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High-Dose Therapy and Autologous Stem Cell Transplantation for Chemoresistant Hodgkin Lymphoma: The Seattle Experience

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Abstract

Background—High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment for patients with chemosensitive relapsed/refractory Hodgkin lymphoma (HL), but this therapy is commonly denied to patients with resistant disease. We explored the utility of HDT and ASCT for chemoresistant HL since there are few established therapies for these patients.

Patients and Methods—Sixty-four chemoresistant HL patients underwent HDT followed by ASCT at our center. Baseline characteristics included: median age = 35 years (range, 14–59 yrs), stage III/IV = 49 (77%), nodular sclerosis histology = 51 (80%), and prior radiation = 32 (50%). Twenty-six patients (41%) received total body irradiation (TBI)-based regimens and 38 (59%) underwent non-TBI conditioning.

Results—The estimated 5-year overall survival (OS) and progression-free survival (PFS) were 31% and 17%, respectively, (median follow-up = 4.2 years). Multivariable analysis only identified year of transplant as independently associated with improved OS (p=.008) and PFS (p=.04), with patients transplanted in later years having better outcome. The probabilities of 3-year PFS for patients transplanted between 1986–1989, 1990–July 1993, August 1993–1999, and 2000–2005 were 9%, 21%, 33%, and 31%, respectively.

Conclusions—These data suggest that HDT and ASCT may result in prolonged remissions and survival for a subset of chemoresistant HL pts, with improved outcomes in patients transplanted more recently.

Introduction

Over 7500 patients are diagnosed with Hodgkin's lymphoma (HL) each year in the United States with 70–90% achieving cure with initial therapy[1–3]. Patients with early relapse or primary refractory disease have a much worse prognosis with long-term disease-free survival rates reported at 5–20% if they are treated with conventional salvage chemotherapy or radiotherapy alone [4, 5]. Over the past two decades several phase II trials, numerous case series from bone marrow transplant registries, and two phase III trials have established high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) as the preferred treatment for these high-risk patients in chemosensitive relapse, with cure rates around 40–60%[6–14].

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Several series have identified chemoresistant disease as a poor prognostic factor for survival in HL patients undergoing HDT and ASCT, and many centers therefore deny this treatment to HL patients that do not achieve at least a partial response to salvage therapy [1, 12, 13, 15–19]. The current study reviewed our experience treating patients who have chemoresistant HL with HDT and ASCT to better define the overall efficacy in this setting and to attempt to identify characteristics associated with improved overall survival (OS) and progression-free survival (PFS).

Patients and methods

Patients

Patients were identified from the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) computerized database. Clinical and research records of all HL patients were reviewed and only those with chemoresistant disease were included in this analysis. Patients were considered to have chemoresistant HL if they achieved less than a partial remission (less than 50% reduction in tumor bulk) with the salvage chemotherapy regimen administered immediately preceding conditioning for ASCT. All patients provided informed consent for treatment on transplant protocols approved by the appropriate institutional review board. In addition, separate institutional approval was obtained to retrospectively gather data from patient records and databases.

Study variables

The specific variables evaluated included: age, gender, stage, histology, tumor bulk at transplant, date of transplant, number of extranodal sites (ENS), number of prior chemotherapy regimens, prior radiotherapy (RT), use of total body irradiation (TBI) conditioning, and stem cell source. Tumor bulk was defined based on the greatest long-axis diameter of the largest tumor mass by computerized tomography noted following salvage therapy and before initiation of transplant conditioning. Flurodeoxyglucose (FDG) positron emission tomography (PET) results were gathered prior to transplant when performed but were not used to define chemosensitivity. A prior regimen was defined as one or more cycles of specific chemotherapy or radiotherapy.

Definition of endpoints and statistical analysis

OS and PFS were computed from the date of stem cell infusion to the date of death or progression using the method of Kaplan and Meier[20]. Events for the endpoint of OS included deaths from any cause, while events for PFS included death from any cause or progressive disease. Univariate and multivariable Cox regression models were fit to examine the association between various factors and the outcomes of OS and PFS. Reported two-sided p-values from regression models were obtained from the Wald test, and no adjustments were made for multiple comparisons.

Results

Baseline characteristics

Between November 1981 and May 2005, we treated 167 patients with HL using HDT and ASCT at our Center with 64 (38%) of these patients meeting the definition of chemoresistant disease. Baseline characteristics for this group are summarized in Table 1. In addition, front-line chemotherapy consisted of ABVD in 25 patients, an ABVD/MOPP hybrid in 22 patients, MOPP in 5 patients, Stanford V in 3 patients, other ABVD hybrids in 2 patients, and a combination of other therapies in 7 patients. Twenty-nine patients (45%) were refractory to their initial chemotherapy regimen. The median number of prior regimens was 2 (range 1–5).

Thirty-two patients (50%) had received prior RT and all patients had a Southwest Oncology Group (SWOG) performance status of 0 or 1 prior to transplant. Eight patients had PET imaging prior to conditioning, of these 7 had FDG-avid foci of active disease.

Regimens immediately prior to transplant to which the HL was deemed resistant included ICE in 14 patients, DHAP in 9 patients, MOPP/ABVD in 7 patients, CED in 7 patients, ABVD in 4 patients, MOPP in 3 patients, and COPP in 2 patients with the remaining 18 patients receiving 17 various other regimens. When all prior regimens were assessed for responses in each patient, 40 (63%) patients were found to be resistant to anthracyclines, 33 (52%) to high-dose alkylating agents (cyclophosphamide [CY] and ifosfamide), 33 (52%) to platinum (cisplatin and carboplatin), and 19 (30%) to high-dose cytarabine.

Conditioning regimens and stem cell sources

Twenty-six patients (41%) were treated with TBI-based preparatory regimens, including 23 receiving TBI/CY/etoposide (VP16) and three patients treated with CY/TBI. The remaining 38 patients (59%) were treated with chemotherapy-only regimens including: busulfan (Bu)/melphalan (Mel)/thiotepa (TT) (n=18), carmustine/CY/VP-16 (n=12), Bu/CY (n=3), carmustine/VP-16/cytararbine/Mel (n=3), Bu/TT (n=1), and Bu/CY/Lithium (n=1). Twenty-four patients received autologous bone marrow, 39 received autologous mobilized peripheral blood stem cells (PBSC), and 1 received both.

Overall and progression-free survival

The 5-year OS and PFS were estimated to be 31% (95% confidence intervals [CI] 18–44%) and 17% (95% CI 6–27%) respectively, with median follow-up of 4.2 years (range 1–16.2 years) among surviving patients (Figure 1). At the last follow up, 21 patients (33%) were alive and 13 (20%) were alive and progression-free. Thirty of the 43 deaths during this study period followed relapse. Non-relapse causes of death included: respiratory failure (5 patients), infections (2 patients), AML/MDS (2 patients), hepatic toxicity (1 patient), renal failure (1 patient), and unknown causes (2 patients). Therapy for the 8 patients surviving following relapse included non-myeloablative allogeneic transplantation (3 patients), chemotherapy alone (2 patients), chemotherapy and radiation (1 patient), radiation alone (1 patient) and surgical resection (1 patient). Of the 7 patients with positive PET imaging pre-transplant, 4 are alive and progression-free from 5 months-2.1 years after transplant, 1 died of AML without relapse of HL at 4 yrs, and 2 suffered progression at 5 and 9 months, respectively. The one patient with a negative PET is alive and progression-free at 2.6 years.

Univariate and multivariable analyses

Hazard ratios (HR) for mortality from univariate analyses included: mixed cellularity (MC) histology, 0.42 (95% CI 0.16–1.07, p=.07 vs. all other); prior radiation, 2.05 (95% CI 1.11–3.79, p=.02); male gender, 1.05 (95% CI 0.57–1.92, p=.88); use of TBI, 0.65 (95% CI 0.34–1.21, p=.17); use of bone marrow-derived stem cells, 1.85 (95% CI 1.01–3.38, p=.05); ≥ 2 extranodal sites (ENS) of disease, 2.10 (95% CI 1.03–4.29, p=.04); and tumor bulk ≥ 5 cm, 1.39 (95% CI 0.75–2.56, p=.30). The HR for death for stage III disease was 0.94 (95% CI 0.39–2.27, p=.89) and for stage IV was 1.13 (95% CI 0.54–2.38, p=.75) when compared to patients with stage I/II disease. Age at transplant (p=.30) and number of cycles of previous chemotherapy (p=.79) were not statistically significantly associated with mortality in univariate models when evaluated as a continuous linear variable. In contrast, the year of transplant was correlated with mortality, with improved survival occurring following more recent transplants (p=.008). After adjusting for year of transplant, none of the other factors were statistically significantly associated with OS, while year of transplant remained associated with survival even after adjusting for the other factors (Table 2). Similar results were observed when PFS was evaluated, with no other factors statistically significantly associated with

outcome after adjusting for year of transplant with later transplants being associated with improved PFS (p=.04). The presence of >1 ENS of disease approached statistical significance for PFS when adjusted for transplant year (HR=1.89 (95% CI 0.92–3.88), p=.08).

Because of the strong correlation between era of transplant and source of stem cells (all recent transplants were done with PBSC) we evaluated the impact of year of transplant within and between the PBSC (August 1993–2005) and bone marrow (1986-July 1993) periods (Table 3). Overall survival appeared to improve over time within both the bone marrow and peripheral blood stem cell source eras as did PFS though the only statistically significant differences were between the most recent and most distant time periods (OS p=.003, PFS p=.02). The absolute risk of relapse in general decreased over time, though demonstrating statistically significant differences were likely limited by the small number of events. The estimated probabilities of 3-year survival for patients transplanted between 1986–1989, 1990-July 1993, August 1993–1999, and 1999–2005 were 9%, 36%, 33%, and 49%, respectively (Figure 2). Likewise, the estimated 3-year PFS for patients transplanted between 1986–1989, 1990-July 1993, August 1993–1999, and 1999–2005 were 9%, 21%, 33%, and 31%, respectively (Figure 2).

Discussion

Chemoresistant HL continues to represent a challenge for clinicians. Several series have repeatedly identified chemoresistance prior to ASCT as a major adverse prognostic factor for HL and, thus, many patients whose disease displays this feature are currently denied ASCT [1, 12, 13, 15–19]. Our study sought to specifically evaluate the outcomes of these patients following ASCT and potentially define a cohort that could attain prolonged remission and survival. Despite chemoresistance, the estimated the 5-year OS and PFS were 31% and 17%, respectively, suggesting a meaningful clinical benefit may be afforded to about one in six patients.

Multivariable analysis identified the year of transplant as a major predictor of survival with patients transplanted more recently having improved outcomes. The estimated OS and PFS at 3 years was 49% and 31%, respectively, among patients treated in the last 5 years as compared to a 9% 3-year OS and PFS in the earliest time period. Assessment of the impact of both transplant era and stem cell source on outcome suggested that the improvement cannot be attributed solely to the use of PBSC, as the OS and PFS among BM vs. PBSC patients are similar in the two time windows that span the change in stem cell source (1989–1999). One could postulate that the etiology of these improvements is likely multifactorial including both more effective supportive care as well as refined patient selection, though the retrospective nature of this study was not able to confirm this hypothesis. For example, differentiating outcomes based on the exact percent response or progression in these chemoresistant cases following salvage therapy was not within the scope of this project, but may have had a major impact on outcome. It is possible that those transplanted in the most recent era had a larger proportion of patients with minor responses to cytoreductive chemotherapy than in earlier times. Improvements in OS could also arise from improved post-relapse therapies, as 3 individuals that attained prolonged survival after relapse in our series underwent non-myeloablative allogeneic transplantation and 3 others had their disease effectively controlled with gemcitabine-based chemotherapy.

Most importantly, our recent data can be more useful than more distant historical results in counseling those with chemoresistant HL about prognosis after ASCT as one-third of the patients in our series transplanted since August 1993 were expected to be alive and progression-free at 3 years. Similarly, these findings would also suggest that caution should be used when comparing outcomes from novel transplant regimens in HL to historical data, as superior results may not be solely due to a change in the intervention being studied. Along these lines, we were

not able to directly compare transplant outcomes in this patient population to best available non-transplant therapies, leaving definitive conclusions to future prospective randomized comparisons.

Despite the fact that some of our patients with resistant HL attained prolonged PFS, new effective approaches are critically needed in this population as the vast majority will still relapse and succumb to their disease. Recent data suggest that gemcitabine-based regimens can induce remissions in patients that have not responded to more traditional salvage therapies [21, 22]. Such secondary pretransplant responses could both improve outcomes via tumor debulking and better identify disease that may respond to high-dose therapies. Individuals with resistant disease could be considered for investigational strategies using novel agents such as anti-CD30 monoclonal antibodies or transplants via reduced intensity allografting or tandem ASCT [23–28]. Future directions should also attempt to take advantage of the radiosensitivity of HL by means of radioimmunotherapy-based transplant-conditioning regimens, as has been successfully employed in non-Hodgkin's lymphoma [29–32]. Furthermore, optimized patient selection with the use of PET may also yield refined risk stratification and determine who may benefit the most from ASCT and who should proceed directly to other therapies. Prior series have suggested that lymphoma patients with CT-defined chemoresistant disease but PET negativity may have comparable outcomes to those with CT-defined responsive disease following ASCT [33, 34]. Unfortunately, the small number of individuals that had pre-transplant PET imaging in our series limited our ability to test this hypothesis. Nevertheless, 7 of 8 patients did have PET scanning that revealed residual disease with only 2 of these 7 experiencing relapse thus far.

Until novel effective therapies are developed the outcome for individuals with chemoresistant HL will be continue to be limited. Our data suggest that high-dose therapy and ASCT could be considered for and will likely benefit a significant subset of patients with HL, with nearly 1 in 3 patients transplanted in the last decade achieving prolonged remissions and survival. Longer follow up of the recently transplanted patients and results from other similar cohorts of transplanted and non-transplanted patients will be needed to confirm these findings.

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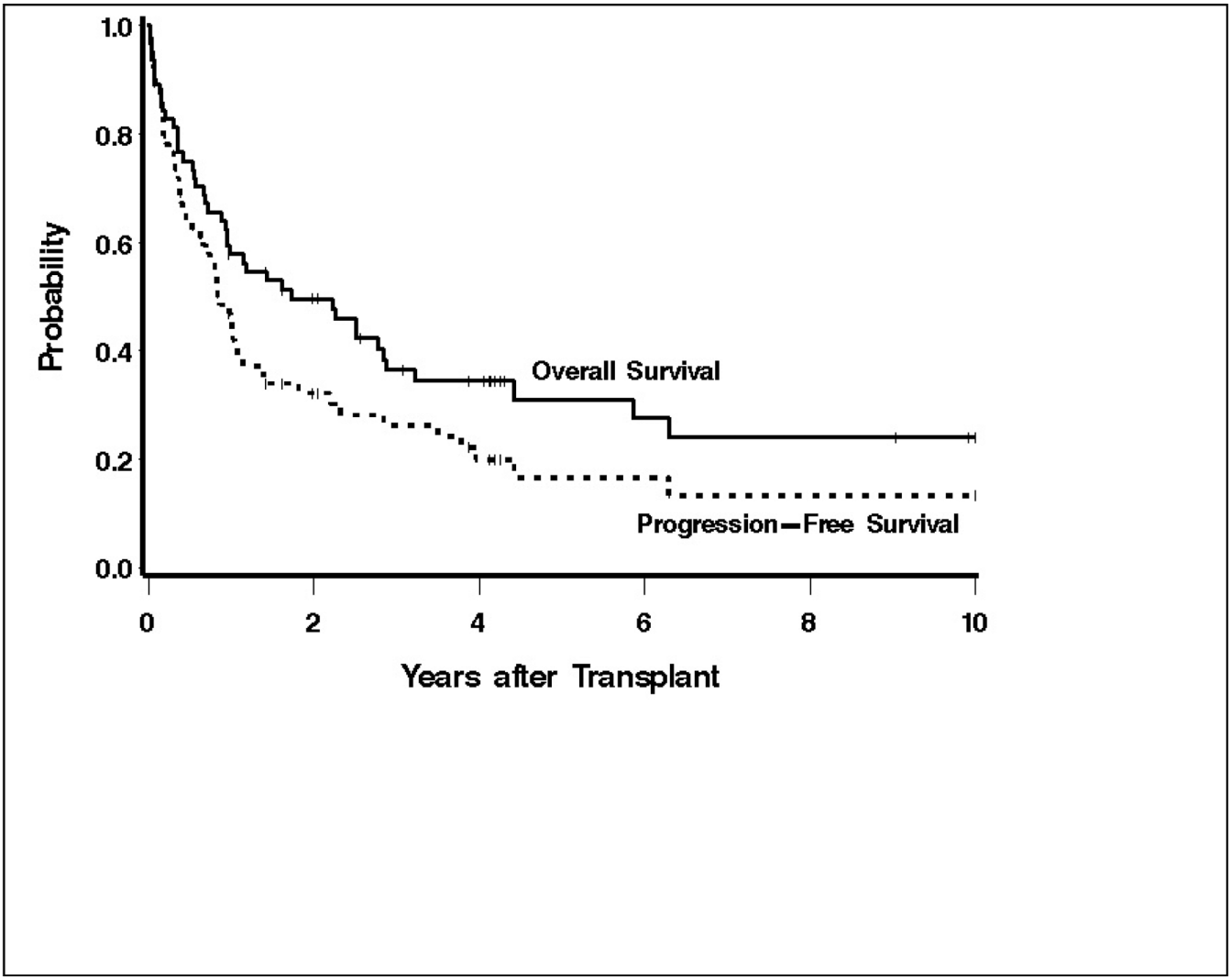

Figure 1.
Overall and progression-free survival of 64 patients with chemoresistant Hodgkin's lymphoma following high-dose therapy and autologous stem cell transplantation.

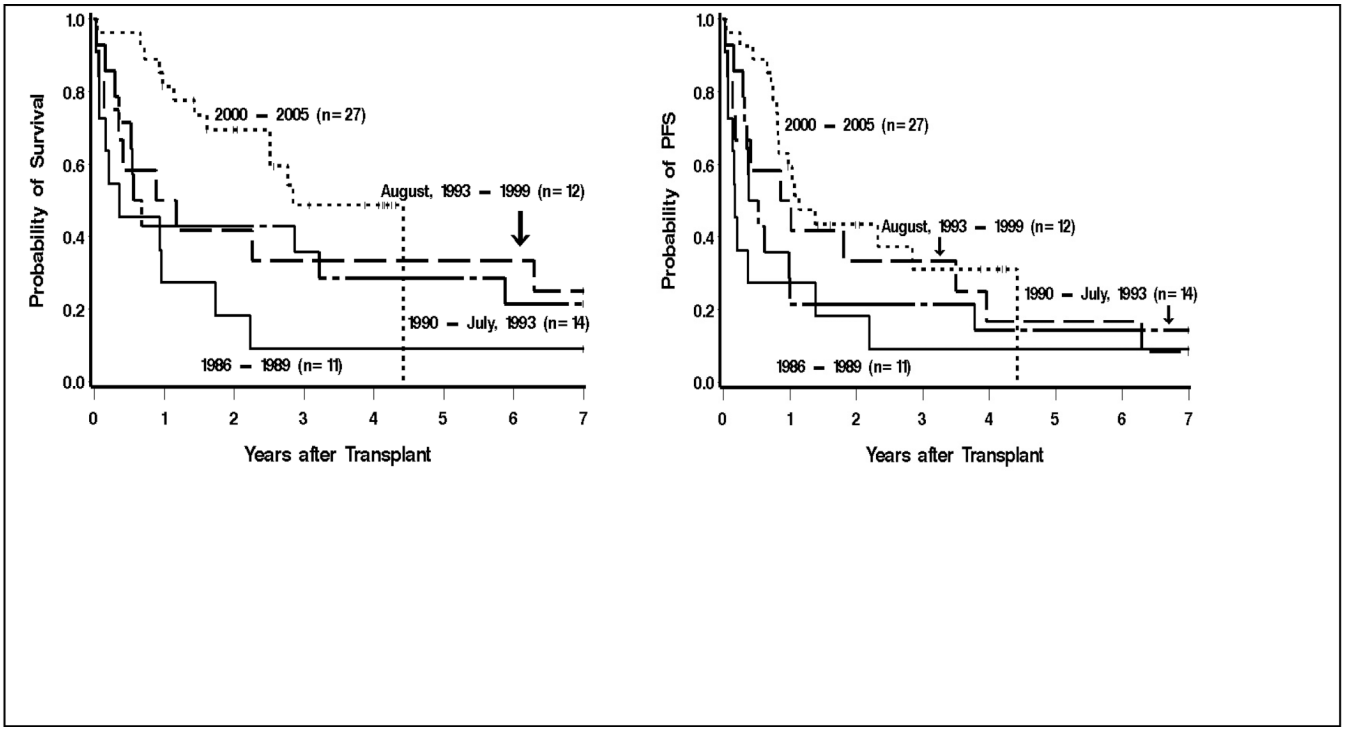

Figure 2.
Overall survival (left) and progression-free survival (right) of 64 chemoresistant Hodgkin's lymphoma patients treated with high-dose therapy and autologous transplantation stratified by year of transplant.

Table 1

Baseline Characteristics of the 64 patients with chemoresistant Hodgkin's lymphoma who underwent autologous stem cell transplantation.

Characteristic	Number	Percent
Median age at transplant	35 years	Range 14–59
Male sex	37	58
Histology		
Nodular Sclerosis	51	80
Mixed Cellularity	11	17
Lymphocyte Predominant	2	3
Number of extranodal sites		
0	31	48
1	22	34
2	10	16
3	1	2
Median number of prior regimens	2	Range 1–5
Prior radiation therapy	32	50
Stage at transplant		
I–II	15	23
III	17	27
IV	32	50
Bulk at transplant		
< 5 cm	42	66
≥ 5 cm	22	34
Preparatory regimens		
Chemotherapy and TBI	26	41
Chemotherapy only	38	59
Stem cell source		
Bone marrow	24	38
Peripheral blood	39	61
Both	1	2

Table 2

Multivariable analysis of associations of baseline factors with mortality adjusted for year of transplant in chemoresistant Hodgkin's lymphoma patients undergoing high-dose therapy and autologous transplantation.

Baseline Factor				Year of transplant
Factor	**Hazard Ratio**	**95% CI**	**p-value**	**p-value***
Stem cell source				
PBSC	1			
BM	0.77	0.28–2.17	.63	.05
Histology				
Non-MC	1			.01
MC	0.44	0.17–1.13	.09	
Prior radiation				
No	1			.06
Yes	1.58	0.80–3.12	.18	
Gender				
Female	1			.007
Male	1.09	0.60–2.00	.78	
Use of TBI				
No	1			.02
Yes	.76	0.40–1.44	.40	
Number of prior regimens*	--	--	.74	.007
Disease Bulk				
<5cm	1			.01
≥5cm	0.95	0.49–1.86	.88	
Extranodal sites				
0–1	1			.02
≥2	1.73	0.84–3.58	.14	
Stage				
I–II	1			
III	1.82	0.64–5.14	.26	.006
IV	1.22	0.57–2.60	.60	
Age*				
	--	--	.70	.01

*P-value for year of transplant modeled as a continuous linear variable after adjusting for the corresponding factor.

Table 3

Hazard ratios from a multivariable analysis of outcomes stratified by year of transplant and stem cell source.

Transplant era	Stem Cell Source	Hazard Ratios			
		Mortality	Mortality or Relapse	Relapse	Non-relapse Mortality
2000–2005 (n=27)	PBSC	1	1	1	1
July 1993–1999(n=12)	PBSC	1.85 (p=.16)	1.44 (p=.34)	1.42 (p=.43)	1.45 (p=.63)
1990-August 1993(n=14)	BM*	1.92 (p=.12)	1.64 (p=.19)	1.95 (p=.11)	0.90 (p=.90)
1986–1989(n=11)	BM	3.56 (p=.003)	2.46 (p=.02)	2.17 (p=.11)	2.98 (p=.13)

* One patient in this era received PBSC.