



BEAM versus BUCYVP16 Conditioning before Autologous Hematopoietic Stem Cell Transplant in Patients with Hodgkin Lymphoma

Sara Singer¹, Robert Dean², Qijuhong Zhao³, Nidhi Sharma³, Donna Abounader², Patrick Elder³, Craig C. Hofmeister³, Don M. Benson³, Ashley Rosko³, Sam Penza³, Leslie Andritsos³, Sumithira Vasu³, Samantha Jaglowski³, Basem M. William³, Brian Bolwell², Brad Pohlman², Matt Kalaycio², Deepa Jagadeesh², Brian Hill², Ronald Sobecks², Steven M. Devine³, Navneet S. Majhail², Yvonne A. Efebera^{3,*}

¹ Department of Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio

² Blood and Marrow Transplant Program, Department of Hematology and Oncology, Cleveland Clinic, Cleveland, Ohio

³ Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio

Article history:

Received 18 December 2018

Accepted 29 January 2019

Key Words:

Hodgkin lymphoma
Autologous transplant
BEAM
BUCYVP16

A B S T R A C T

High-dose chemotherapy followed by autologous hematopoietic stem cell transplant (AHSCT) is a standard of care for patients with relapsed Hodgkin lymphoma. Different conditioning regimens before AHSCT have been used, with the 2 most common being BEAM (carmustine, etoposide, cytarabine, and melphalan) and BUCYVP16 (busulfan, cyclophosphamide, and etoposide). We retrospectively compared the outcomes of patients treated with BEAM (n = 128) or BUCYVP16 (n = 105) followed by AHSCT. After a median follow-up of 4.2 years for BEAM and 3.8 for BUCYVP16 from AHSCT, the 5-year cumulative incidence of relapse was 29% with BEAM compared with 56% with BUCYVP16 ($P < .001$). Median progression free survival (PFS) and overall survival (OS) were not reached with BEAM and were 2.0 and 7.8 years with BUCYVP16, respectively. Improved PFS ($P < .001$) and OS ($P = .001$) were observed with BEAM for patients who needed transplant within 24 months from diagnosis and for patients not in complete remission (non-CR; $P = .001$ and $P < .001$, respectively) at AHSCT. In this large retrospective comparison the use of BEAM conditioning before AHSCT resulted in a statistically significant improved PFS and OS and lower relapse compared with BUCYVP16. This supports the use of BEAM as a frontline conditioning regimen before AHSCT for early-relapsed and non-CR Hodgkin lymphoma.

© 2019 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Hodgkin Lymphoma (HL) accounts for approximately 10% of lymphomas and .5% of cancer cases in the United States. An estimated 8260 new cases and 1070 deaths annually occur due to HL, with most patients affected being young adults [1]. Due to advances in treatment, the prognosis for patients diagnosed with HL is excellent, and most patients are cured with first-line therapy. However, despite the relatively high long-term overall survival (OS) for HL patients, approximately 20% to 30% of patients have refractory or relapsed disease [2]. High-dose chemotherapy

followed by autologous hematopoietic stem cell transplant (AHSCT) is the standard of care for these patients, as established by randomized trials [3,4].

Significant research in the last few years has focused on maximizing outcomes with high-dose chemotherapy. Conditioning regimens reported from single-institution studies with comparable efficacy and toxicities include BEAM (carmustine, etoposide, cytarabine, melphalan), BUCYVP16 (busulfan, cyclophosphamide, etoposide), CBV (cyclophosphamide, carmustine, etoposide), CBV with reduced doses of carmustine with cisplatin, and lomustine, cytarabine, cyclophosphamide, and etoposide [5–8]. Total body irradiation has fallen out of favor because of the high incidence of secondary malignancies and transplant-related mortality [9–12]. Busulfan-based regimens have not been widely explored, and mixed results have been observed with the limited number of studies in HL patients. A study from the

Financial disclosure: See Acknowledgments on page 1114.

* Correspondence and reprint requests: Yvonne Efebera, MD MPH, The Ohio State University Comprehensive Cancer Center, Department of Hematology, A357 Starling-Loving Hall, 320 W. 10th Avenue, Columbus, OH 43210.

E-mail address: Yvonne.Efebera@osumc.edu (Y.A. Efebera).

Cleveland Clinic and Ohio State University reported favorable outcomes from 127 HL patients treated with oral busulfan, etoposide, and cytarabine. Results showed 5-year progression-free survival (PFS) in approximately 48%, 5-year OS in approximately 51%, and 5.5% treatment-related mortality at 100 days post-transplant [13]. A report from Emory University also showed comparable results [14]. Preliminary efficacy data from a retrospective study done at Ohio State University reported at the EBMT annual meeting of 2012 showed that cumulative incidence of relapse (CIR) was significantly increased for the BUCYVP16 group and median OS was significantly longer at 3 and 5 years for the BEAM cohort [15]. In addition, a more recent study showed a busulfan-based regimen to have only marginally improved PFS/OS in HL patients compared with BEAM [16].

Despite the advances in treatment, there are limited data comparing regimens in the current era when significant advances in pre- and post-transplant therapy for HL have occurred. Hence, the goal of the present study was to investigate the efficacy and toxicities of BEAM (from The Ohio State University) compared with BUCYVP16 (from The Cleveland Clinic) in relapsed HL patients undergoing AHST.

METHODS

Patients

This was a retrospective study analyzing 233 consecutive HL patients who underwent AHST at The Ohio State University using BEAM (n = 128) and the Cleveland Clinic using BUCYVP16 (n = 105) between 2006 and 2014. The Institutional Review Board at both universities approved the study. Patients over age 18 years who had relapsed or refractory disease, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate cardiac (left ventricular ejection fraction \geq 45%), pulmonary (diffusing capacity of the lung for carbon monoxide \geq 50%), and hepatic (bilirubin, transaminases < 2 times upper limit of normal) function were included.

Transplant Procedures and Supportive Care

Peripheral blood progenitor cells were collected using standard institutional mobilization protocol and apheresis techniques. Patients treated with BEAM were given carmustine 300 mg/m² on day -6, etoposide 100 mg/m² from days -5 to -2, cytarabine 100 mg/m² from days -5 to -2, and melphalan 140 mg/m² on day -1. Patients treated with BUCYVP16 were given i.v. busulf 0.8 mg/kg every 6 hours for 14 doses on days -8 to -5, etoposide 40 mg/kg on days -5 to -4, and cyclophosphamide 60 mg/kg on days -3 to -2. Hematopoietic stem cells were infused on day 0. Therapeutic drug monitoring was not done in the busulfan group. Disease surveillance was done at both centers with a positron emission tomography/computed tomography scan every 3 to 6 months. All patients received supportive care as per institutional guidelines.

Definitions and Response Evaluation

Response, relapse, and disease progression were defined based on the International Working Group criteria [17]. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count \geq $.5 \times 10^9$ /L. Platelet engraftment was defined as the first of 7 days with a platelet count \geq 20×10^9 /L without platelet transfusion.

Statistical Analysis

Patient characteristics were summarized using median and range for continuous variables and frequency and percentage for categorical variables. The comparison of patient characteristics between BEAM and BUCYVP16 were conducted using the Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and Fisher's exact or chi-square test for categorical variables, whichever was appropriate. Primary endpoints were PFS and OS. PFS was defined as the time from day of transplant to day of documented relapse or death. OS was defined as the time from day of transplant to death from any cause, with censoring at date of last contact. The Kaplan-Meier survival function was used to estimate the PFS and OS rates, and the log-rank test was used for the comparison between treatment groups.

Cox proportional hazard regression model was used to evaluate the association between patient characteristic and risk of death. Age, gender, race, prior treatment, prior radiation, disease stage, remission status at transplant, Karnofsky performance status score, comorbidity index,

CD34 dose infused, and length of stay at hospital after transplant were the covariates tested for association with survival using univariable regression. Confounding was defined as a greater than 10% relative change in the association between conditioning regimen and outcome of interest with or without the potential confounding covariate in the model. Confounders and other risk factors deemed important and potential confounding in the literature were included in the final multivariable model.

CIR was measured from transplant date until relapse, treating death as a competing risk, and CIR was compared between BEAM and BUCYVP16 using the Pepe and Mori test. The Fine and Gray regression model accounting for competing risks was used to examine the association between covariates and risk of relapse. Multiple imputation procedure was applied to calculate the missing values and get the combined results from 15 multiply imputed data sets.

All statistical analyses were performed using Stata 14 (Stata Corp, College Station, TX). Statistical significance was defined as $P < .05$.

RESULTS

Baseline Characteristics

Baseline characteristics were similar between the 2 groups with the exception of median number of prior treatments (Table 1). The number of prior treatments was higher for BEAM (median, 3; range, 1 to 10) than for BUCYVP16 (median, 2; range, 1 to 5; $P < .01$). There were 3 nonclassic HL patients in the BEAM group and 7 patients in the BUCYVP16 group. Median age in the BEAM cohort was 34 years (range, 19 to 73) compared with 38 years (range, 19 to 69) in the BUCYVP16 cohort ($P = 0.51$). Men made up 49% of the BEAM cohort and 55% of the BUCYVP16 cohort ($P = .36$). Patients were predominantly white in both groups ($P = .16$). Disease stage ($P = .17$), prior radiation therapy ($P = .21$), comorbidity index ($P = .08$),

Table 1
Patient Characteristics

	BEAM (n = 128)	BUCYVP16 (n = 105)	P
Median age, yr (range)	34 (19-73)	38 (19-69)	.51
Gender			.36
Male	63 (49)	58 (55)	
Female	65 (51)	47 (45)	
Race			.16
Asian	2 (2)	0 (0)	
Black	13 (10)	6 (6)	
Hispanic	0 (0)	1 (1)	
White	113 (88)	97 (92)	
Multirace	0 (0)	1 (1)	
Disease stage			.17
I	8 (6)	3 (3)	
II	52 (41)	35 (34)	
III	38 (30)	30 (29)	
IV	29 (23)	36 (25)	
Median number of prior treatments (range)	3 (1-10)	2 (1-5)	<.01
Prior radiation			.21
No	75 (59)	70 (67)	
Yes	53 (41)	35 (33)	
Remission status at transplant			.83
CR	48 (37)	43 (41)	
PR	66 (52)	51 (49)	
Primary/relapse refractory	14 (11)	10 (10)	
KPS score			.08
70-80	24 (19)	27 (29)	
90-100	104 (81)	67 (71)	
Median comorbidity index (range)	2 (0-12)	3 (0-7)	.65
Comorbidity index (category)			.58
0-1	40 (33)	23 (36)	
2-3	56 (46)	32 (51)	
4-5	21 (17)	7 (11)	
>5	5 (4)	1 (2)	

Values are n (%) unless otherwise defined. PR indicates partial response; KPS, Karnofsky performance status.

Table 2
Response and Toxicity

	BEAM (n = 128)	BUCYVP16 (n = 105)	<i>p</i>
Median CD34 dose infused, 10 ⁶ /kg (range)	4.45 (1.27-19.25)	7.25 (1.62-47.97)	<.01
Median length of stay (range)	18 (15-51)	21 (19-29)	<.01
Median day of ANC engraft- ment (range)	10 (8-13)	10 (9-12)	<.01
Median day of platelet engraftment (range)	18 (13-70)	16 (7-49)	<.01
Relapse	35(28)	52 (50)	<.01
Death	23 (18)	36 (34)	<.01
SOS	4 (3)	0 (0)	.13
Grade 3 or 4 oral mucositis	19 (26)	25 (50)	.01
Hemorrhagic cystitis	0 (0)	1 (1)	.99
Second malignancy	2 (2)	5 (5)	.25

Values are n (%) unless otherwise defined. ANC indicates absolute neutrophil count; SOS, sinusoidal obstruction syndrome.

and remission status at transplant ($P = .83$) were similar between both groups.

Hematopoietic Engraftment

The CD34 dose infused was higher in the BUCYVP16 group (median, 7.25×10^6 cells/kg; range, 1.62 to 47.97) compared

with the BEAM group (median, 4.45×10^6 cells/kg; range, 1.27 to 19.25; $P < .01$). Platelet engraftment was significantly faster for the BUCYVP16 group (median, day 16; range, 7 to 49 days) compared with BEAM (median, day 18; range, 13 to 70 days; $P < .01$). Earlier platelet engraftment in the BUCYVP16 group might be due to the higher CD34 dose compared with that in BEAM group.

Length of Hospital Stay

Length of hospital stay was significantly shorter for the BEAM group, with median stay of 18 days (range, 15 to 51), compared with the BUCYVP16 group (median, 21 days; range, 19 to 29; $P < .01$) (Table 2). Length of hospital stay continued to be significantly longer in the BUCYVP16 group after deducting 2 days from the BUCYVP16 group to account for the differences in the conditioning start day -8 for BUCYVP16 versus day -6 for BEAM.

Toxicity

Grade 3 or 4 mucositis was statistically greater in the BUCYVP16 group, affecting 50% of patients compared with 26% of patients in the BEAM group ($P = .01$). This could perhaps be attributed to administration of cryotherapy before melphalan in the BEAM group. There were no statistically significant differences in sinusoidal obstruction syndrome ($P = .13$), hemorrhagic cystitis ($P = .99$), or second primary malignancy ($P = .25$) (Table 2).

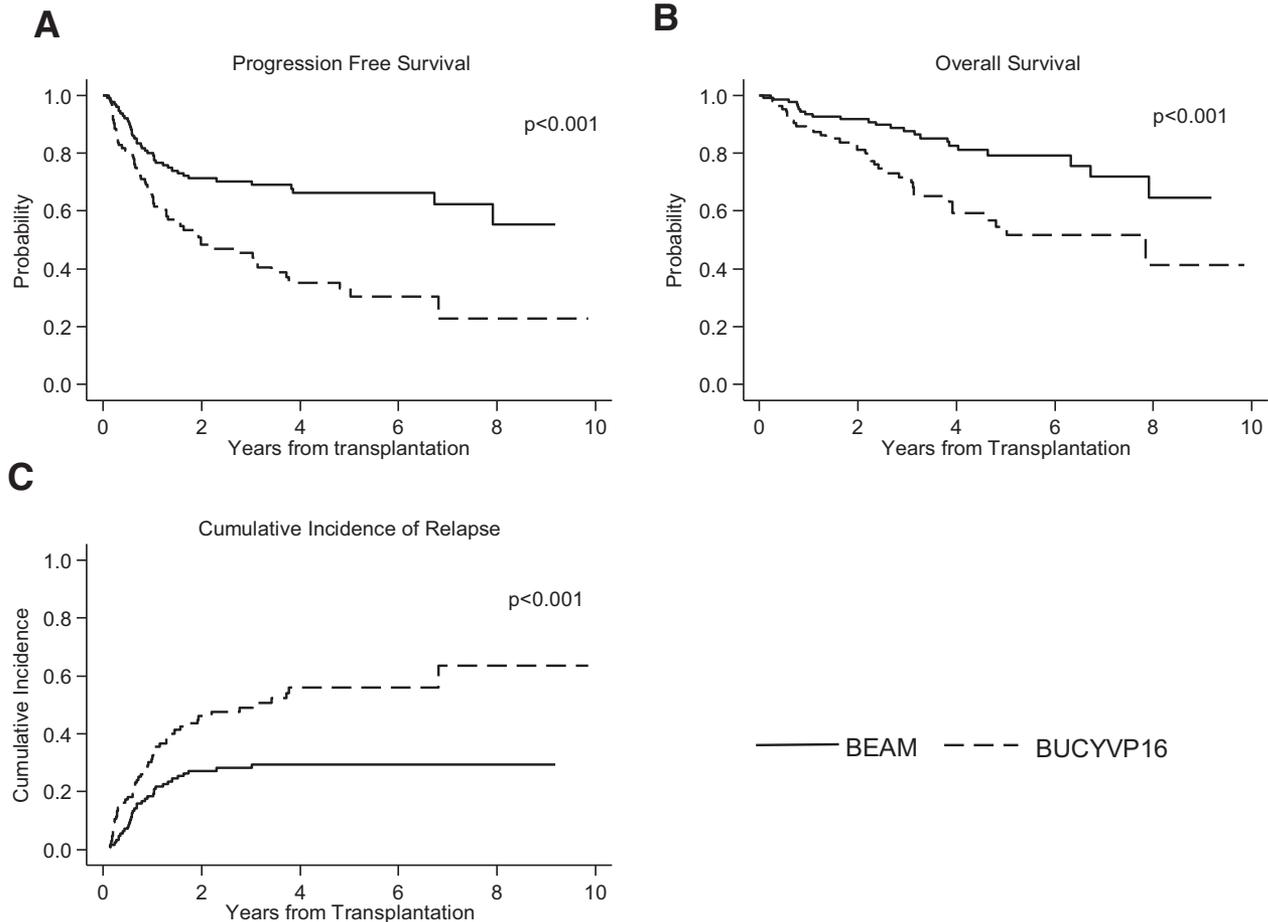


Figure 1. Outcomes from transplantation. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

Table 3
Median PFS and OS

	From Transplant		From Diagnosis	
	PFS	95% CI	PFS	95% CI
BEAM				
Median follow-up, yr	4.1	3.2-5.0	7.1	6.5-8.5
Median PFS, yr	NR	7.9-NR	15.4	13.3-NR
BUCYVP16				
Median follow-up, yr	3.8	2.6-5.0	7.0	5.1-8.9
Median PFS, yr	2.0	1.3-3.4	4.2	3.5-6.8
	From Transplant		From Diagnosis	
	OS	95% CI	OS	95% CI
BEAM				
Median follow-up, yr	4.2	3.9-4.9	7.0	6.5-8.1
Median OS, yr	NR	7.9-NR	NR	13.3-NR
BUCYVP16				
Median follow-up, yr	3.8	3.0-4.9	6.5	5.1-8.0
Median OS, yr	7.8	3.9-NR	11.2	7.8-NR

NR indicates not reached.

Survival and Relapse

With a median follow-up of 4.2 years for BEAM and 3.8 years for BUCYVP16 from time of AHSCT, the median PFS was not reached (95% confidence interval [CI], 7.9 to not reached) for BEAM versus 2.0 years (95% CI, 1.3 to 3.4) for

BUCYVP16 (Figure 1A, Table 3). The estimated rates of 1-, 3-, and 5-year PFS were 80%, 70%, and 66% with BEAM versus 65%, 45%, and 33% with BUCYVP16 ($P < .001$) (Figure 1A). The CIR from AHSCT was higher with BUCYVP16 (hazard ratio [HR], 2.71; 95% CI, 1.71 to 4.29) compared with BEAM ($P < .01$) (Figure 1C, Table 3). Patients with BEAM conditioning at 1, 3, and 5 years had a CIR of 18%, 28%, and 29% compared with 32%, 49%, and 56% for patients with BUCYVP16 conditioning ($P < .001$) (Figure 1C). The cumulative incidence for nonrelapse mortality was similar among the 2 groups ($P = .22$). The 1-, 3-, and 5-year cumulative incidence of nonrelapse mortality for BEAM was 1.6%, 2.7% and 5.3% compared with 2%, 4.5%, and 11.7% for BUCYVP16 (data not shown). The median OS from AHSCT was not reached (95% CI, 7.9 to not reached) for BEAM versus 7.8 years (95% CI, 3.9 to not reached) for BUCYVP16 (Figure 1B, Table 3). The 1-, 3-, and 5-year OS was 94%, 88%, and 79% for BEAM compared with 88%, 72%, and 54% for BUCYVP16 ($P < .001$) (Figure 1C). The PFS, OS, and CIR from diagnosis were also improved for BEAM compared with BUCYVP16 (Figure 2, Table 3).

At the time of AHSCT, 48 patients (38%) and 80 patients (63%) were in complete remission (CR) and non-CR, respectively, for the BEAM group. In the BUCYVP16 group 43 patients (41%) were in CR and 61 (59%) in non-CR. For patients in CR at AHSCT, there was a statistical difference in PFS in favor of BEAM ($P = .037$) but no difference in OS ($P = .24$) and CIR ($P = .16$) between the 2 regimens (Figure 3). Patients in non-CR

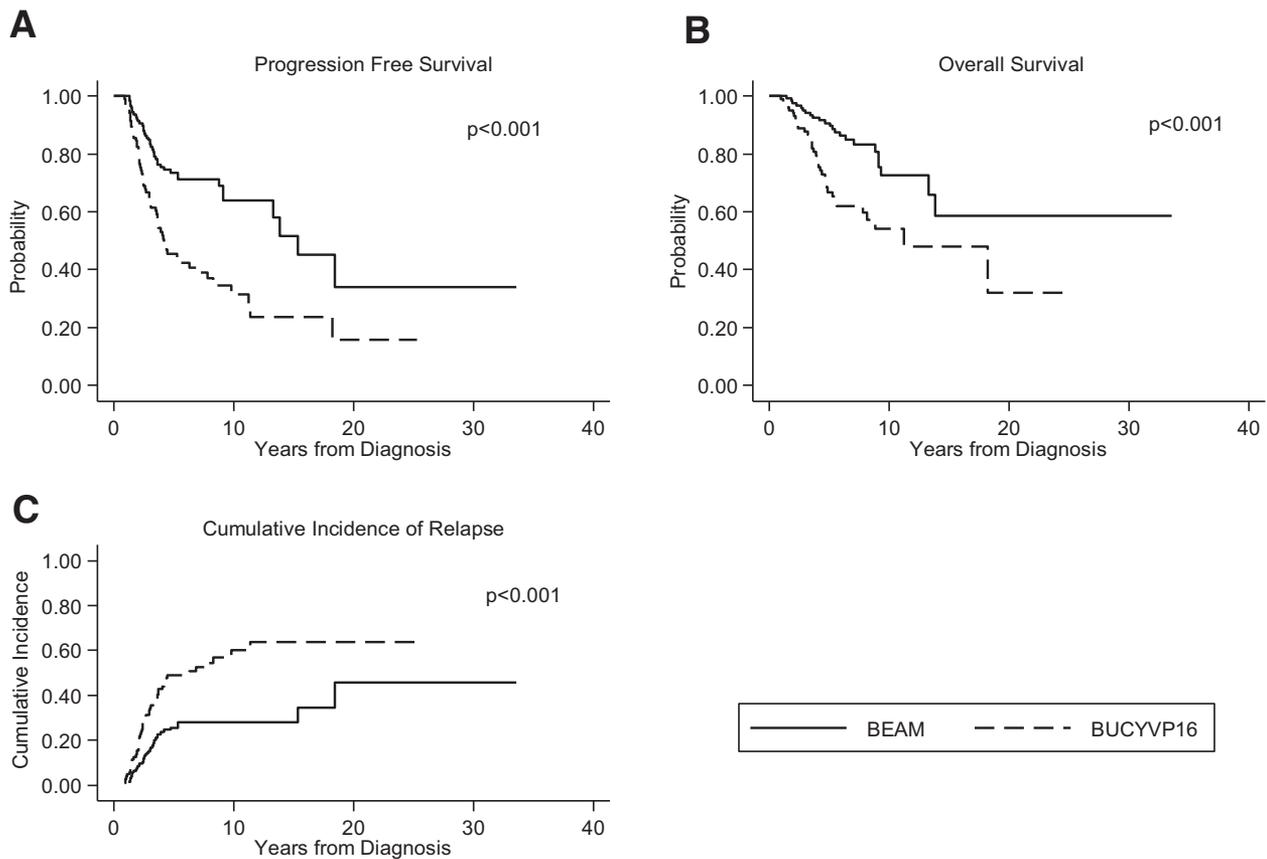


Figure 2. Outcomes from diagnosis. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

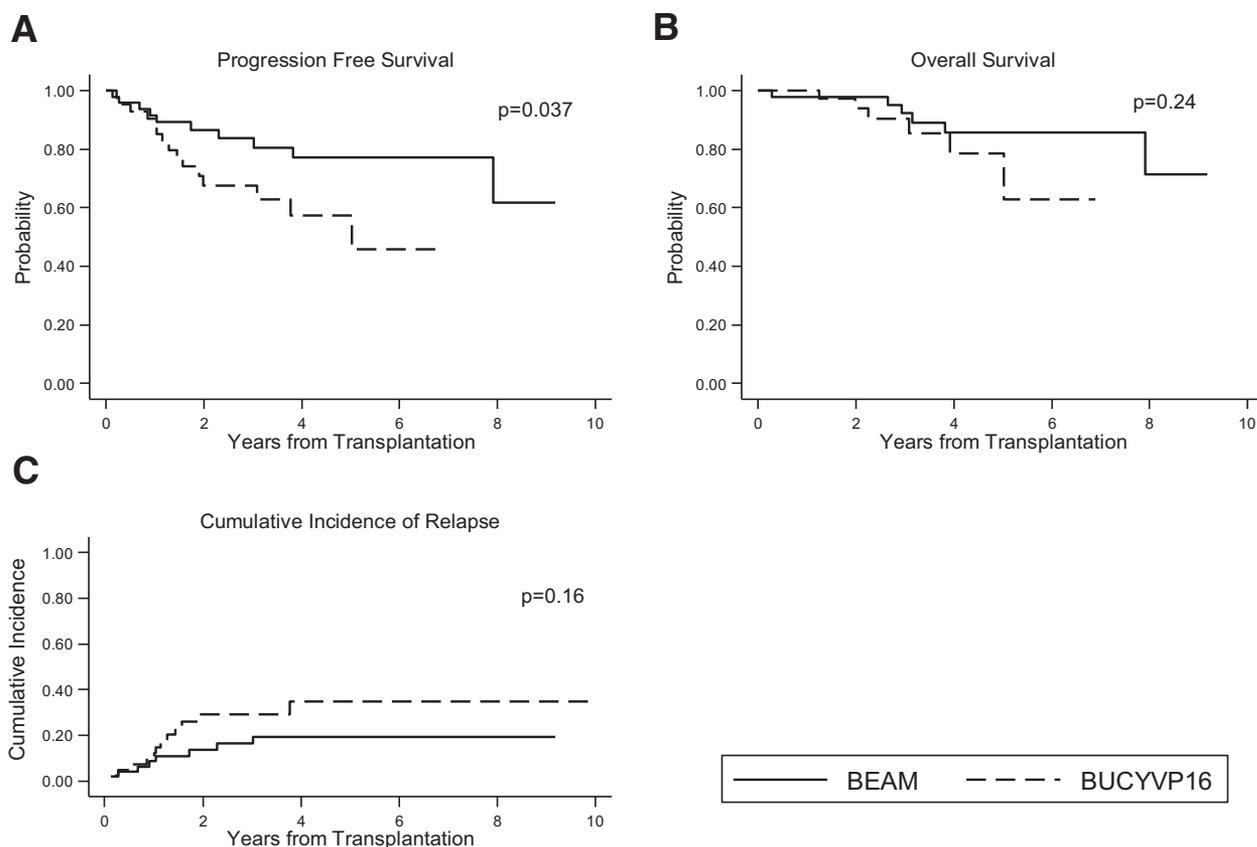


Figure 3. Outcomes for patients in CR going to transplantation. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

at AHSCT had statistically significant improved PFS ($P = .001$), OS ($P < .001$), and CIR ($P < .001$) with BEAM compared with BUCYVP16 (Figure 4).

We further compared the outcomes of those who received AHSCT within 24 months of diagnosis (early relapse) and those who received AHSCT at 24 months or later (late relapse) between the 2 groups. For patients who needed AHSCT within 24 months from diagnosis, PFS ($P < .001$), OS ($P = .001$), and CIR ($P = .003$) were superior with BEAM compared with BUCYVP16 (Figure 5, Table 4). However, for patients who needed AHSCT 24 months or later from diagnosis, there was no difference in outcomes between the 2 regimens (PFS, $P = .115$; OS, $P = .435$; CIR, $P = .095$) (Figure 6, Table 4).

Multivariable analysis for PFS, accounting for age, gender, race, remission status, Karnofsky performance status, comorbidity index, transplant year, and length of stay after transplant, showed worse outcome for BUCYVP16 compared with BEAM (HR, 2.83; 95% CI, 1.81 to 4.40) and for patients in partial remission (HR, 2.89; 95% CI, 1.76 to 4.74) or less (HR, 6.34; 95% CI, 3.21 to 12.51) at the time of transplant compared with CR (Table 5). Factors associated with worse OS were BUCYVP16 (HR, 2.70; 95% CI, 1.48 to 4.91) and partial remission (HR, 3.12; 95% CI, 1.50 to 6.50) or less (HR, 7.55; 95% CI, 2.87 to 19.84) at AHSCT, and factors associated with worse CIR were also BUCYVP16 (HR, 2.71; 95% CI, 1.71 to 4.29) and partial remission (HR, 2.76; 95% CI, 1.61 to 4.71) or less (HR, 7.38; 95% CI, 3.64 to 14.96) at AHSCT (Table 5).

DISCUSSION

Despite expanded knowledge, no evidence demonstrates superiority for any particular conditioning regimen before AHSCT for HL. In the present study we compared the outcomes of BEAM with BUCYVP16 conditioning followed by AHSCT in a cohort of patients transplanted at 2 institutions. We show that patients with relapsed HL have significantly better outcomes with BEAM compared with BUCYVP16, with significantly improved PFS, lower CIR, and better OS. Overall toxicities did not differ significantly between treatments except for high rates of mucositis and longer hospitalization in patients receiving BUCYVP16. We noted that patients who received BUCYVP16 had faster platelet engraftment, which may be due to higher CD34 dose. The length of stay was significantly longer in the BUCYVP16 group, likely because of a longer time to adequate oral intake from mucositis.

Time from diagnosis to AHSCT and remission status at the time of AHSCT were prognostic for outcome. Schmitz et al. [4] reported longer freedom from treatment failure in patients after BEAM-AHSCT compared with conventional aggressive chemotherapy without stem-cell transplantation (Dexa-BEAM), irrespective of the length of initial remission. We found that patients who needed AHSCT within 24 months from diagnosis had statistically improved PFS and OS with decreased CIR with BEAM conditioning compared with BUCYVP16. In addition, we showed that patients in less than CR at the time of transplant had statistically improved outcomes with BEAM as

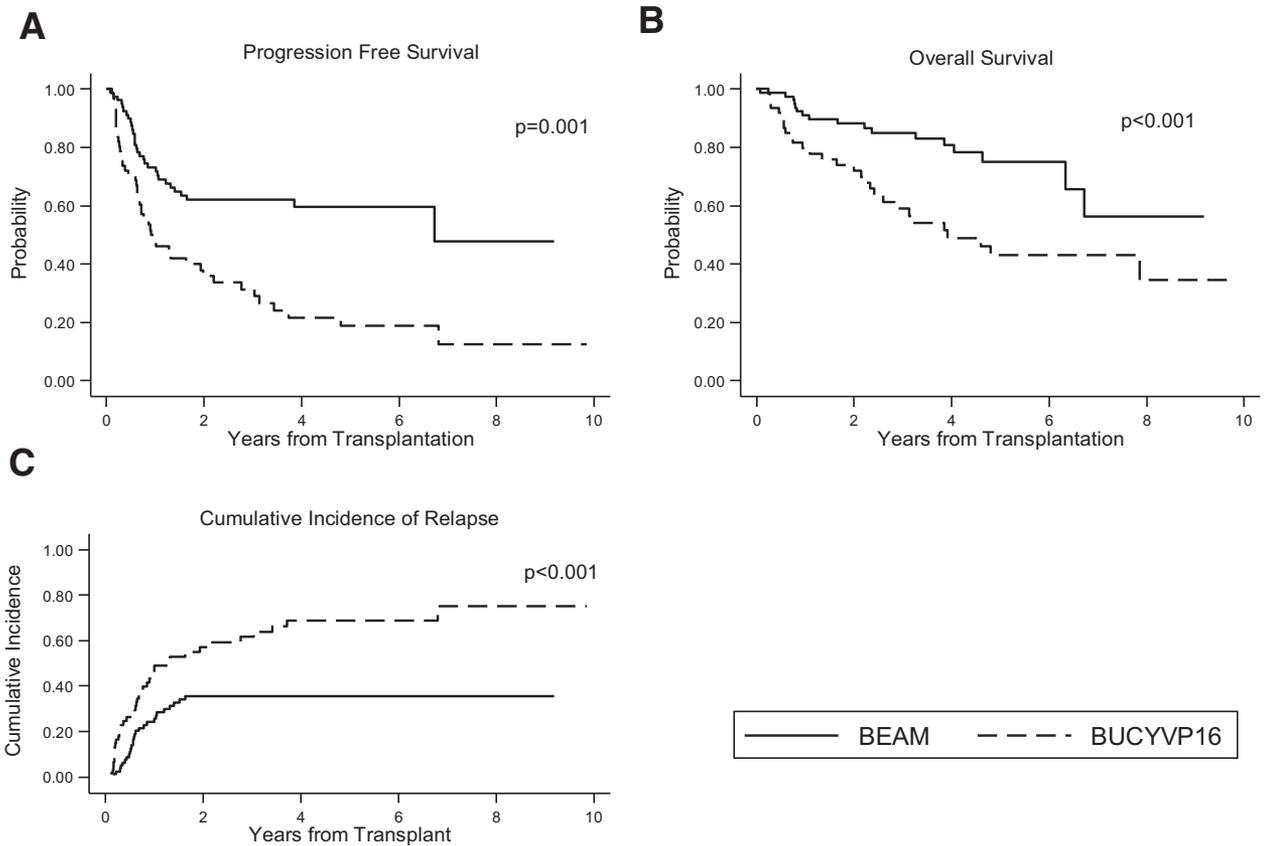


Figure 4. Outcomes for patients in non-CR going to transplantation. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

conditioning regimen compared with BUCYVP16. These data support BEAM as the preferred conditioning regimen before AHSCT for HL patients who require AHSCT within 24 months from diagnosis and for patients in less than CR after salvage therapy.

Several studies have reported promising results with new conditioning regimens, but very few comparisons with standard regimens are available. A multicenter phase II trial reported a comparison of 184 lymphoma patients treated with BUCYVP16 with 729 matched control recipients of BEAM registered with the Center for International Blood and Marrow Transplant Research database [18]. Outcomes for patients with HL treated with BEAM ($n=253$) had improved 2-year PFS of 59% compared with 33% with BUCYVP16 ($n=64$; $P<.001$) but no difference in OS ($P=.82$) [18]. A large retrospective study looking at outcomes of different conditioning regimen in lymphoma patients showed that for patients with HL, the probabilities of 3-year PFS were BEAM 62%, CBVlow 60%, CBVhigh 57%, BuCy 51%, and total body irradiation TBI 43%, and the probabilities of 3-year OS were BEAM 79%, CBVlow 73%, CBVhigh 68%, BuCy 65%, and total body irradiation 47% [9]. Multivariable analysis demonstrated that patients receiving BuCy (HR, 1.51; $P=.003$) and total body irradiation (HR, 2.01; $P=.007$) had worse PFS compared with those receiving BEAM and that patients with HL receiving BEAM had superior OS compared with all other regimens; however, this study did not assess BUCYVP16 [9].

A study performed at M.D. Anderson involved a cohort analysis of 180 consecutive patients with relapsed HL given BEAM ($n=57$), busulfan and melphalan ($n=39$), or Gemcitabine-Busulfan-melphalan (GemBuMel) ($n=84$) showed improved PFS and OS [19]. Although the GemBuMel regimen appeared to be a promising regimen, more studies are needed to confirm the data. Our study comparing the 2 most commonly used transplant conditioning regimens for HL is the first to show both statistically significant improved PFS and OS with BEAM compared with BUCYVP16, especially for patients needing transplant within 24 months from diagnosis and for patients in less than CR at time of transplant.

Our study has several limitations, including its retrospective design, allocation of treatment according to institution, and busulfan levels not monitored for patients in the BUCYVP16 group. Despite these constraints, the disease-related characteristics were similar between the 2 groups. One could argue that superiority of BEAM observed could be due to institutional/geographic effect. To address this we tried to account for all possible confounding variables such as age, gender, race, remission status, Karnofsky performance status, comorbidity index, transplant year, and length of stay into our final multivariable model. It should be noted that the differences between age, sex, race, and transplant year were not statistically different between the 2 groups. In addition, we performed a similar retrospective analysis of non-Hodgkin lymphoma patients between

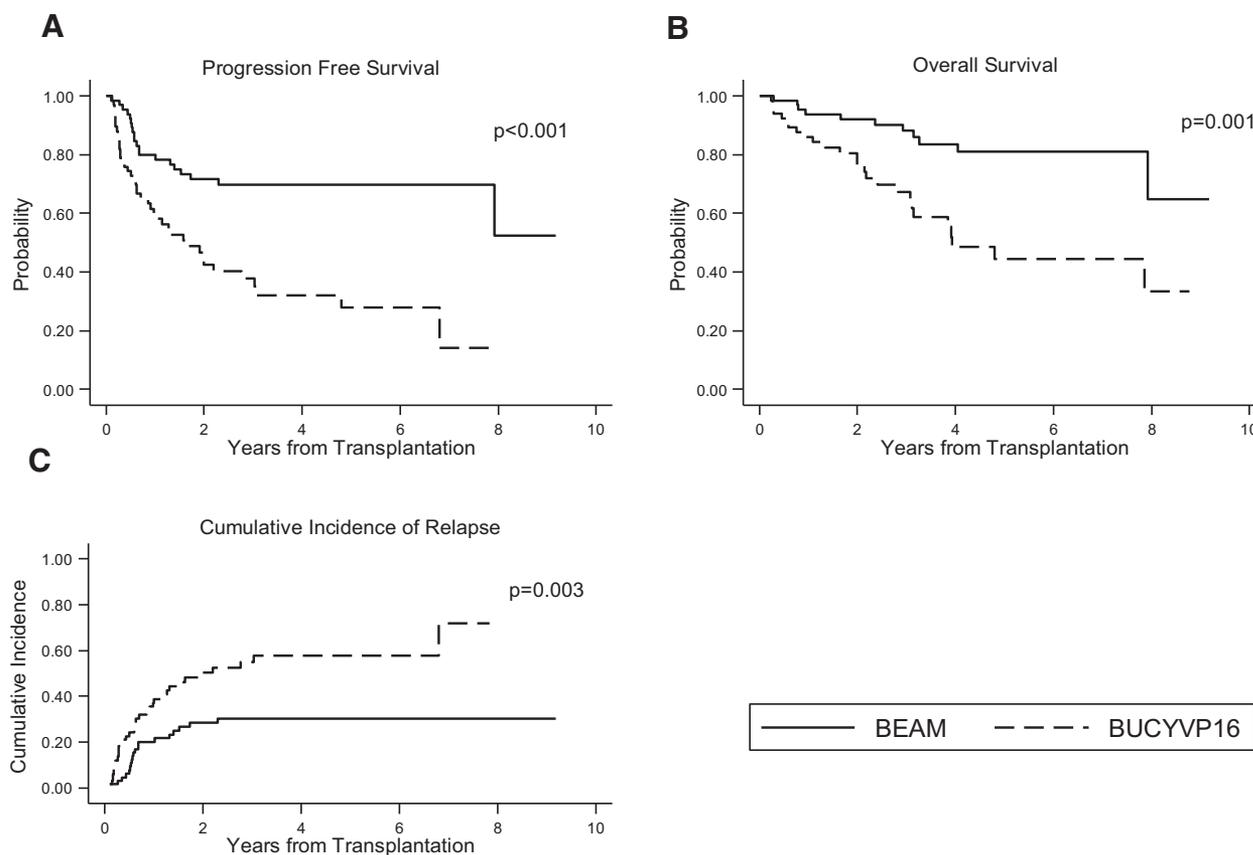


Figure 5. Outcomes for patients < 24 months from diagnosis to transplantation. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

Table 4
Outcome Analysis for Patients Needing AHSCT within or after 24 Months from Diagnosis

	Treatment	Endpoint	Median	95% CI	P
Transplant within 24 months from diagnosis (early relapse)	BEAM	PFS	NR	7.92-NR	<.001
	BUCYVP16		1.64	.91-3.04	
	BEAM	OS	NR	7.92-NR	.001
	BUCYVP16		3.92	3.09-NR	
Transplant at ≥ 24 months from diagnosis (late relapse)	BEAM	CIR	NR		.003
	BUCYVP16		1.91	.98-6.80	
	BEAM	PFS	NR	3.85-NR	.115
	BUCYVP16		3.73	1.28-NR	
Transplant at ≥ 24 months from diagnosis (late relapse)	BEAM	OS	NR	6.33-NR	.435
	BUCYVP16		NR	4.61-NR	
	BEAM	CIR	NR		.095
	BUCYVP16		3.78	1.28-NR	

the 2 institutions during the same period comparing the 2 regimens. We found no statistically significant differences between the 2 conditioning regimens in non-Hodgkin lymphoma (manuscript in review), which further supports our results for HL.

In conclusion, we found that BEAM conditioning before AHSCT is superior to BUCYVP16 in HL patients and especially in patients with early relapse from diagnosis and in patients in less than CR at the time of AHSCT. In the era of novel therapies there is room to further improve outcomes

with high-density chemotherapy and AHSCT for HL patients. More randomized studies are needed to determine the optimal treatment regimen. In fact, to improve responses and remission duration, novel maintenance regimens have also been of key focus. The AETHERA study [20] demonstrated success with brentuximab after transplant in HL. Our findings establishes BEAM as the standard to which newer regimens should be compared and suggests that the components of high-dose conditioning regimens are important for optimal outcomes after AHSCT.

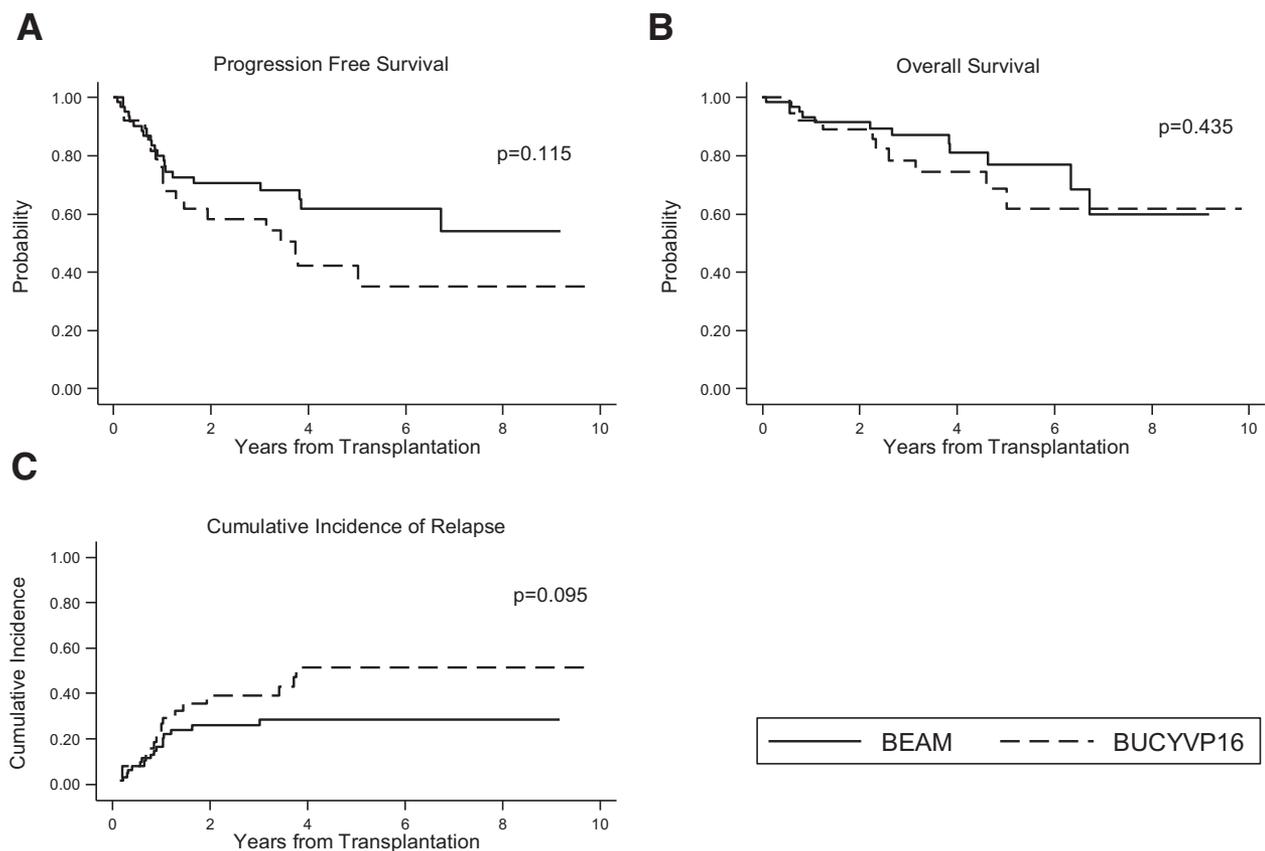


Figure 6. Outcomes for patients ≥ 24 months from diagnosis to transplantation. (A) Kaplan-Meier estimate of PFS. (B) Kaplan-Meier estimate of OS. (C) CIR. Solid line indicates patients who were on BEAM, and broken line indicates patients who were on BUCYVP16.

Table 5

Multivariable Cox Proportional Hazard Regression Model for PFS, OS, and Relapse with Death as Competing Risk

	HR	P	95% CI
<i>PFS</i>			
Conditioning regimen (BUCYVP16 vs. BEAM)	2.83	<.01	1.81-4.40
Age	.99	.43	.98-1.01
Gender (female vs. male)	.70	.12	.45-1.09
White race	1.32	.50	.59-2.95
Remission status at transplant PR vs. CR	2.89	<.01	1.76-4.74
Primary/relapse refractory	6.34	<.01	3.21-12.51
KPS score (90-100 vs. 70-80)	.69	.16	.42-1.15
Comorbidity index	1.10	.18	.96-1.27
Transplant year	1.00	.96	.91-1.09
Length of stay	1.03	.15	.99-1.08
<i>OS</i>			
Conditioning regimen (BUCYVP16 vs. BEAM)	2.70	<.01	1.48-4.91
Age	1.02	.07	1.00-1.04
Gender (female vs. male)	.88	.69	.48-1.64
White race	1.02	.97	.34-3.08
Remission status at transplant PR vs. CR	3.12	<.01	1.50-6.50
Primary/relapse refractory	7.55	<.01	2.87-19.84
KPS score (90-100 vs. 70-80)	.42	.01	.22-.80
Comorbidity index	1.22	.02	1.03-1.43
Transplant year	.96	.59	.83-1.11
Length of stay	1.05	.04	1.00-1.11
<i>CIR</i>			
conditioning Regimen (BUCYVP16 vs. BEAM)	2.71	<.01	1.71-4.29
Age	.98	.04	.96-1.00
Gender (female vs. male)	.68	.09	.43-1.07
White race	1.30	.53	.57-2.96
Remission status at transplant PR vs. CR	2.76	<.01	1.61-4.71
Primary/relapse refractory	7.38	<.01	3.64-14.96
KPS score (90-100 vs. 70-80)	.74	.27	.44-1.26
Transplant year	1.00	.95	.92-1.09
Length of stay	1.01	.61	.97-1.05

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: Y.A.E. and S.S. designed the research study. S.S. and Q.Z. analyzed the results. N.S. and Y.A.E. wrote the paper. P.E., D.A., and S.S. collected the data. M.K., S.M.D., and N.S.M. edited and provided scientific discussions. R.D., C.C. H., D.M.B., A.R., S.P., L.A., S.V., S.J., B.M.W., B.B., B.P., D.J., B.H., and R.S. all reviewed and provided scientific discussions

REFERENCES

- National Cancer Institute. SEER stat fact sheets: Hodgkin lymphoma. Available at: <http://seer.cancer.gov/statfacts/html/hodg.html>. 2018.
- Townsend W, Linch D. Hodgkin's lymphoma in adults. *Lancet*. 2012; 380:836-847.
- Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341:1051-1054.
- Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359:2065-2071.
- Colpo A, Hochberg E, Chen YB. Current status of autologous stem cell transplantation in relapsed and refractory Hodgkin's lymphoma. *Oncologist*. 2012;17:80-90.
- Lavoie JC, Connors JM, Phillips GL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: long-term outcome in the first 100 patients treated in Vancouver. *Blood*. 2005;106:1473-1478.
- Perz JB, Giles C, Szydlo R, et al. LACE-conditioned autologous stem cell transplantation for relapsed or refractory Hodgkin's lymphoma: treatment outcome and risk factor analysis in 67 patients from a single centre. *Bone Marrow Transplant*. 2007;39:41-47.
- Benekli M, Smiley SL, Younis T, et al. Intensive conditioning regimen of etoposide (VP-16), cyclophosphamide and carmustine (VCB) followed by

- autologous hematopoietic stem cell transplantation for relapsed and refractory Hodgkin's lymphoma. *Bone Marrow Transplant*. 2008;41:613–619.
9. Chen YB, Lane AA, Logan B, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2015;21:1046–1053.
 10. Majhail NS, Ness KK, Burns LJ, et al. Late effects in survivors of Hodgkin and non-Hodgkin lymphoma treated with autologous hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor study. *Biol Blood Marrow Transplant*. 2007;13:1153–1159.
 11. Sureda A, Arranz R, Iriando A, et al. Autologous stem-cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. *J Clin Oncol*. 2001;19:1395–1404.
 12. Subira M, Sureda A, Martino R, et al. Autologous stem cell transplantation for high-risk Hodgkin's disease: improvement over time and impact of conditioning regimen. *Haematologica*. 2000;85:167–172.
 13. Wadehra N, Farag S, Bolwell B, et al. Long-term outcome of Hodgkin disease patients following high-dose busulfan, etoposide, cyclophosphamide, and autologous stem cell transplantation. *Biol Blood Marrow Transplant*. 2006;12:1343–1349.
 14. Santos EC, Sessions J, Hutcherson D, Flowers C, Langston A, Waller EK. Long-term outcome of Hodgkin disease patients following high-dose busulfan, etoposide, cyclophosphamide, and autologous stem cell transplantation—a similar experience. *Biol Blood Marrow Transplant*. 2007;13:746–747.
 15. Galena S, Neil D, Lai W, et al. Busulfan, cyclophosphamide, etoposide is not superior to carmustine, etoposide, cytarabine, melphalan conditioning prior to autologous stem cell transplantation in patients with Hodgkin's lymphoma and is associated with increased toxicity. *EBMT 2012 Congress Oral presentation*. 2012;47(S84). abstract #0365.
 16. Sakellari I, Mallouri D, Batsis I, et al. Carmustine, etoposide, cytarabine and melphalan versus a newly designed intravenous busulfan-based Busulfex, etoposide and melphalan conditioning regimen for autologous hematopoietic cell transplant: a retrospective matched-pair analysis in advanced Hodgkin and non-Hodgkin lymphomas. *Leuk Lymph*. 2015;56:3071–3081.
 17. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244.
 18. Flowers CR, Costa LJ, Pasquini MC, et al. Efficacy of pharmacokinetics-directed busulfan, cyclophosphamide, and etoposide conditioning and autologous stem cell transplantation for lymphoma: comparison of a multicenter phase II study and CIBMTR outcomes. *Biol Blood Marrow Transplant*. 2016;22:1197–1205.
 19. Nieto Y, Popat U, Anderlini P, et al. Autologous stem cell transplantation for refractory or poor-risk relapsed Hodgkin's lymphoma: effect of the specific high-dose chemotherapy regimen on outcome. *Biol Blood Marrow Transplant*. 2013;19:410–417.
 20. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385:1853–1862.