

The evolution of stem-cell transplantation in multiple myeloma

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Ther Adv Hematol

2018, Vol. 9(5) 123–133

DOI: 10.1177/
2040620718761776

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Abstract: Autologous stem-cell transplantation (ASCT) remains an integral part of treatment for previously untreated, and may have value in the treatment of relapsed patients with, multiple myeloma (MM). The addition of novel agents like immunomodulators and proteasome inhibitors as induction therapy before and as consolidation/maintenance therapy after ASCT has led to an improvement in complete response (CR) rates, progression-free survival (PFS) and overall survival (OS). With advances in supportive care, older patients and patients with renal insufficiency are now able to safely undergo the procedure. The data concerning the timing of ASCT (early in the disease course or at first relapse), single *versus* tandem (double) ASCT and the role and duration of consolidation and maintenance therapy post ASCT remain conflicting. This review aims to discuss the evolution of stem-cell transplant over the past 3 decades and its current role in the context of newer, safer and more effective therapeutic agents.

Keywords: allogenic, autologous, multiple myeloma, stem-cell transplant

Received: 24 August 2017; revised manuscript accepted: 6 February 2018

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy accounting for nearly 10% of all hematological malignant disorders and 0.9% of all cancer deaths every year.^{1,2} Until the mid 90s, a combination of corticosteroids and melphalan was the standard treatment for patients with MM which gave a median survival of 3 years or less.³ However, the introduction of autologous stem-cell transplant (ASCT) in combination with high-dose chemotherapy (HDCT) improved the median survival to 7 years.^{4,5} With the emergence of safer and more effective novel therapies like immunomodulatory drugs (IMiDs) including thalidomide, lenalidomide and proteasome inhibitors (PIs) including bortezomib, the outcomes have vastly improved.⁶ More recently, pomalidomide, carfilzomib, ixazomib, daratumumab and elotuzumab have been approved for treatment of MM.⁷ The availability of these safer and more effective agents has raised doubts about using ASCT as first-line therapy, especially because both chemotherapy and ASCT only prolong progression-free survival (PFS) and overall survival (OS), and do not produce a cure.

Though allogeneic transplant offers a potential for cure, it is at a cost of increased treatment-related morbidity and mortality.

In this review, we aim to discuss the evolution of stem-cell treatment for the management of MM, including its role as part of initial therapy, in relapsed and refractory patients, associated complications, pros and cons of early *versus* delayed ASCT as well as single *versus* tandem ASCT.

Conventional chemotherapy *versus* stem-cell transplant

ASCT has been the mainstay of therapy in young (<65 years) transplant-eligible patients with MM. The trials comparing chemotherapy alone with ASCT have conflicting results. The impact of ASCT on complete response (CR) rates as well as on PFS and OS as compared with chemotherapy according to various studies are shown in Table 1.

A meta-analysis comprising 2411 patients indicated that the combined hazard of progression

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Table 1. Conventional chemotherapy *versus* ASCT.

Author	Patient population (chemotherapy <i>versus</i> ASCT)	Treatment regimen (chemotherapy <i>versus</i> ASCT)	Response (chemotherapy <i>versus</i> ASCT)	Progression-free survival (chemotherapy <i>versus</i> ASCT)	Overall survival (chemotherapy <i>versus</i> ASCT)
Attal <i>et al.</i> ⁴	200 patients <65 years (100 <i>versus</i> 100)	Alternating cycles of VMCP/BVAP × 18# and IFN <i>versus</i> Alternating cycles of VMCP/BVAP × 4–6# and ASCT	57% <i>versus</i> 81% ($p < 0.0001$)	5 years: 10% <i>versus</i> 28% ($p = 0.01$)	5 years: 52% <i>versus</i> 12% ($p = 0.03$)
Child <i>et al.</i> ⁵	401 patients <65 years (200 <i>versus</i> 201)	ABCM × 4–12# and IFN <i>versus</i> doxorubicin, cyclophosphamide and methyl prednisone × 3# and ASCT	CR: 8% <i>versus</i> 44% ($p < 0.0001$)	Median: 19.6 m <i>versus</i> 31.6 m ($p < 0.0001$)	Median: 42.3 m <i>versus</i> 54.1 m ($p = 0.04$)
Blade <i>et al.</i> ⁸	164 patients (83 <i>versus</i> 81)	Alternating cycles of VBMCP/VBAD followed by VBMCP/VBAD × 8# <i>versus</i> ASCT	CR: 11% <i>versus</i> 30% ($p = 0.002$)	Median: 33 m <i>versus</i> 42 m ($p = \text{NS}$)	Median: 66 m <i>versus</i> 61 m ($p = \text{NS}$)
Fernand <i>et al.</i> ⁹	190 patients 55–65 years (94 <i>versus</i> 96)	VMCP till plateau <i>versus</i> VAMP × 3–4# and ASCT	CR: 20% <i>versus</i> 36%	Median: 19 m <i>versus</i> 25 m ($p = 0.07$)	Median: 47.6 m <i>versus</i> 47.8 m ($p = 0.91$)
Barlogie <i>et al.</i> ¹⁰	516 patients <70 years (255 <i>versus</i> 261)	VAD × 4# and VBMCP <i>versus</i> VAD × 4# and with/without IFN maintenance		7 years: 16% <i>versus</i> 17% ($p = \text{NS}$)	7 years: 42% <i>versus</i> 37% ($p = \text{NS}$)
Palumbo <i>et al.</i> ¹¹	273 patients <65 years (132 <i>versus</i> 141)	RD × 4# and MPR × 6# <i>versus</i> RD × 4# and ASCT with/without R maintenance		Median: 22.4 m <i>versus</i> 43 m ($p < 0.001$)	4 years: 65.3% <i>versus</i> 81.6% ($p = 0.02$)
Gay <i>et al.</i> ¹²	256 patients <65 years (129 <i>versus</i> 127)	RD × 4# and RCD × 6# <i>versus</i> RD × 4# and ASCT with/without R maintenance		Median: 28.6 m <i>versus</i> 43.3 m ($p < 0.0001$)	4 years: 73% <i>versus</i> 86% ($p = 0.004$)

ABCM, adriamycin; ASCT, autologous stem-cell transplant; BCNU, cyclophosphamide and melphalan; BVAP, BCNU, vincristine, adriamycin, prednisone; CR, complete response; IFN, interferon; MPR, melphalan, prednisolone, revilimid; NS, nonsignificant; R, revilimid; RCD, revilimid, cyclophosphamide, dexamethasone; RD, revilimid, dexamethasone; VAD, vincristine, adriamycin, dexamethasone; VAMP, vincristine, adriamycin, melphalan, prednisolone; VBAD, vincristine, BCNU, adriamycin, dexamethasone; VMCP, vincristine, melphalan, cyclophosphamide, prednisolone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone.

was 0.75 [95% confidence interval (CI) 0.59–0.96] and death was 0.92 (95% CI 0.74–1.13) with upfront ASCT as compared with standard-dose chemotherapy. However, most of the studies included in the meta-analysis were conducted using older lesser effective chemotherapeutic regimens. Also, the impact of ASCT at relapse may have led to similar OS among those who received chemotherapy.¹³ As novel therapies can produce CR rates comparable with ASCT, a question arose: whether the use of these newer agents, alone or in combination, will delay or eliminate the need for ASCT. Palumbo and colleagues showed a survival advantage with high-dose melphalan plus ASCT *versus* consolidation with

melphalan, prednisone, lenalidomide after IMiD-based doublet induction.¹¹ However, these two subgroups were not a part of the original four-group design of the study. Also, a recent study by Attal and colleagues showed that the use of ASCT after induction with a triplet regimen using a combination of PIs and IMiDs delays progression but doesn't improve OS.¹⁴ Therefore, although ASCT is considered a part of initial therapy, delaying the same until relapse remains an acceptable approach.

Eligibility for transplant

The eligibility for ASCT varies widely among countries, but is based largely upon patient's

Table 2. Early *versus* delayed ASCT.

Author	Patient population (early ASCT <i>versus</i> delayed ASCT)	Induction regimen (early ASCT <i>versus</i> delayed ASCT)	Response (early <i>versus</i> delayed ASCT)	Progression-free survival (early <i>versus</i> delayed ASCT)	Overall survival (early <i>versus</i> delayed ASCT)
Fernand <i>et al.</i> ¹⁶	185 patients (91 <i>versus</i> 94)	VAMP × 3–4# and ASCT <i>versus</i> VMCP till plateau and ASCT at relapse	85.7% <i>versus</i> 55.5%	Median: 39 m <i>versus</i> 13 m	Median: 64.6 m <i>versus</i> 64 m (<i>p</i> = 0.92)
Kumar <i>et al.</i> ¹⁷	285 patients (173 <i>versus</i> 112)	TD (<i>n</i> = 123) or RD (<i>n</i> = 167) × 4–6# followed by early or delayed ASCT		Median: 20 m <i>versus</i> 16 m (<i>p</i> = NS)	4 years: 73% <i>versus</i> 73% (<i>p</i> = 0.3)
Dunavin <i>et al.</i> ¹⁸	167 patients (102 <i>versus</i> 65)	T-, R- or V-based induction followed by early or delayed ASCT	≥VGPR: 77% <i>versus</i> 55% (<i>p</i> = 0.003)	Median: 28 m <i>versus</i> 18 m (<i>p</i> = 0.11)	Median: NR <i>versus</i> 83 m (<i>p</i> = 0.45)
Remenyi <i>et al.</i> ¹⁹	548 patients (377 <i>versus</i> 171)	57% in early ASCT and 53.2% in delayed ASCT group received novel therapies	CR: 58.1% <i>versus</i> 46.8% (<i>p</i> = 0.016)	Median: 30.2 m <i>versus</i> 23.3 m (<i>p</i> = 0.036)	Median: 97.2 m <i>versus</i> 99.1 m (<i>p</i> = 0.77)
Attal <i>et al.</i> ¹⁴	700 patients (350 <i>versus</i> 350)	VRD × 3# and ASCT + VRD × 2# <i>versus</i> VRD × 8# and ASCT at relapse	CR: 59% <i>versus</i> 48% (<i>p</i> = 0.03)	Median: 50 m <i>versus</i> 36 m (<i>p</i> < 0.001)	4 years: 81% <i>versus</i> 82%

ASCT, autologous stem-cell transplant; CR, complete response; NR, not reached; NS, non-significant; R, revlimid; RD, revlimid, dexamethasone; T, thalidomide; TD, thalidomide, dexamethasone; V, Velcade; VAMP, vincristine, adriamycin, melphalan, prednisolone; VGPR, very good partial response; VMCP, vincristine, melphalan, cyclophosphamide, prednisolone; VRD, Velcade, revlimid, dexamethasone.

age, comorbidities and performance status. In the United States, the upper age limit is flexible up to 75 years for patients with adequate organ function, but in Europe and most other countries, ASCT is performed till the age of 65 years.¹⁵ ASCT is usually avoided for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4 or a New York Heart Association functional status of class III or IV.

Timing of transplant

After stem-cell collection, the patients can either proceed with ASCT upfront (early ASCT) or continue with chemotherapy with a plan to pursue ASCT at the time of relapse (delayed ASCT). There have been various studies which compared the outcomes of early *versus* delayed ASCT, as shown in Table 2. Although the earlier studies reported an improvement in both PFS and OS with the use of ASCT in initial therapy,¹⁶ the incorporation of novel therapies as triplet regimens in the first-line treatment resulted in an improvement in PFS which did not translate into an OS benefit with early ASCT as compared with delayed ASCT.¹⁴

Induction therapy

Patients eligible for ASCT are given induction therapy for 2–4 m prior to stem-cell collection, in order to reduce the tumor burden, to improve the quality of the graft, lessen symptoms, and diminish end-organ damage.

In the past, melphalan-containing regimens were avoided due to their hematopoietic toxicity and increased risk of myelodysplasia following transplantation. The induction regimen was either dexamethasone based or a combination of steroids with non-alkylators like the vincristine, doxorubicin and dexamethasone (VAD) regimen.²⁰

In the era of novel therapies, the most commonly used regimens for initial treatment include bortezomib, dexamethasone and lenalidomide (VRD), bortezomib, thalidomide and dexamethasone (VTD), bortezomib, cyclophosphamide and dexamethasone (VCD), and carfilzomib, lenalidomide, dexamethasone (KRD).^{21–23} Two studies showed the superiority of the triplet regimen, like VRD, over the doublet regimen, like thalidomide–dexamethasone (TD)²⁴ and bortezomib–dexamethasone (VD) in achieving a better PFS and OS.²¹ Other studies have reported improved

responses and delayed progression with the use of VTD over other doublet regimens.^{25,26} Among the triplet regimens, a regimen containing both a PI and an IMiD like VTD and VRD was found to be superior to VCD.^{21,23}

The data concerning impact of the response to induction therapy on outcomes after ASCT remains limited. The Intergroupe Francophone de Myelome (IFM) group evaluated 482 patients enrolled in the IFM 2005-01 trial of induction therapy followed by early ASCT. They found that patients who achieved a very good partial response (VGPR) or better after induction chemotherapy had a longer PFS as compared with those who achieved a VGPR after ASCT (41 m *versus* 31 m, $p = 0.01$).²⁷

Stem-cell mobilization

Apheresis is performed with a goal of collecting a minimum of 2×10^6 CD34+ cells/kg and an optimal dose of 5×10^6 CD34+ cells/kg.²⁸

The standard regimen used for stem-cell mobilization is granulocyte colony stimulating factor (G-CSF) or G-CSF with cyclophosphamide.^{29,30} Plerixafor, a chemokine receptor type 4-inhibitor, is mostly reserved for the patients who fail to collect stem cells to G-CSF and G-CSF/cyclophosphamide.^{31,32}

In addition, it should be noted that there have been some data to suggest that prolonged initial therapy with a lenalidomide-based regimen may impair hematopoietic stem-cell collection. Hence, an early mobilization of stem cells, preferably within the first four cycles of initial therapy with lenalidomide is recommended.³³

Conditioning regimen

The standard preparative conditioning regimen used for ASCT in MM is melphalan at a dose of 200 mg/m², with dose reductions based on age and renal function. In a randomized controlled trial by the IFM group, patients who received melphalan at 200 mg/m² had a higher survival at 45 m (65.8% *versus* 45.5%, $p = 0.05$) with significantly faster hematologic recovery, lower rate of severe mucositis and shorter hospitalizations as compared with those who received melphalan at 140 mg/m² with 8 Gy total body irradiation (TBI).³⁴

The impact of reducing the dose of conditioning melphalan on outcomes of patients with MM has been evaluated. Palumbo and colleagues randomized 298 patients to receive tandem ASCT after conditioning with melphalan at a dose of 200 and 100 mg/m². Melphalan at 200 mg/m² resulted in a longer PFS (31.4 m *versus* 26.2 m, $p = 0.01$) and a trend towards improved OS at 5 years (62% *versus* 48%, $p = 0.13$) as compared with 100 mg/m². The treatment-related mortality was similar in both the groups (3.1% *versus* 2.9%).³⁵

There have been several attempts to study the effect of intensification of preparative regimens before ASCT. Studies using conditioning with cyclophosphamide and melphalan (BCNU), etoposide, cytarabine, and melphalan (BEAM),³⁶ high-dose idarubicin, cyclophosphamide, and melphalan,³⁷ thiotepa, busulfan, and cyclophosphamide,³⁸ and busulfan and melphalan³⁹ did not result in better outcomes while increasing the incidence of toxicities as compared with melphalan at 200 mg/m². Ongoing trials are currently testing whether outcomes can be improved by augmenting the conditioning with use of newer agents, especially in patients with relapses. Three phase I/II trials used escalated doses of bortezomib along with melphalan as conditioning in patients undergoing ASCT. The overall response rate (ORR) in these studies ranged from 44% to 87% with 51–70% of the patients achieving VGPR or better without any increase in hematological toxicity.^{40–42} A phase I trial showed that high-dose lenalidomide in combination with melphalan may offer significant potential as a conditioning regimen before ASCT in patients with relapsed MM.⁴³

Transplant-related toxicity

Savani and colleagues evaluated the complications among 6957 patients with MM who underwent ASCT from 1998 to 2011 in United States using the Nationwide Inpatient Sample (NIS) database. The most common in-hospital complications included stomatitis (44.7%), anemia requiring transfusion (28.5%), febrile neutropenia (16.5%) and bacteremia (15.0%). Despite temporal increase in mean age and comorbidities of patients undergoing ASCT, transplant-related mortality (TRM) reduced (2.9% *versus* 0.7%, $p < 0.01$) significantly from 1998 to 2011. Higher Charlson comorbidity index, female sex and use of TBI were associated with higher complications, while

mechanical ventilation, acute respiratory failure, acute kidney injury, bacteremia and use of TBI predicted in-hospital mortality post ASCT.⁴⁴ Various studies have shown that ASCT can be conducted safely as an outpatient procedure. This not only leads to reduction in morbidity but also provides better cost effectiveness.^{45–47} At the Mayo clinic, a multidisciplinary model involving nurses, physicians, pharmacists and dieticians and utilizing an electronic database for ordering diagnostic tests and chemotherapy was used in 716 patients undergoing ASCT. A total number of 278 patients treated in an outpatient setting with this model had a 100-day survival rate of 98.9% (99.5% for low risk and 97.2% for high risk).⁴⁷

Consolidation therapy

The data regarding the use of consolidation post ASCT in an effort to improve outcomes by deepening the response are limited. Ladetto and colleagues showed that the use of VTD in patients achieving VGPR or better post ASCT led to an increase in CR rates from 15% to 49% and molecular remission from 3% to 18%.⁴⁸ However, it was not known whether this deepening of response influenced survival and progression. A recent per-protocol analysis of the Italian myeloma study showed that consolidation with VTD post ASCT resulted in increased CR rates (60.6% *versus* 46.6%) and prolonged 3-year PFS (62% *versus* 42%, $p = 0.042$) as compared with TD.⁴⁹ The Nordic Myeloma Study Group randomized bortezomib-naïve patients to bortezomib *versus* no consolidation after ASCT. There was a trend towards an improvement in PFS (27 m *versus* 20 m, $p = 0.05$), but there was no difference in OS between both the groups.⁵⁰

Maintenance therapy

Maintenance therapy with lenalidomide and bortezomib appears to be promising in the post-ASCT scenario. Two randomized studies established that the use of low-dose lenalidomide after ASCT until progression led to an improvement in PFS (41 m *versus* 23 m, $p < 0.001$ and 50 m *versus* 27 m, $p < 0.001$) which also translated into an OS benefit (3 years, 88% *versus* 80%) in one of the studies. This survival benefit was largely limited to patients who received lenalidomide as induction therapy.^{51,52} A meta-analysis of 1208 patients also confirmed an improvement in OS (not reached *versus* 86 m, $p = 0.001$) with lenalidomide maintenance, but the risk of second primary malignancies was increased

(hematological, 6.1% *versus* 2.8% and solid, 7.3% *versus* 4.2%).⁵³ Also, it should be noted that the abovementioned trials did not have a planned crossover in which the placebo arm was treated with lenalidomide upon relapse. In all these studies, lenalidomide was superior to the comparator arm but it cannot be recommended to all patients because the OS benefit has not been widely established and because of concerns of long-term safety. Two randomized trials have also evaluated the role of bortezomib maintenance after ASCT. In the Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON) 65/German Multicenter Myeloma Group (GMMG)-HD4 trial, bortezomib maintenance for 2 years resulted in improved PFS (35 m *versus* 28 m, $p < 0.001$) as compared with thalidomide maintenance, especially in patients with renal failure, 13q deletion and 17p deletion.⁵⁴ Another study by the Spanish myeloma (PETHEMA) group showed a significant PFS benefit for bortezomib–thalidomide maintenance as compared with thalidomide or interferon- α 2b alone.⁵⁵ Although these results indicate a benefit for bortezomib maintenance, they are complicated by multidrug treatment during induction and maintenance. Further randomized studies are needed before this can be recommended.

Single *versus* tandem transplant

With tandem (double) ASCT, patients receive a planned second transplant after recovery from the first procedure. Various studies have been conducted comparing single with tandem ASCT, as shown in Table 3. Earlier studies found a significant improvement in PFS and OS with single transplant *versus* tandem ASCT. This benefit was largely restricted to patients who did not achieve VGPR or better with the first transplant.¹⁵ With the incorporation of novel therapies as induction prior to ASCT, the majority of patients achieved a deep response. Hence, the role of tandem transplant has become limited over the past decade. Also, a meta-analysis of 1803 patients concluded that tandem transplant was not associated with any advantage in PFS and OS over a single transplant. The response rate was statistically significantly better with tandem ASCT (risk ratio 0.79, 95% CI 0.67–0.93), but with a statistically significant increase in transplant-related mortality (TRM; risk ratio 1.71, 95% CI 1.05–2.79).⁵⁶ Despite these results, there has been some evidence that patients with high-risk cytogenetics like 17p deletion do benefit with a tandem transplant.^{54,57}

Table 3. Single versus tandem ASCT.

Author	Patient population (single versus tandem ASCT)	Response (single versus tandem ASCT)	Progression-free survival (single versus tandem ASCT)	Overall survival (single versus tandem ASCT)
Attal <i>et al.</i> ⁵⁸	399 patients (199 versus 200)	≥VGPR: 42% versus 50% ($p = 0.1$)	7 years: 10% versus 20% ($p = 0.03$)	7 years: 21% versus 42% ($p = 0.01$)
Cavo <i>et al.</i> ⁵⁹	321 patients (163 versus 158)	≥VGPR: 33% versus 47% ($p = 0.008$)	Median: 23 m versus 35 m ($p = 0.001$)	Median: 65 m versus 71 m ($p = 0.9$)
Sonneveld <i>et al.</i> ⁶⁰	303 patients (148 versus 155)		Median: 27 m versus 24 m ($p = 0.006$)	Median: 50 m versus 55 m ($p = 0.51$)
Fermand <i>et al.</i> ⁶¹	225 patients (112 versus 113)		$p = 0.61$	$p = 0.6$
Mai <i>et al.</i> ⁶²	358 patients (177 versus 181)	CR: 16% versus 19.4% ($p = 0.04$)	Median: 25 m versus 28.7 m ($p = 0.53$)	Median: 73 m versus 75.3 m ($p = 0.33$)

ASCT, autologous stem-cell transplant; CR, complete response; VGPR, very good partial response.

Transplant as salvage therapy

Second ASCT is a safe and effective therapy in eligible patients with relapsed MM. Alvarez and colleagues found that patients with a PFS of <18 m after first ASCT had a median OS of <6 m whereas those with a PFS of ≥18 m showed a median OS approaching 3 years.⁶³ A Mayo Clinic study which reviewed 345 patients who relapsed after ASCT found that the median OS was 10.8 m for patients in the early relapse group (≤12 m from ASCT) as compared with 41.8 m in the late relapse group (>12 m from ASCT; $p < 0.001$). Hence, the authors recommended offering novel trials for patients in the early relapse group due to poor outcomes.⁶⁴ Sellner and colleagues evaluated 200 patients with MM who relapsed after upfront ASCT and were treated with a second transplant at salvage therapy. The ORR was 80.4% at day 100, while the median PFS and OS after salvage ASCT were 15.2 m and 42.3 m, respectively. Factors associated with improved survival after salvage ASCT included an initial PFS of >18 m after upfront ASCT, bortezomib-containing or lenalidomide-containing therapies for reinduction, response to reinduction, and an International Staging System stage I before salvage ASCT.⁶⁵ Most of these studies are based on single-arm data and a Center for International Blood and Marrow Transplant Research (CIBMTR) study is underway which may provide cut offs for duration of remission to undergo salvage transplant. Also, it should be noted that recent clinical trials have shown impressive results with the use of triplet therapy like the carfilzomib, lenalidomide and dexamethasone (KRd)

regimen and daratumumab, lenalidomide and dexamethasone (DRD) regimen in patients with relapsed/refractory MM.^{66,67} Hence, the benefit of ASCT in patients with relapsed myeloma may be of limited value with the availability of highly efficacious triplet regimens using novel agents.

Role in special populations

Autologous stem-cell transplantation in elderly patients

With improvement in supportive care, the percentage of MM patients aged 70 years and above undergoing ASCT has increased from 6% in 1994–1995 to 25% in 2004–2005.⁶⁸ However, there remains a paucity of prospective studies among this patient population owing to exclusion of elderly patients from most randomized trials based on their selection criteria.

Stem-cell mobilization is scant in the elderly population, with a need for more apheresis sessions.⁶⁹ Plerixafor has been found to be promising in this situation.⁷⁰ The other concern is their ability to withstand the toxicity incurred with myeloablative regimens. Most of the studies done in elderly population have used reduced doses of conditioning melphalan. A retrospective study evaluated survival after ASCT in patients over the age of 70 years. The rate of CR was 20 and 27% after a single or tandem ASCT with a median OS of 13 and 33 m, respectively. Treatment-related mortality was 16% in patients receiving conditioning melphalan at a dose of 200 mg/m² of melphalan

and 2% in patients receiving 140 mg/m².⁷¹ The CIBMTR analyzed 11,430 MM patients who underwent ASCT between 2008 and 2011. The 3-year PFS and OS were at 42% and 78% for patients in age group 18–59 years, 38% and 75% in age group 60–69 years, and 33% and 72% in age group >70 years, respectively. In a multivariate analysis, increasing age was associated with worse survival ($p = 0.0006$).⁷² Palumbo and colleagues used a scoring system based on age, comorbidities, and cognitive and physical conditions to categorize elderly patients in three groups, namely, fit, intermediate fit and frail, and found that their 3-year OS rates were 84%, 76% and 57%, respectively.⁷³ However, the relevance of this scoring system has not been demonstrated on the outcomes of the patients undergoing ASCT.

Autologous stem-cell transplantation in renal impairment

In a study of 81 MM patients with serum creatinine > 2 mg/dl who underwent ASCT, it was shown that renal failure has no impact on the quality of stem-cell collections and engraftment. Early TRM was seen in 7% of patients who received melphalan at a dose of 200 mg/m² (MEL-200) and in 5% of those who received a dose of 140 mg/m² (MEL-140). All patients had grade III–IV neutropenia, thrombocytopenia and fever. Mucositis was seen in 93% of patients, while vomiting and diarrhea affected 67% of the patients. Mucositis, pulmonary complications, cardiac complications, specifically atrial dysrhythmias, and neurological complications, particularly encephalopathy, were more frequent in the MEL-200 group as compared with the MEL-140 group. Hence, ASCT is feasible in patients with creatinine > 2 mg/dl; the toxicities are more severe and more frequent. It was also found that conditioning with melphalan at a dose of 140 mg/m² was equally efficacious and had a better toxicity profile as compared with 200 mg/m² in this patient population.⁷⁴ The CIBMTR also studied 1492 MM patients who underwent ASCT for MM between 2008 and 2013. Among these, 1240 patients had normal/mild (≥ 60 ml/min) renal insufficiency (RI), 185 patients had moderate RI (30–59 ml/min), and 67 patients had severe RI (<30 ml/min), based on modification of diet in renal disease. It was found that the 5-year PFS for normal, moderate and severe RI was 35%, 40% and 27%, respectively, ($p = 0.42$); while the 5-year OS was 68%, 68% and 60%, respectively, ($p = 0.69$).⁷⁵

Allogenic stem-cell transplant in multiple myeloma

The only therapy with a potential to produce cure in patients with MM is allogenic stem-cell transplant. The advantages of using an allogeneic graft are the absence of tumor cells and its ability to produce a graft *versus* myeloma effect.⁷⁶ The results from data comparing the efficacy of allogenic stem-cell transplant with ASCT have been conflicting. Krishnan and colleagues evaluated 625 patients with standard-risk MM who received a myeloablative ASCT followed by a nonmyeloablative allogeneic transplant ($n = 189$, those with matched sibling donor) and tandem ASCT ($n = 436$, those without a donor). The 3-year PFS (46% *versus* 43%) and OS (80% *versus* 77%) were similar between both the groups. Even in a subgroup of 85 patients with high-risk MM, there was no benefit to ASCT followed by nonmyeloablative allogeneic HCT.⁷⁷ The PETHEMA group also confirmed that there is no survival benefit with the use of reduced-intensity allogeneic transplant as compared with a second ASCT in patients who failed to achieve a VGPR after first ASCT.⁷⁸ In contrast, two other studies have shown an improvement in PFS and OS with nonmyeloablative allogeneic transplantation after ASCT as compared with tandem ASCT.^{79,80} It should be noted in all these trials, the treatment-related mortality is approximately 10–20% and the rates of acute and chronic graft *versus* host disease are high. At present, allogenic transplant is reserved for young patients with high-risk myeloma in first or second relapse who are willing to accept the high treatment-related morbidity and mortality risk.²

Summary

ASCT remains an integral part of treatment for previously untreated, and may have value in the treatment of relapsed patients with, MM. The addition of novel agents before and after ASCT have led to an improvement in CR rates, delay in progression and prolonged OS. Ongoing studies are looking at how the newer drugs can be incorporated in the treatment paradigm as a part of initial therapy, or as conditioning or as consolidation/maintenance to further improve outcomes.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Becker N. Epidemiology of multiple myeloma. *Recent Results Cancer Res* 2011; 183: 25–35.
2. Vincent Rajkumar S. Multiple myeloma: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2014; 89: 999–1009.
3. Sporn JR and McIntyre OR. Chemotherapy of previously untreated multiple myeloma patients: an analysis of recent treatment results. *Semin Oncol* 1986; 13: 318–325.
4. Attal M, Harousseau JL, Stoppa AM, *et al.* A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; 335: 91–97.
5. Child JA, Morgan GJ, Davies FE, *et al.* High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003; 348: 1875–1883.
6. Kumar SK, Dispenzieri A, Lacy MQ, *et al.* Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014; 28: 1122–1128.
7. Rajan AM and Kumar S. New investigational drugs with single-agent activity in multiple myeloma. *Blood Cancer J* 2016; 6: e451.
8. Blade J, Rosinol L, Sureda A, *et al.* High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood* 2005; 106: 3755–3759.
9. Fermand JP, Katsahian S, Divine M, *et al.* High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol* 2005; 23: 9227–9233.
10. Barlogie B, Kyle RA, Anderson KC, *et al.* Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol* 2006; 24: 929–936.
11. Palumbo A, Cavallo F, Gay F, *et al.* Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med* 2014; 371: 895–905.
12. Gay F, Oliva S, Petrucci MT, *et al.* Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. *Lancet Oncol* 2015; 16: 1617–1629.
13. 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: 183–196.
14. Attal M, Lauwers-Cances V, Hulin C, *et al.* Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med* 2017; 376: 1311–1320.
15. Rajkumar SV and Kumar S. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2016; 91: 101–119.
16. Fermand JP, Ravaud P, Chevret S, *et al.* High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood* 1998; 92: 3131–3136.
17. 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: 1585–1592.
18. Dunavin NC, Wei L, Elder P, *et al.* Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma* 2013; 54: 1658–1664.
19. Remenyi P, Varga G, Mikala G, *et al.* Early versus delayed autologous stem cell transplantation and interferon maintenance in multiple myeloma: single-center experience of 18 years. *Transplant Proc* 2016; 48: 177–184.
20. Mohty M and Harousseau JL. Treatment of autologous stem cell transplant-eligible multiple myeloma patients: ten questions and answers. *Haematologica* 2014; 99: 408–416.
21. Chakraborty R, Muchtar E, Kumar S, *et al.* The impact of induction regimen on transplant outcome in newly diagnosed multiple myeloma in the era of novel agents. *Bone Marrow Transplant* 2017; 52: 34–40.
22. Richardson PG, Weller E, Lonial S, *et al.* Lenalidomide, bortezomib, and dexamethasone

- combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010; 116: 679–686.
23. Moreau P, Hulin C, Macro M, *et al.* Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial. *Blood* 2015; 126: 393.
 24. Durie BGM, Hoering A, Abidi MH, *et al.* Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017; 389: 519–527.
 25. Cavo M, Di Raimondo F, Zamagni E, *et al.* Short-term thalidomide incorporated into double autologous stem-cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. *J Clin Oncol* 2009; 27: 5001–5007.
 26. Moreau P, Facon T, Attal M, *et al.* Comparison of reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as induction treatment prior to ASCT in de novo multiple myeloma (MM): results of IFM2007-02 study. *J Clin Oncol* 2010; 28: 8014.
 27. Moreau P, Attal M, Pegourie B, *et al.* Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. *Blood* 2011; 117: 3041–3044.
 28. Duong HK, Savani BN, Copelan E, *et al.* Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2014; 20: 1262–1273.
 29. Hosing C, Qazilbash MH, Kebriaei P, *et al.* Fixed-dose single agent pegfilgrastim for peripheral blood progenitor cell mobilisation in patients with multiple myeloma. *Br J Haematol* 2006; 133: 533–537.
 30. Awan F, Kochuparambil ST, Falconer DE, *et al.* Comparable efficacy and lower cost of PBSC mobilization with intermediate-dose cyclophosphamide and G-CSF compared with plerixafor and G-CSF in patients with multiple myeloma treated with novel therapies. *Bone Marrow Transplant* 2013; 48: 1279–1284.
 31. DiPersio JF, Stadtmauer EA, Nademanee A, *et al.* Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood* 2009; 113: 5720–5726.
 32. Giralt S, Stadtmauer EA, Harousseau JL, *et al.* International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia* 2009; 23: 1904–1912.
 33. Kumar S, Giralt S, Stadtmauer EA, *et al.* Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. *Blood* 2009; 114: 1729–1735.
 34. Moreau P, Facon T, Attal M, *et al.* Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood* 2002; 99: 731–735.
 35. Palumbo A, Bringhen S, Bruno B, *et al.* Melphalan 200 mg/m² versus melphalan 100 mg/m² in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study. *Blood* 2010; 115: 1873–1879.
 36. Veeraputhiran M, Jain T, Deol A, *et al.* BEAM conditioning regimen has higher toxicity compared with high-dose melphalan for salvage autologous hematopoietic stem cell transplantation in multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2015; 15: 531–535.
 37. Fenk R, Schneider P, Kropff M, *et al.* High-dose idarubicin, cyclophosphamide and melphalan as conditioning for autologous stem cell transplantation increases treatment-related mortality in patients with multiple myeloma: results of a randomised study. *Br J Haematol* 2005; 130: 588–594.
 38. Anagnostopoulos A, Aleman A, Ayers G, *et al.* Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. *Cancer* 2004; 100: 2607–2612.
 39. Blanes M, Lahuerta JJ, Gonzalez JD, *et al.* Intravenous busulfan and melphalan as a conditioning regimen for autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: a matched comparison to a melphalan-only approach. *Biol Blood Marrow Transplant* 2013; 19: 69–74.

40. Lonial S, Kaufman J, Tighiouart M, *et al.* A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. *Clin Cancer Res* 2010; 16: 5079–5086.
41. Roussel M, Moreau P, Huynh A, *et al.* Bortezomib and high-dose melphalan as conditioning regimen before transplantation for de novo multiple myeloma patients: updated data of the IFM phase II study. *J Clin Oncol* 2010; 28: 8129.
42. Biran N, Rowley SD, Vesole DH, *et al.* A phase I/II study of escalating doses of bortezomib in conjunction with high-dose melphalan as a conditioning regimen for salvage autologous peripheral blood stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant* 2016; 22: 2165–2171.
43. Mark TM, Guarneri D, Forsberg P, *et al.* A phase I trial of high-dose lenalidomide and melphalan as conditioning for autologous stem cell transplantation in relapsed or refractory multiple myeloma. *Biol Blood Marrow Transplant* 2017; 23: 930–937.
44. Savani BN, Mukherjee A, Savani GT, *et al.* Utilization trend and in-hospital complications of autologous hematopoietic stem cell transplantation in multiple myeloma in the United States: 13 years perspective. *Blood* 2014; 124: 3978.
45. Paul TM, Liu SV, Chong EA, *et al.* Outpatient autologous stem cell transplantation for patients with myeloma. *Clin Lymphoma Myeloma Leuk* 2015; 15: 536–540.
46. Holbro A, Ahmad I, Cohen S, *et al.* Safety and cost-effectiveness of outpatient autologous stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant* 2013; 19: 547–551.
47. Gertz MA, Ansell SM, Dingli D, *et al.* Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. *Mayo Clin Proc* 2008; 83: 1131–1138.
48. 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: 2077–2084.
49. Cavo M, Pantani L, Petrucci MT, *et al.* Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood* 2012; 120: 9–19.
50. Mellqvist UH, Gimsing P, Hjertner O, *et al.* Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood* 2013; 121: 4647–4654.
51. Attal M, Lauwers-Cances V, Marit G, *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; 366: 1782–1791.
52. McCarthy PL, Owzar K, Hofmeister CC, *et al.* Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; 366: 1770–1781.
53. McCarthy PL, Holstein SA, Petrucci MT, *et al.* Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol* 2017; 35: 3279–3289.
54. Sonneveld P, Schmidt-Wolf IG, van der Holt B, *et al.* Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 2012; 30: 2946–2955.
55. Rosinol L, Oriol A, Teruel AI, *et al.* Bortezomib and thalidomide maintenance after stem cell transplantation for multiple myeloma: a PETHEMA/GEM trial. *Leukemia* 2017; 31: 1922–1927.
56. Kumar A, Kharfan-Dabaja MA, Glasmacher A, *et al.* Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2009; 101: 100–106.
57. Van der Graaf AWM, Bhagirath P, de Hooge J, *et al.* Non-invasive focus localization, right ventricular epicardial potential mapping in patients with an MRI-conditional pacemaker system: a pilot study. *J Interv Card Electrophysiol* 2015; 44: 227–234.
58. Attal M, Harousseau JL, Facon T, *et al.* Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003; 349: 2495–2502.
59. Cavo M, Tosi P, Zamagni E, *et al.* Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol* 2007; 25: 2434–2441.
60. Sonneveld P, Van der Holt B, Segeren CM, *et al.* Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma:

- long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. *Haematologica* 2007; 92: 928–935.
61. Fermand JP, Desseaux K and Marolleau JP. Single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD34-enriched ABSC: long-term results of a two by two designed randomized trial in 225 young patients with multiple myeloma (MM). For the Group “Myelome-Autogreffe”, Caen, Creteil, Limoges, Paris, Strasbourg, France. *Blood* 2009; 114: 917.
 62. Mai EK, Benner A, Bertsch U, *et al.* Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. *Br J Haematol* 2016; 173: 731–741.
 63. Alvares CL, Davies FE, Horton C, *et al.* The role of second autografts in the management of myeloma at first relapse. *Haematologica* 2006; 91: 141–142.
 64. Kumar S, Mahmood ST, Lacy MQ, *et al.* Impact of early relapse after auto-SCT for multiple myeloma. *Bone Marrow Transplant* 2008; 42: 413–420.
 65. Sellner L, Heiss C, Benner A, *et al.* Autologous retransplantation for patients with recurrent multiple myeloma: a single-center experience with 200 patients. *Cancer* 2013; 119: 2438–2446.
 66. Stewart AK, Rajkumar SV, Dimopoulos MA, *et al.* Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015; 372: 142–152.
 67. Dimopoulos MA, Oriol A, Nahi H, *et al.* Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 1319–1331.
 68. McCarthy PL, Hahn T, Hassebroek A, *et al.* Trends in use of and survival after autologous hematopoietic cell transplantation in North America, 1995–2005: significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age. *Biol Blood Marrow Transplant* 2013; 19: 1116–1123.
 69. Morris CL, Siegel E, Barlogie B, *et al.* Mobilization of CD34+ cells in elderly patients (>= 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. *Br J Haematol* 2003; 120: 413–423.
 70. Micallef IN, Stiff PJ, Stadtmauer EA, *et al.* Safety and efficacy of upfront plerixafor + G-CSF versus placebo + G-CSF for mobilization of CD34(+) hematopoietic progenitor cells in patients ≥60 and <60 years of age with non-Hodgkin’s lymphoma or multiple myeloma. *Am J Hematol* 2013; 88: 1017–1023.
 71. Badros A, Barlogie B, Siegel E, *et al.* Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *Br J Haematol* 2001; 114: 600–607.
 72. Sharma M, Zhang MJ, Zhong X, *et al.* Older patients with myeloma derive similar benefit from autologous transplantation. *Biol Blood Marrow Transplant* 2014; 20: 1796–1803.
 73. Palumbo A, Bringhen S, Mateos MV, *et al.* Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood* 2015; 125: 2068–2074.
 74. Badros A, Barlogie B, Siegel E, *et al.* Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol* 2001; 114: 822–829.
 75. Mahindra A, Hari P, Fraser R, *et al.* Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a center for international blood and marrow transplant research analysis. *Bone Marrow Transplant* 2017; 52: 1616–1622.
 76. Mehta J and Singhal S. Graft-versus-myeloma. *Bone Marrow Transplant* 1998; 22: 835–843.
 77. Krishnan A, Pasquini MC, Logan B, *et al.* Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol* 2011; 12: 1195–1203.
 78. Rosinol L, Perez-Simon JA, Sureda A, *et al.* A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood* 2008; 112: 3591–3593.
 79. Bruno B, Rotta M, Patriarca F, *et al.* A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med* 2007; 356: 1110–1120.
 80. Bjorkstrand B, Iacobelli S, Hegenbart U, *et al.* Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol* 2011; 29: 3016–3022.