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REVIEWS

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Symposium Report

2017 BMT TANDEM MEETINGS

Optimal Use of Stem Cell Mobilization in Patients with Hematologic Malignancies

Adapted from a continuing medical education symposium presented at the 2017 BMT Tandem Meetings on February 25, 2017, in Orlando, Florida.
This program is supported by an educational grant from Sanofi Genzyme.

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Program Overview

The goal of this educational program is to enhance the efficacy and safety of stem cell mobilization for donors of patients with multiple myeloma (MM) by spreading information of the most current and effective methods to physicians. Collecting stem cells for transplantation is necessary for many patients, as transplantation persists as an effective strategy for myeloma. New collection methods are arising and improving stem cell mobilization, and physicians should be kept up to date on the new options and guidelines for protecting donor safety.

Learning Objectives

The following are the learning objectives in CME format for this program. Upon completion of this program, participants will be able to:

- Identify existing and emerging strategies for optimizing stem cell mobilization

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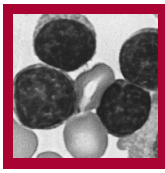

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- Select optimal CD34 goals and strategies to achieve the best results
- Identify barriers to autologous transplants in MM

Target Audience

This activity has been developed and is intended for transplant specialists, oncologists, hematologists, and other healthcare professionals involved in the treatment of patients with hematologic malignancies.

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Parameswaran N. Hari, MD, MRCP, MS, discloses that he has received honoraria and served as a consultant for Sanofi, Celgene, and Takeda.

Luciano Costa, MD, discloses that he has received honoraria and research funding from Sanofi and from Amgen, and has received honoraria from Celgene. He has served also as a consultant for Sanofi.

John R. Wingard, MD, has no relevant financial relationships to disclose.

Hemant Murthy, MD, has no relevant financial relationships to disclose.

Jack W. Hsu, MD, has no relevant financial relationships to disclose.

FROM THE EDITOR'S DESK

Stem Cell Transplantation in Multiple Myeloma: Expanding Access to a Highly Effective, Yet Underutilized Treatment

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Multiple myeloma remains an incurable illness however, the future is bright as continued progress is made. Once a disease whose life expectancy could only be measured in weeks, we now routinely speak of survival with myeloma in years. The introduction of novel therapies has resulted in deeper remissions following induction, prolonged survival with maintenance therapy, and improved responses in relapsed setting.

Despite novel therapies, autologous stem cell transplant remains a cornerstone of myeloma therapy, adding incremental benefits to the novel therapies. Multiple prospective, randomized controlled trials have shown improvement in progression free survivals in newly diagnosed myeloma patients who received autologous transplant consolidation versus novel therapies alone. This can be in large part attributed to incorporation of these novel therapies with autologous transplant, as well as continued advances in supportive care associated with stem cell collection and transplantation.

However, autologous stem cell transplantation is still underutilized in the management of patients with multiple myeloma. Efforts are needed to enhance access to this important modality of treatment to mirror the efforts made to enhance the efficacy of treatments. One large barrier to access to autologous transplantation centers around referral practices. Age and comorbidities may unduly restrict one's ability to receive a transplant if a referral is not made. Economic, racial, and other social barriers may unknowingly exist as well as apparent barriers to referral to transplant centers. Another significant barrier exists once a transplant is planned with regards to mobilization of hematopoietic stem cells. Late referrals to transplant centers, prolonged exposure to therapies which may impact mobilization and lack of early consideration of autologous transplantation when creating treatment algorithms may often complicate the ability to organize transplantation and remove a therapy which can significantly improve outcomes. Even when planned accordingly, however, strategies to prevent and overcome mobilization failure are still necessary. With the availability of plerixafor and the use of pre-apheresis circulating CD34+ cell concentrations, our ability to identify patients at high risk for mobilization failure is enhanced, and potentially preventable. The availability of pegfilgrastim and biosimilars, in addition to other mobilization strategies, has further complicated the issue of determining the optimal regimen for mobilization and fostered the need for more studies to inform consensus guidelines.

In this issue, Dr. Parameswaran N. Hari describes the patterns and causes for underutilization of autologous transplantation and strategies to overcome this, while Dr. Luciano J. Costa reviews the current concepts and strategies in stem cell mobilization, which are critical for successful stem cell transplantation. With continued efforts to remove barriers and improve access to transplantation, these clinical advancements and improved outcomes can hopefully be experienced by many more affected by myeloma today.

Parameswaran N. Hari, MD, MRCP, MS

Introduction

Transplantation for multiple myeloma (MM) is the most common use of hematopoietic stem cells in the United States. Nonetheless, autologous stem cell transplantation (ASCT) remains a vastly underutilized treatment modality in MM. This issue of *Blood and Marrow Transplantation Reviews* focuses on the key barriers to hematopoietic stem cell transplantation (HSCT) for patients with hematologic malignancies, with a focus on ASCT procedures in patients with MM. Strategies for optimizing stem cell mobilization in patients undergoing ASCT are also reviewed.

Barriers to Autologous Transplantation for Myeloma

Parameswaran N. Hari, MD, MRCP, MS

The current standard of care for patients with newly diagnosed MM involves an assessment of transplant eligibility based on patient age, performance status, and the presence of certain comorbidities. Ideally, patients are evaluated at the time of diagnosis, and transplant physicians are consulted to select the optimal induction regimen for each patient. For most patients in the community however, induction therapy is initiated without considering the potential impact of the induction regimen on subsequent treatment options. For transplant-eligible patients, hematopoietic stem cells can be harvested and used within the first several cycles of induction treatment (i.e., early or upfront transplant), or stored for use at first relapse (i.e., late transplant). Following transplant, options for consolidation and/or maintenance therapy are also evolving.

For patients with MM who are not candidates for transplantation, treatment algorithms are well established for induction and extended therapy. Notably, many patients who are initially considered poor candidates for transplant may crossover to transplant eligibility. Fewer patients will transition from transplant-eligible to transplant-ineligible due to complications and other barriers.

Upfront Transplantation in Newly Diagnosed Multiple Myeloma

Several recent clinical trials have reinforced the central role of autologous stem cell transplant (ASCT) for patients with MM who are undergoing induction therapy. The prospective, randomized, phase III European Myeloma Network (EMN) EMN02/H095 trial enrolled 1510 patients aged ≤65 years with newly diagnosed, symptomatic, transplant-eligible multiple myeloma [1]. Patients were stratified according to baseline International Staging System (ISS) risk criteria and the presence of high-risk cytogenetics (t(4;14), del(17p), del(1p), or 1q gain). All patients underwent indication therapy with 3-4 cycles of bortezomib, cyclophosphamide, and dexamethasone (VCD). After induction, 1211 eligible patients were randomly assigned to 4 cycles of bortezomib, melphalan, and prednisone (VMP; n = 505) or high-dose melphalan (HDM) plus single or double ASCT (n = 706). Patients then underwent a second randomization to consolidation therapy with 2 cycles of bortezomib, lenalidomide, and dexamethasone (VRD; n = 444) or no consolidation (n = 459). All patients were then treated with lenalidomide 10 mg/day on days 1-21 every 4 weeks as continuous maintenance therapy. The primary endpoint was progression-free survival (PFS) after the first and second randomizations.

Cavo and colleagues presented preplanned interim findings from the EMN02/H095 trial at the 2016 American Society of Clinical Oncology (ASCO) annual meeting (Table 1) [1]. The median follow-up was 26 months (range, 19-37 months) from the first randomization. Compared with VMP, upfront ASCT was associated with a significant improvement in median PFS in the overall study population (HR, 0.73; 95% CI, 0.61-0.88; P = .001). Patients with high-risk cytogenetics derived the greatest benefit front upfront transplantation, with the median PFS increasing more than two-fold from 20.3 months in the VMP group to 42.3 months in the ASCT (HR, 0.53; 95% CI, 0.37-0.76; P = .001). The most common adverse events in the ASCT group were gastrointestinal (GI) concerns and mucositis.

The EMN02/H095 trial is the most recent in a series of clinical trials highlighting the benefit of upfront ASCT in patients with newly diagnosed MM [2-5]. Even in the era of highly potent triplet induction regimens such as VRD and VCD, upfront ASCT appears to be an effective strategy for debulking MM, leading to improved PFS compared with late transplant across all studies (Table 2) [2-5]. In the trials from GIMEMA and Gay et al, early transplant was also associated with a significant improvement in overall survival (OS) [2,3].

Implications of Novel Induction Regimens

Upfront ASCT also appears to improve the efficacy of emerging regimens such as carfilzomib, lenalidomide, and dexamethasone (KRd) [6,7]. In 2012, Jakubowiak et al presented findings from a phase I/II trial demonstrating the benefit of frontline KRd without transplantation in patients with newly diagnosed MM (N = 53) [7]. In that study, 61% of patients achieved a stringent complete response (sCR) after completing at least 8 cycles of KRd, and the 2-year PFS rate was 92% [7].

More recently, Jakubowiak and colleagues conducted a phase II trial designed to assess whether ASCT improved the efficacy of extended KRd in newly diagnosed MM [6]. The phase II KRd plus ASCT trial enrolled 76 patients with newly diagnosed

Table 1. Progression-Free Survival Following Upfront Autologous Stem Cell Transplant or Bortezomib, Melphalan, and Prednisone After Induction Therapy [1]

	All Patients		High-Risk Patients	
	ASCT (n = 695)	VMP (n = 497)	ASCT (n = 133)	VMP (n = 87)
Median PFS, months	Not reached	42.5 months	42.3 months	20.3 months
3-year PFS	65%	57.1%	52.4%	29.5%
HR (95% CI)	0.73 (0.61-0.88)		0.53 (0.37-0.76)	
P value	.001		.001	

ASCT, autologous stem cell transplant; CI, confidence interval; HR, hazard ratio; PFS, progression free survival; VMP, bortezomib, melphalan, and prednisone.

Table 2. Recent Studies of Upfront Transplantation or Novel Agent-Based Regimens in Newly Diagnosed Multiple Myeloma [2-5]

Group/Trial	Patients (N)	Induction Regimen	Comparison	Response ≥VGPR	Progression-free survival	Overall survival
GIMEMA MM-03-05	402	RD x 4	MPR x 6 ASCT x 2	63% 59%	Median: 22 months 43 months*	At 4 years: 65% 81%*
Gay et al multicenter trial	389	RD x 4	CRD x 6 ASCT x 2	50% 54%	Median: 29 months 43 months*	At 4 years: 86% 73%*
IFM/DFCI 2009	700	VRD x 3	VRD x 5 ASCT + VRD x 2	78% 88%*	Median: 34 months 43 months*	At 4 years: 83% 81%
EMN02/ HO95 MM	1192	VCD x 3-4	VMP x4 ASCT 1 or 2	74% 85%*	At 3 years: 57% 65%*	NS; short follow-up

*Statistically significant (P < .05).

ASCT, autologous stem cell transplant; CDR, cyclophosphamide, lenalidomide, and dexamethasone; EMN, European Myeloma Network; GIMEMA, Italian Group for Hematologic Diseases in Adults; IFM/DCFI, Intergroupe Francophone Du Myelome/Dana-Farber Cancer Institute; MPR, melphalan, prednisone, and lenalidomide; NS, nonsignificant; RD, lenalidomide plus dexamethasone; VCD, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

Table 3. Responses During Treatment with Upfront Carfilzomib, Lenalidomide, and Dexamethasone with and without Autologous Stem Cell Transplantation [6]

Responses	KRd with ASCT			KRd without ASCT		
	4 cycles (n = 75)	8 cycles (n =70)	18 cycles (n = 50)	4 cycles (n = 49)	8 cycles (n =44)	18 cycles (n = 41)
≥sCR	11%	63%*	84%	8%	30%*	51%
≥CR	16%	67%	86%	18%	34%	59%
≥nCR	23%	81%	94%	43%	66%	80%
≥VGPR	73%	91%	94%	69%	89%	90%

*Primary endpoint.

ASCT, autologous stem cell transplantation; CR, complete response; KRd, carfilzomib, lenalidomide, and dexamethasone; nCR, near complete response; sCR, stringent complete response; VGPR, very good partial response.

MM who were eligible for ASCT with no age limitations [6]. All patients received 4 cycles of KRd followed by HDM and ASCT. After transplantation, patients also received 4 additional cycles of KRd consolidation (cycles 5-8) and 10 additional cycles of KRd maintenance therapy (cycles 9-10). Patients received off protocol maintenance after completing 18 cycles of KRd. The primary endpoint was the sCR rate at the end of post-ASCT consolidation. Response rates among patients treated with KRd plus ASCT were compared with those among patients enrolled in the phase I/II trial of KRd without transplantation.

At the 2016 American Society of Hematology (ASH) annual meeting, Zimmerman and colleagues presented results demonstrating deep responses with extended KRd and transplantation [6]. Patients treated with ASCT and KRd achieved higher response rates those treated without ASCT across all treatment cycles, including the primary endpoint of sCR after KRd cycle 8 (63% versus 30%) (Table 3). After a median follow-up of 17.5 months, the 2-year estimated PFS and OS rates were 97% and 99%, respectively, for all patients treated with KRd and ASCT. The most common grade 3-4 adverse events among patients treated with KRd plus ASCT included lymphopenia (28%), neutropenia (18%), and infections (8%).

These findings demonstrate the continued value of ASCT, even in the setting of highly potent, novel induction regimens. Future research may assess the role of additional therapies, such as monoclonal antibodies, added to the backbone of regimens such as KRd plus ASCT.

Maintenance, Consolidation or Second transplant?

The phase III StaMINA trial examined the role of additional treatment, including consolidation therapy or second ASCT, among patients with newly diagnosed who completed standard upfront HDM and ASCT [8]. The trial enrolled 758 patients aged ≤70 years with MM requiring therapy. Although the induction regimen was not specified, all patients were required to complete at least 2 cycles of systemic therapy, and were within 2-12 months of treatment initiation at the time of study enrollment. Autograft requirements included the availability of ≥ 4 × 106 CD34+ cell/kg. The median patient age was 57 years (range, 20 to 70 years). After completing treatment with melphalan 200 mg/m2 plus ASCT, patients were randomly assigned to 1 of 3 groups: no consolidation (n = 257), consolidation with 4 cycles of RVD (n = 254), or a second ASCT (n = 247). All patients were also treated with standard lenalidomide maintenance therapy until progression. The primary endpoint was PFS.

After a median follow-up of 37.8 months, there was no difference in the estimated PFS or OS rates across treatment arms (Table 4) [8]. These findings indicate that upfront treatment with single ASCT followed by lenalidomide maintenance should remain the standard of care for patients with newly diagnosed MM treated with modern induction therapy.

Transplantation Trends and Barriers

As described in the previous section, clinical trial findings consistently support ASCT to prolong the first PFS following diagnosis. Whenever possible, upfront transplantation is preferable to improve patient outcomes. Despite its role as the standard of care for initial therapy in MM,

however, ASCT remains widely underutilized. Data from the Center for International Blood and Marrow Transplant Research database (CIBMTR) show that fewer than one-third of all patients who are potentially eligible for ASCT in the US will proceed to transplantation (Table 5) [9]. At present, approximately 6,500 transplants are performed each year in the US for patients with MM. Those who are most likely to undergo HCT are white male patients, whereas black women are least likely to be treated with transplantation. In addition, few patients with MM aged ≥65 years are receiving transplants, despite increased treatment access via Medicare coverage. If all patients who needed HCT received one, the number of transplants for MM would increase to approximately 15,000 each year.

Recent research has focused on understanding the complex barriers to transplantation. The majority of HSCT procedures are autologous, and therefore not limited by donor availability. Regardless, certain patient groups, including Hispanic patients, black patients, elderly patients, and women, remain particularly vulnerable to disparities in cancer care. The specific barriers to ASCT among patients with MM appear to span economic, social, provider, and health-system factors (Table 6) [10].

Table 4. Survival Outcomes After First Transplant and Randomization to Maintenance Alone, Consolidation and Maintenance, or Second Transplant and Maintenance [8]

Endpoint	Induction Therapy and First ASCT Followed By:		
	Len Maintenance Only	RVD Consolidation and Len Maintenance	Second ASCT and Len Maintenance
All patients	(n = 257)	(n = 254)	(n = 247)
Estimated PFS at 38 months	52.2%	56.7%	56.5%
Estimated OS at 38 months	83.4%	85.7%	82.0%
High-risk patients	(n = 59)	(n = 65)	(n = 57)
Estimated PFS at 38 months	40.2%	48.3%	42.2%
Estimated OS at 38 months	79.5%	77.5%	79.3%

ASCT, autologous stem cell transplant; len, lenalidomide; OS, overall survival; PFS, progression-free survival; RVD, bortezomib, lenalidomide, and dexamethasone.

Table 5. Hematopoietic Stem Cell Transplantation Utilization Rates in the United States [9]

Year	Estimated Transplant Utilization Among Transplant-Eligible Patients, %			
	Hispanic	Non-Hispanic Black	Non-Hispanic White	Overall
2008	8.6	12.2	22.6	19.1
2009	9.8	13.2	26.6	21.9
2010	11.9	15.7	29.4	24.7
2011	11.4	18.2	34	27.8
2012	14.2	19	35.4	29.5
2013	16.9	20.5	37.8	30.8

Table 6. Barriers to Transplantation Access in Multiple Myeloma [10]

Economic Factors	Health-System Factors	Provider Factors	Social Factors
· Socioeconomic status · Education · Number of wage earners · Employment status · Insurance coverage · Place of residence · Transportation	· Limited number of transplant centers · Workforce shortage · Capacity limitations · Infrastructure issues	· Physician referral · Provider attitudes/biases · Provider expertise · Provider diversity	· Age · Ethnicity and race · Language · Culture · Health literacy · Patient/family attitudes · Caregiver availability

Race, Gender, and Transplantation

In 2010, Joshua and colleagues evaluated the effect of race and gender on HSCT utilization in patients with leukemia, lymphoma and MM [11]. The analysis included all patient data captured between 1997 and 2002 by the CIBMTR, the Surveillance, Epidemiology, and End Results (SEER) database, and the US Census Bureau. In total, the analysis included 27,725 patients with leukemia, lymphoma or MM aged ≤70 years.

Results showed a significant interaction between patient race and HCT utilization [11]. The age-adjusted odds ratio (OR) of undergoing HCT for any hematologic malignancy was significantly higher for white patients than for black patients (OR, 1.40; 95% CI, 1.35-1.46; P <.0001). The racial disparity was consistent for all HCT subtypes, including ASCT (OR, 1.24; P < .0001), HLA identical sibling HCT (OR, 1.59; P < .0001), and unrelated donor HCT (OR, 2.02; P < .0001). In the subgroup of patients with MM (n = 6912), white patients were 75% more likely than black patients to undergo any type of HCT as part of their treatment plan (OR, 1.75; 95% CI, 1.64-1.86; P < .0001).

Patient gender also influenced treatment selection [11]. Among patients with MM, men were 10% more likely than women to undergo HCT (OR, 1.1; 95% CI, 1.05-1.15; P < .0001). In a closer analysis of HCT subtypes among patients with MM, the gender disparity remained statistically significant only for ASCT (HR, 1.10; 95% CI, 1.05-1.15; P < .0001). Together, these findings indicate substantial underutilization of HCT in African American and female patients with multiple types of cancer, including MM.

Patient Age and Transplantation

Older patient age is another key barrier to transplantation. In another retrospective analysis of the CIBMTR database, Costa and colleagues examined trends among patients with MM who underwent HCT within 12 months of diagnosis in 3 cohorts: 1995 to 1999, 2000 to 2004, and 2005 to 2009 [12]. In each cohort, the rates of HCT

utilization were the lowest among patients in the oldest age group (P < .001 for trend). Across the time periods, however, the number of upfront transplants for patients with MM increased across all age groups (Table 7). These trends indicate increased acceptance of transplant as an upfront treatment strategy in MM, although transplant remains underutilized in older patients.

Transplant Outcomes Across Patient Subgroups

Several studies have examined whether HCT is underutilized in certain groups due to an adverse relationship between patient demographics and transplant outcomes. To date, the evidence suggests that all patients with MM can benefit from transplantation, regardless of race, sex, age, and the presence of certain comorbidities [13-15].

Transplant Outcomes by Race/Ethnicity

At the 2016 ASH annual meeting, Schriber and colleagues presented findings from another analysis of the CIBMTR database examining the interaction between patient ethnicity and transplant outcomes [13]. The analysis included 28,450 patients with MM who underwent ASCT between 2008 and 2014. Of these, 24,102 patients received peripheral blood with melphalan conditioning and had at least 100 days of follow-up data. The study cohort included 18,046 non-Hispanic white patients, 4,123 non-Hispanic black patients, and 1,933 Hispanic patients.

Transplant utilization increased across all groups during the 6-year observational period, and was highest for white patients (37.8%), followed by black patients (20.5%) and Hispanic patients (16.9%). Despite differences in utilization, there were no differences in PFS (P = .2) or OS (P = .24) across patient subgroups. In a multivariate analysis, ethnicity had no effect on survival. By comparison, several other patient and disease characteristics adversely affected post-transplant survival, including:

- Increasing age
- Male gender
- Karnofsky performance status <90
- Hematopoietic Cell Transplantation-Specific Comorbidity Index score > 3
- Longer duration (>12 months) from diagnosis to AHCT
- Dose of Melphalan conditioning 140 mg/m2 (versus 200 mg/m2)
- Pre-transplant response <CR

Transplant Outcomes by Age

Sharma and colleagues conducted a similar analysis of ASCT outcomes by patient age, showing the potential benefit of transplantation across all age groups [14]. The study included data from 11,430 patients with plasma cell myeloma who underwent AHCT between 2008 and 2011. Patients were stratified by age at transplant: 18 to 59 years (n = 5818), 60 to 69 years (n = 4666), or ≥70 years (n = 946). Although a multivariate analysis identified increasing age as a risk factor for mortality (P = .0006), the myeloma-specific mortality rate was similar among all age cohorts. This suggests an age-related effect on non-myeloma mortality. Overall, the estimated 3-year OS rates were 78%, 75%, and 72% for patients aged 18 to 59 years, 60 to 69 years, or ≥70 years, respectively (P < .001). The estimated 3-year PFS rates were 42%, 38%, and 33%, respectively, across these cohorts (P = non-significant). These findings indicate that older patients who are selected for transplant derive a similar anti-myeloma benefit compared with younger patients, without an increased risk in PFS [14].

Transplantation is an important strategy for extending survival even among elderly patients with MM. In the general population, individuals who reach age 65 years have a life expectancy of approximately 80 to 85 years. For those who reach age 75 years, the life expectancy increased to 85 to 88 years. Therefore, most older patients who are diagnosed with MM had a further life expectancy of 10 or more years prior to their diagnosis. By achieving an estimated median PFS of 4 years with ASCT, elderly patients can reclaim a significant portion of their expected lifespan. Age alone should not guide treatment decisions around ASCT in patients with MM.

Transplant Outcomes and Comorbidities

Transplantation remains an important option for patients with MM and certain comorbidities, such as renal impairment [15]. Another recent analysis of the CIBMTR database examined the interaction between renal function and transplant outcomes among 1492 patients who underwent AHCT between 2008 and 2013. Patients were stratified by glomerular filtration rate (GFR) into the following groups: normal/mild renal impairment (GFR >60 ml/min) (n = 1240); moderate renal impairment (GFR 30-60 ml/min) (n = 185); or severe renal impairment (GFR <30 ml/min) (n = 67). The analysis found no differences in PFS (P = .124) or OS (P = .602) across patient subgroups defined by renal function at the time of transplant. Furthermore, 85% of patients with severe renal insufficiency at baseline achieved dialysis independence following AHCT, underscoring the benefit of transplantation in this patient population [15].

Transplant Outcomes in the Salvage Setting

In a recent multicenter, phase III, open-label trial, Cook and colleagues demonstrated the benefit of salvage ASCT in patients with relapsed MM [16]. The

Table 7. Trends in the Upfront Utilization of Autologous Hematopoietic Cell Transplantation in Multiple Myeloma by Age [12]

Patient Characteristics	1995-1999	2000-2004	2005-2010
Median age at transplant (range)	54 years (27-73 years)	57 years (22-80 years)	57 years (22-80 years)
< 50 years	32%	21%	21%
50 to 64 years	60%	59%	59%
≥65 years	7%	20%	20%

BSBMT/UKMF Myeloma X trial enrolled 297 patients with MM relapsing at least 18 months after previous ASCT. All patients underwent 2 to 4 cycles of induction with bortezomib, doxorubicin and dexamethasone (PAD), and 174 patients were randomly assigned to receive HDM and salvage ASCT (n = 89) or oral weekly cyclophosphamide (n = 85). The median OS was 67 months among patients who underwent salvage ASCT, compared with 52 months among those treated with weekly cyclophosphamide (HR, 0.56; 95% CI, 0.35-0.90; P = .0169). Therefore, findings from the BSBMT/UKMF Myeloma X trial support the role of salvage ASCT in patients with MM at first relapse after first ASCT. The study investigators noted that delay of salvage ASCT to the third-line setting or beyond may not result in a similar survival benefit [16].

Another study examined outcomes among 5,047 patients in the CIBMTR database who underwent salvage autologous (n = 3536) or salvage allogeneic (n = 1511) HSCT for MM between 2004 and 2014. The 3-year probability of OS was 54% and 40% in the autologous and allogeneic groups, respectively (P < .001) [9]. Therefore, HSCT remains an important strategy for prolonging survival in the salvage setting.

Trends in Transplant Referral

The underutilization of AHCT begins for many patients with MM with low referral rates. Pidala and colleagues surveyed 113 hematologists/oncologists in the United States about their referral practices for allogeneic HCT among patients with hematologic malignancies [17]. Clinicians were less likely to refer older patients and black patients for HCT evaluation, relative to younger patients and white patients, respectively (Table 8). Patients without insurance coverage were also less likely to receive referrals for allogeneic HCT.

In addition to non-referral, late referral may contribute to mobilization issues due to prolonged therapy. Patients who achieve a partial response to upfront therapy tend to undergo treatment with additional cycles of the induction regimen rather than referred for transplantation. Prolonged induction therapy itself can impair future mobilization attempts, making patients ineligible for late transplant (See the next section, *Mobilizing Strategies and Goals*).

Table 8. Likelihood of Not Receiving a Referral for Allogeneic Hematopoietic Cell Transplantation [17]

Patient Characteristics	OR (95% CI)	P Value
Race: African American versus Caucasian	2.35 (1.93, 2.87)	< .0001
Insurance coverage: no coverage versus coverage	6.9 (5.2-9.1)	< .0001
Age: 60 years versus 30 years	8.29 (5.89, 11.69)	< .0001

CI, confidence interval; OR, odds ratio.

Table 9. Recommendations for Addressing Barriers to Transplantation [18]

Barriers	Recommendations
Delayed HCT referral	Improve education for referring HCPs
Lack of cells mobilized	Target minorities to become donors
Financial burden	Make search assistance funds available Advocate for patients for insurance appeals
Lack of social support and caregiver Issues	Engage in advocacy efforts
Poor access to health care, including geographic barriers	Research disparities in healthcare access Target at-risk populations for outreach
Barriers in language, culture, literacy	Use culturally sensitive patient education materials

Addressing Barriers to Transplantation

In 2010, an expert working group from the National Marrow Donor Program (NMDP) identified opportunities to overcome common barriers to HSCT access (Table 9) [18]. The NMDP working group focused on the 3 urgent priorities for improving HSCT utilization: encouraging clinicians to refer patients to transplant centers early; expanding access to resources that facilitate the donation process; and helping to alleviate financial complications associated with transplantation. The NMDP working group also identified strategies to address barriers within vulnerable populations, including racial minorities, elderly patients, nonnative English speakers, and patients who lack insurance coverage. For these patients, the working group recommended 3 additional priorities: supporting ongoing research on disparities in transplant access; targeting at-risk populations for outreach; and improving communication efforts with such patients [18].

Summary

The underutilization of autologous HSCT among patients with MM remains a major challenge in current oncology practice. Certain patient populations, particularly racial and ethnic minorities, are especially vulnerable to HSCT disparities. Despite a higher median age at MM diagnosis compared with other hematologic malignancies, increasing patient age appears to be a persistent barrier to transplant referral. Additional barriers to transplant referral, access, and utilization are not well described, but likely involve the complex interactions of race, education, income, geographic distribution, and physician and patient bias. Understanding the underlying factors that contribute to underutilization is critical for designing strategies that improve access to transplantation and ultimately improve clinical outcomes for patients with MM.

Mobilizing Strategies and Goals

Luciano J. Costa, MD, PhD

Despite ongoing underutilization, the number of ASCT procedures performed each year in the United States has steadily increased, in part due to improved mobilization strategies [19]. The evolution of mobilization began more than 40 years ago with the identification of a small number of hematopoietic stem cells in the peripheral blood (PB) during homeostasis [20]. In the 1970s, investigators observed that the number of stem cells in the PB increased following chemotherapy [21]. Chemomobilized PB stem cells were first used in autologous HSCT in the 1980s, and soon because a widely-used alternative to bone marrow [22]. At the same time, growth factors (GFs) such as granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) were shown to mobilize high numbers of PB stem cells, and GF mobilization was incorporated into autologous HSCT protocols [23-25]. By 1995, stem cell mobilization with GF alone or GF plus chemotherapy because the standard of care for autologous HSCT [26,27]. More recently, the CXCR4 antagonist plerixafor and other novel small molecules have been evaluated as mobilization agents.

Hematopoietic stem cells reside in the bone marrow, where multiple chemokines and cytokines traffic their movement from the extracellular matrix into the peripheral blood [28]. By manipulating this process, stem cell mobilization enables the collection of stems cells via apheresis for both autologous and allogeneic transplantation. Chemotherapeutic agents stimulate cell mobilization by inducing a state of severe neutropenia that triggers an influx of endogenous growth factors. Exogenous growth factors also degrade the links within the extracellular matrix that tether stem cells to the bone marrow. Plerixafor directly antagonizes CXCR4 to release stem cells from the bone marrow into the peripheral blood. When used concurrently, 2 or 3 mobilization agents act synergistically to break the links between stem cells and the bone marrow and to prevent their reattachment [28].

Target Stem Cell Dosing

The question of the optimal number of stem cells for collection and transplant is controversial. Advocates of collecting a greater number of stem cells cite advantages such as faster engraftment, shorter hospital stays, fewer transfusions, reduced antimicrobial use, and the potential for better survival. The limitations of collecting more cells include a higher number of apheresis procedures, higher costs and resource utilization, and potential tumor contamination.

Glaspy and colleagues evaluated the relationship between CD34+ cell yield and the probability of engraftment [29]. Infusion of 5 x 106 CD34+ cells/kg is associated with an 85% probability of platelet engraftment to 20 x 109/L by day 14 post-transplant and a very low incidence of platelet recovery beyond 28 days. The probability of engraftment decreases with infusions of fewer cells. Among patients infused with 5 x 106 CD34+ cells/kg, the probability of engraftment is 65% by day 14, with approximately 10% of patients experiencing delayed platelet recovery.

In 2014, Giralt and colleagues developed expert consensus recommendations regarding optimal autologous stem cell mobilization [30]. The guidance includes recommendations for minimum and ideal target stem cell doses for a single autologous HSCT procedure (Table 10). Of note, increasing evidence suggests that patients with MM may benefit from a second salvage transplant.

Options for Stem Cell Mobilization

Successful ASCT requires the procurement and cryopreservation of hematopoietic progenitor cells (HPCs) to ensure safe engraftment. The simplest method for mobilizing HPCs involves the use of hematopoietic GF, such as G-CSF or GM-CSF. Additional options have also been utilized to increase CD34+ cell yield and reduce mobilization failure.

Table 10. Minimum and Ideal Target Stem Cell Doses for Autologous Hematopoietic Stem Cell Transplantation [30]

	Minimum Recommendation	Ideal Target
Stem cell dose	2 x 106 CD34+ cells/kg	3-5 x 106 CD34+ cells/kg
Additional considerations	· Use of collection yields of 1-2 x 106 CD34+ cells/kg for autologous HSCT should be individualized to each patient's clinical circumstances · Such doses may be used if needed and if benefit of autologous HSCT is compelling	· Yield of 2.5 x 106 CD34+ cells/kg in a single apheresis session may be reasonable to avoid prolonging mobilization by several days to reach ideal target dose · Higher targets necessary if multiple transplantations are planned

HSCT, hematopoietic stem cell transplantation.

Table 11. Advantages and Limitations of Mobilization Strategies

Regimen	Advantages	Limitations
Growth factor	· Simple · Low toxicity · Less expensive	· High risk of failures · Low cell yields
Growth factor plus chemotherapy	· Possible "anti-tumor" effects · High cell yields	· Toxicity · High cost · Risk of failure
Growth factor plus plerixafor	· Low toxicity · Low risk of failure · High cell yields	· Cost · Plerixafor-specific toxicity

Each of the 3 main strategies for stem cell mobilization has advantages and limitations for different patient populations (Table 11). The first strategy involves the use of cytokine mobilization agents alone, most commonly G-CSF. Other agents such as GM-CSF and pegylated filgrastim are also used. Second, the combination of cytokines (G-CSF of GM-CSF) plus chemotherapy can increase stem cell yield. Cyclophosphamide and etoposide are the most common chemotherapeutic agents used in current practice. Disease-specific regimens have been developed for patients with lymphoma and other tumor types. Third, the combination of cytokines plus plerixafor is also emerging as an important option for stem cell mobilization.

Predicting Mobilization Failure

Given the potential limitations of each mobilization strategy, it is important to identify patients who are most likely to benefit from GF alone, GF plus chemotherapy, or GF plus plerixafor. Several factors are associated with poor mobilization, including increasing age, history of diabetes or smoking, and lower steady-state platelet count. In general, patients with lymphoma are typical worse mobilizers than patients with MM. Treatment history can jeopardize mobilization, including prior exposure to lenalidomide (>4 cycles), fludarabine, or bendamustine, extensive radiation, and radioimmunotherapy. Delayed recovery from prior chemotherapy also predicts poor mobilization.

Based on known risk factors for impaired mobilization, Costa and colleagues evaluated whether a prediction model could be developed to direct mobilization strategies [31]. In the multicenter retrospective study of 477 patients with MM undergoing first autologous mobilization with GF, investigators included 2 definitions of poor mobilization: <20/mm3 PB-CD34+ cells and <10/mm3 PB-CD34+ cells at day 4 after GF initiation. A predictive model incorporating known clinical risk factors performed poorly in identifying the <20/mm3 and <10/mm3 thresholds for poor mobilization, with areas under the curve of 0.710 and 0.747, respectively. Further, a multiple regression analysis showed no correlations between either threshold and any other clinical characteristics at the time of mobilization, including treating institution, patient gender, time between diagnosis and mobilization, or plasma cells in the bone marrow. Therefore, clinical characteristics were not useful for developing a predictive model to stratify patients for different mobilization regimens.

Growth Factor Plus Plerixafor

Several trials have shown that adding plerixafor to G-CSF increased the yield of CD34+ cell mobilization and decreased the number of apheresis days compared with G-CSF alone [32,33]. One multicenter, double-blind, placebo-controlled phase III trial evaluated plerixafor in patients with non-Hodgkin lymphoma (NHL) undergoing autologous HSCT [32]. The trial enrolled 298 patients with NHL who required autologous HSCT during first or second complete or partial remission. All patients were treated with G-CSF 10 µg/kg daily for up to 8 days. Patients were randomly assigned to receive plerixafor 240 µg/kg (n = 150) or placebo (n = 148) beginning on day 4 and continuing for up to 4 days. The primary endpoint was the percentage of patients who collected ≥5 x 106 CD34+ cells/kg within 4 apheresis days.

Compared with G-CSF plus placebo, G-CSF plus plerixafor enabled significantly more patients to achieve the target stem cell collection goals at each apheresis time point (HR, 3.64; 95% CI, 2.39-5.45; P < .0001) (Table 12). Patients treated with G-CSF plus plerixafor were also more likely to meet the secondary endpoint of collecting ≥2 x 106 CD34+ cells/kg within 4 apheresis days. For all patients, the median number of CD34+ cells collected in the G-CSF plus placebo and G-CSF plus plerixafor groups was 5.69 x 106 cells/kg and 1.98 x 106 cells/kg, respectively.

In another phase III trial of patients with MM undergoing autologous HSCT (N = 302), adding plerixafor on day 4 of G-CSF treatment led to a significant 3-5-fold increase in the yield of CD34+ cells on day 1 of apheresis [33]. In total, 71.6% of patients in the plerixafor plus G-CSF group achieved the primary endpoint of collecting ≥6 x 106 CD34+ cells/kg in ≤2 aphereses, compared with 34.4% of patients in the placebo plus G-CSF group (P < .001) (Table 13). Furthermore, 54% of patients in the plerixafor group reached the target mobilization after 1 apheresis, whereas 56% of patients in the placebo group required at least 4 apheresis to reach the target CD34+ cell yield.

Preemptive Plerixafor

To minimize the costs of treatment and the risk of adverse events, several centers have adopted the strategy of preemptive plerixafor. Using this approach, patients are treated with G-CSF for 4 days. If the CD34+ yield is sufficient on day 4, patients proceed to immediate apheresis. Otherwise, evening plerixafor is given in preparation for next-day apheresis.

The preemptive plerixafor approach is feasible given that the concentration of CD34+ cells measured in the peripheral blood (PB-CD34+ cells/mm3) strongly predicts the apheresis yield (CD34+ cells/kg) (r2, 0.899;

Table 12. Mobilization with or without Plerixafor in Patients with Non-Hodgkin Lymphoma [32]

Results	Apheresis Day				Hazard Ratio (95% CI)	P Value
	Day 1	Day 2	Day 3	Day 4		
Patients reaching ≥5 x 106 CD34+ cells/kg						
Plerixafor + G-CSF	27.9%	49.1%	57.7%	65.6%	3.64 (2.39-5.45)	< .0001
Placebo + G-CSF	4.2%	14.2%	21.6%	24.2%		
Patients reaching ≥2 x 106 CD34+ cells/kg						
Plerixafor + G-CSF	56.5%	81.0%	87.9%	90.9%	2.50 (1.86-3.36)	< .0001
Placebo + G-CSF	20.4%	35.3%	56.9%	59.8%		

CI, confidence interval; G-CSF, granulocyte-colony stimulating factor.

P < .01) [34]. Centers can predict the effects of adding plerixafor prior to apheresis based on data showing that plerixafor increases the CD34+ cell yield by 3-5-fold [33]. Based on this experience, Costa and colleagues developed and validated a decision-support algorithm for identifying which patients are most likely to benefit from the addition of plerixafor prior to apheresis [34]. For a given collection target (e.g., ≥6 x 106 CD34+ cells/kg), the algorithm identifies the threshold of PB-CD34+ cells on day 4 (e.g., 25 cells/mm3) that favors G-CSF alone versus G-CSF plus plerixafor for the most cost-effective mobilization.

As applied in clinical practice, the algorithm recommends plerixafor use for approximately 68% of patients [34]. On average, the apheresis product is 103% of the predicted yield, enabling 94% of patients to meet their mobilization target. Only 3% of patients require remobilization. The mean interval between mobilization and transplantation is 14 days.

Chemotherapy-Based Mobilization

In 2011, Shaugnessy and colleagues retrospectively evaluated mobilization outcomes among patients treated with plerixafor plus G-CSF (n = 33) or chemotherapy plus G-CSF (n = 33) [35]. The median total yield of CD34+ cells was similar in the chemotherapy and plerixafor groups (11.6 versus 10.7 x 106/kg; P = .50), as was the likelihood of collecting ≥6 x 106 CD34+ cells/kg (90% versus 100%; P = .49). By comparison, there were more weekend apheresis procedures in the chemotherapy group than the plerixafor group (19 versus 0; P ≤ .0001), underscoring the decreased predictability of chemotherapy-based mobilization. In addition, patients in the chemotherapy were more likely than those in the plerixafor group to require mobilization-related hospitalization (58% versus 0%; P ≤ .0001), suggesting increased toxicity. All patients proceeded to autologous HSCT, with no difference between the chemotherapy and plerixafor groups in engraftment outcomes. The median total costs of mobilization were similar in the chemotherapy and plerixafor groups ($18,824 versus $14,244, respectively; P = .45).

Table 13. Mobilization with or without Plerixafor in Patients with Multiple Myeloma [33]

Results	Apheresis Day				Hazard Ratio	P Value
	Day 1	Day 2	Day 3	Day 4		
Patients reaching ≥6 x 106 CD34+ cells/kg						
Plerixafor + G-CSF	54.2%	77.9%	86.8%	86.8%	2.54	< .0001
Placebo + G-CSF	17.3%	35.3%	49.0%	55.9%		

G-CSF, granulocyte-colony stimulating factor.

Table 14. Mobilization Outcomes Following Filgrastim or TBO-Filgrastim [39]

Outcome	TBO-Filgrastim (n = 99)	Filgrastim (n = 86)	P Value
Median CD34+ cells on day 4	12.5 cells/μL	12.5 cells/μL	.78
Median plerixafor utilization	66%	60%	.61
Mean plerixafor doses, n	.96	1.06	.31
Mean total collection days	1.57 days	1.65 days	.24
Median CD34+ cells/μL on day 5	50 cells/μL	43 cells/μL	.15
Median total collected CD34+ cells	5.85 x 106 cells/kg	5.56 x 106 cells/kg	.59

Table 15. Mobilization Outcomes Following Filgrastim or Pegfilgrastim [40]

Characteristic	Filgrastim (n = 74)	Pegfilgrastim (n = 57)	P Value
Median PB-CD34+ cells on day 4	18.1 cells/μL	28.7 cells/μL	.01
Patients requiring plerixafor	67.5%	45.6%	.01
Mean days of apheresis, n	1.62 days	1.68 days	.6
Mean number of injections, n	13.12	2.68	< .001
Median total CD34+ cells collected	7.26 x 106 cells/kg	7.54 x 106 cells/kg	.6
Patients not meeting mobilization target, %	8.1%	8.8%	1
Mobilization failures (<2 x 106 CD43+ cells/kg), %	1.3%	1.7%	1

PB, peripheral blood.

Chemotherapy-based mobilization appears to increase the risk of mobilization failure. Another retrospective study included 50 patients managed with preemptive plerixafor, as guided via a mobilization decision-support algorithm, and 81 patients from an historic cohort treated with chemotherapy plus G-CSF and GM-CSF [36]. The mobilization failure rate was 2% among those managed with the mobilization algorithm, compared with 22% who were treated with chemotherapy (P < .01). In addition, 2% of patients in the preemptive plerixafor developed complications requiring hospitalization, compared with 30% in the chemotherapy group (P < .01). The estimated cost per patient of successfully completing mobilization was lower in the plerixafor group than in the chemotherapy group ($23,893 versus $29,423, respectively), before accounting for costs associated with multiple mobilization attempts. Given the higher rate of repeat mobilization attempts in the chemotherapy group, the true difference in total costs may be greater.

Mobilization Strategies and Long-Term Disease Control

One proposed advantage of chemomobilization involves improved long-term disease control for patients with lymphoma and MM, due to the use of high doses of alkylating agents. To date, however, the evidence does not support the

Table 16. Consensus Recommendations for Autologous Stem Cell Mobilization [30]

Consideration	Recommendation/Comments
Chemomobilization versus steady-state cytokine mobilization	· Ongoing debate (head-to-head data are equivocal) · Varying response to mobilization regimens between patients with myeloma and NHL growth factor alone often adequate for patients with early-stage myeloma, suboptimal for those with late stage MM and NHL · Stand-alone CM can be a successful strategy but is associated with toxicity and higher cost
Stand-alone chemomobilization	· Limit to patients who have not responded optimally to salvage therapy or in patients who have failed other strategies
Upfront plerixafor	· Suitable option for all patients particularly in the following circumstances: · If goal is highest possible CD34+ cell collection yield · If real-time PB-CD34+ cell counts are not available · If fewer apheresis days is the top priority · Preemptive use of plerixafor based on PB-CD34+ measurements is reasonable in other cases
Use of chemomobilization versus plerixafor + G-CSF	· Firm recommendations cannot be made (lack of data) · Controlled prospective trials comparing the 2 strategies should be considered
Cytokine-alone strategies	· Do not use for remobilization
Plerixafor	· Include in remobilization regimens for patients failing a non–plerixafor-containing mobilization attempt · May be effective in patients who have failed previous plerixafor-based mobilization · Options include plerixafor + G-CSF and chemotherapy + G-CSF + plerixafor · Addition of plerixafor to chemotherapy for remobilization should be explored in prospective trials
Chemotherapy-based remobilization	· Acceptable strategy for patients who have failed cytokine-only mobilization
Bone marrow harvest	· Third-line approach in patients who are ineligible for mobilization clinical trials and in whom the benefit of autologous HSCT is sufficiently compelling to outweigh the potential drawbacks

G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplantation; PB, peripheral blood.

use of chemotherapy-based mobilization as a strategy for preventing disease progression or prolonging survival.

In a retrospective analysis from the CIBMTR database, mobilization strategies were compared among 968 patients with MM who underwent AHCT between 2007 and 2012 [37]. In total, 519 patients were treated with GF alone and 449 were treated with GF plus chemotherapy. Platelet engraftment was slightly faster among patients treated with chemotherapy compared with those treated with GF alone (19 days versus 18 days, respectively; P = .006). However, the estimated 3-year PFS was similar for patients treated with GF with or without chemotherapy (40% versus 43%; P = .33) The estimated 3-year OS was also comparable among those treated with GF with or without chemotherapy prior to transplantation (80% versus 82%; P = .43).

Lenalidomide Exposure and Mobilization

Prior exposure to lenalidomide is associated with suboptimal mobilization of CD34+ cells [38]. In a study of 89 patients with MM, those exposed to a greater number of cycles of prior lenalidomide (> 4 cycles) experienced significantly worse CD34+ cell mobilization than patients exposed fewer cycles of lenalidomide (1-4 cycles) or those with no history of lenalidomide treatment (P < .001 for trend). Increased lenalidomide exposure was also associated with an increase in the number of apheresis sessions required to achieve the mobilization target (P = .008). Despite these challenges, however, GF mobilization with preemptive plerixafor was ultimately successful in these patients, with no patients failing mobilization or requiring remobilization prior to transplantation.

Emerging G-CSF Alternatives

Alternatives to standard G-CSF agents, including TBO-filgrastim and pegfilgrastim, provide more options for patients undergoing mobilization. Experience to date supports the use of these G-CSF alternatives in appropriate patients. Elayan and colleagues evaluated outcomes among 185 patients with lymphoma or plasma cell disorders treated with filgrastim (n = 86) or TBO-filgrastim (n = 99), with or without plerixafor [39]. Compared with filgrastim, TBO-filgrastim demonstrates identical performance across all measures of mobilization, at an average cost savings of $964.25 per patient (Table 14).

Pegfilgrastim, which is currently approved for the prevention of neutropenia and fever following outpatient chemotherapy, has also been studied as a mobilization agent. In a retrospective study of 131 patients with lymphoma or MM, pegfilgrastim significantly increased the median PB-CD34+ cell yield on day 4 compared with filgrastim (P = 0.01) (Table 15) [40]. Pegfilgrastim was also associated with a subsequent reduction in plerixafor utilization (P = .01). The single administration of pegfilgrastim 12 mg also represented improved convenience for patients compared with the filgrastim dosing of 10 μg/kg/day continuing until the completion of collection.

Consensus Recommendations

The 2014 consensus recommendations for stem cell mobilization provide additional guidance for treatment selection (Table 16) [30]. Specific strategies should be selected for individual patients based on 3 central goals: to reduce the overall mobilization failure rate to <5%; to minimize mobilization-related complications; and to optimize resource utilization.

In general, pre-apheresis PB-CD34+ cell-count monitoring is recommended to identify poor mobilizers prior to mobilization failure. The use of preemptive plerixafor, based on PB-CD34+ cell-count monitoring, appears to prevent mobilization failure. To offset the need for remobilization, consider upfront stead-state mobilization with plerixafor plus G-CSF in select patients. Emerging strategies such as chemotherapy plus plerixafor plus G-CSF merit further evaluation in prospective trials [30].

The consensus guidelines also outline treatment considerations based on tumor type. For patients with multiple myeloma, it is appropriate to limit steady-state mobilization with G-CSF alone (10-16 μg/kg/d) to patients with ≤1 previous line of therapy who have not been treated previously with melphalan or >4 cycles of lenalidomide. Instead,

PB CD34+ cell-count monitoring with preemptive plerixafor will facilitate successful collection in most patients. For patients with NHL, steady-state mobilization with G-CSF alone (10-16 µg/kg/d) is associated with higher failure rates in some cases. At present, this approach remains an option due to low toxicity and ease of scheduling, but it should be limited to patients who are at low risk for mobilization failure. By comparison, PB-CD34+ cell-count monitoring with preemptive plerixafor will allow for successful stem cell collection in most patients.

Summary

Autologous HSCT is the established standard of care for improving survival in patients with MM, but this treatment approach first requires successful stem cell mobilization. The development of several novel mobilization regimens has improved access to transplantation by increasing stem cell yield and decreasing the need for remobilization. Each mobilization strategy is associated with advantages and limitations, and therefore treatment must be individualized for each patient with MM. Consensuses recommendations are available to guide the selection of an optimal mobilization strategy in patients with MM and other hematologic malignancies who are candidates for autologous HSCT.

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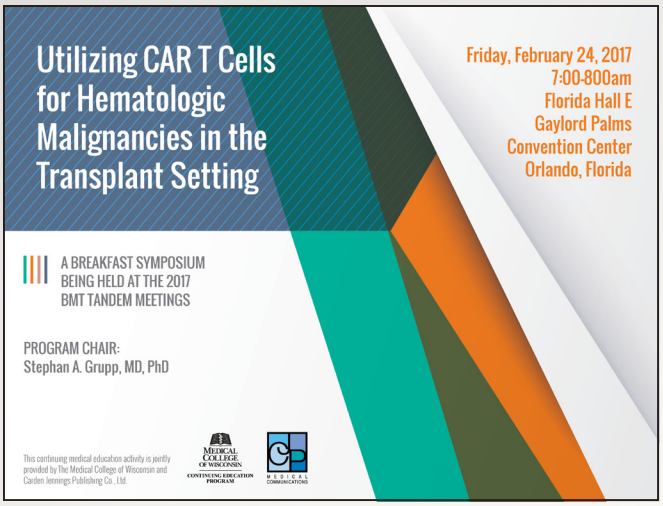

Utilizing CAR T Cells for Hematologic Malignancies in the Transplant Setting

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ASBMT
Symposium Report
2016 BMT TANDEM MEETINGS
Examining Targeted Therapies for Hodgkin Lymphoma in the Post-Transplant Setting: Reason for Optimism
Activity Chairs
Program Overview
Hodgkin lymphoma (HL) is a pathologically and clinically heterogeneous hematologic malignancy. In the United States, an estimated 185,000 people are currently living with this disease, and it accounted for more than 9,000 new cases of cancer in 2015. Chemotherapy and radiation provide long-term benefit to the majority of patients with HL; however, some patients will eventually relapse.
High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is the standard of care for relapsed disease, resulting in complete remission rates of approximately 50%. However, patients who relapse after ASCT generally have poor outcomes, with 3-year overall survival rates as low as 12% in patients with multiple poor prognostic factors. In an attempt to prolong the benefit of ASCT in relapsed/refractory HL, chemotherapy and targeted therapy regimens have been tested as consolidation therapy. However, finding an appropriate balance between efficacy and tolerability has remained challenging. Since therapy options in the relapsed/refractory setting are limited, the discovery of new, well-tolerated agents that may
continued on page 3

Blood and Marrow Transplantation Reviews: Examining Targeted Therapies for Hodgkin Lymphoma in the Post-Transplant Setting: Reason for Optimism

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1. **Recent data indicate that ASCT does not add value in terms of survival or PFS in patients receiving potent novel agent induction therapies.**
   A. True
   B. False; Studies have shown PFS advantage but no OS benefit for ASCT
   C. False; Studies have shown both PFS and OS benefit for ASCT even after novel agent induction

2. **Majority of ASCT eligible MM patients in the US receive transplants irrespective age; sex or ethnicity**
   A. True
   B. False; Majority receive transplant but age; sex and race remain barriers to transplant
   C. False; Only a minority among those eligible receive transplant but with further decrements attributed to older age, female sex and minority ethinicity.

3. **Which of these factors best predict the yield of CD34+ apheresis collection in patients with multiple myeloma or non-Hodgkin lymphoma undergoing G-CSF mobilization?**
   A. Age
   B. Prior use of lenalidomide
   C. CD34+ in peripheral blood on the 4th day of G-CSF administration
   D. Prior radiation to pelvis and spine

4. **In regards to the use of high dose chemotherapy for mobilization of CD34+ cells in patients with multiple myeloma, which of the following statements is correct.**
   A. Chemotherapy mobilization is associated with more toxicity than other mobilization strategies
   B. Chemotherapy mobilization is more effective and less expensive than mobilization with G-CSF plus plerixafor.
   C. Chemotherapy is necessary for adequate CD34+ mobilization in patients previously treated with lenalidomide
   D. Chemotherapy mobilization is necessary in patients with suboptimal response to induction therapy to improve disease control.

5. **The minimum recommended number of autologous CD34+/kg for a safe transplant is:**
   A. 5 x 10^5/Kg
   B. 1 x 10^6/kg
   C. 2 x 10^6/kg
   D. 1 x 10^7/kg