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Guideline

Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation

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A B S T R A C T

Therapeutic strategies for multiple myeloma (MM) have changed dramatically over the past decade. Thus, the role of hematopoietic stem cell transplantation (HCT) must be considered in the context of this evolution. In this evidence-based review, we have critically analyzed the data from the most recent clinical trials to better understand how to incorporate HCT and when HCT is indicated. We have provided our recommendations based on strength of evidence with the knowledge that ongoing clinical trials make this a dynamic field. Within this document, we discuss the decision to proceed with autologous HCT, factors to consider before proceeding to HCT, the role of tandem autologous HCT, post-HCT maintenance therapy, and the role of allogeneic HCT for patients with MM.

INTRODUCTION

The landscape of multiple myeloma (MM) has changed dramatically over the last several years, with numerous new therapies and improved patient outcomes [1]. Since the last publication of American Society for Blood and Marrow Transplantation (ASBMT) guidelines for MM (2003) the

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Table 1
Levels of Evidence [4]

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2−	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Nonanalytic studies, eg, case reports or case series.
4	Expert opinion.

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paradigm for therapy (induction and after transplantation) has evolved significantly. As the utilization of autologous hematopoietic stem cell transplantation (auto-HCT) for MM has increased, the demographics of this therapy have shifted to provide improved outcomes for patients over 40 and 60 years old [2]. These exciting changes require a critical review of the role of hematopoietic stem cell transplantation (HCT) for this disease.

Data published between June 1, 2002 and December 31, 2014 were reviewed. We searched the PubMed database using the terms *multiple myeloma* and *transplant* as well as topics relevant to each particular discussion section. Only finalized peer-reviewed publications were included for review. Studies were graded according to the criteria set forth by the Steering Committee for Evidence-Based Reviews from ASBMT [3], adapted from the original recommendations of the Scottish Intercollegiate Guidelines Network Grading Review Group [4]. Levels of evidence were assessed and a grade was assigned to each recommendation following the criteria in Tables 1 and 2.

AUTO-HCT VERSUS CONVENTIONAL CHEMOTHERAPY

A significant survival advantage of high-dose chemotherapy (HDC) and auto-HCT over conventional chemotherapy was reported in the pivotal Intergroupe Francophone du Myelome (IFM) trial in 1996 [5]. Thereafter, several additional trials have been published to support these findings, the details of which are outlined in Table 3. Of the 6 trials presented, 4 have shown a benefit in progression-free survival (PFS) and 3 have shown a benefit in overall survival (OS) for auto-HCT. Of note, only 1 of these studies was published after 2010. A meta-analysis from 2007 also found an improvement for PFS in the auto-HCT arm but no benefit in OS [12]. Although the most recently published prospective trial by Palumbo et al. employed 2 cycles of melphalan 200 mg/m^2, patients received a more relevant lenalidomide-based induction [11]. In addition, an analysis of toxicity done by Fermand et al. [8] also favored the auto-HCT arm.

Based on these data, in conjunction with the previously reported results from the IFM study, we recommend HDC and auto-HCT as consolidative therapy for patients with MM (grade A recommendation). Prospective studies are in progress to further clarify if this recommendation will be upheld in the era of novel agents for induction therapy.

Table 2
Grades of Recommendation [4]

A	At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

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TIMING OF AUTO-HCT: EARLY VERSUS LATE

A systematic literature search did not identify any prospective, randomized trials comparing early versus delayed auto-HCT in MM since the publication of 2003 guidelines. Although the randomized study by Fermand et al. [8] showed a significant event-free survival (EFS) benefit and longer time without symptoms, treatment, or treatment toxicity with early transplantation in MM patients receiving conventional inductions, no such prospective data are available for MM patients receiving modern (immunomodulatory drug (IMiD)- or proteasome inhibitor-based) induction regimens.

Two retrospective studies have examined this issue more recently. Kumar et al. and Dunavin et al. retrospectively evaluated the role of early (within 12 months of diagnosis) versus delayed auto-HCT in MM patients (n = 290) who received IMiD-based inductions [13] or any novel induction [14]. The time to progression and OS from time of diagnosis were similar between the 2 groups in both studies.

These retrospective studies suggest feasibility of delayed auto-HCT in the modern era, but they are not a substitute for randomized data. The reason for employing early versus delayed transplantation in individual patients in these studies is not clear. Hence, which subset of MM patients is likely to benefit the most from delayed auto-HCT remains unknown. More importantly, no patient-reported outcome or quality of life data comparing early versus late auto-HCT in the modern era are available. Similarly, reliable cost effectiveness data comparing early transplantation against continuation of often expensive novel agent inductions are not available. Finally, in carefully selected MM patients receiving lenalidomide-based inductions with intent for a delayed auto-HCT, the importance of early stem cell collection and cryopreservation cannot be overemphasized [15-17]. Further recommendations on stem cell mobilization are discussed in the recently published ASBMT guidelines [18,19].

Therefore, based on available prospective data, we continue to recommend early (up-front) auto-HCT. However, given the recent and rapid changes in induction therapy, it is also reasonable to consider enrollment on a clinical trial that addresses the question of transplantation timing. The multicenter DFCI 10-106 (NCT01208662) trial is ongoing to address this exact question in the era of novel combination therapy.

Table 3
Summary of Prospective Randomized Trials Comparing Conventional Chemotherapy with Auto-HCT

Author	Study Details	Response Data	PFS Data	OS Data	Level of Evidence	Comments
Child, 2003 [6]	Pts < 65 yr ABCM→IFN maintenance vs Dox-Methylpred-Cy → auto-HCT	CR 8% versus 44% favoring auto-HCT group ($P = .04$)	Favoring auto-HCT group ($P < .001$)	Favoring auto-HCT group ($P < .04$)	1++	
Blade, 2006 [7]	Pts < 65 yr VBMCP/VBAD→ 8 additional cycles versus auto-HCT (high dose Mel ± TBI)	CR 11% versus 30% favoring auto-HCT group ($P = .002$)	No difference	No difference	1++	
Fermand, 2005 [8]	Pts < 65 yr VMCP versus CHOP/VAMP→ auto-HCT with Mel versus Bu/Mel	*P* value not reported	EFS favoring auto-HCT group ($P = .07$)	No difference	1++	Time without symptoms, treatment, and treatment toxicity (TwiSTT) longer in auto-HCT arm ($P = .03$).
Palumbo, 2004 [9]	Pts 50-70 yr MP × 6 versus Mel 100 mg/m^2 × 2	nCR = 6% versus 25% ($P = .002$)	EFS at 3 yr favoring auto-HCT group 16% versus 37% ($P < .001$)	OS at 3 yr favoring auto-HCT group 62% versus 77% ($P < .001$)	1++	
Barlogie, 2006 [10]	VAD→ VBMCP versus auto-HCT with Mel/TBI→ ± IFN maintenance	No difference	No difference	No difference	1++	
Palumbo, 2014 [11]	Len-Dex +Cy- mob→ MPR × 6 versus Mel 200 mg/m^2 auto-HCT × 2; all randomized to ± Len maintenance	*P* value not reported	Favoring auto-HCT group ($P < .001$)	Favoring auto-HCT group ($P < .02$)	1++	Maintenance improved PFS but not OS

Pts indicates patients; ABCM, doxorubicin, carmustine, cyclophosphamide, melphalan; Dox, doxorubicin; methylpred, methylprednisolone; Cy, cyclophosphamide; VBMCP, vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VBAD, vincristine, BCNU, doxorubicin, dexamethasone; Mel, melphalan; TBI, total body irradiation; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; VAMP, vincristine, doxorubicin, methylprednisolone; Bu, busulfan; TwiSTT, time without symptoms, treatment, or treatment toxicity; MP, melphalan, prednisone; nCR, near complete response; VAD, vincristine, doxorubicin, dexamethasone; Len, lenalidomide; Dex, dexamethasone; MPR, melphalan, prednisone, lenalidomide.

AUTO-HCT FOR REFRACTORY MYELOMA

The evidence to support a first auto-HCT for refractory disease (defined as < partial response to induction therapy) is generally limited to older retrospective studies (Table 4). Based on this literature, even patients with refractory disease can gain some benefit from auto-HCT, though this is probably less true for patients with overtly progressive disease [23]. It is also important to mention that data from these studies are from the early 2000s, such that a patient refractory to novel therapies may have a different clinical course. Retrospective analysis also suggests that, although additional lines of therapy before auto-HCT may improve response depth in patients with less than a partial remission, this does not seem to impact long-term survival [24]. Though prospective evidence is lacking, we recommend consideration of a first auto-HCT for patients with refractory disease (grade C).

FACTORS TO CONSIDER FOR AUTO-HCT: AGE AND COMORBIDITIES

Several groups have retrospectively examined whether age should be considered as a factor in patient selection for auto-HCT [25-27]. In all of these studies, age > 65 years has *not* been found to be a limiting factor for transplantation success. The hematopoietic cell transplantation–specific comorbidity index (HCT-CI) has been shown to predict risk of nonrelapse mortality and survival after allo-HCT. Saad et al. analyzed outcomes of 1156 patients in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry after auto-HCT and high-dose melphalan [28]. On multivariate analysis, OS was inferior in groups with HCT-CI score of 1 to 2 (relative risk, 1.37, [95% confidence interval, 1.01 to 1.87]; $P = .04$) and HCT-CI score > 2 (relative risk, 1.5 [95% confidence interval, 1.09 to 2.08]; $P = .01$). OS was also inferior with Karnofsky performance status < 90 ($P < .001$). However, it is important to note that the treatment-related mortality at 1 year was equivalent (2%) for patients with a HCT-CI score of 0 or >2.

We recommend that age not be used as a selection factor (grade C). However, an HCT-CI score of >2 or Karnofsky performance status <90 can warrant additional consideration before proceeding with auto-HCT. Though the evidence is mainly retrospective, it is unlikely that prospective randomized data will be forthcoming to truly answer this question.

Table 4
Summary of Studies Examining Role of Auto-HCT for Patients with Refractory MM

Author	Study Details	Response Data	PFS Data	OS Data	Level of Evidence
Singhal, 2002 [20]	n = 43 refractory pts; C-VAMP→auto-HCT	40% CR		Similar between refractory and responsive pts	2+
Kumar, 2004 [21]	n = 50 refractory pts versus n = 101 chemosensitive pts, all receiving auto-HCT	20% versus 35% CR ($P = .063$)	1-yr PFS similar between groups		2+
Alexanian, 2004 [22]	89 refractory pts; VAD→ auto-HCT versus 45 refractory pts without auto-HCT	16% CR in auto-HCT group	27 mo longer in auto-HCT group ($P < .01$)		2+
Rosinol, 2012 [23]	n = 80 primary refractory: 49 with SD and 31 with PD. VBMCP/VBAD Mel-based auto-HCT and second auto	No difference in response after first auto-HCT	PFS shorter in PD pts (.6 versus 2.3 yr, $P = .0004$)	OS shorter in PD pts (1.1 versus 6 yr, $P = .00002$)	2+

C-VAMP indicates vincristine, doxorubicin, methyleprednisolone; SD, stable disease; PD, progressive disease.

Table 5
Summary of Studies Examining Impact of Cytogenetics on Outcomes after Auto-HCT

Author	Cytogenetics/FISH Studied	Effect on PFS	Effect on OS	Level of Evidence
Falcon, 2001 [29]	Abnormality of 13 by FISH		Adverse prognostic factor ($P < .001$)	2+
Chang, 2004 [30]	t(4:14)	Significantly worse ($P = .0003$)	Significantly worse ($P = .0001$)	2+
Moreau, 2002 [31]	t(4:14)	EFS Significantly worse ($P < .000$)	Significantly worse ($P = .002$)	2+
Chang, 2005 [32]	p53 deletion	Significantly worse ($P = .0324$)	Significantly worse ($P = .0008$)	2+
Chang, 2010 [33]	Del 1p21	Significantly worse ($P < .001$)	Significantly worse ($P = .001$)	2+
Avet-Loiseau, 2007 [34]	Composite FISH for del(13), t(11;14), t(4;14), hyperdiploidy, MYC translocations, and del(17p)	Adverse results for t(4;14), del(17p) (EFS)	Adverse results for t(4;14), del(17p) (EFS)	2++
Fonseca, 2003 [35]	Composite of t(4;14), t(14; 16) and del17p		Significantly worse ($P < .001$)	2+
Neben, 2010 [36]	Composite of t(4;14) and del17p with ISS II or III		Significantly worse ($P < .001$)	2+

ISS indicates International Staging System.

FACTORS TO CONSIDER FOR AUTO-HCT: CYTOGENETICS

Several investigators have reported retrospective analyses of cytogenetic data for MM patients undergoing auto-HCT (Table 5). Although these studies of auto-HCT patients confirm the inferior outcome expected with high-risk cytogenetics, there are no prospective studies to determine if patients with any particular cytogenetic abnormality should *not* undergo auto-HCT or, conversely, whether any particular cytogenetic abnormality gains specific benefit from auto-HCT over conventional chemotherapy. However, the poor outcomes associated with some of these abnormalities make a case for alternative options for these patients. Therefore, we recommend serious consideration of a clinical trial for patients with high-risk cytogenetics, particularly del17p or t(4:14) (grade C).

WHAT IS THE OPTIMAL PREPARATIVE REGIMEN FOR HDC AND AUTO-HCT?

The IFM trial established melphalan 200 mg/m^2 (Mel 200) as the standard to which all other MM preparative regimens for auto-HCT are compared [37]. Table 6 summarizes the clinical trials with the highest degree of evidence in comparing alternative regimens to Mel 200. These studies focus on agents traditionally used for conditioning or add chemotherapy agents more often used in the treatment of hematologic malignancies other than myeloma. More recently, several single-arm studies have incorporated novel agents used routinely in the induction treatment of MM [42,43]. Although this may be a promising approach, no prospective controlled studies are available for higher level evidence.

Based on the studies performed, no combination of agents to date has proven safer or more effective than Mel 200 mg/m^2 as a preparative regimen. Thus, we recommend Mel 200 as the standard regimen for MM conditioning, outside of clinical trials (grade A). However, ongoing research that incorporates novel agents such as bortezomib may ultimately lead to increases in PFS and OS without contributing to excessive toxicity. Though beyond the scope of this review, recommendations on chemotherapy dosing in obese patients or patients with renal insufficiency are discussed in a recent review and ASBMT guidelines on these topics [44,45].

THE ROLE OF TANDEM AUTO-HCT FOR MULTIPLE MYELOMA

The advantage of an auto-HCT strategy that routinely incorporates tandem transplantations remains an open question. Table 7 details the prospective, randomized controlled trials of single versus tandem auto-HCT for MM. The landmark IFM trial demonstrated a benefit from the tandem auto-HCT in all parameters: EFS, relapse-free survival (RFS), and OS [46]. A subset analysis indicated that the group achieving less than a very good partial response benefited most from the tandem procedure. However, the Bologna 96 and the HOVON 24 trials showed the tandem arm to benefit EFS but not OS [47,48]. Finally, in the HOVON-65/GMMG-HD4 trial, a separate analysis comparing the single versus tandem approach showed an improvement in PFS but not in OS [49]. However, assignment to the treatment arm was based on geographic location and the trial had not been designed to prospectively ask this question.

In addition to the trials listed in Table 7, there have been several single-arm trials that have examined this question with comparisons made to historical controls [50-53]. The vast majority of these have not suggested superiority of the tandem approach, though the conditioning regimens vary

Table 6
Summary of Prospective Studies Examining Preparative Regimens for Auto-HCT in MM

Author	Regimens Studied	PFS/OS	Level of Evidence	Comments
Lahuerta, 2010 [38]	BuMel versus Mel 200	Median PFS 41 mo versus 31 mo; median OS 77 versus 70 mo ($P = .40$)	1–	Excessive VOD caused closing of Bu/Mel arm
Fenk, 2005 [39]	Idarubicin/Mel/Cy versus Mel 100 mg/m^2 × 2; IFN maintenance for all patients	No difference in EFS and OS TRM 20% versus 0% in Mel 200 arm	1+	Standard therapy better, less toxicity
Vela-Ojeda, 2007 [40]	BCNU/etoposide/Mel versus Mel 200	Median OS 36 mo versus 86 mo ($P = .08$)	1–	No benefit for oral Mel regimen
Palumbo, 2010 [41]	Mel 200 mg/m^2 × 2 versus Mel 100 mg/m^2 × 2	Median PFS 31.4 versus 26.2 mo ($P = .01$); 5-yr OS 61.8 versus 47.7% ($P = .13$)	1++	Mel 200 mg/m^2 should be considered standard, though was in tandem approach in this study

VOD indicates veno-occlusive disease; TRM, treatment-related mortality.

Table 7
Prospective Studies Examining Single versus Tandem Auto-HCT

Author	Conditioning Regimen	TRM/ORR	EFS	OS	Level of Evidence
Attal, 2003 [46]	TBI 8 Gy and Mel 140 mg/m^2 versus Mel 140 mg/m^2 followed by TBI 8 Gy and Mel 140 mg/m^2; IFN maintenance offered to all pts	TRM 4% versus 6% ORR 84% versus 88%	Favoring tandem arm; 25 mo versus 36 mo ($P = .03$)	Favoring tandem arm 48 versus 58 mo ($P = .01$)	1++
Cavo, 2007 [47]	Mel 200 mg/m^2 d-2 versus Mel 200 mg/m^2 followed by Mel 140 mg/m^2 d-2 and Bu 1 mg/kg PO × 12 d-5-to -3; maintenance IFN offered to all pts	TRM 3% versus 4% ORR NS CR + nCR 33% versus 47% ($P = .01$)	Favoring tandem arm; 23 versus 35 mo ($P = .001$)	65 mo versus 71 mo ($P = .9$)	1++
Sonnevold, 2007 [48]	Mel 70 mg/m^2 i.v. × 2 versus Mel 70 mg/m^2 i.v. × 2; Cy 120 mg/kg i.v. and TBI 9 Gy; maintenance IFN offered to all pts	TRM not stated; ORR 88% for entire group CR 13% versus 32%	Favoring tandem arm; 21 mo versus 22 mo ($P = .013$)	55 mo versus 50 mo ($P = .51$)	1++

ORR indicates overall response rate; NS, not significant; PO, orally.

between trials. Not surprisingly, a number of investigators have included novel agents, such as thalidomide or bortezomib, in a tandem transplantation algorithm [54-57]. Although the results of these trials are encouraging, the lack of a single HCT control arm makes their results difficult to interpret, particularly as induction regimens evolve rapidly.

Finally, Barlogie et al. have published their updated results with the total therapy approach [58-61]. With incorporation of novel therapeutics to rigorous induction followed by tandem HCT, consolidation, and maintenance, the single-center results have continued to improve. However, the treatment algorithms are complex and the contribution of each component, specifically the importance of using a tandem HCT platform, to the overall response is difficult to ascertain.

Two meta-analyses addressing the role of tandem HCT for MM have been published [62,63], both of which suggest that there is no apparent improvement in either EFS or OS using a tandem approach. Based on the conflicting data from the prospective randomized trials and the above meta-analyses, there is insufficient evidence to support tandem auto-HCT as the standard of care for myeloma patients. However, there are cases when this may be considered, based in the IFM data, in patients with less than a very good partial response after a first auto-HCT (grade D) or as part of a clinical trial. It is important to note that in the current era of IMiDs and proteasome inhibitors, the role of up-front tandem transplantation has not yet been decided. Results from an upcoming integrated analysis of 4 phase III European trials [64] and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 trial (NCT01109004), in which one third of patients have been randomized to a tandem melphalan 200 mg/m^2 arm, may ultimately alter future transplantation algorithms.

AFTER AUTO-HCT: RECOMMENDATIONS FOR FOLLOW-UP

Although not based on prospective, randomized studies, there have been guidelines established for timing and tests for follow-up [65,66]. Our recommendations are thus based mainly on consensus opinion in the setting of retrospective data. At present, the International Myeloma Working Group (IMWG) uniform response criteria [67] are the preferred criteria to determine the best response to treatment.

For measureable serum or urine myeloma proteins, the first measurement is taken 2 to 3 months after auto-HCT, and then followed every 3 to 4 months thereafter [65]. Although bone marrow (BM) aspiration/biopsy is required to document any complete response (CR), there is no evidence to indicate that it is required for follow-up if there are measurable serum or urine markers [66]. It should be noted that retrospective data suggests that patients with less BM disease burden have improved outcomes, even with negative serum and urine markers [68].

The role of various imaging modalities after transplantation is controversial. Current retrospective data suggest that serial skeletal survey is not useful for earlier detection of disease relapse or progression [69] and this is the opinion upheld by the IMWG. Although serial magnetic resonance imaging may assist in following response to therapy [70], its role in routine surveillance is not defined. In patients with known lesions at diagnosis, positron emission tomography-computed tomography (PET/CT) after transplantation can be useful to predict long-term outcome [71]. However, PET/CT imaging as a routine surveillance for asymptomatic patients after transplantation is not yet recommended.

Recently, the IMWG panel approved definitions of immunophenotypic CR and molecular CR to be incorporated into the IMWG criteria [72]. In addition, several studies have prospectively employed multiparameter flow cytometry and shown improved outcome in minimal residual disease (MRD)–negative patients after auto-HCT [73,74]. The European Myeloma Network has developed a consensus on for plasma cell enumeration, sample preparation, gating, and immunophenotype for clonality assessment [75]. However, there is still considerable variability in the United States regarding flow cytometric definitions of abnormal plasma cells [76].

Recommendations for Follow-up after Auto-HCT: A Position Statement Reviewed and Agreed upon by a Consensus Panel from the ASBMT

1. In patients with measurable disease, monitoring should start 2 to 3 months after auto-HCT and continue every 3 months thereafter with serum and/or urine M-protein, serial involved free light chain (FLC) assay, and serum FLC ratio. BM biopsy may be required in patients with oligosecretory plasma cell disorder and in patients with no measurable disease.
2. If documentation of response is desired, BM examination and FLC ratio are required to document CR, near CR, and stringent CR status or to assess cause of persistent cytopenias.
3. IMWG uniform response criteria should be used to determine disease status after auto-HCT.

Table 8
Summary of Prospective, Randomized Studies using Consolidation after Auto-HCT

Author	Study Details	Response Data	PFS Data	OS Data	Level of Evidence	Comments
Mellqvist, 2013 [77]	Bortezomib × 20 doses versus no consolidation	Upgrade from PR favoring consolidation arm ($P = .007$)	Favoring consolidation arm ($P = .05$)	No difference	1++	More fatigue in consolidation arm; benefits mainly for pts in < VGPR
Spencer, 2009 [78]	Thal-pred versus prednisone	CR + VGPR rate favoring Thal-pred arm ($P < .001$)	Favoring Thal-pred arm ($P < .001$)	Favoring Thal-pred arm ($P = .004$)	1++	
Cavo, 2012 [79]	VTD versus TD consolidation; dex maintenance for all	CR/nCR rate favoring VTD arm ($P = .02$)	Favoring VTD arm ($P = .042$)	No difference	1++	Tandem auto-HCT setting

PR indicates partial response; VGPR, very good partial response; Thal, thalidomide; VTD, bortezomib, thalidomide, dexamethasone; TD, thalidomide, dexamethasone.

4. In asymptomatic patients not suspected to have relapse or progression of disease after HCT, serial radiography/magnetic resonance imaging or PET scan is not routinely required. However, these tests may be used to follow response to therapy or evaluate new symptoms.
5. MRD testing after auto-HCT in MM can reveal patients at risk for poorer outcomes and should be considered for disease evaluation (grade B). If MRD testing is attempted, multiparametric flow cytometry following the European Myeloma Network consensus guidelines should be the method of choice.

AFTER AUTO-HCT: RECOMMENDATIONS FOR TREATMENT

In the era of novel agents, consolidation and maintenance strategies are attractive options after auto-HCT. Table 8 summarizes prospective, randomized trials examining post-transplantation consolidation, defined as a planned course of full or intermediate dose cycles. Of note, only the study by Mellqvist et al. [77] compared consolidation bortezomib with no treatment, whereas the other 2 studies compared consolidation strategies [78,79]. In the first trial, consolidation bortezomib improved PFS but not OS. Maintenance strategies with glucocorticoids [80,81] or interferon [10,82,83] have largely been abandoned because of excessive toxicity and/or absence of benefit. Table 9 summarizes prospective randomized trials using novel agents for maintenance therapy after auto-HCT. We included only trials that studied the effect of additional therapy after auto-HCT with no randomization before auto-HCT.

Maintenance thalidomide was associated with improved OS in at least 1 trial [84]; however, the increased toxicities and inferior outcomes in health-related quality of life [86] have made this strategy less appealing. Three randomized controlled trials have examined maintenance lenalidomide [11,88,89]. Although all showed improved PFS, only the CALGB trial demonstrated an improvement in OS. It should be noted that 2 of these trials [88,89] demonstrated an increase in second primary malignancies (SPM) in the maintenance lenalidomide arms. In a recently published meta-analysis of 8 randomized controlled trials, a benefit in both PFS and OS was seen for IMiD-based maintenance [90]. This was largely based on data with thalidomide but suggested that longer follow-up with lenalidomide was needed. Though there has been data to suggest that bortezomib maintenance may also be used [49], it has not been as rigorously studied as maintenance alone against an appropriate control.

Recommendations for Therapy after Auto-HCT

1. Consolidation after auto-HCT is not routinely recommended but can be considered in the setting of a clinical trial.

Table 9
Summary of Prospective Studies Using Novel Agents for Maintenance Therapy after Auto-HCT

Author	Study Details	Response Data	PFS Data	OS Data	Level of Evidence	Comments
Attal, 2006 [84]	No maintenance versus pamidronate versus Thal-pamidronate	CR favoring Thal-pamidronate ($P = .03$)	EFS favoring Thal-pamidronate ($P < .009$)	Favoring Thal-pamidronate ($P < .04$)	1++	Increased neuropathy, fatigue, constipation, neutropenia in Thal-pamidronate arm
Maiolino, 2012 [85]	Dex versus Thal-dex	No difference	Favoring Thal-dex ($P = .002$)	No difference	1++	
Stewart, 2013 [86]	No maintenance versus Thal-pred	Not reported	Favoring Thal-pred ($P < .0001$)	No difference	1++	Worse HRQoL in Thal-pred arm
Morgan, 2012 [87]	No maintenance versus Thal		Favoring Thal ($P < .001$)	No difference	1++	Meta-analysis suggested benefit of Thal on OS
McCarthy, 2012 [88]	Len versus placebo	Not reported	Favoring Len ($P < .001$)	Favoring Len ($P = .03$)	1++	More toxicities and SPMs in Len arm
Attal, 2012 [89]	Consolidation Len→Len maintenance versus placebo	CR/VGPR rates favoring Len maintenance ($P = .009$)	Favoring Len maintenance ($P < .001$)	No difference	1++	More toxicities and SPMs in Len arm
Palumbo, 2014 [11]	MPR × 6 and Mel 200 auto-HCT × 2 arms both randomized to ± Len maintenance	Not reported for non-maintenance arms	For auto-HCT group PFS favored maintenance arm: 64.7 versus 37.4 mo	No difference due to maintenance for auto-HCT group	1+	Maintenance improved PFS but not OS; SPMs not increased in maintenance arm

HRQoL indicates health-related quality of life.

2. Maintenance with an immunomodulatory drug (thalidomide or lenalidomide) is recommended unless a contraindication exists (grade A). In most cases, lenalidomide is preferred because of improved survival data in the era of novel agents.
3. In patients with high-risk disease with renal failure or adverse chromosome changes, post–auto-HCT bortezomib consolidation and maintenance may be considered (grade D).

LONG-TERM MANAGEMENT OF MM PATIENTS AFTER AUTO-HCT

After auto-HCT, patients are often referred back to their community oncologist. It is imperative that the transplantation physician collaborate with referring hematologists to determine a follow-up plan. With improving survival, patients now face concerns for SPM, thrombosis, anticoagulation, bone complications, and economic and relationship issues.

Though there are very little prospective data on the post-transplantation population, our experience suggests that the principles from the induction period can apply. Thus, based on expert panel consensus, we recommend resumption of bisphosphonate therapy [91] as per IMWG recommendations [92] and prophylactic anticoagulation or antiplatelet therapy for patients receiving thalidomide or lenalidomide therapy [93,94]. Because of the increased risk of SPMs in the setting of lenalidomide maintenance therapy [88,89], patients should be followed closely and monitored for hematological and nonhematological cancers.

SECOND TRANSPLANTATION AS SALVAGE THERAPY FOR RELAPSED MM

Unfortunately, the majority of patients treated with an initial auto-HCT eventually relapse. Although there are a number of new drugs for treating relapsed disease, a second transplantation remains a viable treatment option for patients and should be considered in the arsenal of available therapeutic options for these patients. Current National Comprehensive Cancer Network guidelines recommend that all patients who are eligible for auto-HCT be considered for peripheral blood apheresis sufficient for 2 autografts in the event a second autograft is necessary in the salvage setting [95].

Until recently, most of the data regarding the efficacy of a second auto-HCT have been limited to single-institution, retrospective studies that include a relatively small number of patients (Table 10). However, the first prospective phase III study of second salvage auto-HCT was recently reported [110]. Salvage auto-HCT was compared with salvage cyclophosphamide in patients who had relapsed disease after previous auto-HCT. Patients in the salvage auto-HCT had a superior PFS ($P < .0001$) but not OS.

The retrospective studies have consistently shown that salvage second auto-HCT is a viable and safe option for patients with relapsed disease. The most consistent finding among these studies is that longer progression-free interval from first auto-HCT is associated with better outcomes for PFS and OS. In contrast to this, patients with rapid relapse (<12 months) do not derive significant benefit from a second auto-HCT. When examined as a group, the overall response rate was 64.3% (95% confidence interval, 27.3% to 97.4%) with a median PFS of 12.3 months and median OS of 12.3 months, which are comparable to outcomes with other salvage regimens [111]. Of note, there are no prospective data regarding the use of maintenance therapy after second salvage auto-HCT. Finally, when comparing second auto-HCT to allogeneic HCT (allo-HCT), patients who undergo allo-HCT may suffer higher nonrelapse mortality with inferior OS [109].

Table 10
Recent Retrospective Studies Evaluating Second Salvage Auto-HCT for Relapsed MM

Authors	Years of Study	N	NRM, %	Median PFS, mo	Median OS, mo
Auner, 2013 [96]	1994-2001	83	—	15.5	31.5
Chow, 2013 [97]	1992-2011	30	7	22	45
Gonsalves, 2013 [98]	1994-2009	98	4	25.3	33
Lemieux, 2013 [99]	1995-2009	81	—	18	48
Michaelis, 2013 [100]	1995-2008	187	4	11.2	30
Jimenez-Zepeda, 2012 [101]	1992-2009	81	2.6	16.4	53
Shah, 2012 [102]	1992-2008	44	2	12.3	31.7
Blimark, 2011 [103]	1996-2007	66	NR	8.5	24
Cook, 2011 [104]	1990-2002	106	7	—	46.8
Fenk, 2011 [105]	1993-2008	55	5.9	14	52
Burzynksi, 2009 [106]	1999-2007	25	8	12	19
Olin, 2006 [107]	1998-2007	41	7	8.5	20.7
Elice, 2006 [108]	1993-2003	26	—	14.8	38.1
Qazilbash, 2006 [109]	1992-2004	14	7	6.8	29.5

Recommendations on the Role of Salvage Second Auto-HCT

Second auto-HCT is a safe and efficacious treatment modality for relapsed MM and should be considered (grade B). We note that this grade is based on data with superior PFS as an outcome, but think that this is an appropriate endpoint in the relapsed setting.

Patients with longer progression-free interval after first auto-HCT have better outcomes after salvage second auto-HCT. It is recommended that the minimum length of remission be at least 12 months for consideration of second auto-HCT as salvage therapy (grade D).

The role of maintenance therapy after salvage second auto-HCT is unclear.

ALLOGENEIC TRANSPLANTATION FOR MYELOMA

The role allo-HCT in MM remains controversial and poorly defined. Interest in allo-HCT for MM has been sustained by the promise of a myeloma-free donor cell graft and the possibility of an immune-mediated graft-versus-myeloma effect [112-114]. Traditional myeloablative conditioning and its associated toxicities have given way to more tolerable reduced-intensity conditioning (RIC) regimens. Often performed after optimal cytoreduction with a conventional auto-HCT, this approach uncouples myeloablation (achieved by the auto-HCT) from the graft-versus-myeloma effect mediated by establishing donor chimerism more safely through reduced-intensity allo-HCT. However, it should be noted that marked improvements have been over the past decade in supportive care and typing. As such, the role of conditioning (myeloablative versus RIC) remains an open question.

Several randomized trials (Table 11) have utilized biological assignment of patients to prospectively compare tandem auto-HCT-allo-HCT versus tandem auto-HCT in the upfront transplantation setting [115-123]. Unrelated donors were permitted in 1 study [121], whereas all the remaining studies assigned patients to auto-HCT-allo-HCT if a matched sibling donor was available. These trials vary substantially in design, eligibility, pretransplantation induction therapy, use

Table 11
Summary of Randomized Trials Comparing Tandem Auto-HCT-Allo-HCT versus Tandem Auto-HCT

Authors	Cooperative Group	Population, Including Cytogenetic Abnormalities	Follow-Up, mo	Conditioning						GVHD Prophylaxis	Outcomes
				Auto, n	Auto/ RIC, n	AHCT, median age	AHCT/allo-HCT, median age	Auto	RIC		
Bjorkstrand, 2011 [115]; Gahrton, 2013 [116]	EBMT-NMAM	Newly diagnosed MM patients, <70 yr	96	249	108	57	54	Mel 200	Flu+TBI 200 cGy	CSA + MMF	Better 8-yr PFS (22% versus 12%) and OS (49% versus 39%) for auto-HCT/allo-HCT
Garban, 2006 [117], Moreau, 2008 [118]	IFM	del13 del +/ or B2 microglobulin > 3 mg/L and <65 yr	56	219	65	58	54	Mel 200, Mel 220	Bu + Flu + ATG	CSA + MTX	No difference in PFS or OS
Giaccone [119], Bruno [120]	NA	Newly diagnosed MM patients, ≤65 yr	86	82	80	54 (mean)	54 (mean)	Mel 200, Mel 100-200	TBI 200 cGy	CSA + MMF	Median PFS (35 versus 29 mo) and OS (80 versus 54 mo) superior in AHCT/ allo-HCT
Knop [121]	DSMMM	del13 del by FISH, ≤ 60 yr	41	73	126	56	52	Mel 200	Flu + Mel ± ATG	NA	No difference is OS, PFS not reported.
Krishnan, 2011 [122]	BMT-CTN	Not meeting criteria for high risk, ≤70 yr	40	436	189	55	53	Mel 200	TBI 200 cGy	CSA + MMF	No difference in 3-yr PFS or OS
Krishnan, 2011 [122]	BMT-CTN	del13 del by cytogenetics or B2microglobulin> 4 mg/L, ≤70	40	48	37	57	51	Mel 200	TBI 200 cGy	CSA + MMF	No difference in 3-years PFS or OS
Rosinol, 2008 [123]	PETHEMA	Not achieving CR/nCR after first autologous, <65 yr	62	85	25	55	52	Mel 200 or CVB	Flu + Mel	CSA + MTX	More CR in AHCT/allo-HCT, no difference in PFS or OS

EBMT-NMAM indicates European Group for Blood and Marrow Transplantation Non-Myeloablative Allogeneic Stem Cell Transplantation in Multiple Myeloma (NMAM)2000 study; Flu, fludarabine; CSA, cyclosporine A; MMF, mycophenolate mofetil; ATG, antithymocyte globulin; NA, not available; PETHEMA, Programa para el Estudio de la Terapéutica en Hemopatía Maligna; CVB, cyclophosphamide, etoposide, BCNU.

of total body irradiation in the conditioning regimen, use of anti-hymoglobulin, and graft-versus-host disease (GVHD) prophylaxis.

The 2 trials with the longest duration of follow up [115,116,119,120] (96 and 86 months) are also the only trials reporting superior PFS and OS among patients assigned to auto-HCT-allo-HCT. All the remaining studies, including the largest of the trials performed [122], found no PFS or OS difference between the 2 approaches. Meta-analyses of the published allo-HCT versus auto-HCT studies have confirmed that although CR rates are higher for allo-HCT, so are the rates of treatment-related mortality [124,125]. Thus, a consistent PFS or OS benefit for allo-HCT cannot be demonstrated.

Although allo-HCT has been considered for high-risk groups, the optimal patient population for this strategy is not known and requires further investigation. Data on late allo-HCT is scarce, with no prospective randomized trial. A recent CIBMTR analysis [126] and several single-center studies [127,128] have suggested that for the multiply relapsed patient in the salvage setting, allo-HCT does not offer significant advantages in survival or a prospect of cure.

There are also no prospective studies reporting on the outcome of allo-HCT for plasma cell leukemia (PCL). A retrospective CIBMTR study of 50 PCL patients who received allo-HCT or auto-HCT in the first 18 months from diagnosis did not show any advantage of allo-HCT [129], despite lower relapse rate. Although inconclusive, these data suggest that in PCL, as in MM, the benefits of lower relapse rates after allo-HCT are often offset by the high treatment-related mortality. More tolerable conditioning regimens and advances in supportive care may ultimately allow allo-HCT to have a greater impact on this high-risk disease.

Lenalidomide maintenance is more controversial in the allo-HCT setting (versus auto-HCT). It was not feasible and associated with higher GVHD rates in 1 study [130] whereas a more recent prospective phase 2 study suggested benefit in a high-risk MM population with a 18 month PFS of 68% [131]. Proteasome inhibitors have been shown to be safe after allo-HCT and are known to reduce the risk of GVHD in clinical and experimental settings [132,133]. Newer trials of allo-HCT incorporating maintenance of either immune modulators or proteasome inhibitors are being conducted and designed (ISRCTN16228367 Lena RIC study and BMT CTN1302).

Recommendations on the Role of Allo-HCT

Upfront myeloablative allo-HCT is not routinely recommended (grade A). It may be appropriate for further study in young patients with very high-risk MM, in the context of a clinical trial.

Planned RIC-allo-HCT after auto-HCT has not been found to be superior in the majority of clinical trials and is, therefore, not recommended over auto-HCT (grade A). Its role in high-risk subgroups requires further study.

Allo-HCT salvage therapy for relapsed MM has not been shown to be superior to salvage auto-HCT and is not routinely recommended outside of a clinical trial (grade D). For younger patients with a good performance status, allo-HCT can be considered, ideally in the context of a clinical trial.

The role and choice maintenance after allo-HCT has not been adequately studied and is not known.

CONCLUSIONS

The recent advances in therapy for MM have ushered in an era in which clinical data cannot always dictate clinical experience. Although HDC with auto-HCT is still considered a valuable tool for tumor reduction and remission consolidation, the true data to support this modality in the current framework of novel therapies are being developed. In these guidelines, we have attempted to present an objective review of the existing data so that practitioners can make an educated recommendation to their patients.

The limitations of these recommendations should not be overlooked. Much of the randomized, controlled, prospective data comes from trials done before novel triple therapy induction regimens. Much of the data from trials with novel regimens is single-arm or retrospective. In addition, advances in supportive care and disease detection increasingly influence our decision-making process to tailor treatment for each individual patient. As patients with MM live longer, the importance of quality of life cannot be overemphasized. Future clinical trials with quality of life endpoints will likely have a significant impact on the decision to proceed with transplantation options.

We await the results of several pivotal trials (BMT CTN 0702, 1304) to further clarify the role and timing of auto-HCT for MM in the setting of novel therapeutics. In addition, the equivocal data with allo-HCT combined with poor outcomes for high-risk patients, regardless of treatment choice, justify investigating allo-HCT as an up-front therapy for these patients. This is also being developed as a multicenter clinical trial (BMT CTN 1302).

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SUPPLEMENTARY DATA

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