

Autologous stem cell transplantation for multiple myeloma: history and future

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Over the last decade, high-dose therapy supported by autologous stem cell transplantation (ASCT) has been the standard frontline therapy for younger patients with multiple myeloma (MM). But recently, the treatment strategy has been dramatically changed after the introduction of novel agents such as thalidomide, bortezomib and lenalidomide. These agents have been incorporated into induction therapies before ASCT and into consolidation and maintenance after ASCT, resulting in improvements in the complete remission (CR) rate with the prolongation of progression-free (PFS) and overall survival (OS). Now the best available strategy to achieve high CR rate and prolong PFS seems induction with three-drug bortezomib-based combinations followed by ASCT with bortezomib or immunomodulatory drugs-based consolidation, and lenalidomide maintenance. However, the best timing of ASCT in the era of novel agents represents an area of active debate and major interest. Currently several new agents are being developed, and more effective induction regimens using these agents with ASCT will upgrade responses and prolong PFS and OS in the near future.

Key words: multiple myeloma, autologous stem cell transplantation, thalidomide, bortezomib, lenalidomide

Introduction

The outcome of patients with multiple myeloma (MM) treated with conventional chemotherapy is poor¹⁾. However, the survival of patients with newly diagnosed MM, particularly those younger than 60 years, has significantly improved recently due to the introduction of high-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT)²⁾. The concept of HDT supported by ASCT for MM was developed in the 1980's^{3,4)}, and over the last decade has become the standard frontline therapy for younger patients with MM⁵⁾. About 20 to 50% of patients who received ASCT achieved complete response (CR); however, almost all patients eventually relapse with a median survival of 5 years.

More recently, novel agents such as thalidomide, bortezomib, and lenalidomide have been introduced into the clinical setting and have markedly changed the management of MM⁶⁾.

These agents have been incorporated into induction therapies before ASCT and into consolidation and maintenance after ASCT, resulting in improvements in the CR rate with the prolongation of progression-free (PFS) and overall survival (OS). The use of these novel agents in combination with dexamethasone and alkylating agents is producing CR and PFS rates that are comparable to those achieved with HDT. In this review, the history and role of ASCT in the era of novel agents have been discussed.

History of ASCT

The beginning of modern chemotherapy for MM was initiated by the introduction of melphalan in 1958 (Figure 1). Another important step was the introduction of steroids. The combination of melphalan with prednisolone became the standard care for patients with MM for nearly 30 years.

Changes in treatment standards began when HDT in MM was reported by McElwain and Powles in 1983³⁾. They demonstrated that a single infusion of high-dose melphalan could induce CR in patients with high-risk diseases, and this dose-response effect of melphalan was later confirmed in a larger study⁴⁾. To overcome the prolonged myelosuppression induced by high-dose melphalan, systematic autologous stem cell support, which was initially explored in a relapse setting, but

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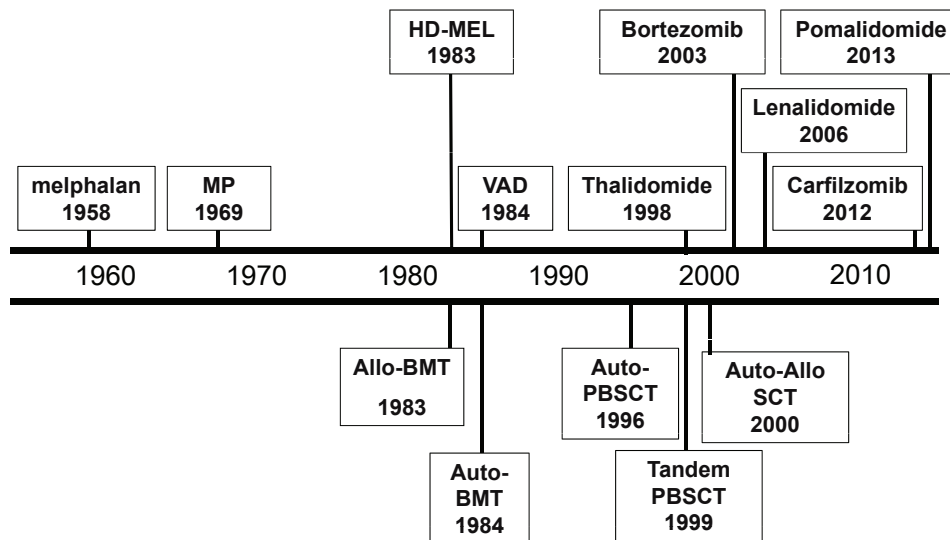


Figure 1. Timeline depicting the treatment of multiple myeloma from 1958 to the present day. MP: melphalan/prednisolone, HD-MEL: high-dose melphalan, VAD: vincristine/doxorubicin/dexamethasone, BMT: bone marrow transplantation, PBSCT: peripheral blood stem cell transplantation, SCT: stem cell transplantation.

was recently introduced in an upfront setting, was proposed by Barlogie et al.^{7,8)}. In the 1990's, peripheral blood stem cell transplantation (PBSCT) was introduced and was shown to be superior to bone marrow transplantation in terms of hematopoietic recovery, which suggests that peripheral blood is a recommended source of ASCT in MM. With a single HDT followed by ASCT, 20–50% patients achieved CR; however, almost all patients eventually relapsed. To decrease the risk of relapse after ASCT, the feasibility and efficacy of purging methods aimed at providing a tumor-free source of hematopoietic stem cells were investigated in a prospective randomized trial. Although approximately 3 logs of reduction in the number of myeloma cells contaminating the graft was reported, purged autologous stem cell transplantation (SCT) did not improve the OS over that produced by unpurged SCT⁹⁾.

In 1999, the Arkansas group first reported the concept of double intensification therapy for newly diagnosed MM, and prospective randomized trials comparing double versus single HDT have subsequently been investigated¹⁰⁾.

Single ASCT versus conventional chemotherapy

The first prospective randomized trial comparing HDT with conventional chemotherapy (CC) was conducted by Inter-groupe Francophone du Myelome (IFM)¹¹⁾ (Table 1). They demonstrated the superiority of HDT with ASCT over that of CC in 200 patients aged less than 65 years old (IFM 90 trial). In this trial, HDT significantly improved the response rate, event-free survival (EFS), and OS. These results were confirmed 7 years later by the British group in a larger cohort involving 407 patients (MRCVII trial)¹²⁾. Based on these two trials, ASCT

become the standard care for frontline therapy in patients aged less than 65 years old. Thus far, six randomized trials comparing HDT followed by ASCT with CC have been published^{11–16)}; however, the results across these studies have not been consistent. In four of the five studies^{11–14,16)}, the CR rate was superior in the HDT arm, and in four of the six studies^{11,12,14,15)}, this superior CR rate translated into a significant benefit in terms of EFS. However, OS was significantly improved in only three of the six trials^{11,12,14)}. A systematic review and meta-analysis of randomized trials, including 2411 patients, of ASCT versus CC showed a significant longer PFS in favor of ASCT, with no significant impact on OS, which may have been due to salvage ASCT at the time of relapse in the CC arm¹⁷⁾. This suggests the benefit of delayed ASCT at the time of relapse^{16,18)}. One randomized trial comparing early versus delayed ASCT demonstrated an equivalent OS, but early ASCT was associated with longer EFS and better quality of life¹⁹⁾.

Tandem (double) transplantation

Tandem stem cell transplantation refers to a planned second course of HDT and SCT within six months of the first. The concept of this approach in newly diagnosed patients was first investigated by the Arkansas group and was found to yield encouraging results, with median EFS and OS of 43 and 68 months, respectively¹⁰⁾. The IFM was the first to conduct a randomized trial comparing single versus double ASCT in 399 patients up to 60 years of age (IFM94 trial)²⁰⁾ (Table 2). On an intention-to-treat analysis, the 7-year EFS and OS were significantly improved in the double ASCT arm. The benefit

Table 1 Conventional chemotherapy versus high-dose therapy for multiple myeloma

Study Author	No. of patients	Age (years)	CR (%)		P value	EFS (months)		P value	OS (months)	
			CC vs HDT			CC vs HDT			CC vs HDT	P value
IFM90 Attal	200	< 65	5 vs 22		< 0.001	10 vs 28 (5-year)		0.01	12 vs 52 (5-year)	0.03
PETHEMA Blade	164	< 65	11 vs 30		0.002	33 vs 42		NS	66 vs 61	NS
Italian MMSG Palumbo	195	50–70	6 vs 25 (nCR)		0.000	15.6 vs 28		< 0.0001	42 vs 58+	< 0.0001
MRCVII Child	407	< 65	8 vs 44		< 0.001	20 vs 32		< 0.01	42 vs 54	0.04
MAG95 Ferland	190	55–65	20 vs 36		nr	19 vs 25		0.07	48 vs 48	NS
US S9321 Barlogie	516	≤ 70	15 vs 17		NS	14% vs 17% (7-year)		NS	38% vs 38% (7-year)	NS

CC: conventional chemotherapy, HDT: high-dose therapy, CR: complete response, EFS: event-free survival, OS: overall survival, nr: not reported, NS: not significant

Table 2 Single versus tandem ASCT for multiple myeloma

Study Author	No. of patients	CR (%)		P value	EFS (months)		P value	OS (months)	
		single vs tandem			single vs tandem			single vs tandem	P value
IFM94 Attal	399	42 vs 50		0.1	25 vs 30		0.03	48 vs 58	0.01
MAG95 Ferland	227	39 vs 37		NS	31 vs 33		NS	49 vs 73	0.14
Bologna96 Cavo	321	33 vs 47 (CR + nCR)		0.008	23 vs 35		0.001	65 vs 71	NS
GMMG Goldschmidt	261	nr		nr	23 vs not reached		0.03	nr	nr
HOVON 24 Sonneveld	303	13 vs 28		0.002	20 vs 22		0.01	55 vs 50	NS

ASCT: autologous stem cell transplantation, CR: complete response, EFS: event-free survival, OS: overall survival, nr: not reported, NS: not significant

of EFS, but not OS, was confirmed by two other randomized trials^{21,22}. A meta-analysis of data pooled from controlled clinical trials (one of which was retracted), including 1803 patients, failed to show superior OS with tandem ASCT, which was associated with an improved response rate²³. The feasibility of double ASCT was good because 75% of patients underwent the second ASCT, with a toxic death rate of less than 5%. In both the IFM94 and Bologna 96 trials, the benefit of survival of tandem ASCT was only observed among patients failing to achieve CR or very good partial response (VGPR) after the first transplantation^{20,21}. On the other hand, patients who already achieved VGPR after the first transplant did not significantly benefit from a second ASCT. However, these two studies were not adequately powered to evaluate the equivalence on one versus two transplants in patients achieving CR or VGPR after

the first ASCT. The NCCN guidelines (2013, ver. 1) recommended collecting enough stem cells for two transplants in all transplant-eligible patients, and that a second ASCT could be considered in patients achieving less than VGPR after the first HDT²⁴. The role of single versus tandem ASCT is currently being explored in a prospective randomized trial conducted by the Bone Marrow Transplant Clinical Trials Network (BMT/CTN0702 trial) (Figure 2).

Pre-transplant conditioning regimen

High-dose melphalan 200 mg/m² (Mel200) is considered to be the standard preconditioning regimen for ASCT in MM. A prospective randomized trial comparing Mel200 versus melphalan 140 mg/m² (Mel140) plus 8Gy of total body irradiation

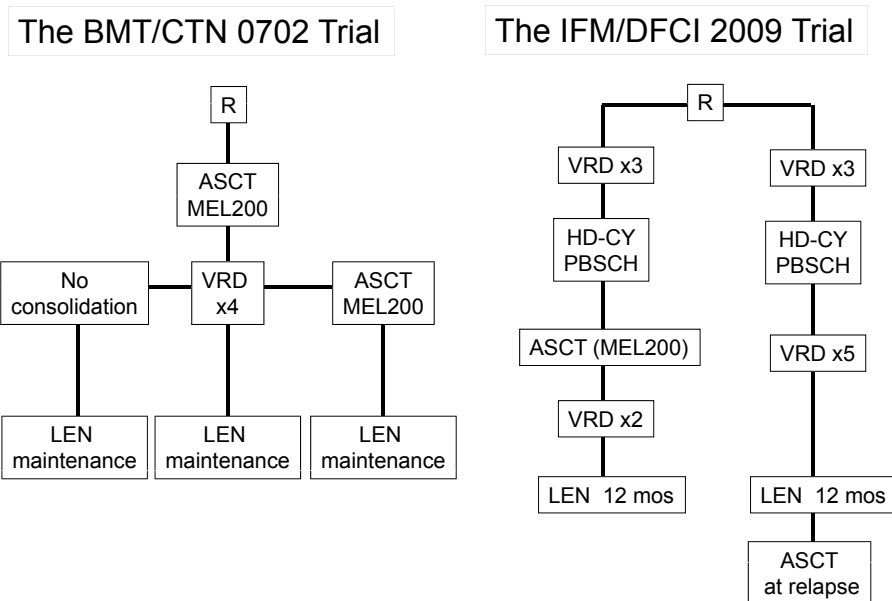


Figure 2. Ongoing prospective randomized trials comparing early versus late ASCT. The BMT/CTN 0702 trial (left) and IFM/Dana-Farber Cancer Institute [DFCI] 2009 trial (right). R: randomization, VRD: bortezomib/lenalidomide/dexamethasone, LEN: lenalidomide, HD-CY: high-dose cyclophosphamide, PBSCH: peripheral blood stem cell harvest, ASCT: autologous stem cell transplantation

(TBI) showed that Mel200 was at least as effective and better tolerated than the regimen containing TBI²⁵⁾ (IFM9502 trial). Although EFS was identical in both groups, OS was significantly longer with Mel200 as a result of a longer OS after the first relapse. Although higher doses of melphalan have been tested, no randomized trials have been conducted. In the PETHEMA/GEM2000 trial, the first 225 patients receiving the combination of oral busulfan 12 mg/kg plus melphalan 140 mg/m² (BuMel) were retrospectively compared with the subsequent 542 patients receiving Mel200 as a preconditioning regimen for ASCT. They demonstrated that transplant-related mortality was significantly increased in the BuMel group due to the increased incidence of veno-occlusive disease. Although the median PFS was significantly longer in the BuMel group, OS was similar in both groups²⁶⁾.

Thus far, no randomized trial has shown the superiority of any other conditioning regimen over that of Mel200.

Impact of CR after ASCT

The achievement of CR is a crucial step in obtaining long-lasting disease control and prolonged survival in MM^{27,28)}. In the IFM90 trial, patients achieving CR or at least VGPR had a longer OS than patients who only achieved partial response (PR). Moreover, patients who achieved immunofixation (IFE)-negative CR after ASCT had significantly longer PFS and OS than those who remained in near CR (nCR; negative electrophoresis but positive IFE) or VGPR²⁹⁾. A review of retrospective and prospective studies on almost 5000 patients treated with

HDT indicated a highly significant association between the maximal response and long-term outcomes³⁰⁾. Recently, the Spanish PETHEMA group has shown that the achievement of a negative minimal residual disease (MRD) by multicolor flow cytometry (MFC) is a stronger predictor of EFS and OS than that of IFE-negative CR^{31,32)}, while the Italian group showed that 18% of patients in at least VGPR after ASCT achieved molecular remission by qualitative and quantitative polymerase chain reactions with intensification therapy using VTD (bortezomib, thalidomide, and dexamethasone). After a median follow-up of 27 months, no patient in molecular remission had relapsed³³⁾. In addition, sustained CR has been reported to be predictive of long-term survival³⁴⁾. These observations suggest that the goal of myeloma therapy exists in the achievement of deeper and sustained responses, and that more refined and sensitive response criteria for MM, including not only negative IFE, but also MFC and molecular CR, is needed³⁵⁾.

Prognostic factors in the context of ASCT

Despite major improvements in the survival of patients treated with HDT, significant variability has been observed in the outcomes achieved. Many factors have been reported as being responsible for the lack of the efficacy of HDT. Most of these factors are linked to the biology of myeloma cells.

The International Staging System (ISS), which is based on the β 2-microglobulin (β 2M) and albumin levels, can predict outcomes well after either conventional or HDT³⁶⁾. Restricted to patients treated with HDT, the OS was 111 months, 66

months, and 45 months, respectively for patients with stage 1, 2, or 3.

Cytogenetic abnormalities are the most important prognostic factors in MM. With conventional cytogenetics, hypodiploidy and del(13) have been shown to be negative prognostic factors with HDT³⁷. FISH analysis showed that t(4;14), del(17p) and t(14;16) were also poor prognostic factors³⁸. The negative prognostic factor del(13), as detected by FISH, may be associated with a poor outcome only when associated with t(4;14) or del(17p)³⁸.

One of the other factors related with poor outcomes is the proliferative index. However, this laboratory parameter is not always available or routinely evaluated.

Introduction of novel agents

The introduction of novel agents such as thalidomide, bortezomib, and lenalidomide has markedly changed the management of MM. These agents have been incorporated into induction therapies before ASCT, and into consolidation and maintenance treatments after ASCT.

Induction regimens using novel agents

Until recently, the combination of vincristine, doxorubicin, and dexamethasone (VAD) was the standard induction regimen before ASCT, but now its use has ceased.

Thalidomide was the first novel agent to be compared with VAD or dexamethasone, in combination with dexamethasone (TD) or with doxorubicin plus dexamethasone (TAD)³⁹⁻⁴¹ (Table 3). Although TD or TAD were superior to VAD in terms of overall response or the VGPR rate, the CR rate was low at less than 10%^{40,41}. Post-ASCT results were analyzed in two trials; although the VGPR rates with TD and VAD were similar³⁹, they were better with TAD than with VAD⁴¹. In conclusion, the benefits of TD or TAD over VAD remained modest. Recently, another combination of thalidomide with cyclophosphamide and dexamethasone (CTD) has been reported from the MRC IX trial, in which CTD was shown to have a higher CR rate than that of VAD both before (13%) and after (50%) ASCT⁴².

The second novel agent that became available was the proteasome inhibitor bortezomib (Table 3). In the IFM2005-01 trial, 482 patients were randomly assigned to receive bortezomib/dexamethasone (BD) or VAD as induction therapy⁴³. Patients were then randomized to receive consolidation therapy consisting of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) or not, followed by ASCT. Patients not achieving VGPR underwent a second transplantation. After induction therapy, the rates of CR/nCR, at least VGPR, and overall response were significantly higher with BD than with

VAD. CR/nCR and at least the VGPR rates were higher regardless of the disease stage or adverse cytogenetic abnormalities, and response rates were similar in patients who did or did not receive DCEP consolidation. These superior response rates in the BD induction arms translated into better response rates after HDT. At a median follow-up of 32.2 months, median PFS was modestly, but not significantly prolonged; 36 months versus 30 months with BD versus VAD.

Triple combination therapy including BD has been extensively tested in phase 3 studies. Three prospective randomized studies have shown that VTD (BD plus thalidomide) is superior to TD or BD⁴⁴⁻⁴⁶. The Italian group prospectively compared TD versus VTD in 474 patients with newly diagnosed MM before tandem ASCT and found that VTD was superior in terms of CR or at least the VGPR rate, which translated into better PFS after HDT (GIMEMA MMY-3006 trial)⁴⁴. The major toxicity of this trial using bortezomib and thalidomide was peripheral neuropathy (10% in grade 3-4). The Spanish group also compared TD versus VTD versus a more complex chemotherapy regimen before ASCT in 390 patients, using the higher number of six cycles of induction, and demonstrated that VTD was able to achieve the best pre- and post-ASCT CR rates (PETHEMA/GEM05MENS65 trial)⁴⁵. In the IFM2007-02 trial, four cycles of BD induction were compared with four cycles of a lower dose of VTD (bortezomib, 1 mg/m² instead of 1.3 mg/m², and thalidomide 100 mg/day instead of 200 mg/day as the Italian and Spanish trials) to reduce the rate of neuropathy⁴⁶. A total of 199 patients were enrolled and VTD was found to result in superior CR plus VGPR rates both before and after ASCT. A reduction in the rates of severe neuropathy was observed with the VTD arm with a grade 3 to 4 peripheral neuropathy of 3%.

In the HOVON-65/GMMG-HD4 trial, a combination of BD plus doxorubicin (PAD) was compared with VAD as induction therapy before ASCT⁴⁷. PAD had a superior CR/nCR rate over that of VAD after both induction (11% vs. 5%) and ASCT (30% vs. 15%). Other triple combination therapies included BCD (BD plus cyclophosphamide) or VRD (BD plus lenalidomide). A phase II trial of BCD demonstrated an overall response rate of 88%, including at least VGPR of 61% and CR/nCR of 39%⁴⁸. A phase I/II trial with VRD demonstrated that response rate was 100% with 67% at least VGPR and 39% CR/nCR rates⁴⁹. However, no results by prospective randomized trials are available yet.

A four-drug combination has been tested in phase 2 randomized trials. One study comparing VTD plus cyclophosphamide (VTDC) with VTD has demonstrated that both regimens were highly active induction regimens producing high CR/nCR and MRD-negative rates with a 3-year OS rate of 80% (both arms)⁵⁰. However, VTDC was associated with increased toxicity and transient decreases in the Global Health score, without an

Table 3 Novel agent-based induction regimen for transplant-eligible patients

Study Author	Regimen	No. of patients	Postinduction		P value	Post-Transplantation		P value	PFS (month)	P value
			CR (%)	≥ VGPR (%)		CR (%)	≥ VGPR (%)			
IFM2005-01 Harrousseau	BD	240	15	38	< 0.001	35	54	< 0.001	36	0.064
	VAD	242	6 (+ nCR)	15		18 (+ nCR)	37		30	
HOVON-65/ GMMG-HD4 Sonneveld	PAD	371	7	42	< 0.001	21	62	< 0.001	35%	0%
	VAD	373	2	14		9	36		28%	
GIMEMA MMY-3006 Cavo	VTD	236	19	62	< 0.0001	42	82	< 0.0001	68%	0.0057
	TD	238	5	28		30	64		56% (3y-PFS)	
PETHEMA/ GEM05MEN0S65 Rosinol	VTD	130	35	60	0.001 (CR)	46	nr	0.004	56	0.01
	TD	127	14	29		24	nr		28	
IFM2007-02 Moreau	vtD	100	13	49	0.05	31	74	0.02	26	NS
	BD	99	12	36		29	58		30	
SWOG S0232 Zonder	LD	97	–	63	< 0.01	–	–	–	–	–
	D	95	–	16		–	–		–	
ECOG E4A03 Rajkumar	LD	223	5	50	0.04	–	–	–	–	–
	Ld	222	4	40		–	–		–	
MAG Macro	TD	100	–	25	0.0027	–	44	NS	–	–
	VAD	104	–	7		–	42		–	
HOVON50 Lokhorst	TAD	268	3	37	< 0.001	14	54	0.03	34	< 0.001
	VAD	268	2	18		12	44		25	
MRCIX Morgan	CTD	553	13	43	0.00083 (CR)	50	74	0.00052 (CR)	27	NS
	CVAD	540	8	27		37	62		25	
Ludwig	VTD	49	31	69	NS	76	89	NS	25	NS
	VTDC	48	35	67		70	82		24	
Reeder	BCD	33	39 (+nCR)	61	–	70 (+nCR)	74	–	nr	–
Richardson	VRD	66	29	67	–	nr	nr	–	nr	–

CR: complete response, VGPR: very good partial response, PFS: progression-free survival, OS: overall survival, nr: not reported, NS: not significant
BD: bortezomib/dexamethasone, VAD: vincristine/doxorubicin/dexamethasone, PAD: bortezomib/doxorubicin/dexamethasone, VTD: bortezomib/thalidomide/dexamethasone, TD: thalidomide/dexamethasone, LD: lenalidomide/high-dose dexamethasone, D: dexamethasone, Ld: lenalidomide/low-dose dexamethasone, TAD: thalidomide/doxorubicin/dexamethasone, CTD: cyclophosphamide/thalidomide/dexamethasone, CVAD: cyclophosphamide/vincristine/doxorubicin/dexamethasone, VTDC: bortezomib/thalidomide/cyclophosphamide/dexamethasone, BCD: bortezomib/cyclophosphamide/dexamethasone, VRD: bortezomib/lenalidomide/dexamethasone

increase in activity. In another trial, VRD or BCD, or VRD plus cyclophosphamide (VRDC) were tested⁵¹. The regimens were equally effective: the CR rate was 24% with VRD, 22% with BCD, and 25% with VRDC, and the corresponding 1-year PFS were 83%, 93%, and 86%, respectively.

The third novel agent was a lenalidomide; an analog of tha-

lidomide (Table 3). A randomized trial comparing lenalidomide plus high-dose dexamethasone (40mg/day on days 1–4, 9–12, and 17–20 of a 28-day cycle) (LD) versus lenalidomide plus low-dose dexamethasone (40 mg/day, on days 1, 8, 15, and 22 of a 28 day-cycle) (Ld) in 445 newly diagnosed myeloma patients demonstrated that Ld was associated with better

short-term OS and lower toxicity (ECOG E4A03 trial)⁵².

Based on these observations, the NCCN guidelines (version 1, 2013) recommended BD, VTD, PAD, and Ld as a Category 1 induction regimen for younger myeloma patients eligible for ASCT²⁴. However, no data were available to draw conclusions regarding the superiority of one combination over the other. Currently, randomized trial comparing PAD with BCD is ongoing (GMMG-MM5 trial).

Effect of novel agents on the peripheral blood stem cell harvest

Recently, novel agents have been integrated as a first-line treatment; however, there is concern about their safety regarding the ability to collect sufficient numbers of stem cells from the peripheral blood. Several studies have suggested that lenalidomide markedly decreases the number of stem cells collected^{53,54}. Kumar et al. reported that among those mobilized with granulocyte colony-stimulating factor (G-CSF) alone, the total number of CD34⁺ cells collected, average daily collection, and day 1 collection were significantly lower and the amount of apheresis was higher in patients treated with lenalidomide than those receiving dexamethasone, TD, or VAD⁵⁴. A trend was seen towards a decreasing PBSC yield with an increasing duration of lenalidomide therapy as well as increasing age. They recommended the collection of PBSC within 6 months of the initiation of therapy with lenalidomide to minimize the risk of mobilization failure⁵⁴. However, stem cells were mobilized with cyclophosphamide and G-CSF in a prospective study that included 346 newly diagnosed patients who received four cycles of Ld as induction⁵⁵. Patients failing to collect a minimum of 4×10^6 CD34⁺ cells/kg received a second mobilization course. After mobilization, a median yield of 8.7×10^6 CD34⁺ cells/kg was obtained from patients receiving the Ld induction⁵⁵. These results show that a short induction with lenalidomide allowed the sufficient collection of stem cells for autologous transplantation in most newly diagnosed patients when mobilized with cyclophosphamide plus G-CSF.

While there are contradictory findings on the impact of thalidomide on stem cell mobilization and collection, the effect, if any, appears to be relatively small with a limited impact on the ability to proceed with SCT⁵³.

The effect of bortezomib on the ability to collect PBSC has also been examined in the context of clinical trials. In a randomized trial, there was slightly lower stem cell number in patients who received BD; median yield was 6.8×10^6 CD34⁺ cells/kg in the bortezomib group versus 8.5×10^6 CD34⁺ cells/kg in the control group receiving VAD⁵⁶. In another randomized trial, PAD did not have any negative impact, and the median yield of stem cells harvested was 10.48×10^6 CD34⁺ cells/kg⁵⁷.

Conditioning regimen containing novel agents

As previously described, Mel200 is a standard preconditioning regimen for ASCT. The addition of bortezomib with Mel200 has recently been studied because bortezomib was shown to have synergistic effects with melphalan. The IFM group reported a phase 2 study involving 54 newly diagnosed patients who received the combination of bortezomib ($1 \text{ mg/m}^2 \times 4$) with Mel200 as a conditioning regimen (BorMel)⁵⁸. Overall, 70% of patients achieved at least VGPR, including 17 patients with CR (34%). No toxic death was observed, and bortezomib did not increase the hematological toxicity. A matched control analysis comparing this cohort with patients from the IFM2005-01 trial (Mel200 alone) demonstrated that the CR rate was higher in the BorMel group (35% vs. 11%) regardless of the induction therapy. This observation suggests that BorMel is a safe and promising regimen. Similar results were reported in a phase I/II study involving 39 patients⁵⁹. A prospective randomized study is required to evaluate the role of the BorMel conditioning regimen.

Post-transplantation consolidation with novel agents

Recently, novel agents are being tested soon after ASCT to further improve the quantity and quality of responses. Ladetto et al. treated 39 patients who achieved at least VGPR after ASCT and who had an available molecular marker based on the immunoglobulin heavy chain rearrangement with VTD³³. Responses were assessed by qualitative nested polymerase chain reaction (PCR) and real-time quantitative PCR (RQ-PCR) using tumor-clone-specific primers. IFE-negative CR increased from 15% after ASCT to 49% after VTD, and molecular remissions increased from 3% after ASCT to 18% after VTD. With a median follow-up of 42 months after consolidation, no patient in molecular remission has relapsed. VTD consolidation induced the additional depletion of 4.14 natural logarithms of tumor burden by RQ-PCR. Patients with a tumor load less than the median value after VTD had better outcomes than those who had tumor loads above the median value after VTD. Recently, the efficacy and safety of consolidation with VTD or TD was assessed using a per-protocol analysis of the data from the GIMEMA MMY-3006 trial, which compared VTD versus TD as induction therapy before, and consolidation after, double ASCT for newly diagnosed myeloma patients⁶⁰. Before starting consolidation, CR/nCR rate was not significantly different in the VTD (63.1%) and TD arms (54.7%). After consolidation, CR/nCR (73.1% vs 60.9%) rate was significantly higher for VTD treated versus TD-treated patients. VTD consolidation significantly increased CR and CR/nCR rates, but TD did not.

Single-agent bortezomib has been tested as a consolidation

Table 4 Maintenance therapy with novel agents

Study Author	Regimen	No. of patients	CR (%)	P value	EFS or PFS (%)	P value	OS (%)	P value
			W vs WO		W vs WO		W vs WO	
IFM9902 Attal	thalidomide + pamidronate none or pamidronate	597	67 vs 55	0.03	52 vs 36 (3-year)	0.002	87 vs 77 (4-year)	0.04
TT2 Barlogie	thalidomide none	668	62 vs 43	< 0.001	56 vs 44 (5-year)	0.01	57 vs 44 (8-year)	0.09
ALLG MM6 Spencer	thalidomide + PSL PSL	269	63 vs 40	< 0.001	42 vs 23 (3-year)	< 0.001	86 vs 75 (3-year)	0.004
HOVON50 Lokhortst	thalidomide interferon	556	66 vs 54	0.005	34 vs 25 (months)	< 0.001	73 vs 60 (months)	0.77
MRCIX Morgan	thalidomide none	493	nr	nr	30 vs 27 (months)	0.003	75 vs 80 (3-year)	0.26
NCIC CTG MY10 Stewart	thalidomide + PSL none	332	nr	nr	32 vs 14 (4-year)	< 0.0001	68 vs 60 (4-year)	NS
IFM2005-02 Attal	lenalidomide none	614	84 vs 76 (≥ VGPR)	0.009	43 vs 22 (4-year)	< 0.001	73 vs 75 (4-year)	NS
CALGB10040 McCarthy	lenalidomide none	460	nr	nr	66 vs 39 (3-year)	< 0.001	88 vs 80 (3-year)	0.03

W: with maintenance, WO: without maintenance, CR: complete response, EFS: event-free survival, PFS: progression-free survival, OS: overall survival, nr: not reported, NS: not significant

treatment after ASCT in a phase III trial conducted by the Nordic Myeloma Group⁶¹. A total of 392 patients were randomly assigned after ASCT to receive no treatment or bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 for two 3-week cycles, and then again on days 1, 8, and 15 for four 4-week cycles. The median number of bortezomib infusions was 19 and toxicity was low, with 3% grade 3 to 4 neuropathy related to the consolidation phase. The response after ASCT was improved, and the 6-month post randomization CR/nCR rate was 35% in the observation arm versus 54% in the bortezomib arm ($P < .005$).

These observations suggest that consolidation therapy may enhance responses after ASCT; however, no data regarding PFS and OS are available yet. Trials studying the impact of novel agent-containing consolidation regimens after ASCT are currently ongoing. In the BMT/CTN0702 trial, patients aged less than 70 years old who receive ASCT will be randomly assigned to receive Mel200 (tandem ASCT), or four courses of VRD or no consolidation, followed by lenalidomide maintenance (Figure 2). Another important international, prospective trial, which has been designed to assess the VRD regimen in combination with or without ASCT (the IFM/Dana-Farber Cancer Institute [DFCI] 2009 trial), will also examine the impact of two cycles of RVD given as consolidation after ASCT.

Maintenance therapy

Maintenance treatment is given for a prolonged time period with the goal of extending the duration of the response, PFS, and OS, while maintaining a good quality of life. Thus far, several trials tested chemotherapy as maintenance treatment without any positive results, and preliminary findings regarding the efficacy of interferon alpha as maintenance could not be confirmed¹⁶.

The availability of novel agents has renewed the concept of maintenance. The first novel agent tested was thalidomide. Six randomized studies have been reported on thalidomide maintenance^{41,62-67} (Table 4). The IFM 9902 trial was the first to show that thalidomide as maintenance after tandem ASCT was superior to no maintenance or pamidronate alone⁶². Thalidomide increased the CR + VGPR rate (67% vs. 55%), the 3-year PFS (52% vs. 36%), and the 4-year OS (87% vs. 77%). The Australian group obtained similar results⁶³. In the Total Therapy 2 trial, the Arkansas group initially reported that the CR rate and 5-year PFS were significantly better in the thalidomide arm, but there was no improvement in OS⁶⁴. However, in an updated analysis, with a median follow-up of 72 months, prolonged OS was confirmed in a subgroup of patients with poor-risk cytogenetics⁶⁵. In all 6 trials, a significant benefit was observed in terms of PFS with thalidomide maintenance, whereas OS was improved in 2 of 6 trials. In addition, in the

IFM trial, only patients who failed to achieve at least VGPR had significantly longer PFS in the thalidomide arm, indicating that thalidomide may further reduce the tumor mass after HDT, consistent with a consolidation rather than a maintenance effect⁶². The shorter OS duration observed in several studies appears to be a result of a shorter survival time after relapse, which may be caused by the duration of the maintenance treatment, possible selection of more resistant clones, and the availability of effective salvage treatments. One major concern with thalidomide maintenance is cumulative toxicity such as peripheral neuropathy (PN). The PN observed with thalidomide is related to the duration of the treatment and is cumulative. In the IFM99-02 trial, patients received thalidomide for a median duration of 15 months and the PN observed in 68% of these cases (7% in grade 3 to 4) was the main reason for the discontinuation of treatment⁶². In the Australian trial, thalidomide was planned to be administered for 12 months, and the most common reason for the withdrawal of thalidomide was PN, which occurred in 52% of patients (10% in grade 3 to 4)⁶³. Recently, Stewart et al. reported that maintenance therapy with thalidomide plus prednisolone following ASCT was associated with deteriorations in the patient-reported health-related quality of life⁶⁷. Future studies should be aimed at identifying patients who may benefit from thalidomide maintenance and establishing the appropriate dose and optimal duration of therapy.

The more favorable toxicity profile of lenalidomide makes it an ideal agent for maintenance therapy. Two prospective randomized trials have been reported^{68,69}. In the CALGB 100104 trial, 460 patients who had stable disease or a marginal, partial, or complete response 100 days after ASCT, were randomly assigned to receive lenalidomide or placebo, which was administered until disease progression⁶⁸. The starting dose of lenalidomide was 10 mg per day. The median time to progression was 46 months in the lenalidomide group and 27 months in the placebo group ($P < 0.001$). The OS at 3 years was 88% and 80% among patients in the lenalidomide and placebo groups, respectively ($P = 0.03$). OS was significantly increased with lenalidomide maintenance therapy despite a crossover to lenalidomide by some of the placebo patients after unblinding of the study in January 2010. More grade 3 or 4 hematologic adverse events and grade 3 non-hematologic adverse events occurred in the lenalidomide arm. Second primary cancers occurred in 18 patients who received lenalidomide (8%) and 6 patients who received placebo (3%). In the IFM2005-02 trial, 614 patients who had non-progressive disease after ASCT were treated with 2 cycles of lenalidomide consolidation and were randomized to either lenalidomide maintenance or placebo until relapse⁶⁹. Lenalidomide maintenance therapy improved the median PFS (41 months vs. 23

months with placebo; $P < 0.001$). This benefit was observed across all patient subgroups, including those based on the $\beta 2M$ level, cytogenetic profile, and response after transplantation. With a median follow-up period of 45 months, more than 70% of patients in both groups were alive at 4 years. The rates of grade 3 or 4 PN were similar in the two groups. The incidence of second primary cancers was 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group ($P = 0.002$). The median EFS (with events that included second primary cancers) was significantly improved with lenalidomide (40 months, vs. 23 months with placebo; $P < 0.001$).

Maintenance therapy with single agent bortezomib has been reported in patients who had already been exposed to bortezomib during induction therapy. In the HOVON-65/GMMG-HD4 trial, patients who were eligible for ASCT were randomly assigned to receive VAD or PAD before single ASCT⁴⁷. A two-year maintenance therapy was subsequently administered, which consisted of thalidomide for VAD patients and bortezomib (1.3 mg/m² twice a month) for PAD patients. The incorporation of bortezomib before ASCT was advantageous for the response rates, including a CR rate of 24% with VAD and 36% with PAD. After ASCT, bortezomib maintenance was tolerated better than thalidomide, with a lower rate of treatment discontinuation. Although a significant benefit of bortezomib maintenance therapy is likely, the design of the study allows only for the conclusion that the bortezomib-based induction regimen followed by ASCT and bortezomib maintenance was superior to VAD induction followed by ASCT with thalidomide maintenance therapy. Further studies are required to evaluate the role of bortezomib maintenance.

Future directions

The introduction of novel agents such as bortezomib and immunomodulatory drugs (IMiDs) has markedly improved the outcome of ASCT in young MM patients. The prospective randomized trials performed so far suggest that the best available strategy to achieve high CR rates and prolong PFS includes induction with 3-drug bortezomib-based combinations followed by ASCT with bortezomib or IMiDs-based consolidation, and lenalidomide-based maintenance. However, the best timing of ASCT in the era of novel agents represents an area of active debate and major interest. Unless the final results of ongoing clinical trials comparing early versus late ASCT plus novel agents become available, ASCT up-front should continue to be considered the preferred approach for a patient eligible to tolerate HDT (Figure 2). This sequential approach seems the most appropriate strategy to upgrade responses and prolong survival.

Recently, understanding of the biology of MM has markedly increased, and systematic cytogenetic evaluations in clinical trials have revealed critical adverse prognostic factors such as the 17p deletion. The Mayo Clinic group proposed the mSMART (Mayo Stratification for Myeloma and Risk-adapted therapy) algorithm, a consensus opinion taking into account genetically-defined risk statuses, including cytogenetics, gene expression profiling, and plasma cell labeling indices. This classification allows for the definition of three risk groups, high, intermediate and standard, which determines treatment approaches. However, no clinical evidence is available to justify a risk-adapted strategy. Further study is warranted to evaluate the usefulness of a risk-adapted approach.

Currently several novel agents including second generation proteasome inhibitors (carfilzomib, ixazomib, and oprozomib), pomalidomide, and monoclonal antibodies (elotuzumab and daratumumab) are being developed, and some of them have already been tested for their incorporation into induction therapy. More effective induction regimens with less toxicity in combination with ASCT will upgrade responses and prolong PFS and OS in the near future.

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