

## First line vs delayed transplantation in myeloma: Certainties and controversies

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### Abstract

Since the middle of 1990s autologous stem cell transplantation has been the cornerstone for the treatment

of young patients with multiple myeloma (MM). In the last decade the introduction of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PI), has dramatically changed the therapeutic scenario of this yet incurable disease. Due to the impressive results achieved with IMiDs and PI both in terms of response rates and in terms of progression free and overall survival, and to the toxicity linked to high dose therapy and autologous stem cell transplantation (ASCT), a burning question nowadays is whether all young patients should be offered autotransplantation up front or if this should be reserved for the time of relapse. This article provides a review of the data available regarding ASCT in MM and of the current opinion of the scientific community regarding its optimal timing.

**Key words:** Autologous stem cell transplantation; Immunomodulatory drugs; Proteasome inhibitors; High dose therapy; Multiple myeloma

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**Core tip:** Autologous stem cell transplantation (ASCT) is the cornerstone for the treatment of young multiple myeloma patients. This review summarizes the current knowledge on ASCT, with a special focus on the role of ASCT in the era of novel agents for multiple myeloma treatment.

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### INTRODUCTION

Multiple myeloma (MM) is the second most common

hematologic malignancy, accounting for approximately 13% of all blood neoplasm and for approximately 1% of all cancers. The number of new cases diagnosed every year is of approximately 86000 worldwide<sup>[1]</sup>. MM is mainly a disease of the aging population, however young individuals below 65 years of age can also be affected<sup>[1]</sup>.

Traditionally MM patients have been divided in two groups, based on their eligibility and fitness to receive high dose therapy (HDT) and autologous stem cell transplantation (ASCT). Fit patients, usually younger than 65-70 years of age, were offered HDT (with doses ranging from 200 to 100 mg/m<sup>2</sup> based on age and clinical conditions) and ASCT, while conventional treatment with lower doses of chemotherapy (mostly Melphalan) and steroids was given to elderly or unfit patients<sup>[2-9]</sup>.

In the last decade major advances in the management of MM have been made thanks to the introduction of novel agents such as immunomodulatory drugs [the immunomodulatory drugs (IMiDs), such as thalidomide, lenalidomide and pomalidomide] and proteasome inhibitors [the proteasome inhibitors (PI) bortezomib and carfilzomib]<sup>[10-15]</sup>. The introduction of these drugs as part of the frontline treatment in both transplant eligible and non-eligible patients translated into a markedly increased rate of complete remission (CR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS)<sup>[11,13,16-18]</sup>. In patients ineligible to ASCT, the addition of bortezomib to the conventional melphalan and prednisone (MP) treatment translated into a rate of CR of 30%, with an OS at 5 years of 56.4 mo<sup>[19,20]</sup>. These impressive results, comparable to the rate of CR and OS achieved with ASCT, have raised the question whether autologous transplant is nowadays still needed to treat MM patients or if it should be replaced by new drug containing regimens with or without chemotherapy. In this latter case ASCT would be used as a salvage treatment at the time of progression in patients initially treated with novel agents. This review will focus on the current role of ASCT for the treatment of MM patients.

## UP-FRONT TRANSPLANTATION

High dose melphalan supported by ASCT for the treatment of fit MM patients was first developed in the 1980s, and it has been considered the standard of care for this group of patients since the middle of 1990s<sup>[21,22]</sup>. The infusion of harvested and cryopreserved autologous stem cells, first introduced in the relapsed-refractory setting, proved to be able to reduce the prolonged myelosuppression caused by high doses of melphalan<sup>[23,24]</sup>. In consideration of the good results seen in this subset of patients, ASCT was translated in the newly diagnosed setting, and also in this group of patients HDT ASCT demonstrated its superiority in

comparison to conventional chemotherapy<sup>[4,5]</sup>. At present 7 randomised trials have compared ASCT with conventional chemotherapy, and results largely confirm the benefit of a transplant treatment approach (Table 1)<sup>[4,5,9,25-28]</sup>. The majority of the studies demonstrated that treatment with ASCT was associated with a longer PFS<sup>[4,5,9,25-27]</sup>; conversely, the benefit in terms of OS was less clear<sup>[4,5,9]</sup>. This finding can be partly explained by the fact that patients initially treated with only chemotherapy were later rescued with ASCT, thus providing a rationale for reserving ASCT at a later time point in patient's history<sup>[29]</sup>. Similar results were shown in a meta-analysis of 2411 patients, in which a benefit in terms of PFS, but not of OS, was observed<sup>[30]</sup>.

The introduction of novel agents in the induction phase before and in a consolidation or maintenance phase after ASCT, has further improved the outcomes of MM patients, increasing response rates, PFS and OS (Table 2). The combination of thalidomide and dexamethasone (TD) or of thalidomide with conventional chemotherapy has significantly increased the rate of responses compared to chemotherapy alone<sup>[10,17,31-33]</sup>. TD incorporated into double ASCT was able to improve PFS and OS (median PFS 48 mo, OS 65% at 5 years) compared to standard chemotherapy with vincristine, adriamycin and dexamethasone<sup>[10,31]</sup>.

Bortezomib in the context of ASCT gave even more impressive results<sup>[16,34-36]</sup>, with the best combinations being those of bortezomib plus dexamethasone and an IMiDs<sup>[13,37,38]</sup>. The combination of bortezomib, thalidomide and dexamethasone incorporated into ASCT resulted in a PFS of 68% at 3 years<sup>[13]</sup>, and a OS that reached 82% at 2 years<sup>[37]</sup>.

Even more interesting seems the combination of bortezomib and dexamethasone with lenalidomide (VRD) followed by ASCT. A phase I / II study investigating this combination in newly diagnosed MM patients reported impressive results, with an overall response rate of 100% and an estimated PFS and OS at 18 mo of 75% and of 97% respectively. This results have however to be carefully interpreted and confirmed, considering the short follow up that at the time of reporting of only 21 mo<sup>[38]</sup>.

The high rate of good quality responses seen with the incorporation of PI and IMiDs as induction before, and consolidation and maintenance after ASCT translated into an increase of both PFS and OS; in consideration of these results, and of the toxicity associated with HDT and ASCT, a burning question nowadays is whether new treatments alone, without the use of upfront ASCT, would be sufficient to treat young MM patients<sup>[39]</sup>. In this scenario it is worth noting that the majority of patients enrolled in clinical trials that were not treated with ASCT upfront could still receive it at the time of relapse. Furthermore impressive results were seen with the introduction of novel agents in the treatment of MM patients not suitable for ASCT.

**Table 1 Phase III clinical trials of chemotherapy vs transplantation**

Ref.	Publication year	Random	Patients n	ORR (%)	CR (%)	PFS/EFS	OS
Attal <i>et al</i> <sup>[41]</sup> IFM90	1996	ASCT	100	81	<sup>1</sup> 22	28 mo	57 mo
		CCT	100	57	5	18 mo	44 mo
				$P < 0.001$	$P < 0.001$	$P = 0.01$	$P = 0.03$
Child <i>et al</i> <sup>[5]</sup> MRC VII	2003	ASCT	200	86	44	32 mo	54 mo
		CCT	201	48	8	20 mo	42 mo
				$P = \text{NR}$	$P < 0.001$	$P < 0.001$	$P = 0.04$
Ferland <i>et al</i> <sup>[25]</sup> MAG90	1998	ASCT	91	78	57	39 mo	64.6 mo
		CCT	94	58	20	13 mo	64 mo
Barlogie <i>et al</i> <sup>[28]</sup> S9321	2006	ASCT	261	93	17	17%	38%
		CCT	255	90	15	14%	38%
						At 7 yr	At 7 yr
Ferland <sup>[27]</sup> MAG95	2005	ASCT	94	62	36	37 mo	79 mo
		CCT	96	58.5	20	16 mo	43 mo
Bladé <i>et al</i> <sup>[26]</sup> PETHEMA	2005	ASCT	81	82	30	42 mo	66 mo
		CCT	83	83	11	33 mo	61 mo
					$P = 0.002$		
Palumbo <i>et al</i> <sup>[9]</sup> MMSG	2004	ASCT	95	72	<sup>1</sup> 25	28 mo	58 mo
		CCT	99	66	6	16 mo	42 mo
					$P = 0.002$	$P < 0.001$	$P < 0.001$

<sup>1</sup> ≥ nCR. Only statistical significant  $P$  is reported. CCT: Conventional chemotherapy; ASCT: Autologous stem cell transplantation; ORR: Overall response rate; CR: Complete remission; nCR: Near CR; PFS: Progression free survival; EFS: Event free survival; OS: Overall survival; NR: Not reported; IFM: Intergroupe Francophone du Myélome; MRC: Medical Research Council; PETHEMA: Programa Para El Estudio y Tratamiento De Las Hemopatías Malignas; MAG: Myélome Autogreffe.

## RATIONAL FOR DELAYED TRANSPLANTATION: NEW DRUGS COMBINATIONS WITH OR WITHOUT CHEMOTHERAPY FOR PATIENTS NOT CANDIDATE TO ASCT

The advent of new drugs has dramatically changed the outcomes not only of young MM patients, but also, and maybe even more impressively, those of older transplant ineligible patients. Already the implementation of thalidomide into the classic combination of MP was able to improve patients outcomes compared to MP alone<sup>[40]</sup>. The addition of bortezomib to MP led to even more impressive results, increasing the response rate of elderly MM patients to rates previously seen only in patients that received ASCT. Patients treated with Bortezomib, Melphalan and Prednisone (VMP) showed a TTP of 24 mo and a 3- and 5-year OS of 68.5% and 46%, respectively. The addition of bortezomib to MP was able to increase the OS of patients of 13 mo<sup>[19,20,41]</sup>.

Another interesting combination is the one of lenalidomide and dexamethasone. The combination of lenalidomide and dexamethasone was first evaluated both in young and elderly MM patients, identifying the association of lenalidomide with low dose dexamethasone (Ld) as the combination to bring forward in further trials<sup>[11]</sup>. This combination has been proved to be extremely beneficial in the elderly population. A continuous treatment with lenalidomide and dexamethasone was found to be superior not only to MP plus thalidomide, but also to the same regimen given for

a fixed number of cycles (18 cycles); continuous Ld significantly reduced the risk of death ( $HR = 0.78$ ;  $P = 0.02$ ) and the authors speculate that for the first time a regimen without chemotherapy can be considered as a standard of care for the treatment of MM patients<sup>[42]</sup>. The knowledge that ASCT can be given also as a salvage treatment, together with the data coming from the aforementioned trials resulted in the treatment strategy comprehensive of upfront ASCT now being questioned by some centres<sup>[43]</sup>.

## DELAYED TRANSPLANTATION

The best timing of ASCT, whether it should be given as an upfront treatment or as salvage therapy at the time of relapse, was already a burning question before the novel agents era. From 1990 to 1995, Fermand *et al*<sup>[25]</sup> randomly assigned 185 patients to receive early ASCT or conventional chemotherapy with vincristine, melphalan, cyclophosphamide and prednisone (VMPC). In this latter group ASCT was reserved for the time of relapse. Although median event free survival was longer for patients treated with early ASCT (39 mo vs 13 mo) the median OS was not significantly different between the two groups (64.6 mo vs 64 mo,  $P = 0.92$ ), and 90% of the patients randomised to the VMPC arm were able to receive the planned delayed ASCT at the time of relapse<sup>[25]</sup>.

Several analyses, summarised in Table 3, have investigated the role of ASCT as a salvage therapy for MM<sup>[29,44-51]</sup>. These works are not always comparable, due to the different nature of the works (both prospective and retrospective) and to the fact that ASCT was

**Table 2 Improved outcomes with the introduction of novel agents in the upfront treatment of multiple myeloma**

Ref.	Publication's year	Therapy	Patients n	≥ VGPR (%) preASCT	≥ VGPR (%) postASCT	≥ PR %	CR/ nCR %	PFS/EFS OS
<b>Thalidomide</b>								
Rajkumar <i>et al</i> <sup>[32]</sup>	2006	TD vs D	200	63 vs 41 (≥ PR)	NR			NR
Cavo <i>et al</i> <sup>[10]</sup>	2009	TD vs VAD	270	30 vs 15	68 vs 49			PFS 51% vs 31% at 4 yr OS 69% vs 53% at 5 yr
Barlogie <i>et al</i> <sup>[17]</sup>	2006	TT2 + Thal vs TT2	668	NR	62 vs 43			EFS 56% vs 44% at 3 yr OS 65% vs 65% at 5 yr
Lokhorst <i>et al</i> <sup>[33]</sup>	2010	TAD vs VAD	402	32 vs 15	49 vs 32			EFS 34 mo vs 22 mo OS 73 mo vs 60 mo
<b>Lenalidomide</b>								
Richardson <i>et al</i> <sup>[38]</sup>	2010	VRD	35			100	57	NR
Palumbo <i>et al</i> <sup>[56]</sup>	2014	MPR vs HDM	202			NR	NR	PFS 22.4 mo vs 43 mo OS 65.3% vs 81.6%
		Maintenance R vs No maintenance	198			78	23	PFS 41.9 mo vs 21.6 mo
McCarthy <i>et al</i> <sup>[66]</sup>	2012	Lenalidomide vs placebo	204			77	19	OS 79% vs 88% PFS at 3 yr
Attal <i>et al</i> <sup>[67]</sup>	2012	Lenalidomide vs placebo	460					66% vs 39% OS at 3 yr 88% vs 80% PFS at 4 yr
			614					43% vs 22% OS at 4 y 73% vs 75%
<b>Bortezomib</b>								
Harousseau <i>et al</i> <sup>[16]</sup>	2010	*VD vs VAD	482	38 vs 15	54 vs 37			36 m vs 27 m
Sonneveld <i>et al</i> <sup>[34]</sup>	2012	*Induction PAD + maint VEL vs induction VAD + maint Thal	626	NR	75 vs 61			46% vs 42% at 3 yr
Cavo <i>et al</i> <sup>[13]</sup>	2010	*VTD vs TD induction and consolid	480	62 vs 28	82 vs 64			68% vs 56% at 3 yr
Rosiñol <i>et al</i> <sup>[37]</sup>	2012	*VTD vs TD	202	29 vs 14 (CR)	59 vs 40 (CR)			82% at 2 yr (OS)
Moreau <i>et al</i> <sup>[35]</sup>	2011	*VD vs vtD	199	49 vs 39	74 vs 58			30 mo vs 26 mo
Leleu <i>et al</i> <sup>[36]</sup>	2013	VTd-ASCT + consolid VTd vs VTd-ASCT	217	After treatment: 83 vs 64				TTP: 62% vs 29% at 4 yr

VGPR: Very good partial response; TTP: Time to progression; PFS: Progression free survival; NR: Not reported; Thal: Thalidomide; TD: Thalidomide dexamethasone; VAD: Vincristine adriamycin dexamethasone; TAD: Thalidomide adriamycin dexamethasone; MPR: Melphalan prednisone lenalidomide; VTD: Bortezomib thalidomide dexamethasone; VD: Bortezomib dexamethasone; PAD: Adriamycin bortezomib dexamethasone; vtD: Reduced doses bortezomib thalidomide dexamethasone; R: Lenalidomide; VRD: Bortezomib lenalidomide dexamethasone; OS: Overall survival; ASCT: Autologous transplantation; nCR: Near CR; HDM: High dose melphalan; Consolid: Consolidation; Maint: Maintenance.

**Table 3 Major studies of delayed autologous stem cell transplantation (for randomised trials only data regarding delayed autologous stem cell transplantation are reported)**

Ref.	Publication's year	Patients n	Type of trial	Median interval between diagnosis or first ASCT and delayed ASCT	Previous ASCT	ORR (%)	PFS (mo)	OS (mo)
Cook <i>et al</i> <sup>[49]</sup>	2011	106	Retrospective	19 mo (relapse from first transplant)	Yes	63%	NR	37
Jimenez-Zepeda <i>et al</i> <sup>[51]</sup>	2012	81	Retrospective	39 mo (relapse from first transplant)	Yes	97.4%	16.43	53
Sellner <i>et al</i> <sup>[44]</sup>	2013	200	Retrospective	NR	Yes	80.4%	15.2	43.2
Cook <i>et al</i> <sup>[46]</sup>	2014	89	Prospective	2.7 yr	Yes	83%	19	80.3% at 3 yr
Gertz <i>et al</i> <sup>[29]</sup>	2000	64	Prospective	NR	No	97%	11.4	19.6
Michaelis <i>et al</i> <sup>[45]</sup>	2013	187	Retrospective	32 mo	Yes	68%	5% at 5 yr	29% at 5 yr
Shah <i>et al</i> <sup>[68]</sup>	2012	44	Retrospective	30 mo	Yes	90%	12.3	31.7
Kumar <i>et al</i> <sup>[48]</sup>	2012	112	Prospective	> 12 mo	No	32% (≥ VGPR)	16 (TTP)	73.4% at 4 yr
Dunavin <i>et al</i> <sup>[47]</sup>	2013	65	Retrospective	17.7 mo	No	NR	23 (TTP)	63% at 5 yr

VGPR: Very good partial response; TTP: Time to progression; PFS: Progression free survival; ASCT: Autologous stem cell transplant; OS: Overall survival; NR: Not reported; ORR: Overall response rate.

in some cases given as a salvage treatment after a previous ASCT<sup>[44-46]</sup>, whilst in others patients received ASCT after relapsing from a treatment not including transplantation<sup>[29,47,48]</sup>.

One of the biggest records is the one published by Sellner *et al*<sup>[44]</sup>, in which 200 MM patients retreated with ASCT at the time of relapse were retrospectively analysed. In the study a prognostic score was created, based on the International Staging System (ISS) at the time of relapse and on the duration of response after the first ASCT. The analysis showed that the biggest benefit of salvage ASCT was achieved in those patients with a low ISS (ISS 1) and with a first PFS longer than 18 mo. Another interesting finding of the study was that about 50% of the patients presented at the time of relapse with cytogenetic features of high risk, such as the presence of del(17p), t(4;14) or amp(1q), and that these patients had a worst outcome as compared to patients that relapsed with standard risk features<sup>[44]</sup>. These findings are of primary importance in the decision of when to perform an ASCT (upfront or at relapse), taking into account that patients may relapse with a more aggressive disease, and that cytogenetic abnormalities known to confer a dismal outcome are seen more often in patients in advanced stages of disease, probably as the result of an increasing biological risk and clonal selection<sup>[52-54]</sup>.

Most of the studies available were published before IMiDs and PI became available for upfront treatment. In the era of novel agents two studies have retrospective analysed the role of early vs delayed ASCT<sup>[47,48]</sup> and one study prospectively evaluated a second ASCT after relapse from a previous one<sup>[46]</sup>. One study reported the outcomes of 290 patients treated with IMiDs based therapy (thalidomide or lenalidomide) and that received early (within 12 mo of diagnosis) or late ASCT; PFS was similar irrespective of when ASCT was performed (early or late) and no significant difference could be observed in OS, with both groups experiencing a 4-year OS of 73%<sup>[48]</sup>. In a similar study Dunavin *et al*<sup>[47]</sup> retrospectively reviewed the outcome of 167 patients treated with novel agent-based therapy (IMiDs or PI) and receiving early or delayed ASCT. The 5-year OS from diagnosis was similar in the two groups (63% both in early and late ASCT,  $P = 0.45$ ), in accordance with the data reported by Kumar *et al*<sup>[48]</sup>. The English group prospectively evaluated the role of salvage ASCT after relapse from a previous one; patients relapsing after ASCT were randomised between treatment with a second ASCT or chemotherapy with cyclophosphamide (Cy). With a median follow-up of 31 mo, although patients randomised to a second ASCT experienced a longer PFS compared to patients treated with Cy (19 vs 11 mo for ASCT and Cy respectively,  $P < 0.0001$ ) no difference in terms of OS could be seen. It also has to be noted that the comparator chemotherapy arm, comprehensive of only weekly Cy, might not be the standard of care in a time when multiple drugs, such as third generation IMiDs, second generation PI, spindle

kinase inhibitor or monoclonal antibodies are available for the treatment of relapsed MM.

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## NEW DRUGS IN THE CONTEXT OF UP-FRONT VS DELAYED TRANSPLANTATION: PHASE III CLINICAL TRIALS

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As already stated the advent of new drugs has dramatically changed the therapeutic scenario of MM patients. Not only an induction treatment comprehensive of new drugs significantly increased the rate of high quality responses and improved survival outcomes<sup>[11,13,16,34]</sup>, but the manageable toxicity of these compounds make them suitable for a long term and continuous treatment<sup>[42,55]</sup>. In the above mentioned phase I / II VRD trial, a post hoc landmark analysis showed that the risk of progression after one year was low irrespective of whether patients had received or not an ASCT and that in patients who did not wish to undergo transplantation, responses increased prolonging therapy from 4 to 8 cycles<sup>[38]</sup>.

The impressive results obtained with first line treatment comprehensive of IMiDs and PI prompt the investigation of upfront vs delayed transplantation in the context of specifically designed phase III randomised trials.

The Italian Gruppo Italiano Malattie Ematologiche dell'Adulto conducted a phase III clinical trial aimed at comparing melphalan, prednisone and lenalidomide (MPR) vs two courses of HDT with melphalan (melphalan 200 mg/m<sup>2</sup>). All patients had previously received an induction treatment with four courses of Lenalidomide and low dose dexamethasone (Ld). With a median follow-up of 51.2 mo the results showed a clear advantage of the ASCT arm both in terms of PFS (43 vs 22 mo,  $P < 0.001$ ) and of OS (82% vs 65% at 4 years,  $P = 0.02$ )<sup>[56]</sup>. Another factor that might have influenced the outcome of the study was that 41% of the patients randomised in the late transplant arm did not receive the planned salvage ASCT<sup>[56]</sup>. High dose melphalan (HDM) after 4 cycles of induction with Ld was also compared to cyclophosphamide, lenalidomide and dexamethasone (CRD). Similarly to what already seen with the MPR treatment, HDM was superior to CRD in terms of PFS (27 mo vs not reached for CRD and HDM, respectively,  $P = 0.012$ ), whilst no advantage was seen in terms of OS (estimated 3-year OS 81% vs 84% for CRD and HDM, respectively,  $P = 0.891$ )<sup>[57]</sup>. A pooled analysis the two trials showed that in newly diagnosed MM patients, HDM followed by ASCT significantly improved PFS and OS in comparison to MPR or CRD. Patients with favourable baseline conditions, such as a good baseline performance status (PS) (Karnofsky PS  $\geq 80\%$ ), a low ISS (ISS 1), the absence of high-risk cytogenetic abnormalities [del(17p), t(4;14), t(14;16)] and those that had achieved at least a very good partial response

after induction had the most significant benefit in terms of OS<sup>[58]</sup>.

The reported trials seem to favour upfront ASCT, however a possible caveat of these studies is the not-optimal induction treatment, with the rate of complete responses reported after consolidation (with MPR or HDM) that were lower than those reported at the same time point after other chemotherapy-free induction regimens, such as bortezomib-thalidomide-dexamethasone<sup>[13,37,56]</sup>. The most promising induction combinations to be tested in the context of upfront vs delayed transplantation are triplet combinations including two novel agents or a novel agent and a chemotherapeutic drug associated with Dexamethasone<sup>[13,34,37,38]</sup>. Two multicentre randomised phase III trials are currently ongoing, evaluating the role of upfront vs delayed ASCT in the context of a new drug based therapy. The European Myeloma Network (EMN) on one side and the Intergroupe Francophone du Myélome (IFM) in association with the Dana-Farber Cancer Institute (DFCI) on the other, are conducting two trials aimed at assessing the role of ASCT in comparison to a novel agent based consolidation. The EMN02 trial randomises transplant eligible newly diagnosed MM patients, after an induction with 4 cycles of bortezomib, cyclophosphamide and dexamethasone, to receive a consolidation therapy with 4 cycles of VMP or with ASCT to support one or two cycles of HDM. Patients are further randomised to a second consolidation treatment with VRD vs observation; all patients will receive maintenance treatment with lenalidomide. The IFM/DFCI 2009 trial compares VRD with or without transplantation in a subset of patients similar to those included in the EMN02 study. As for patients in the EMN02 study, patients enrolled in the IFM/DFCI 2009 trial will receive maintenance lenalidomide. Both trials are currently closed to recruitment and definitive results with a long follow up results are eagerly awaited.

## CONCLUSION

In the era of novel agents the appropriate timing for performing ASCT, whether upfront or at relapse, is still a burning question. If on one hand it is true that early ASCT improves PFS rates, on the other hand it is associated with a higher toxicity compared to a treatment with novel agents<sup>[56]</sup>. It has to be also acknowledged that, whilst almost all randomized studies showed longer PFS for early ASCT, the benefit on OS was not uniformly reported<sup>[25,56-58]</sup>. The lack of advantage observed in some cases in terms of OS is mainly due to the effective salvage therapy nowadays available, and to the possibility for patients to receive ASCT later in their disease history as a salvage treatment. For this reason some centres nowadays recommend ASCT only for those patients with high-risk features, whilst for standard risk patients a treatment option reserving ASCT for the time of relapse is considered acceptable<sup>[59-61]</sup>. In this context it has to be emphasised, in patients for whom a delayed ASCT may be considered, the extreme importance of

early stem cell collection and cryopreservation; an early stem cell collection is particularly important in those patients receiving lenalidomide based treatments<sup>[62,63]</sup>.

Despite being a feasible option for carefully selected patients, delayed ASCT has some important caveats: Not only a significant percentage of patients might not be able to receive HDM at the time of relapse, due to the worsening of their clinical conditions<sup>[56]</sup>, but also a worst outcome could be expected due to the higher rate of adverse cytogenetic features in more advanced disease phases<sup>[44]</sup>. Furthermore it has to be noted that reliable cost effectiveness data comparing early ASCT vs the continuation of a novel agent based therapy are currently not available<sup>[64]</sup>.

Based on the available data the recent guidelines from the American Society for Blood and Marrow Transplantation recommend performing ASCT early in disease history (within 12 mo)<sup>[64]</sup>, and there is a global consensus strongly in favour of upfront ASCT<sup>[21,65]</sup>. Results of ongoing phase III studies are eagerly awaited to answer the burning question regarding the optimal timing of ASCT in young MM patients and whether, in the era of novel agents, HDM is still a need in order to treat MM.

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