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Salvage Second Hematopoietic Cell Transplantation in Myeloma

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Abstract

Autologous hematopoietic cell transplantation (AHCT) as initial therapy of patients with multiple myeloma (MM) improves survival. However, data to support this approach for relapsed/progressive disease after initial AHCT (AHCT1) are limited. Using Center for International Blood and Marrow Transplant Research data, we report the outcomes of 187 patients who underwent a second AHCT (AHCT2) for the treatment of relapsed/progressive MM. Planned tandem AHCT was excluded. Median age at AHCT2 was 59 years (range, 28 to 72), and median patient follow-up was 47 months (range, 3 to 97). Nonrelapse mortality after AHCT2 was 2% at 1 year and 4% at 3 years. Median interval from AHCT1 to relapse/progression was 18 months, and median interval between transplantations was 32 months. After AHCT2, the incidence of relapse/progression at 1 and 3 years was 51% and 82%, respectively. At 3 years after AHCT2, progression-free survival was 13%, and overall survival was 46%. In multivariate analyses, those relapsing ≥36 months after AHCT1 had superior progression-free ($P = .045$) and overall survival ($P = .019$). Patients who underwent AHCT2 after 2004 had superior survival ($P = .026$). AHCT2 is safe and feasible for disease progression after AHCT1. In this retrospective study, individuals relapsing ≥36 months from AHCT1 derived greater benefit from AHCT2 compared with those with a shorter disease-free interval. Storage of an adequate graft before AHCT1 will ensure that the option of a second autologous transplantation is retained for patients with relapsed/progressive MM.

Keywords

Second autologous; transplantation; Multiple myeloma; Relapsed multiple myeloma

INTRODUCTION

Data support the use of autologous hematopoietic cell transplantation (AHCT) in the up front treatment of eligible patients with plasma cell multiple myeloma (MM). Pivotal studies from the 1990s and 2000s demonstrated prolonged remission and survival when AHCT was compared with chemotherapy alone [1-3]. A benefit in progression-free survival (PFS) has been confirmed in meta-analyses [4], although the success of salvage therapy in the chemotherapy arms likely mitigated demonstration of an overall survival (OS) benefit. Even in the era of novel agents, AHCT remains a cornerstone of therapy [3,5-7].

When patients relapse/progress after an up front single or tandem transplantation, salvage treatment options include additional chemotherapy, clinical trials with investigational agents, and, in select cases, allogeneic hematopoietic cell transplantation, or a second autologous transplantation. Although lenalidomide and bortezomib improve survival in relapsed/progressive myeloma, the development of chemotherapy resistance is a common feature of this disease, and the survival rate of patients refractory to both bortezomib and lenalidomide is dismal [8].

Data regarding outcomes of a second AHCT (AHCT2) performed as salvage therapy for relapse/progression after AHCT1 are primarily limited to retrospective analyses from single institutions [9-15]. Registry data have the advantage of larger numbers of patients in a multi-institutional context. With this in mind, we analyzed data from 187 patients reported to the

Center for International Blood and Marrow Transplant Research (CIBMTR) to clarify the benefits of AHCT2, performed at relapse/progression after AHCT1.

METHODS

Data Source

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program that comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic HCT and AHCT to a statistical center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program Coordinating Center in Minneapolis, Minnesota. Participating centers are required to register all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed up longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the institutional review board and the privacy officer of the Medical College of Wisconsin. All CIBMTR centers contribute to the registration data. Research data are collected on a subset of registered patients and include detailed disease and pre-transplantation and post transplantation clinical information.

Patients

We identified 983 patients who underwent a second AHCT for MM between 1995 and 2008. Patients who had AHCT2 for reasons other than relapsed/progressive disease were removed from the study cohort, including planned tandem transplantation (n = 704), graft failure (n = 10), another malignancy (n = 1), or unknown (n = 23). Patients who had undergone a previous allogeneic stem cell transplantation (n = 10), a third subsequent allogeneic stem cell transplantation (n = 2), and those without a minimum of 100 days of follow-up data (n = 46) were also excluded. A total of 187 patients from 55 centers in North America who received an AHCT2 for relapsed/progressive MM after an initial AHCT1 comprised the final study population. Median follow-up of survivors from the second transplantation in this study was 47 months (range, 3 to 97 months).

Statistical Methods

Outcomes analyzed included relapse/progression, nonrelapse mortality (NRM), PFS, and OS. Relapse/progression was defined according to the standard European Group for Blood and Marrow Transplantation/IBMTR/ABMTR criteria [16]. NRM was defined as death from any cause within the first 28 days after transplantation or death thereafter in the absence of relapse/ progression. OS interval was defined as the time from AHCT2 to death from any cause. Patients alive without evidence of disease relapse/progression were censored at last follow-up and the PFS event summarized by a survival curve. Cumulative incidence of NRM and relapse/progression were calculated using cumulative incidence curves to accommodate competing risks. Associations between patient-, disease-, and transplantation-related factors and survival were assessed using multivariate Cox proportional hazards regression. The variables considered in the multivariate analysis were age (continuous), sex, Karnofsky performance score, Durie-Salmon stage, and immunochemical subtype of MM, disease status before AHCT2, conditioning regimen for AHCT2 (melphalan alone versus others), interval from AHCT1 to relapse/progression, interval from AHCT1 to AHCT2, and the year of AHCT2.

Forward stepwise variable selection at a .05 significance level was used to identify covariates. In the model, the assumption of proportional hazards was tested for each variable using a time-dependent covariate and graphical methods. All variables considered in the multivariate analysis satisfied the proportionality assumption. All computations were made using the statistical package SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. The median age of the cohort was 59 years at AHCT2 (range, 28 to 74), and 53% were of Karnofsky performance score ≥90. Most patients (78%, n = 146) were white. Median interval from AHCT1 to AHCT2 was 32 months (range, 6 to 122 months) and from AHCT1 to first relapse/progression was 18 months (range, 3 to 121 months). A total of 22 patients (12%) underwent the second transplantation within 12 months of AHCT1. Compared with AHCT1, patients were less likely to be in complete or partial remission before AHCT2.

Peripheral blood progenitor cell grafts were collected before AHCT1 in all patients, and no use of remobilized grafts after AHCT1 was reported. High-dose melphalan was used as a preparative regimen in 84%, whereas the use of total body irradiation–based regimens was minimal (3%). The number of reported salvage AHCT2 increased within the time frame of the collected data: 18 transplantations each were reported during the years 1995 to 2000 and 2001 to 2002, 35 transplantations occurred during 2003 to 2004, 53 transplantations were recorded during 2005 to 2006, and 63 transplantations occurred during 2007 to 2008.

Safety and Relapse

Figure 1 shows the cumulative incidence of NRM and relapse/progression. The incidence of NRM after AHCT2 was 2% (95% confidence interval [CI], 1%-5%) at 1 year and 4% (95% CI, 2%-8%) at 3 years, respectively. Of the 187 patients, 10 died from NRM, including infection (n = 4), organ failure (n = 4), and second malignancy (n = 2). The two reported second malignancies were breast cancer and myelodysplastic syndrome. Engraftment rate of neutrophils (absolute neutrophil count ≥500/mm^3 for 3 subsequent days) and platelets (platelet count ≥20,000/mm^3 for 7 subsequent days without platelet transfusion) at 28 days was 96% (range, 93% to 98%) and 88% (range, 83% to 92%), respectively.

Cumulative incidence of relapse/progression after AHCT2 is shown in Figure 1. Incidence of relapse/progression was 51% (95% CI, 43%-58%) at 1 year, 82% (95% CI, 76%-88%) at 3 years, and 91% (95% CI, 85%-95%) at 5 years. In multivariate analysis (Table 2), a longer interval from AHCT1 to initial relapse (≥36 months) was associated with a lower risk of relapse/progression after AHCT2 (relative risk, .63; 95% CI, .49-.97). In individuals with a greater than 36-month interval between AHCT1 and initial relapse/progression, the incidence of relapse/progression was 41% (95% CI, 25%-57%) at 1 year, 68% (95% CI, 51%-82%) at 3 years, and 81% (95% CI, 65%-93%) at 5 years after AHCT2.

PFS and OS

The 1-, 3-, and 5-year PFS after AHCT2 was 47% (95% CI 40% to 54%), 13% (95% CI 9% to 19%), and 5% (95% CI 2% to 11%), respectively. The OS at 1 year was 83% (95% CI, 77%-89%), whereas it was 46% (95% CI, 37%-54%) and 29% (95% CI, 21%-38%) at 3 and 5 years, respectively (Figure 2). In multivariate analysis, a longer interval from AHCT1 to relapse/ progression (≥36 months) was associated with superior PFS and OS (Figure 3). For those relapsing ≥36 months after AHCT1, the PFS at 1, 3, and 5 years was 59% (95% CI, 41%-74%), 26% (95% CI, 13%-41%), and 13% (95% CI, 4%-28%), respectively.

Corresponding OS was 88% (95% CI, 71%-95%) at 1 year, 58% (95% CI, 39%-73%) at 3 years, and 48% (95% CI, 28%-65%) at 5 years. OS stratified by the time from AHCT1 to relapse/ progression is shown in Figure 3. AHCT2 performed after 2004 was associated with superior survival (relative risk, .61; 95% CI, .4-.94).

DISCUSSION

AHCT is used as an up front or salvage treatment for patients with MM [17]. AHCT2 has also been used to salvage patients relapsing after an initial (up front) AHCT [18]. Current National Comprehensive Cancer Network guidelines recommend that AHCT-eligible patients with MM undergo leukopheresis with the intent to collect enough peripheral blood progenitor cell to undergo two AHCTs, in which case the second graft can be cryopreserved for use as salvage AHCT2 [17].

There is considerable heterogeneity in practice patterns, and no current standard of care exists as to whether or when to implement ACHT2 for relapsed/progressive myeloma. ACHT2 is a distinct treatment strategy compared with tandem AHCT, which is defined as two planned cycles of high-dose therapy with peripheral blood progenitor cell support in which a second AHCT is performed within 180 days of the first, with the objective of increasing the likelihood of a complete or very good partial remission [19]. Inconsistent results have been reported by the studies randomizing patients to single versus tandem AHCT [19-22]. The most recent National Comprehensive Cancer Network guidelines are not prescriptive regarding tandem transplantation [17].

Notably, many third-party payers, including Centers for Medicare and Medicaid Services in the United States, reimburse for a single AHCT only (National coverage determination for stem cell transplantation, Centers for Medicare and Medicaid Services, Manual section number 110.8.1. http://www.cms.gov/medicare-coverage-database. Accessed 4/30/ 2012).

Our data provide an estimate of the effectiveness of AHCT2 as salvage therapy in a select group of patients and suggest that it is safe with a relatively low NRM (4%). NRM rates are similar to up front AHCT in reported studies [20,23,24] and previously reported rates after second salvage transplantation [9-15]. About 29% of patients were alive at 5 years, and 25% of these pretreated patients achieved a complete remission after AHCT2. Thus, AHCT2 at first relapse/progression may harness the advantage of durable remission and preserves the option of using other therapies for subsequent relapses/progressions.

We summarize in Table 3 some of the comparable published retrospective analyses of salvage autologous transplantation in patients with MM [9,10,12,14,15]. The most consistent finding among these studies is that a longer progression-free interval after AHCT1 predicts improved survival after AHCT2. In our analysis, patients progressing later than 36 months after AHCT1 had a median OS after AHCT2 of 49 months (95% CI, 34-108) compared with a median OS of 28 months (95% CI, 24-42) in patients who had a shorter progression-free interval after AHCT1. Other published retrospective studies summarized in Table 3 have correlated better outcomes in patients who relapse/progress more than 2 years after ACHT1[9,10,12,15]. It may be that patients who relapse/progress within 2 to 3 years of AHCT1 would be better served by participation in clinical trials rather than a second high-dose melphalan AHCT, although confirmation of this hypothesis would require a randomized study.

Aiming to understand the optimal timing of a second autologous transplantation, researchers with the European Group for Blood and Marrow Transplantation looked at 7,452 patients, of which 2,655 had an up front planned AHCT2, and 4,797 had unplanned AHCT2 in the years between 1993 and 2002. They found superior outcomes when AHCT2 was performed before

relapse (within 6 to 12 months of AHCT1) [25]. In this study, the median OS (from AHCT1) of the unplanned AHCT2 was 51 months. This is not to be confused with our OS of 30 months from AHCT2. This is one of the largest retrospective studies addressing the timing of a second transplantation, but it was performed before the advent of novel agents and aims to answer a different question from that proposed here.

In our multivariate analyses, disease status and chemotherapy sensitivity before AHCT2 did not affect outcomes, because at the time of AHCT2, 46% of patients were in less than a partial remission. Given that the cohort spans 15 years, these data were largely accumulated before the relatively recent era of maintenance therapy after AHCT1. Recently published, high-quality, prospective data demonstrate improvement in PFS and OS when lenalidomide is initiated after AHCT1 [26,27]. Given that the use of novel agents as maintenance therapy improve PFS after AHCT1, it is likely that in the modern era, a greater proportion of relapses/progressions after AHCT1 may be beyond the 36-month interval identified. It is unclear whether the same benefits of AHCT2 would be preserved in patients who receive maintenance after AHCT1. Survival has improved since 2004, although NRM and PFS after AHCT2 were not different. We hypothesize that the improved OS seen in patients who underwent transplantation after 2004 is due to the use of novel agents in treatment of relapse/progression after AHCT2.

MM is as twice as common among African Americans than white Americans [28]. In the US population, about 13% of individuals identify themselves in census rolls as African American/black [29]. The percentage of African Americans who underwent AHCT2 in our study is 12%—which is less than what might be expected. Previous analyses have shown that African Americans are less likely to have access to AHCT1 as a treatment for MM [30], although the outcome after AHCT is similar among blacks and whites [31]. The reasons for this disparity are unclear and probably multifactorial.

Limitations inherent to our analyses include its retrospective nature and incomplete data on maintenance therapy and on modern prognostic factors, such as cytogenetics and International Staging System (ISS) stage. These limitations are because the reported time period predates newer maintenance therapies, ISS staging, and risk stratification. Information about new cytogenetic or molecular characteristics of disease at the time of AHCT2 was unavailable. Retrospective data collection also meant that the dataset includes only patients who actually received an AHCT2. We were not able to determine the characteristics of patients who were excluded on the basis of nonavailability of a graft or other factors such as rapid relapse/progression, poor performance status, age, insurance status, comorbidities, or patient/provider preference. This may account for the relatively low numbers of overall AHCT2 recorded by the registry, and it limits the applicability of the findings compared with prospective data. All AHCT2 were performed using hematopoietic cells collected and stored before AHCT1 and is consistent with current clinical practice recommendations.

These data provide support for the use of late second AHCT in patients with relapsed/progressive MM. We also underscore the need for randomized studies looking at therapies after relapse/progression comparing available options, including AHCT2, chemotherapy combinations, and allogeneic transplantations. One particular unmet need is identifying investigational strategies in patients who have early progression after AHCT1: Do these individuals benefit from newer induction or conditioning regimens? An ongoing phase III clinical trial (myeloma X) in the United Kingdom enrolls patients who relapse/progress at least 18 months after AHCT1 to receive reinduction with bortezomib, doxorubicin, and dexamethasone and randomizes them to AHCT2 versus low-dose maintenance cyclophosphamide (see www.clinicaltrials.gov, NCT00747877). Prospective clinical trials

like these are needed to define the risk-to-benefit ratio as well as the placement and sequencing of AHCT2 relative to other therapies.

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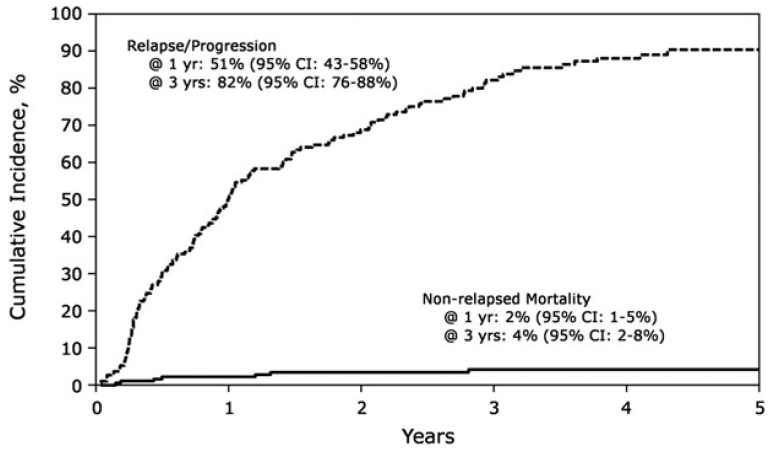

Figure 1.
Cumulative incidence of relapse/progression and NRM after salvage AHCT2.

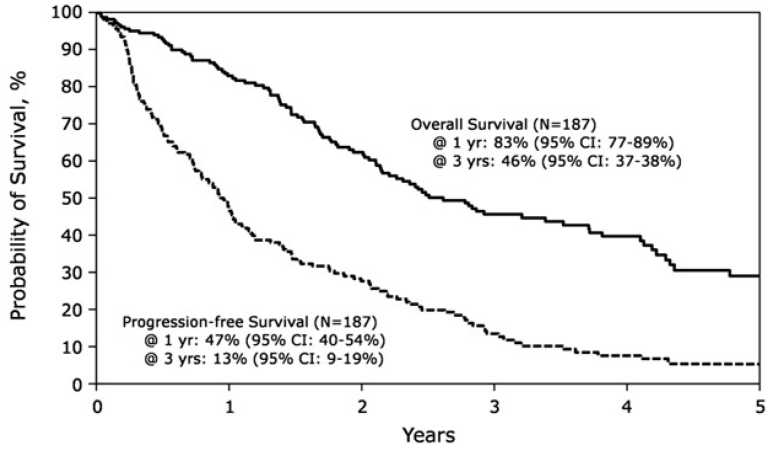

Figure 2.
Probability of PFS and OS after AHCT2.

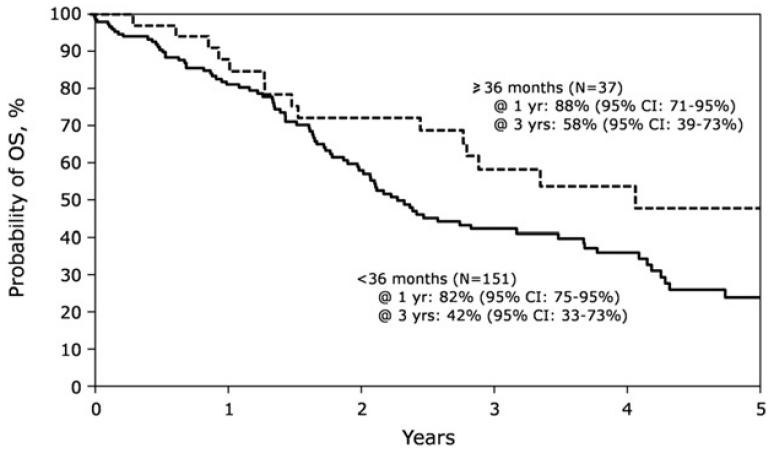

Figure 3.
Probability of OS after AHCT2 stratified by time to relapse/ progression from AHCT1.

Table 1

Characteristics of Patients Receiving AHCT2 for Relapsed/Progressive MM between 1995 and 2008

Patient Characteristics	First Transplantation	Second Transplantation
Demographics		
Number of patients	187	187
Age at transplantation, median (range), yr	57(28-72)	59(28-74)
Male sex		118(63%)
Race		
White		146(78%)
African American		23(12%)
Other		18(10%)
Disease related		
Immunochemical subtype of MM		
IgG		89(48%)
IgA		37(20%)
Light chain/other/unknown		61(33%)
Durie-Salmon stage at diagnosis		
Stage I	12(6%)	–
Stage II	40(21%)	–
Stage III	111(59%)	–
Missing	24(13%)	–
International stage at diagnosis		
Stage I	34(18%)	–
Stage II	26(14%)	–
Stage III	17(9%)	–
Missing	110(59%)	–
Karnofsky score before AHCT2		
≥90%		99(53%)
Transplantation related		
Serum albumin before AHCT		
<3.5 g/L	49(26%)	59(32%)
Serum creatinine before transplantation		
≥1.5 mg/dL	13(7%)	25(13%)
Conditioning regimen for transplantation		
Melphalan alone	149(80%)	158(84%)
Melphalan + TBI ± others	10(5%)	4(2%)
Melphalan ± others	9(5%)	17(9%)
TBI (no melphalan) ± others	5(3%)	2(1%)
Busulfan + cyclophosphamide ± others	12(6%)	5(3%)

Patient Characteristics	First Transplantation	Second Transplantation
Others	2(1%)	1(<1%)
Disease status before transplantation		
CR/PR	153(82%)	74(40%)
MR/NR/SD	21(11%)	86(46%)
Relapse/progression	1(<1%)	27(14%)
Missing	12(6%)	–
Cytogenetics at any time before transplantation		
Abnormal	–	27(14%)
Normal	–	84(45%)
Not assessable/unknown	–	76(41%)
Time from AHCT1 to AHCT2, median (range), mo	–	32(6-122)
6-12	–	22(12%)
12-23	–	36(19%)
24-35	–	51(27%)
≥36	–	78(42%)
Time from AHCT1 to relapse/ progression, median (range), mo	18(3-121)	–
<6	33(18%)	–
6-11	27(14%)	–
12-23	55(29%)	–
24-35	36(19%)	–
≥36	36(19%)	–
Year of transplantation		
1990-1994	7(4%)	–
1995-2000	50(27%)	18(10%)
2001-2002	50(27%)	18(10%)
2003-2004	38(20%)	35(19%)
2005-2006	36(19%)	53(28%)
2007-2008	6(3%)	63(34%)
Post transplantation		
Best response reported after AHCT		
CR	81(43%)	47(25%)
PR	73(39%)	81(43%)
MR	6(3%)	11(6%)
NR/SD	20(11%)	30(16%)
Progression	5(3%)	18(10%)
Missing	2(1%)	–
Maintenance therapy		
None	–	143(71)

Patient Characteristics	First Transplantation	Second Transplantation
Imid (lenalidomide, thalidomide)	–	22(11)
Interferon/interleukin-2	–	14(7)
Steroid	–	10(5)
Bortezomib	–	9(5)
Others (cyclophosphamide, melphalan)	–	3(2)
Median follow-up of survivors, (range), mo	–	47(3-97)

CR indicates complete response; PR, partial response; MR, minimal response; NR, no response; SD, stable disease; TBI, total body irradiation.

Table 2

Multivariate Analysis of Risk Factors for Relapse/Progression, Treatment Failure (Inverse of PFS), and OS

Outcome	n	HR	95% CI	*P* Value
Relapse/progression				
Time from AHCT1 to REL				
≥36 mo	36	1		
<36 mo	151	1.58	(1.03-3.41)	.036
Treatment failure/PFS				
Time from AHCT1 to REL				
≥36 mo	36	1		
<36 mo	151	1.52	(1.01-2.30)	.045
Overall mortality/survival				
Time from AHCT1 to REL				
≥36 mo	36	1		
<36 mo	151	1.91	(1.12-3.28)	.019
Year of AHCT2				
1995-2004	100	1		
2005-2008	87	.61	(.40-.94)	.026

HR indicates hazard ratio; REL, Relapse.

Table 3

Comparison of Our Data with the Major Studies That Evaluated Outcome of Second Salvage AHCT for Myeloma

	CIBMTR (our data)	Toronto/Princess Margaret [10]	MD Anderson [14]	University of Pennsylvania [12]	S. Texas VA [9]	Germany [15]
Year published		2011	2011	2009	2009	2011
Number of patients	187	81	44	41	25	55
Years inclusive	1995-2008	1992-2009	1992-2008	1998-2007	1999-2007	1993-2008
Interval between ASCT1 and ASCT2 (range)	32 (6-122)	NR	30 (2-78)	37 (3-91)	39 (4-74)	
Post-ASCT outcomes						
CR	25%	7.7%			20%	9%
CR/VGPR			11%	16%(6/38 cases)		9%
VGPR		39.7%				
PR	43%	50%	79%		44%	56%
ORR		97% (day 100)	90%	55% (21/38 cases)	64%	85%
NRM	4% (5 yr)	2.6% (100 days)	2% (100 days)	7% (100 d)	8%	5% (100 d)
Median PFS post AHCT2, mo	11.2	16.4	12.3	8.5	12	EFS: 14
Median OS post AHCT2, mo	30	53	31.7	20.7	19	52
Multivariate analysis	Improved OS if interval between AHCT1 relapse ≥36 mo and for AHCT2 after 2004	Improved PFS and OS if interval between AHCT1 and AHCT2 >24 mo	Worse OS associated with AA race, shorter TTP after AHCT1, IgG, and increased number of prior therapies	Worse outcomes if >4 prior therapies, TTP after AHCT1 ≥12 mo	NR	Improved outcomes if remission >12 mo after AHCT1

VA indicates Veterans Administration; CR, complete response; VGPR, very good partial response; PR, partial response; EFS, event-free survival; AA, African American; TTP, time to progression; IgG, immunoglobulin G; NR, not recorded.