Have drug combinations supplanted stem cell transplantation in myeloma?

Antonio Palumbo[1] and Federica Cavallo[1]

[1]Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy

The introduction of proteasome inhibitor and immunomodulatory drugs has considerably changed the treatment paradigm of multiple myeloma. Autologous stem cell transplantation (ASCT) is superior to conventional chemotherapy and is considered the standard of care for patients younger than 65 years. Nevertheless, the favorable results shown by multidrug inductions, consolidations, and long-term maintenance approaches have challenged the role of ASCT. This article provides an overview of recent and ongoing clinical trials and aims to define the role of ASCT in the era of novel agents. (*Blood*. 2012;120(24):4692-4698)

Introduction

Multiple myeloma (MM) is a plasma cell malignancy, accounting for 1% of all cancers and 10% of hematologic neoplasms. Incidence increases greatly with age: the median age at diagnosis is 70 years, with 35% of patients younger than 65 years.[1] In the Western countries, the annual age-adjusted incidence has reached 5.6 cases per 100 000 persons because of the aging of the general population. In the 1990s, treatment efficacy was improved by the use of autologous stem cell transplantation (ASCT) and subsequently by the introduction of proteasome inhibitors and immunomodulatory agents (IMiDs). In the last decade, survival of patients younger than 50 years with newly diagnosed MM has significantly improved, with 10-year survival rate increasing from 24.5% to 41.3%.[2] However, MM is characterized by multiple relapses. Genomic instability and clonal heterogeneity cause the selection of more aggressive subclones responsible for drug resistance and finally dismal outcome.[3] For these reasons, effective treatment should be concentrated at the early phases of disease, when clones are more drug sensitive, long-lasting remissions are more frequent, and serious adverse events are less prominent. This approach significantly improves quality of life and may ultimately prolong overall survival (OS).

Treatment strategy

Achievement of profound cytoreduction and durable response

The efficacy of treatment is mainly related to the achievement of a durable response. The achievement of a complete response (CR) is associated with prolongation of progression-free survival (PFS) and OS in both young and elderly patients.[4,5] Before the introduction of bortezomib and IMiDs, an analysis of 4990 patients with MM receiving ASCT, including 2991 patients in prospective studies, showed that patients achieving CR after transplantation had longer event-free survival (EFS) and OS compared with patients achieving partial response (PR) only: median OS was 59-88.6 months in patients with CR compared with 39-68 months in patients with PR ($P < .001$).[4] Of note, a recent study reported that 35% of patients attaining CR were alive at 12 years after a median follow-up of 153 months.[6] In the elderly patients treated with either conventional chemotherapy or combinations, including thalidomide or bortezomib, the achievement of CR confirmed to be an independent predictor of longer outcome: the 3-year OS rose from 67% in patients in PR to 91% in patients in CR ($P < .001$), regardless of age, International Staging System stage, and treatment received.[5] Conventional chemotherapy, including thalidomide or bortezomib, has shown similar results to high-dose therapy and ASCT. In MM, CR is defined by negative serum and urine immunofixation, disappearance of any soft tissue plasmacytoma, and $< 5\%$ plasma cell on bone marrow examination. This definition has low sensitivity and is somehow inappropriate, because residual tumor is always present despite the achievement of CR. More sensitive techniques are now showing better correlation between a deeper response level and an improved outcome.[7,8] In patients with immunofixation-negative CR the 3-year PFS was 50% as opposed to 95% in patients with immunophenotypic CR ($P = .02$).[7] However, even in patients with stringent, immunophenotypic, or molecular CR, late relapses occur, showing the need for adequate biomarkers to detect the eradication of the tumor clone in vivo. In a recent analysis, after a median follow-up of 65 months, the 6-year PFS was 46%, despite the previous achievement of a molecular CR. It is important not only to achieve CR but also to maintain a sustained CR. Patients with sustained CR for ≥ 3 years had a longer OS than patients who had unsustained CR (5-year OS, 82% vs 24%; $P < .001$).[9] These data support a treatment strategy tailored to increase both CR rates and duration of response.

Early treatment discontinuation

Excessive toxicities are the main cause of early discontinuation that significantly affect cumulative dose intensity and efficacy. In the Total Therapy 3 (TT3) program, the premature discontinuation of bortezomib increased the risk of progression by 6 times ($P < .001$).[10] In the exploratory analysis of 134 patients receiving twice-weekly bortezomib compared with 369 patients on the once-weekly schedule, the twice-weekly bortezomib schedule resulted in a

Submitted May 4, 2012; accepted June 14, 2012. Prepublished online as *Blood* First Edition paper, June 22, 2012; DOI 10.1182/blood-2012-05-423202.

This article was selected by the *Blood* and *Hematology 2012 American Society of Hematology Education Program* editors for concurrent submission to *Blood* and *Hematology 2012*. It is reprinted in *Hematology Am Soc Hematol Educ Program*. 2012;2012:335-341.

higher rate of nonhematologic grade 3-4 adverse events (51% vs 36%; $P = .003$), mainly peripheral neuropathy (16% vs 3%; $P = .001$). The twice-weekly schedule had a higher rate of discontinuation (15% vs 5%; $P < .001$), consequently the cumulative delivered dose of bortezomib was similar (40.1 mg/m^2 for twice-weekly schedule and 39.4 mg/m^2 for once-weekly schedule) and so was the 3-year PFS rate (47% vs 50%; P value is not significant).[11]

Low-dose dexamethasone in combination with lenalidomide (Ld) reduced the frequency of adverse events and improved treatment adherence compared with high-dose dexamethasone with lenalidomide (LD): 30% of patients in the Ld group remained on treatment for > 1 year compared with 14% in the LD group. The 1-year OS was 96% for the Ld group compared with 87% for the LD group ($P < .001$).[12] In a randomized trial, the cumulative dose intensity of the combination melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPL-L) was 88% in patients younger than 75 years but only 56% in those older than 75 years, with a negative effect on median PFS.[13] These data clearly show the need to avoid excessive toxicities, to reduce discontinuation rate to < 20%, and to maintain cumulative dose intensity to ≥ 80%, delivering the appropriate treatment to the appropriate patient subgroups.

Role of early versus late ASCT: an open question

Before the introduction of bortezomib and IMiDs, a meta-analysis performed on 9 randomized trials confirmed a PFS benefit with upfront ASCT in comparison with conventional chemotherapy combinations.[14] Three randomized studies showed that OS was similar whether ASCT was done early or as salvage therapy at relapse.[15] Interestingly, in one trial early ASCT improved median EFS (39 vs 13 months), as well as the average time without symptoms (27.8 vs 22.3 months) compared with late ASCT, but OS was unchanged (64.6 vs 64 months). The early approach was also associated with lower rate of relapse, reduced treatment-related toxicities, and discontinuation. Another trial detected no significant PFS improvement with early ASCT (42 vs 33 months; $P = .57$) and suggested that the greatest benefit from early ASCT was among patients with disease refractory to induction therapy.[15]

In elderly patients with newly diagnosed MM, the combination melphalan-prednisone-thalidomide (MPT) was compared with an intermediate-dose melphalan 100 mg/m^2 (Mel 100) followed by ASCT.[16] The MPT regimen significantly reduced the risk of progression by 46% ($P < .001$) and the risk of death by 31% ($P = .027$). This study questioned the role of ASCT in the era of bortezomib and IMiDs. In recent years the efficacy of both ASCT and combination chemotherapy has been improved by the introduction of more effective induction, consolidation, and maintenance schedules that prolong duration of response.

Stem cell transplantation

Induction treatments

Bortezomib-dexamethasone (BD) induction regimen significantly increased CR/near CR (nCR) rate after ASCT (39.5%) in comparison with dexamethasone-vincristine-adriamicyn (VAD; 39.5% vs 22.5%; $P < .001$; Table 1).[17] However, the PFS improvement induced by BD was modest (36 vs 29.7 months; $P = .064$). Better results were obtained with 3-drug combinations.[18,20,30,31] The addition of cytotoxic drugs such as doxorubicin or cyclophosphamide to both thalidomide (TAD, CTD)[30,31] or bortezomib (PAD, BCD)[18,20] improved response rate. The TAD regimen prolonged PFS in comparison with VAD (34 vs 22 months; $P < .001$), whereas the PFS induced by CTD was similar to cyclophosphamide-VAD (median, 27 vs 25 months; $P = .59$). The regimen of BCD led to 70% CR/nCR rate after ASCT.[20] The combination of PAD significantly improved PFS compared with VAD (35 vs 28 months; $P = .002$).[18] The combination of bortezomib and IMiDs has shown similar results.[21,32] Bortezomib-thalidomide-dexamethasone (BTD) was superior to thalidomide-dexamethasone (TD).[21] The CR/nCR rate was increased with BTD induction compared with TD (55% vs 41%; $P = .002$) and so was also the 3-year PFS (68% vs 56%; $P < .006$).[21,32] Grade 3-4 neuropathy was higher with BTD (10% vs 2%; $P < .001$). The TT program consisted of induction, consolidation with combination chemotherapy plus thalidomide (TT2) or bortezomib (TT3), and double ASCT. In the TT3 program the cumulative frequency of CR increased with time and reached 56% at 2 years, with a 5-year EFS of 69%.[10,22]

Consolidation treatments

In several studies, the double ASCT extended PFS in comparison with single ASCT, but OS benefit was found in only 2 of them.[33] The role of the double ASCT is being questioned by the availability of novel effective combinations, although it is currently recommended in patients who fail to achieve VGPR or better after the first ASCT. In a recent study, tandem ASCT improved OS in comparison with single ASCT (5-year OS, 70% vs 55%; $P = .03$), the treatment regimen included PAD as induction and bortezomib or thalidomide as maintenance; unfortunately, the tandem versus single ASCT option was not randomized and only depended on insurance reimbursement.[18] Consolidation with bortezomib and IMiDs is currently under evaluation. BTD consolidation increased CR from 15% to 49% in patients who achieved VGPR after double ASCT.[8] Recently, the role of BTD versus TD consolidation after double ASCT was assessed. BTD consolidation increased the CR/nCR rate from 63% to 73%, but 3-year PFS was marginally improved (60% vs 48%; $P = .042$).[32] Four cycles of lenalidomide-prednisone have been adopted as consolidation after double ASCT; this approach increased the CR rate from 38% to 66%.

Maintenance treatments

After ASCT, thalidomide maintenance therapy improved the quality of response and increased PFS. In a recent meta-analysis, maintenance therapy with thalidomide reduced both the risk of progression (36%) and death (27%).[34] However a significant rate of grade 3-4 polineuropathy (7%-19%) was reported, and the rate of discontinuation reached 52.2%.[35] Median time on therapy was ~ 1 year.[36] The role of lenalidomide maintenance after ASCT was assessed.[27,28] In one study, lenalidomide reduced the risk of progression by 50% ($P < .001$), whereas OS was similar to the placebo group ($P = .29$).[27] In another study, lenalidomide reduced the risk of progressive disease by 52% ($P < .001$) and the risk of death by 38% ($P < .03$; Figure 1A-B).[28] In both studies, the most frequent grade 3-4 adverse events were neutropenia (45%-51%) and infections (1%-13%), and a higher incidence of second primary cancers in the lenalidomide arm was detected (7.8%-8.5% at 3 years; Table 2). Despite the high toxicities associated with this approach, a PFS improvement was detected. Median time on treatment was ~ 2 years. Data on single-agent bortezomib maintenance are available in one trial only. Patients who were randomly assigned to PAD or VAD induction followed by ASCT received bortezomib or thalidomide as maintenance therapy, respectively. Bortezomib maintenance significantly improved CR/nCR, from

Table 1. Efficacy of selected regimens

Regimen	Patients, n	Schedule	CR, %	PFS/EFS/TTP, %	OS, %
Stem cell transplantation					
BD	121	B: 1.3 mg/m^2 days 1, 4, 8, 11; D: 40 mg days 1-4 (cycles 1-4), days 9-12 (cycles 1-2); for four 21-d cycles	6	50 at 36 mo	81 at 36 mo
Mel 200[17]		Mel 200: 200 mg/m^2 (double if $<$ VGPR)	39 $\geq$ nCR		
PAD induction	413	P: 1.3 mg/m^2 days 1, 4, 8, 11; A: 9 mg/m^2 days 1-4; D: 40 mg days 1-4, 9-12, 17-20; for three 28-d cycles	7	50 at 35 mo	61 at 60 mo
Mel 200		Mel 200: 200 mg/m^2 (single-double)	21		
B maintenance[18]		B: 1.3 mg/m^2 days 1, 15; for 2 y	36		
PAD induction	102	P: 1.3 mg/m^2 days 1, 4, 8, 11; A: 30 mg/m^2 day 4; D: 40 mg days 1-4, 8-11, 15-18 (cycles 1-2), days 1-4 (cycles 2-4)	12	66 at 36 mo	85 at 36 mo
Mel 100		Mel 100: 100 mg/m^2 (double)	33		
LP consolidation		L: 25 mg days 1-21; P: 50 mg qod; for four 28-d cycles	40		
L maintenance[19]		L: 25 mg days 1-21 until disease progression	40		
BCD induction	33	B: 1.3 mg/m^2 days 1, 4, 8, 11; C: 300 mg/m^2 days 1, 8, 15, 22; D: 40 mg days 1-4, 9-12, 17-20; for four 28-d cycles	46 $\geq$ nCR*		
Mel 200[20]		Mel 200: 200 mg/m^2 (single)	70 $\geq$ nCR*		
BTD induction	236	B: 1.3 mg/m^2 days 1, 4, 8, 11; T: 100-200 mg/d; D: 40 mg days 1, 2, 4, 5, 8, 9, 11, 12; for three 21-d cycles	19	68 at 36 mo	90 at 36 mo
Mel 200		Mel 200: 200 mg/m^2 (double)	42		
BTD consolidation[21]		B: 1.3 mg/m^2 days 1, 8, 15, 22; T: 100 mg/d; D: 40 mg days 1, 2, 8, 9, 15, 16, 22, 23; for two 35-d cycles	61		
BTD PACE induction	303	B: 1.0 mg/m^2 days 1, 4, 8, 11; T: 200 mg days 1-4; D: 40 mg/m^2 days 1-4; P: 10 mg/m^2 days 1-4; A: 10 mg/m^2 days 1-4; C: 400 mg/m^2 days 1-4; E: 40 mg/m^2 days 1-4; for two $\leq$ 56-d cycles		69 at 60 mo	72 at 60 mo
Mel 200		Mel 200: 200 mg/m^2 (double)			
BTD PACE consolidation[22]		BTD as induction; P: 7.5 mg/m^2 days 1-4; A: 7.5 mg/m^2 days 1-4; C: 300 mg/m^2 days 1-4; E: 30 mg/m^2 days 1-4; for two 56-d cycles	56†		
Drug combinations					
MPT induction[23]	1685	M: 0.18 or 0.25 mg/kg days 1-7 or 1-4; P: 2 mg/kg days 1-4; T: 100-200 mg/d; M (0.18 mg) T (100 mg) for six 28-d cycles; M (0.25 mg) T (200 mg) for twelve 42-d cycles	25 $\geq$ VGPR	43 at 24 mo	50 at 39 mo
BMP induction[24]	344	B: 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1-4), days 1, 8, 22, 29 (cycles 5-9); M: 9 mg/m^2 days 1-4; P: 60 mg/m^2 days 1-4; for nine 42-d cycles‡	30	50 at 24 mo	68 at 36 mo
BMPT induction	254	B: 1.3 mg/m^2 days 1, 8, 15, 22; M: 9 mg/m^2 days 1-4; P: 60 mg/m^2 days 1-4; T: 50 mg/d; for nine 35-d cycles	38	56 at 36 mo	89 at 36 mo
BT maintenance[11]		B: 1.3 mg/m^2 every 14 d; T: 50 mg/d for 2 y	42		
BLD induction[25]	35	B: 1.3 mg/m^2 days 1, 4, 8, 11; L: 25 mg days 1-14; D: 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 (or days 1, 8, 15); for eight 28-d cycles	37	75 at 18 mo	97 at 18 mo
LD induction[12]	223	L: 25 mg days 1-21; D: 40 mg days 1-4, 9-12, 17-20; for four 28-d cycles	5	50 at 19 mo	75 at 24 mo
Ld induction[12]	222	L: 25 mg days 1-21; d: 40 mg days 1, 8, 15, 22; for four 28-d cycles	4	50 at 25 mo	76 at 24 mo
MPL induction	152	M: 0.18 mg/kg d 1-4; P: 2 mg/kg d 1-4; L: 10 mg days 1-21; for nine 4-wk cycles	10	50 at 31 mo	70 at 36 mo
L maintenance[13]		L: 10 mg days 1-21 until disease progression	33 $\geq$ VGPR		
CLd induction[26]	53	C: 36 mg/m^2 days 1, 2, 8, 9, 15, 16; L: 25 mg days 1-21; d: 40-20 mg weekly (cycles 1-4/5-8) for eight 28-d cycles	79 $\geq$ nCR*		
Maintenance regimens after stem cell transplantation					
L maintenance[27]	307	L: 10-15 mg days 1-21 until disease progression	29	50 at 41 mo	73 at 48 mo
L maintenance[28]	231	L: 10-15 mg days 1-21 until disease progression		50 at 46 mo	88 at 36 mo

TTP indicates time to progression; VGPR, very good partial response or better; PAD, bortezomib-adriamicyn-dexamethasone (in this schedule, P stands for bortezomib); BCD, bortezomib-cyclophosphamide-dexamethasone; BTD, bortezomib-thalidomide-dexamethasone; BLD, bortezomib-lenalidomide-dexamethasone; BTD-PACE, bortezomib-thalidomide-dexamethasone and cisplatin-doxorubicin-cyclophosphamide-etoposide; LP, lenalidomide-prednisone; qod, every other day; L, lenalidomide; B, bortezomib; BMP, bortezomib-melphalan-prednisone; BMPT, bortezomib-melphalan-prednisone-thalidomide; BT, bortezomib-thalidomide; BP, bortezomib-prednisone; CLd, carfilzomib, lenolidomide, and low-dose dexamethasone; Mel, melphalan; CR, complete response; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; BD, bortezomib-dexamethasone; LD, lenalidomide plus high-dose dexamethasone; Ld, lenalidomide plus low-dose dexamethasone; MPT, melphalan-prednisone-thalidomide; and MPL, melphalan-prednisone-lenalidomide.

*In per-protocol population.

†Percentage at 2 years.

‡Alternative BMP schedule[11] was B 1.3 mg/m^2 days 1, 8, 15, 22; M 9 mg/m^2 days 1-4; P 50 mg/m^2 days 1-4.

Table 1. (continued)

Regimen	Patients, n	Schedule	CR, %	PFS/EFS/TTP, %	OS, %
Maintenance regimens after drug combinations					
BT maintenance[29]	91	B:1.3 mg/m^2 twice weekly days 1, 4, 8, 11, every 3 mo; T: 50 mg/d up to 3 y	44	50 at 32 mo	
BP maintenance[29]	87	B: 1.3 mg/m^2 twice weekly; days 1, 4, 8, 11, every 3 mo; P: 50 mg qod up to 3 y	39	50 at 24 mo	

TTP indicates time to progression; VGPR, very good partial response or better; PAD, bortezomib-adriamicyn-dexamethasone (in this schedule, P stands for bortezomib); BCD, bortezomib-cyclophosphamide-dexamethasone; BTD, bortezomib-thalidomide-dexamethasone; BLD, bortezomib-lenalidomide-dexamethasone; BTD-PACE, bortezomib-thalidomide-dexamethasone and cisplatin-doxorubicin-cyclophosphamide-etoposide; LP, lenalidomide-prednisone; qod, every other day; L, lenalidomide; B, bortezomib; BMP, bortezomib-melphalan-prednisone; BMPT, bortezomib-melphalan-prednisone-thalidomide; BT, bortezomib-thalidomide; BP, bortezomib-prednisone; CLd, carfilzomib, lenolidomide, and low-dose dexamethasone; Mel, melphalan; CR, complete response; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; BD, bortezomib-dexamethasone; LD, lenalidomide plus high-dose dexamethasone; Ld, lenalidomide plus low-dose dexamethasone; MPT, melphalan-prednisone-thalidomide; and MPL, melphalan-prednisone-lenalidomide.

*In per-protocol population.

†Percentage at 2 years.

‡Alternative BMP schedule[11] was B 1.3 mg/m^2 days 1, 8, 15, 22; M 9 mg/m^2 days 1-4; P 50 mg/m^2 days 1-4.

31% to 49%, and reduced the risk of progression on a landmark analysis ($P = .04$). With bortezomib maintenance, grade 3-4 peripheral neuropathy was 5% and grade 3-4 infections were 24%. The median time on therapy was ~ 2 years in the bortezomib group and 1 year in the thalidomide group.[18]

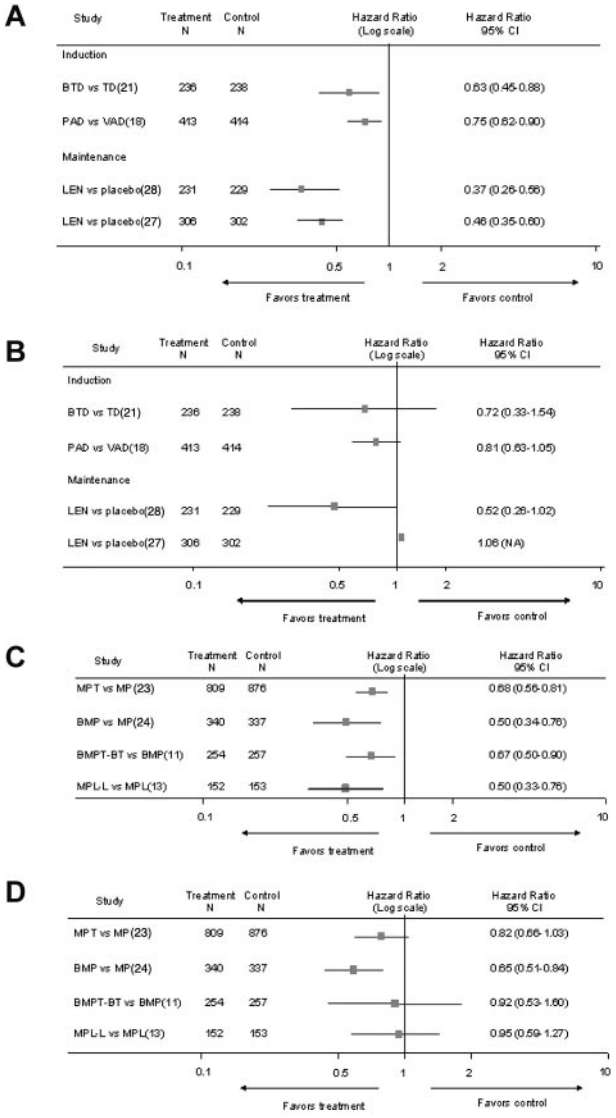

Figure 1. Hazard ratios. (A) PFS with regimens, including stem cell transplantation and novel agents; (B) OS with regimens, including stem cell transplantation and novel agents; (C) PFS with drug combinations, including novel agents; and (D) OS with drug combinations, including novel agents. Len indicates lenalidomide; NA, not available; and MP, melphalan-prednisone.

The 3-drug combinations, such as BCD, BTD, or BRD inductions, improved response rate. These results might be further improved with the introduction of novel proteasome inhibitors as shown by the combination of carfilzomib-lenalidomide-dexamethasone. The role of the second ASCT has been questioned and is currently limited to patients who do not reach VGPR after a single ASCT. Future trials to assess the role of single versus double ASCT are warranted. Consolidation with BTD improved CR rates and PFS, but data are limited and randomized studies for consolidation regimens are lacking. Maintenance therapy with IMiDs reduced the risk of progression by ~ 50%. In patients aged 65-75 years, PAD induction followed by tandem Mel 100, ASCT, lenalidomide-prednisone consolidation, and lenalidomide maintenance induced a CR rate of 40%, 3-year PFS of 66%, and 3-year OS of 85%.[19] Overall, the available data show that effective induction, consolidation, and maintenance therapy have greatly improved the efficacy of high-dose therapy and ASCT. With these approaches the CR/nCR rates are ranging from 36% to 70%, the 5-year PFS from 62% to 69%, and the 5-year OS from 61% to 72%.

Drug combinations

A meta-analysis of the 6 randomized controlled trials that compared MPT with MP showed that MPT improved both PFS and OS of ~ 6 months.[23] Peripheral neuropathy (6%-23%) and venous thromboembolism (3%-12%) were the main adverse events associated with thalidomide. The combination bortezomib-melphalan-prednisone (BMP) improved the median time to next therapy by 8 months ($P < .001$) and reduced the risk of death by 32% in comparison with MP.[24] Grade 3-4 peripheral neuropathy was 13%.

BMP plus thalidomide followed by bortezomib-thalidomide maintenance (BMPT-BT) was compared with BMP alone. BMPT-BT significantly increased the CR rate (38% vs 24%; $P < .001$) and prolonged the 3-year PFS (56% vs 41%; $P = .008$), but the 3-year OS was similar (89% vs 87%; $P = .77$).[11] The median PFS for BMPT-BT was 37.2 months. Thalidomide did not increase the hematologic toxicity of BMP, and the weekly dose of bortezomib plus 50 mg/d thalidomide did not increase the risk of grade 3-4 peripheral neuropathy (4%). In another study BTP versus BMP inductions were followed by BT or bortezomib-prednisone (BP) maintenance. From start of maintenance, the median PFS was

Table 2. Safety of selected regimens

Regimen	Grade 3-4 hematologic toxicities			Grade 3-4 nonhematologic toxicities			
	Neutropenia, %	Thrombocytopenia, %	Anemia, %	Thromboembolism, %	Neuropathy, %	Infection, %	Second primary cancer, %
Stem cell transplantation							
BD[17]	5	2.9	4.2	1.7	7.1	8.8	
PAD induction	3	10	8	4	24	26	
B maintenance[18]	0	4	1	1	5	24	
PAD induction	10	17	3	5	16	17	
LP consolidation							
L maintenance[19]	16	6	0	2	1	9	
BCD induction[20]	13	25	12	7	7		
BTD induction				3	10	3	
BTD consolidation[21]				0.6	0.6	1.2	
BTD PACE induction				11	14		
BTD PACE consolidation[22]				6	10		
Drug combinations							
MPT induction	17-43 (any hematologic toxicity)			2-6	1-6	4-20	
BMP induction[24]	40	37	19	1	13	10	6*
BMPT induction	38	22	10	5	8	13	
BT maintenance[11]	2.6	0.6	0	2	5.3	1.3	
BLD induction[25]	9	6	2	4.5	7.5	2	
LD induction[12]	12	6	8	26	2	16	
Ld induction[12]	20	5	7	12	2	9	
MPL induction	35†	11†	3†	3	0	11	7‡
L maintenance[13]	7†	6†	4†	2	0	3	
CLd induction[26]	12	10	18	10	0	6	
Maintenance regimens after stem cell transplantation							
L maintenance[27]	51	14	3	3	1	8	8.5§
L maintenance[28]	45	14	5				7.8§
Maintenance regimens after drug combinations							
BT maintenance[29]	0	0	0	1	7	2	
BP maintenance[29]	0	0	0	0	2	2	

Abbreviations are explained in Table 1.
*Incidence in the BMP arm at 5 years.
†Grade 4 only.
‡Incidence in the whole MPL-L arm at 3 years.
§Incidence in the lenalidomide arm at 3 years.

32 months for patients receiving BT and 24 months for those receiving BP ($P = .1$).[29]

In a randomized phase 2 study, bortezomib-lenalidomide-dexamethasone (BLD), bortezomib-cyclophosphamide-dexamethasone (BCD) or bortezomib-cyclophosphamide-lenalidomide-dexamethasone (BCLD) was tested. The regimens were equally effective; CR rate was 24% with BLD, 22% with BCD, and 25% with BCLD, and the corresponding 1-year PFS was 83%, 93%, and 86%, respectively. BCLD increased the frequency of hematologic toxicities and the discontinuation rate (21%); the excessive toxicities did probably reduce the efficacy of the 4-drug combination.[37] In another study, BLD induced 100% at least PR, including 37% of CRs; the 1.5-year PFS rate was 75% and the 1.5-year OS rate was 97%; the frequency of grade 3-4 neuropathy was 3%.[25]

MPL-L prolonged the median PFS of 17 months in comparison with MPL and MP alone (31 vs 14 vs 13 months; $P < .001$).[13] The 3-year OS was similar (70% vs 62% vs 66%). The most common adverse events were hematologic, with grade 4 neutropenia reported in 35% and 32% patients in the MPL-L and MPL groups, respectively. The 3-year rate of second primary cancers was 7% with MPL-L.

The combination of the new proteasome inhibitor carfilzomib with lenalidomide and low-dose dexamethasone was effective and well tolerated. Responses were rapid, with 46 of 49 patients achieving PR after 1 cycle; after 4 cycles, the PR rate was 100%; after 12 cycles, the VGPR rate was 100%, including 79% CR/nCR. No overlapping toxicities were recorded, with no grade 3-4 peripheral neuropathy.[26]

In conclusion, MPT or BMP has improved median PFS of ~ 6-8 months in comparison with MP. The latest 3- or 4-drug combinations, and particularly maintenance therapy, have further prolonged PFS approximately by another 10-17 months. OS advantage will require longer follow-up to be clearly assessed. Drug combinations, including proteasome inhibitors and IMiDs, have led to at least PR of 100% and high rates of CRs (24%-38%). Maintenance therapy with bortezomib or lenalidomide induced a median PFS of ~ 31-37 months and 3-year OS of ~ 70%-89% (Figure 1C-D). Despite these improvements and the difficult comparison of studies conducted in patients younger than 65 years versus studies conducted in patients older than 65 years, ASCT still seems to add clinical value to current induction, consolidation, and maintenance regimens.

Comparison between stem cell transplantation and drug combination: available data

In a retrospective analysis, OS was evaluated in patients receiving lenalidomide-dexamethasone followed by ASCT or lenalidomide-dexamethasone as continuous treatment, the 3-year OS was 94% in

patients receiving early ASCT and 78% in those receiving lenalidomide-dexamethasone. Although this trial was not designed to assess early ASCT versus drug combination, OS with early ASCT appeared to be superior.[38] In a posthoc landmark analysis of 53 patients who received BLD induction at diagnosis, PFS was unchanged in patients treated with early ASCT or continuous treatment ($P = .38$).[25] In a retrospective analysis of 290 patients who received early versus delayed ASCT after IMiD-based initial therapy, the 4-year OS rate was 73% in both groups ($P = .03$).[39]

In the first prospective randomized trial, patients received Ld induction therapy and were then randomly assigned to tandem ASCT or MPL. After a median follow-up of 26 months, the CR rate was 25% for ASCT and 20% for MPL ($P = .49$). ASCT reduced the risk of progression by ~ 50% ($P < .001$). The 2-year PFS was 73% for ASCT and 54% for MPL. The 2-year OS was comparable in the 2 groups (90% vs 87%; $P = .19$).[40] In a similar study, 390 patients received Ld induction regimen and were then randomly assigned to receive tandem ASCT or cyclophosphamide-lenalidomide-dexamethasone, followed by lenalidomide maintenance therapy. Patient accrual was completed in May 2011, and preliminary data should be available soon (NCT01091831 at www.clinicaltrials.gov).

Two ongoing large studies are currently enrolling patients. The IFM/DFCI2009 study addresses the question of whether high-dose therapy and ASCT or conventional chemotherapy should be preferred. In this trial 1000 patients are receiving BLD induction and are then randomly assigned to continue BLD treatment or to receive ASCT plus BLD consolidation. Afterward, the role of fixed-duration maintenance therapy will be investigated, and patients will receive lenalidomide maintenance for 1 year (NCT01191060 and NCT01208662 at www.clinicaltrials.gov). The EMN02 study not only aims to compare ASCT with conventional chemotherapy, but it also investigates the role of second ASCT and the advantages associated with consolidation therapy after transplantation. In this study, 1500 patients are receiving BCD induction and are then randomly assigned to BMP or ASCT and further randomly assigned to receive consolidation or no consolidation with BLD. The benefits of maintenance therapy will be assessed as well, but, compared with the previous study, patients will receive lenalidomide maintenance until disease progression (NCT01208766 at www.clinicaltrials.gov).

Conclusions and future perspectives

The introduction of effective regimens, including bortezomib and IMiDs, has greatly improved the outcome observed with ASCT in young patients with MM. The achievement of CR is an independent predictor of prolonged PFS and OS. Despite the improvement reported with conventional chemotherapy plus IMiDs, ASCT remains a necessary component of therapy to attain CR and consequently superior PFS. The data from prospective trials performed so far suggest that the best available strategy to achieve high CR rates and to prolong their duration includes induction with 3-drug bortezomib-based combinations followed by ASCT and consolidation/maintenance with IMiDs. This sequential approach seems the most appropriate strategy to upgrade response and prolong survival. Longer follow-up is needed to evaluate whether the timing of ASCT is relevant for OS. Results from ongoing large collaborative studies that compare effective drug combinations with stem cell transplantation are awaited and will shed further light on this important clinical question.

Acknowledgments

The authors thank the editorial assistant Giorgio Schirripa.

Authorship

Contribution: A.P. and F.C. collected and analyzed the data and wrote the manuscript.

Conflict-of-interest disclosure: A.P. has received honoraria from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Millennium, Merck, and Onyx and has served on the advisory boards of Celgene and Janssen-Cilag. F.C. has received honoraria from Celgene, Janssen-Cilag, and Onyx and has served on the advisory committee of Celgene.

Correspondence: Antonio Palumbo, Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliera S. Giovanni Battista, Via Genova 3, 10126 Torino, Italy; e-mail: appalumbo@yahoo.com.

References

1. Altekruse SF, Kosary C, Krapcho M, Neyman N, Aminou R, Waldron W. *SEER Cancer Statistics Review, 1975-2007.* Bethesda, MD: National Cancer Institute; 2008. http://www.seercancer-gov/csr/1975_2008. Accessed April 14, 2012.
2. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood.* 2008;111(5): 2521-2526.
3. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood.* 2012;120(5):1067-1076.
4. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica.* 2007;92(10):1399-1406.
5. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood.* 2011;117(11):3025-3031.
6. Martinez-Lopez J, Blade J, Mateos MV, et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. *Blood.* 2011;118(3):529-534.
7. Paiva B, Martinez-Lopez J, Vidriales MB, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. *J Clin Oncol.* 2011;29(12):1627-1633.
8. Ladetto M, Pagliano G, Ferrero S, 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(12): 2077-2084.
9. Hoering A, Crowley J, Shaughnessy JD Jr, et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in total therapy protocols. *Blood.* 2009;114(7):1299-1305.
10. van Rhee F, Szymonifka J, Anaissie E, et al. Total Therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy. *Blood.* 2010; 116(8):1220-1227.
11. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol.* 2010;28(34):5101-5109.
12. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 2010;11(1):29-37.
13. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med.* 2012;366(19): 1759-1769.
14. Koreth J, Cutler CS, Djulbegovic B, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. *Biol Blood Marrow Transplant.* 2007;13(2):183-196.
15. Giralt S. Stem cell transplantation for multiple myeloma: current and future status. *Hematology Am Soc Hematol Educ Program.* 2011;2011:191-196.
16. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan

and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209-1218.

17. Harousseau JL, Attal M, Avet-Loiseau H, 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(30):4621-4629.
18. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al. HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, doxorubicin, dexamethasone (PAD) vs VAD followed by high-dose melphalan (HDM) and maintenance with bortezomib or thalidomide in patients with newly diagnosed multiple myeloma (MM) [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21): Abstract 40.
19. Palumbo A, Gay F, Falco P, et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *J Clin Oncol*. 2010;28(5):800-807.
20. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia*. 2009;23(7):1337-1341.
21. Cavo M, Tacchetti P, Patriarca F, 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(9758):2075-2085.
22. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol*. 2007;138(2):176-185.
23. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood*. 2011;118(5):1239-1247.
24. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010; 28(13):2259-2266.
25. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116(5):679-686.
26. Jakubowiak AJ, Dytfeld D, Jagannath S, et al. Final results of a frontline phase 1/2 study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in multiple myeloma (MM) [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2011;118(21):Abstract 631.
27. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; 366(19):1782-1791.
28. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19): 1770-1781.
29. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol*. 2010;11(10):934-941.
30. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica*. 2008;93(1):124-127.
31. Morgan GJ, Davies FE, Gregory WM, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood*. 2011;118(5):1231-1238.
32. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy following autologous hematopoietic stem-cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012; 120(1):9-19.
33. Barlogie B, Attal M, Crowley J, 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(7): 1209-1214.
34. Hahn-Ast C, von Lilienfeld-Toal M, van Heteren P, et al. Improved progression-free survival and overall survival with thalidomide maintenance therapy in multiple myeloma: a meta-analyis of randomized trials in 2274 patients [abstract]. *Haematologica*. 2010;95(2):Abstract 0942.
35. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012;119(1):7-15.
36. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006; 108(10):3289-3894.
37. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood*. 2012; 119(19):4375-4382.
38. Siegel DS, Jacobus S, Rajkumar SV, et al. Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21):Abstract 38.
39. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer*. 2012;118(6):1585-1592.
40. Palumbo A, Cavallo F, Hardan I, et al. A phase III study to compare melphalan, prednisone, lenalidomide (MPR) versus melphalan 200 mg/m2 and autologous transplantation (MEL200) in newly diagnosed multiple myeloma patients [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21):Abstract 3573.

2012 120: 4692-4698
doi:10.1182/blood-2012-05-423202 originally published online June 22, 2012

Have drug combinations supplanted stem cell transplantation in myeloma?

Antonio Palumbo and Federica Cavallo

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.