uncommonly seen with lenalidomide. Another major challenge to be considered in patients who receive thalidomide or lenalidomide up-front is the increased risk of thromboembolic complications.[92,93] Adequate guidelines on the most appropriate thromboprophylactic treatments have been provided by the IMWG.[92] Finally, hypothyroidism is an additional important adverse event associated with long-term therapy incorporating thalidomide or lenalidomide. Long-term use of lenalidomide is also associated with severe diarrhea and cramps in a subset of patients.

The effect of newer induction regimens, in particular those incorporating lenalidomide, on peripheral blood stem cell mobilization and the optimal strategies to obtain adequate stem cell harvests have recently been reviewed by the IMWG.[94]

Bortezomib

One of the most important nonhematologic toxicities of bortezomib is PN, which may lead to impaired quality of life. Bortezomib-induced PN is predominantly sensory, although in $< 10\%$ of cases motor neuropathy has been reported.[95] Unlike neurologic toxicity associated with thalidomide, neuropathic pain, mainly located in the fingertips and toes, is a major problem with bortezomib. Major risk factors of bortezomib-induced PN include the cumulative dose of the drug and treatment schedule. Attempts to decrease the rate and severity of neurologic toxicity in transplantation candidates have included either dose reduction of bortezomib given on a twice-weekly basis[63] or once-weekly administration of the drug at a higher dose to maintain activity.[96] In elderly, transplantation-ineligible patients for whom treatment plan was composed of long-term exposure to melphalan and prednisone combined with bortezomib (given twice weekly for 4 cycles, followed by once-weekly administration for the next 5 cycles), the overall risk of PN was 47%, including 13% grade 3 or 4.[8] In 2 recent studies of melphalan and prednisone combined with standard-dose bor-

tezomib given on a weekly basis for 6 to 9 cycles, the incidence of grade 3 or 4 PN was reduced to 6% to 7%, whereas efficacy was retained.[97,98] Whether these favorable results may be obtained in transplantation-eligible patients who usually receive a shorter induction therapy is an issue not yet addressed in clinical trials. Notably, compared with single-agent bortezomib short-term use of combined bortezomib and thalidomide was not associated with a major increase in the frequency of any grade and grade 3 or 4 PN.[53,61,64,66] Besides symptomatic therapy, the optimal management of bortezomib-induced PN requires its early recognition and dose reduction or discontinuation of the drug using a validated algorithm; an alternative option may be to prolong the dosing schedule. Provided these procedures are promptly adopted, approximately 70% of patients have partial or complete reversibility of their neurologic symptoms. The issue of the management of treatment-emergent PN in MM has been recently addressed.[99] Severe thrombocytopenia occurs in approximately 5% or less of patients in the frontline setting. An additional adverse effect commonly seen with bortezomib-based regimens is reactivation of varicella zoster virus,[100] a complication that can be virtually abrogated with acyclovir prophylaxis.[101]

Role of novel agents as consolidation and maintenance therapies after autologous transplantation(s)

Consolidation treatment is generally short-term and aims to improve responses after ASCT. Upgraded rates of CR and CR-nCR, in the range between 10% and 30%, have been recently reported with post-ASCT use of bortezomib or lenalidomide as single agents[102,103] or with VTD.[104] In several of these studies, consolidation therapy with VTD yielded molecular remissions in up to 60% of patients.[38,105]

Maintenance treatment is given for a prolonged time period with the goal of extending the duration of response, PFS, and OS, while maintaining a good quality of life.[106] Several randomized studies showed a PFS benefit with thalidomide as single agent or combined with prednisone as maintenance therapy after ASCT.[46,47,80,81,107,108] In 2 of these studies, OS was extended in the thalidomide arm,[80,107] a gain lost when thalidomide was also given as part of induction therapy before ASCT.[46,47,81] Concerns exist about the use of thalidomide maintenance after ASCT, including the possible emergence of tumor-resistant clones in patients with prolonged exposure to this agents and its lack of efficacy in patients with adverse cytogenetic abnormalities.[109] However, the major caveat that precludes a widespread use of thalidomide maintenance is the toxicity related to long-term administration of this agent, primarily PN. In several studies, thalidomide-induced PN led to discontinuation rates in the 60% range[46,81] and impairment in patients' quality of life.[108] Lenalidomide is an attractive alternative to thalidomide because of the lack of neurologic toxicity. Two independent randomized trials have recently shown a significantly longer PFS[110,111] for patients randomized to lenalidomide maintenance (5-15 mg/day) compared with the placebo group after a single or double ASCT.[105,106] An increased incidence of second primary malignancies, in the 7% range, has been recently reported. Although a concerted effort is needed to better define the underlying mechanisms and identify risk factors, the optimal role and duration of lenalidomide maintenance therapy need to be tested in future clinical trials.

Conclusions

In conclusion, incorporation of IMiDs and/or bortezomib into newer regimens given in preparation for ASCT has been extensively explored using a wide range of different combinations. Doublet therapies combining either an IMiD or bortezomib with dexamethasone (eg, TD or Rd or VD) affected higher overall response rates than traditional treatments,[42,43,45,53] although the lowest rate of high-quality responses was seen with TD. Compared with doublets, such as TD and VD, triplet induction regimens, in particular, bortezomib plus thalidomide and dexamethasone (VTD), further increased the rate of CR and/or at least VGPR, both before and after autotransplantation.[61-63] In the context of triplet regimens combining bortezomib with an IMiD, RVD is an attractive alternative to VTD,[70] although favorable results reported so far are not backed by phase 3 clinical studies. Several newer induction treatments, such as VD, VTD, PAD, and Rd, have been included as a category 1 recommendation, which signifies a high-level of evidence and uniform consensus among panel members, in the United States National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Multiple Myeloma Version 1.2011.[23]

Enhanced high-quality responses affected by newer induction regimens translated into even higher frequencies of CR or at least VGPR after single or double ASCT. Although extended PFS was reported in several of these studies,[45,46,47,53,55,61] no OS benefit was generally seen, a finding that reflects the lack of adequate power and/or follow-up to detect survival differences. Furthermore, proving an OS benefit at this time is probably difficult because of the rapidly increasing availability of effective salvage therapies at the time of relapse.

Based on these considerations and the close relationship between maximal response to induction therapy and favorable prognosis after ASCT, it is likely that many investigators in the IMWG would recommend using one of the bortezomib-containing triplet regimens as up-front induction therapy in a transplantation-eligible MM patient. However, other IMWG investigators might feel that until OS differences emerge, low-risk patients may have the option of choosing either a doublet regimen with low morbidity, such as Rd, or a bortezomib-based triplet, provided that they are properly informed about the pros and cons, particularly the risk of early PN with bortezomib. Besides once-weekly administration of bortezomib, the introduction into the clinical practice of subcutaneous bortezomib that has recently shown a significantly lower risk of PN compared with intravenous bortezomib in patients with relapsed/refractory disease[112] and carfilzomib, a second-generation irreversible proteasome inhibitor with significantly less neurotoxicity than bortezomib, may solve some of these issues in the near future.

In the absence of randomized studies comparing different induction regimens, it is difficult to recommend one induction regimen over another. However, particular patient and disease characteristics may guide the clinician to select the most appropriate therapy. For instance, preliminary data suggest that bortezomib-based regimens, such as VTD, VD, and PAD, can partially or completely abrogate the poor prognosis related to t(4;14),[55,61,78] although more mature data about del(17p) are needed. In patients presenting with acute renal failure, both bortezomib- and thalidomide-based regimens can be safely given, whereas lenalidomide requires appropriate dose reductions and frequent monitoring of blood counts. In patients at high risk of thromboembolic complications, a bortezomib-based regimen may be preferable. In contrast, the presence of neuropathy at baseline might suggest excluding bortezomib-based or thalidomide-based treatments in

favor of a regimen, such as Rd. In the studies reported so far, the dose of dexamethasone was variable. However, high-dose dexamethasone is needed in those patients in whom a prompt reduction in tumor cell mass is required. Finally, it is worth remembering that in many countries novel-agent-based induction therapies for younger, transplantation-eligible patients are not approved as yet. In these cases, the choice of induction regimen should be based on drug availability; furthermore, referral of patients to a specialized myeloma center with access to studies of novel agents is recommended.

The usual choice of giving 3 to 6 cycles of induction therapy to maximize the depth of response before early ASCT represents a reasonable balance between maximum benefit and minimum toxicity. However, an alternative choice that can be discussed with the patient, particularly if response to therapy is favorable and he/she is unwilling to proceed to early ASCT, is to continue induction for as long as maximal tumor reduction is achieved and then to maintain response until relapse or progression, at which time salvage ASCT can be performed. In this scenario, especially in patients treated with lenalidomide-based regimens, peripheral blood stem cells should be collected early, after 4 to 6 cycles of induction therapy. The best timing of ASCT in the novel agent era represents an area of active debate and major interest. Unless final results of ongoing clinical trials comparing early versus late ASCT plus novel agents will be available, ASCT up-front should continue to be considered the preferred approach for a patient who is eligible to tolerate HDT. More recently, the treatment paradigm for transplantation-eligible MM patients has continued to evolve with the introduction of the novel agents as consolidation and maintenance therapies. Mature results demonstrating the role, if any, of consolidation therapy in improving clinical outcomes and the impact of maintenance therapy on OS are needed before these strategies are widely adopted. In the meantime, the choice of using consolidation and/or maintenance therapy outside clinical trials is at the patient's and physician's discretion. If post-ASCT therapy with lenalidomide is planned, the IMWG recommends that the benefits of extended disease control versus potential risks of second malignancies with continued lenalidomide therapy be discussed with each patient. For many other important and still unaddressed questions, prospective randomized phase 3 studies are currently planned or underway.

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Contribution: All authors developed the consensus, provided critical review and edits to the manuscript, gave approval to the final manuscript, and significantly participated in the development and writing of the manuscript.

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