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Improved outcomes of high-risk relapsed Hodgkin lymphoma patients after high-dose chemotherapy: a 15-year analysis

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ABSTRACT

High-dose chemotherapy and autologous stem-cell transplant (HDC/ASCT) is standard treatment for chemosensitive relapsed classical Hodgkin lymphoma, although outcomes of high-risk relapse (HRR) patients remain suboptimal. We retrospectively analyzed all HRR classical Hodgkin lymphoma patients treated with HDC/ASCT at our institution between 01/01/2005 and 12/31/2019. HRR criteria included primary refractory disease/relapse within 1 year, extranodal extension, B symptoms, requiring more than one salvage line, or positron emission tomography (PET)-positive disease at ASCT. All patients met the same ASCT eligibility criteria. We treated 501 patients with BEAM (n=146), busulphan/melphalan (BuMel) (n=38), gemcitabine(Gem)/BuMel (n=189) and vorinostat/Gem/BuMel (n=128). The Gem/BuMel and vorinostat/Gem/BuMel cohorts had more HRR criteria and more patients with PET-positive disease at ASCT. Treatment with brentuximab vedotin (BV) or anti-PD1 prior to ASCT, PET-negative disease at ASCT, and maintenance BV increased over time. BEAM and BuMel predominated in earlier years (2005-2007), GemBuMel and BEAM in middle years (2008-2015), and vorinostat/GemBuMel and BEAM in later years (2016-2019). The median follow-up is 50 months (range, 6-186). Outcomes improved over time, with 2-year progression-free survival (PFS)/overall survival (OS) rates of 58%/82% (2005-2007), 59%/83% (2008-2011), 71%/94% (2012-2015) and 86%/99% (2016-2019) (P<0.0001). Five-year PFS/OS rates were 72%/87% after vorinostat/GemBuMel, 55%/75% after GemBuMel, 45%/61% after BEAM, and 39%/57% after BuMel (PFS: P=0.0003; OS: P<0.0001). These differences persisted within the PET-negative and PET-positive subgroups. Prior BV and vorinostat/GemBuMel were independent predictors of more favorable outcome, whereas primary refractory disease, ≥2 salvage lines, bulky relapse, B symptoms and PET-positivity at ASCT correlated independently with unfavorable outcomes. In conclusion, post-HDC/ASCT outcomes of patients with HRR classic Hodgkin lymphoma have improved over the last 15 years. Pre-ASCT BV treatment and optimized synergistic HDC (vorinostat/GemBuMel) were associated with this improvement.

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Introduction

High-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) is standard treatment of relapsed classical Hodgkin lymphoma (cHL).[1,2] Adverse predictors of post-ASCT outcome include primary refractory disease, short first complete remissions, extranodal extension, bulky lesions or B symptoms at the time of relapse, performance status ≥1 at relapse, relapse within a prior radiation field, requirement for more than one line of salvage chemotherapy and, particularly, the persistence of metabolically active tumor on pre-HDC positron emission tomography (PET).[3-5]

The BEAM regimen (carmustine/etoposide/cytarabine/melphalan) has long been the standard HDC combination for cHL despite its suboptimal results in patients with high-risk relapses (HRR), whose long-term progression-free survival (PFS) rate is around 50%.[3,5,6] Efforts to improve ASCT outcomes have focused mainly in the pretransplant and posttransplant settings. Pretransplant PET-guided use of non-cross-resistant chemotherapy and incorporation of novel drugs, such as brentuximab vedotin (BV), seem to improve results.[7,8] In the post-ASCT setting, a randomized trial of maintenance BV after BEAM for HRR cHL showed improvement of 5-year PFS from 41% to 59% as compared to that with placebo.[9,10]

In contrast, despite clearly suboptimal results obtained with BEAM, little effort has gone into developing a more efficacious HDC program, save for the notable exceptions of attempts to deliver HDC in a tandem fashion.[11-13] We have systematically sought to develop more effective HDC regimens based on investigations of synergistic interactions between its components. We started with a combination of pharmacokinetically-guided intravenous busulfan with melphalan (BuMel), which was as safe as BEAM but appeared not to be more effective.[14] Following the demonstration of marked preclinical synergy between gemcitabine and BuMel, we next investigated clinically the GemBuMel combination.[15,16] Finally, our preclinical work on epigenetic modulation, the synergistic interactions between nucleoside analogs and bifunctional DNA-alkylating agents used in HDC[17] led us to clinically test vorinostat/GemBuMel[18] and azacytidine/vorinostat/ GemBuMel.[19]

We herein report our experience with HDC with ASCT for HRR cHL over the last 15 years, analyzing patient-, tumor-, and treatment-related factors (pre-ASCT, HDC regimens, and post-ASCT) associated with outcome.

Methods

We retrospectively analyzed all patients with HRR cHL treated at MD Anderson Cancer Center with HDC and ASCT between 01/01/2005 and 12/31/2019. This analysis was approved by the Institutional Review Board. As in our sequential GemBuMel trials, HRR was defined for this analysis by one or more of the following criteria: relapse within 1 year or refractoriness to frontline therapy, extranodal extension at relapse, B symptoms at relapse, failure to achieve a complete remission in response to the most recent therapy, or requiring two or more lines of salvage therapy. Lines of salvage chemotherapy were defined as different regimens used to treat persistent/progressive disease and did not include a different regimen given to mobilize peripheral blood progenitor cells following a complete remission. Patients not meeting any HRR criteria were excluded from this analysis. Bulky lesions at relapse were defined as those ≥5 cm. All demographic and tumor-related variables were captured prospectively in our departmental database.

During this 15-year period we studied new HDC regimens for HRR cHL in sequential Institutional Review Board-approved clinical trials: a phase II trial of BuMel (NCT00427765),[14] a phase I trial of GemBuMel (NCT00410982),[15] a phase II study of GemBuMel (NCT01200329),[16] a phase I/II trial of vorinostat/GemBuMel (NCI-2011-02891),[18] and a phase I/II trial of azacytidine/vorinostat/GemBuMel (NCT01983969).[19] The upper age limit of participants in these trials was 65 years and the patients had to have had a performance status 0-2 and normal renal, pulmonary, cardiac and hepatic function (*Online Supplementary Material*).

BuMel,[14] GemBuMel,[15] vorinostat/GemBuMel,[18] and azacytidine/vorinostat/GemBuMel[19] were administered as previously described (*Online Supplementary Material*). Since azacytidine did not improve the activity of vorinostat/GemBuMel, we included those patients with the vorinostat/GemBuMel group in this analysis.

Patients with HRR cHL who were eligible for those trials but who instead received standard BEAM were prospectively registered in our database. In addition, both GemBuMel and vorinostat/Gem/Bu/Mel were adopted as standard regimens at our institution upon publication of their trials. Reasons for treating patients off study included their declining trial participation, patients' lack of clinical trial insurance benefits or periods when no trial was open to enrollment. The choice of HDC regimen off study was at the treating physician's discretion.

Institutional guidelines for supportive care and follow-up visits were followed (*Online Supplementary Material*). All patients in this analysis had undergone pre-ASCT PET/computed tomography scans, prospectively interpreted as positive (active tumor) or negative (no active tumor) using the International Harmonization Project in Lymphoma (IHPL) criteria up to 2013 (with mediastinal blood pool activity as the reference background),[20] and the Deauville score from 2014 thereafter (with a score 1-3 considered a complete remission).[21]

Post-transplant radiotherapy, delivered at 30-41.4 Gy, was considered for bulky relapses and/or PET-positive lesions at ASCT. Maintenance BV was considered for all patients after the results of the AETHERA study became available.[9]

Statistical analyses

Differences in variables by cohort were assessed with Wilcoxon rank-sum and χ^2 tests for continuous and categorical variables, respectively.[22] PFS and overall survival (OS) were measured from the initiation of HDC to relapse or death, respectively, or last follow-up visit. The Kaplan-Meier method estimated 12-, 24-, and 60-month PFS and OS,[23] and differences in outcomes were assessed using the log-rank test.[24] Univariable and multivariable Cox regression analyses identified factors associated with PFS and OS. Statistical significance was defined by α=0.05 and all analyses used SAS v.9.4 (Cary, NC, USA).

Results

A total of 501 patients with HRR cHL were treated with HDC and ASCT between 01/01/2005 and 12/31/2019 and all are included in this analysis: 189 received GemBuMel (159 on two clinical trials and 30 off study), 128 received vorinostat-GemBuMel (± azacytidine) (41 on trial, 87 off trial), 146 received BEAM (all standard of care), and 38 BuMel (all on study). Thirty-seven patients (7.3%) received maintenance BV.

Over a median follow-up of 50 months (range, 6-186), a

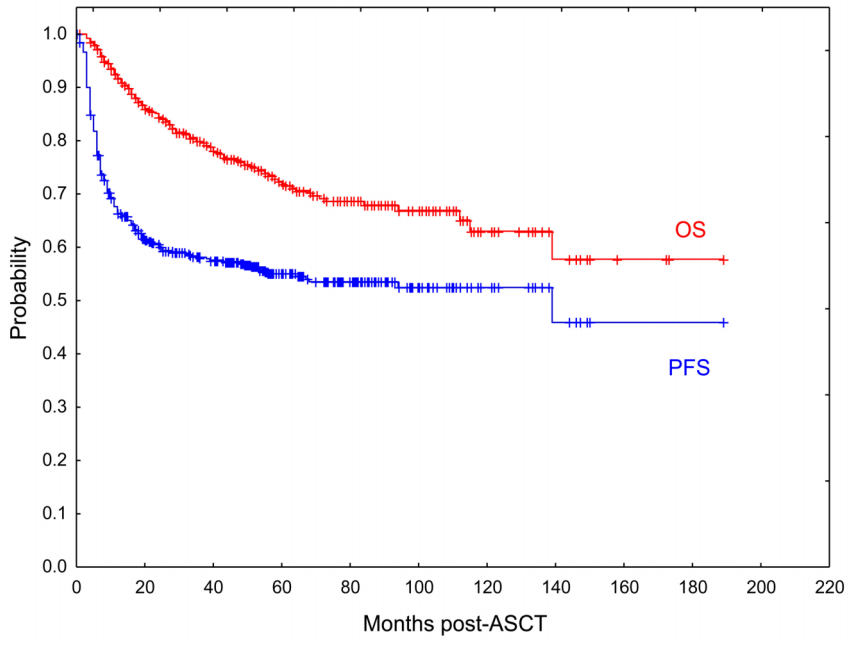

Figure 1. Progression-free survival and overall survival of all patients. PFS: progression-free survival; OS: overall survival; ASCT: autologous stem-cell transplantation.

total of 205 patients (40.9%) experienced relapse and 130 patients (25.9%) died. Treatment-related mortality from HDC/ASCT was the cause of death of two patients, aged 40 and 45, who died from infectious complications, both around 3 months after BEAM therapy. Other causes of death were progressive disease (n=96), second primary malignancies (n=8), toxicity from post-ASCT salvage therapies (n=21, 19 after allogeneic stem cell transplantation, 2 after BV), unrelated late events (n=2), and unknown (n=1). The causes of death did not vary across the different time periods (*Online Supplementary Table S1*).

The overall 1-year, 2-year and 5-year PFS rates for the whole population were 67% (95% confidence interval [95% CI]: 63-71%), 60% (95% CI: 56-64%), and 55% (95% CI: 50-59%), respectively. The 1-year, 2-year and 5-year OS rates were 92% (95% CI: 89-94%), 84% (95% CI: 81-87%), and 73%, respectively (Figure 1). There was a gradual improvement in PFS and OS over time (Figures 2 and 3). The 2-year PFS rates were 48% for those transplanted between 2005-2007, 50.6% for those transplanted between 2008-2010, 64.3% for those transplanted between 2011-2015 and 78.7% for those transplanted between 2016-2019 (P<0.0001) (Figure 2A). Their respective 2-year OS rates were 74.6%, 76.8%, 89.7% and 96.2% (P<0.0001) (Figure 2B).

Seven BEAM patients were ineligible for the clinical trials due to age older than 65 years. Three of them are alive in complete remission at 15 months, 3 years and 5 years after ASCT. The other four relapsed at a median of 17 months after ASCT (range, 4-39 months), and three died from tumor progression. We excluded these seven patients from the cohort and prognostic analyses described below, for which all patients met the same eligibility criteria.

Cohort analyses

There were significant differences in disease characteristics among the four cohorts (Table 1). The GemBuMel and vorinostat/GemBuMel groups included more patients with primary refractory disease (P=0.001), bulky relapse (P<0.0001) and more patients with three or more high-risk criteria (P=0.0006), as well as more patients with PET-positive disease at ASCT (P=0.0002), as compared to patients treated with BEAM or BuMel.

Patient- and tumor-related variables did not change substantially over time but there was an increase in the use of pre-ASCT BV (P<0.0001) and anti-PD1 (P<0.0001), a decrease in PET-positive disease at ASCT (P=0.0008), and an increase in post-transplant BV (P<0.0001) (Table 2). BEAM and BuMel predominated in earlier years (2005-2007), GemBuMel and BEAM in middle years (2008-2015), and vorinostat/GemBuMel and BEAM in the last 4 years (2016-2019) (P<0.0001). Consequently, the use of post-ASCT maintenance BV was largely restricted to the vorinostat/GemBuMel and BEAM cohorts (P<0.0001). These two cohorts, in particular the one treated with vorinostat/GemBuMel, also received more prior BV (P<0.0001) and anti-PD1 (P=0.0001).

To discern a possible confounding effect of having followed two different sets of criteria for interpretation of PET scans (IHPL from 2005-2013 and the Deauville score from 2014-2019) we retrospectively reviewed all patients from the earlier period who had a positive PET at ASCT by IHPL criteria. Thus, those whose PET showed uptake greater than mediastinum but not than liver were reassigned as negative (Deauville score 3). Of 115 patients with a positive PET by IHPL, 23 were reassigned as PET-negative: 15 in the GemBuMel cohort (21.7% of PET-positive patients by IHPL in this cohort), two in the vorinostat/GemBuMel cohort (18.1%), four in the BEAM cohort (16.6%), and two in the BuMel cohort (18.1%).

There were significant differences among the four cohorts in PFS (P=0.0003) (Figure 3A) and OS (P<0.0001) (Figure 3B), with patients receiving vorinostat/GemBuMel having the best outcomes, followed by those treated with GemBuMel, BEAM and BuMel. The respective 2-year and 5-year PFS rates were 73.2% and 71.9% (vorinostat/GemBuMel), 57.3% and 55% (GemBuMel), 56.3% and 45% (BEAM), and 47.4% and 38.9% (BuMel) (Figure 4). Likewise, the respective 2-year and 5-year OS rates were 93.8% and 87.3%

(vorinostat/GemBuMel), 85.5% and 75.5% (GemBuMel), 75.2% and 60.8% (BEAM), and 78.9% and 57.2% (BuMel) (Figure 5). The differences among regimens persisted within the subgroups with PET-negative (PFS: *P*=0.0002; OS: *P*<0.0001) (Figure 4A) and PET-positive disease at ASCT (PFS: P=0.002; OS: *P*<0.0001) (Figure 4B). Likewise, these differences were also seen when patients were analyzed by number of risk factors (*Online Supplementary Figures S1-3*).

Overall responses to HDC, determined around day +30 after ASCT in patients with measurable active disease at the time of transplantation, did not vary among the cohorts: BEAM 76.9%; BuMel 72.7%, GemBuMel 88.3%, and vorinostat/GemBuMel 88.6% (*P*=0.48). However, complete remission rates were higher after vorinostat/GemBuMel (82.8%) than after GemBuMel (70.1%), BuMel (63.6%) or BEAM (50%) (*P*=0.03).

The median follow-up times of the four cohorts were 97 months (range, 3-189) for those transplanted between 2005-2007, 93 months (range, 6-138) for those transplanted between 2008-2011), 57 months (range, 6-91) for those transplanted between 2012-2015, and 26 months (range, 3-55) for those transplanted between 2016-2019.

Prognostic analyses

Univariate analyses of PFS showed that primary refracto-

Table 1. Patient and clinical features of the matched cohorts of patients (n=494).

	All (N=494)	BEAM (N=139)	BuMel (N=38)	GemBuMel (N=189)	Vorinostat/GemBuMel (N=128)	*P*
Age in years, median (range)	34.5(8-65)	36 (10-65)	36 (20-63)	34 (13-65)	33 (8-62)	0.31
Gender, male/female, %	57.5 / 42.5	58.2 / 41.8	65.8 / 34.2	56.1 / 43.9	56.3 / 43.8	0.72
ASCT year interval						
2005-2007	97 (19.6%)	57 (41%)	38 (100%)	2 (1.1%)	0 (0%)	<0.0001
2008-2011	138 (27.9%)	37 (27.2%)	0 (0%)	97 (51.3%)	4 (3.1%)	
2012-2015	157 (31.7%)	25 (17.9%)	0 (0%)	88 (46.6%)	44 (34.4%)	
2016-2019	102 (20.6%)	20 (14.7%)	0 (0%)	2 (1.1%)	80 (62.5%)	
N. of modified AETHERA criteria						
Median (range)	2 (1-4)	1 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	0.001
1	198 (40%)	72 (51.8%)	13 (34.2%)	72 (38%)	41 (32%)	0.0006
2	196 (39.6%)	48 (34.5%)	19 (50%)	77 (40.7%)	52 (40.6%)	
3	84 (17%)	16 (11.5%)	5 (13.1%)	35 (18.5%)	28 (21.9%)	
4	16 (3.2%)	3 (2.1%)	1 (2.6%)	5 (2.6%)	7 (5.5%)	
Primary refractory disease	218 (44.1%)	45 (34.5%)	12 (31.5%)	100 (53.4%)	61 (50%)	0.001
Prior disease-free interval#						
Median (range)	2 (3-242)	4 (3-115)	1 (3-98)	0 (3-166)	0 (3-242)	0.02
<12 months	186 (67.4%)	65 (69.1%)	24 (92.3%)	59 (66.3%)	38 (56.7%)	0.01
≥12 months	90 (32.6%)	29 (30.9%)	2 (76.9%)	30 (33.7%)	29 (43.2%)	
PS ≥1 at relapse	179 (36.2%)	55 (37.6%)	11 (28.9%)	64 (33.8%)	49 (38.2%)	0.55
Extranodal extension at relapse	205 (41.4%)	44 (31.6%)	13 (34.2%)	84 (44.4%)	57 (44.5%)	0.21
B symptoms at relapse	79 (16%)	21 (15.1%)	5 (13.1%)	26 (13.7%)	27 (21.1%)	0.29
Prior radiotherapy	133 (26.9%)	42 (30.2%)	11 (28.9%)	47 (24.9%)	33 (25.8%)	0.85
Relapse within prior RT field	55 (11.1%)	12 (8.6%)	4 (10.5%)	19 (10%)	21 (16.4%)	0.16
Bulky relapse	150 (30.3%)	22 (15.8%)	7 (18.4%)	74 (39.1%)	47 (36.7%)	<0.0001
Prior BV	120 (24.3%)	25 (18%)	0 (0%)	24 (12.7%)	71 (55.4%)	<0.0001
Prior anti-PD1	19 (3.8%)	3 (2.1%)	0 (0%)	2 (1%)	14 (10.9%)	0.0001
N. of prior lines of therapy						
Median (range)	2 (2-8)	2 (2-8)	2 (2-6)	2 (2-6)	3 (2-7)	<0.0001
>2	206 (41.7%)	44 (31.6%)	16 (42.1%)	72 (38.1%)	74 (57.8%)	<0.0001
N. of prior relapses						
Median (range)	1 (1-7)	1 (1-7)	1 (1-4)	1 (1-5)	1 (1-6)	0.10
>1	165 (33.4%)	41 (29.4%)	10 (26.3%)	63 (33.3%)	51 (39.8%)	0.19
Positive PET at ASCT	141 (28.5%) *	25 (18%) *	11 (28.9%) *	75 (39.7%) *	37 (28.9%) *	0.0002 *
	118 (23.9%) **	21 (15.1%) **	9 (23.6%) **	60 (31.7%) **	35 (27.3%) **	0.007 **
Progressive disease at ASCT	38 (7.6%)	4 (2.8%)	1 (2.6%)	24 (12.7%)	9 (7%)	0.004
Post-ASCT radiotherapy	69 (14%)	11 (7.9%)	4 (10.5%)	28 (14.8%)	27 (21.1%)	0.02
Post-ASCT BV	37 (7.4%)	14 (10.3%)	0 (0%)	1 (0.5%)	20 (15.6%)	<0.001

Values are numbers (percentages) unless otherwise stated. #Disease-free interval excludes patients with primary refractory disease. *PET interpreted per International Harmonization Project in Lymphoma (2005-2013) and Deauville criteria (2014-2019). **All PET interpreted per Deauville criteria. BEAM: carmustine/ etoposide/cytarabine/melphalan; BuMel: busulphan/melphalan; GemBuMel: gemcitabine/busulphan/melphalan; ASCT: autologous stem-cell transplant; PS: performance status; RT: radiotherapy; BV: brentuximab vedotin; PET: positron emission tomography.

ry disease (*P*=0.005), B symptoms at relapse (*P*=0.009), performance status ≥1 at relapse (*P*=0.01), more than one prior relapse (*P*=0.0001), more than two prior lines of therapy (*P*=0.0004), positive PET at ASCT (*P*<0.0001), and progressive disease at ASCT (*P*<0.0001) correlated with an adverse PFS. In contrast, prior BV treatment (*P*=0.01), prior anti-PD1 treatment (*P*=0.03), the use of vorinostat/GemBuMel (*P*=0.0004), and post-ASCT maintenance therapy with BV (*P*=0.01) were associated with a favorable PFS (Table 3).

In multivariable analyses of PFS, primary refractory dis-

Table 2. Patient and clinical characteristics by treatment year interval (entire population, n=501).

	Treatment year interval				
	2005-2007 (N=98)	2008-2011 (N=138)	2012-2015 (N=158)	2016-2019 (N=107)	*P*
Age in years, median (range)	30 (18-72)	35 (10-69)	32 (13-70)	34 (8-71)	0.58
Gender, male/female (%)	62 (63%) / 36 (37%)	80 (58%) / 58 (42%)	87 (55%) /71 (45%)	59 (55%) /48 (45%)	0.57
HDC regimen					
BEAM	58 (59.2%)	37 (26.8%)	26 (16.5%)	25 (23.4%)	<0.0001
BuMel	38 (100%)	0 (0%)	0 (0%)	0 (0%)	
GemBuMel	2 (2%)	97 (70.3%)	88 (55.7%)	2 (1.9%)	
Vorinostat/GemBuMel	0 (0%)	4 (2.9%)	44 (27.8%)	80 (74.8%)	
Primary refractory disease	41 (41.8%)	69 (50%)	74 (46.8%)	43 (40.2%)	0.39
Prior disease-free interval *					
Median (range)	1 (3-108)	0 (3-166)	3 (3-145)	3 (3-242)	0.11
<12 months	43 (75.4%)	45 (65.2%)	45 (53.5%)	83 (62.5%)	0.16
PS ≥1 at relapse	37 (37.7%)	48 (34.4%)	61 (38.6%)	33 (30.8%)	0.59
Bulky relapse	19 (19.4%)	45 (32.6%)	60 (38%)	27 (25.2%)	0.008
Extranodal extension at relapse	33 (33.7%)	64 (46.4%)	68 (43%)	40 (37.4%)	0.19
B symptoms at relapse	14 (14.3%)	19 (13.8%)	24 (15.2%)	22 (20.6%)	0.48
N. of prior relapses					
Median (range)	1 (1-4)	1 (1-6)	1 (1-7)	1 (1-5)	0.24
>1	27 (27.6%)	54 (39.1%)	51 (32.3%)	34 (31.8%)	0.28
N. of prior lines of therapy					
Median (range)	2 (2-6)	2 (2-7)	2 (2-8)	2 (2-10)	0.29
>2	34 (34.7%)	54 (39.1%)	72 (45.6%)	47 (43.9%)	0.31
Prior BV	0 (0%)	4 (2.9%)	60 (38%)	58 (54.2%)	<0.0001
Prior anti-PD1	0 (0%)	0 (0%)	2 (1.3%)	19 (17.8%)	<0.0001
Positive PET at ASCT	29 (29.6%)	58 (42%)	40 (25.3%)	21 (19.6%)	0.0008
Progressive disease at ASCT	5 (5.1%)	23 (16.7%)	7 (4.4%)	3 (2.8%)	<0.0001
Post-ASCT radiotherapy	7 (7.1%)	28 (20.3%)	16 (10.1%)	19 (17.8%)	0.0089
Post-ASCT BV	0 (0%)	0 (0%)	2 (1.3%)	35 (32.7%)	<0.0001

Values are numbers (percentages) unless otherwise stated. *Disease-free interval excludes patients with primary refractory disease. HDC: high-dose chemotherapy; BEAM: carmustine/etoposide/cytarabine/melphalan; BuMel: busulphan/melphalan; GemBuMel: gemcitabine/busulphan/melphalan; PS: performance status; BV: brentuximab vedotin; PET: positron emission tomography; ASCT: autologous stem-cell transplant.

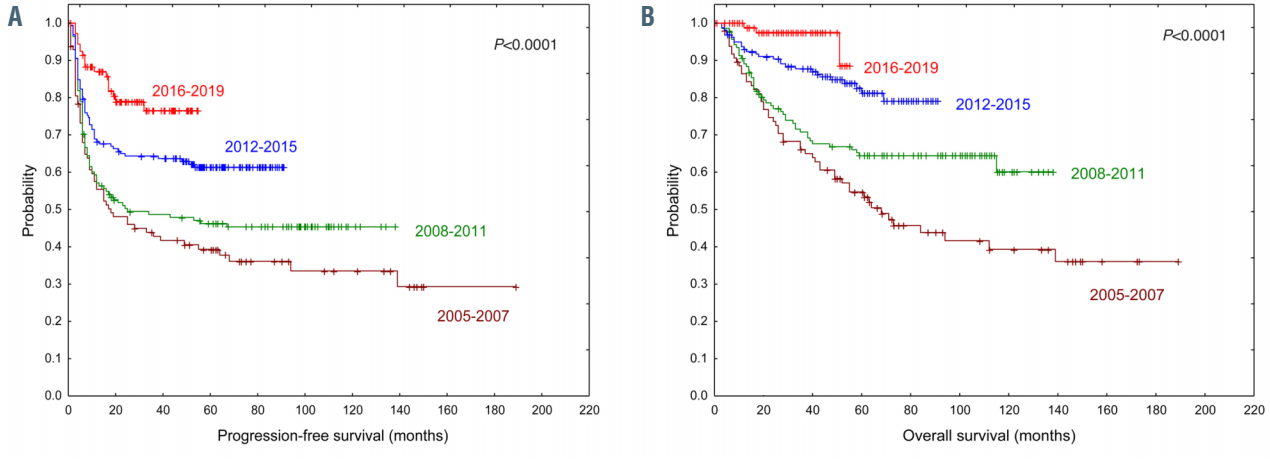

Figure 2. Outcomes by treatment year. (A) Progression-free survival, (B) overall survival.

Table 3. Cox regression univariable and multivariable analyses of progression-free survival of the matched cohorts of patients.

	Univariable				Multivariable			
		95% CI				95% CI		
	HR	LL	UL	P	HR	LL	UL	P
Age >35 years	1.17	0.89	1.54	0.26	1.13	0.85	1.50	0.39
Female gender	0.92	0.70	1.22	0.57	1.02	0.76	1.36	0.9
Treatment year								
2005-2007	3.85	2.27	6.54	<0.0001	–	–	–	–
2008-2011	3.14	1.87	5.28	<0.0001	–	–	–	–
2012-2015	2.07	1.22	3.51	0.006	–	–	–	–
2016-2019	1 (ref)							
Primary refractory disease	1.49	1.14	1.96	0.003	1.41	1.01	1.97	0.04
Prior disease-free interval <1 year	0.76	0.53	1.09	0.14	0.92	0.60	1.40	0.69
N. of prior relapses >1	1.72	1.30	2.27	0.0001	1.19	0.79	1.78	0.4
N. of prior lines of therapy >2	1.65	1.26	2.17	0.0003	1.60	1.08	2.12	0.01
PS ≥1 at relapse	1.28	1.19	1.92	0.01	1.15	0.78	1.52	0.7
Bulky relapse	1.33	1.00	1.77	0.047	1.56	1.15	2.12	0.004
Extranodal extension at relapse	0.97	0.73	1.28	0.81	0.98	0.73	1.31	0.88
B symptoms at relapse	1.58	1.13	2.22	0.008	1.68	1.19	2.37	0.003
Positive PET at ASCT	2.90	2.20	3.83	<0.0001	2.60	1.83	3.69	<0.0001
Progressive disease at ASCT	2.64	1.77	3.94	<0.0001	1.06	0.64	1.76	0.83
Prior BV	0.65	0.45	0.93	0.01	0.58	0.36	0.93	0.02
Prior anti-PD1	0.23	0.06	0.94	0.04	0.35	0.08	1.48	0.15
HDC regimen				global P=0.0006				global P=0.001
Vorinostat/GemBuMel	1 (ref)				1 (ref)			
GemBuMel	1.74	1.16	2.61	0.007	1.33	0.83	2.13	0.23
BEAM	2.10	1.38	3.19	0.0005	2.19	1.35	3.55	0.001
BuMel	2.74	1.63	4.62	0.0002	2.29	1.24	4.23	0.007
Post-ASCT BV	0.23	0.08	0.73	0.01	0.37	0.12	1.20	0.09
Post-ASCT radiotherapy	0.94	0.63	1.39	0.75	0.66	0.43	1.02	0.06

HR: hazard ratio. 95% CI: 95% confidence interval. LL: lower limit. UL: upper limit; ref: reference; PS: performance status; PET: positron emission tomography; ASCT: autologous stem-cell transplant. BV: brentuximab vedotin; HDC: high-dose chemotherapy; GemBuMel: gemcitabine/busulphan/melphalan; BEAM: carmustine/etoposide/cytarabine/melphalan; BuMel: busulphan/ melphalan.

ease (hazard ratio [HR]=1.41 [95% CI: 1.01-1.97], *P*=0.04), more than two prior lines of therapy (HR=1.60 [95% CI: 1.08-2.36], *P*=0.01), bulky relapse (HR=1.56 [95% CI: 1.15-2.12], *P*=0.004), B symptoms (HR=1.68 [95% CI: 1.19-2.37], *P*=0.003) and a positive PET at ASCT (HR=2.60 [95% CI: 1.83-3.69], *P*<0.0001) were independent adverse prognostic factors, whereas prior BV (HR=0.58 [95% CI: 0.36-0.93], *P*=0.02) and vorinostat/GemBuMel (*P*<0.0001) were independently associated with improved PFS. The hazard ratios for the other three HDC regimens compared to vorinostat/GemBuMel were: GemBuMel: 1.33 (95% CI: 0.83-2.13), BEAM: 2.19 (95% CI: 1.35-3.55), and BuMel 2.29 (95% CI: 1.24-4.23) (Table 3).

The following were unfavorably associated with OS in univariate analyses: age >35 years (*P*=0.006), B symptoms (*P*=0.006), performance status ≥1 (*P*=0.002), more than one prior relapse (*P*=0.0001), more than two prior lines of therapy (*P*<0.0001), positive PET at ASCT (*P*<0.0001), and progressive disease at ASCT (*P*<0.0001). In contrast, prior BV treatment (*P*=0.01) and vorinostat/GemBuMel (*P*<0.0001) were associated with a more favorable OS (Table 4).

Multivariable OS analyses identified age >35 years (HR=1.80 [95% CI: 1.24-2.60], *P*=0.002), B symptoms (HR=1.74 [95% CI: 1.13-2.68], *P*=0.01), more than two prior lines of therapy (HR=2.11 [95% CI: 1.26-3.53], *P*=0.004), and positive PET at ASCT (HR=1.88 [95% CI: 1.16-3.04], *P*=0.01) as independent adverse prognostic factors. On the contrary, prior BV treatment (HR=0.46 [95% CI: 0.23-0.90], *P*=0.02) and vorinostat/GemBuMel (*P*<0.0001) were independently associated with better OS. The hazard ratios for the other three HDC regimens compared to vorinostat/GemBuMel were: GemBuMel: 1.63 (95% CI: 0.75-3.57), BEAM: 5.06 (95% CI: 2.30-11.10), and BuMel 5.17 (95% CI: 2.13-12.54) (Table 4).

Of note, evaluation of all PET according to the Deauville score did not change the prognostic effect of this variate in univariate analyses or the results for any variable in the multivariate analyses.

Treatment for post-ASCT relapse

Patients received a median of two (range, 0-12) lines of salvage therapy for post-ASCT recurrence. Salvage therapies included BV (n=85), conventional chemotherapy (n=72), clinical trials of experimental agents (n=67), allogeneic stem cell transplantation (n=64), anti-PD1 (n=37), radiotherapy (n=27), and unknown (n=14). No salvage therapy was administered to 13 patients. Of the 205 patients who relapsed, 53 are currently in a new clinical

complete remission after allogeneic stem cell transplantation (n=26), anti-PD1 (n=13), BV (n=9), radiotherapy (n=3) and chemotherapy (n=2).

Second primary malignancies

Out of the entire population (n=501) eight patients developed therapy-related myelodysplastic syndrome and

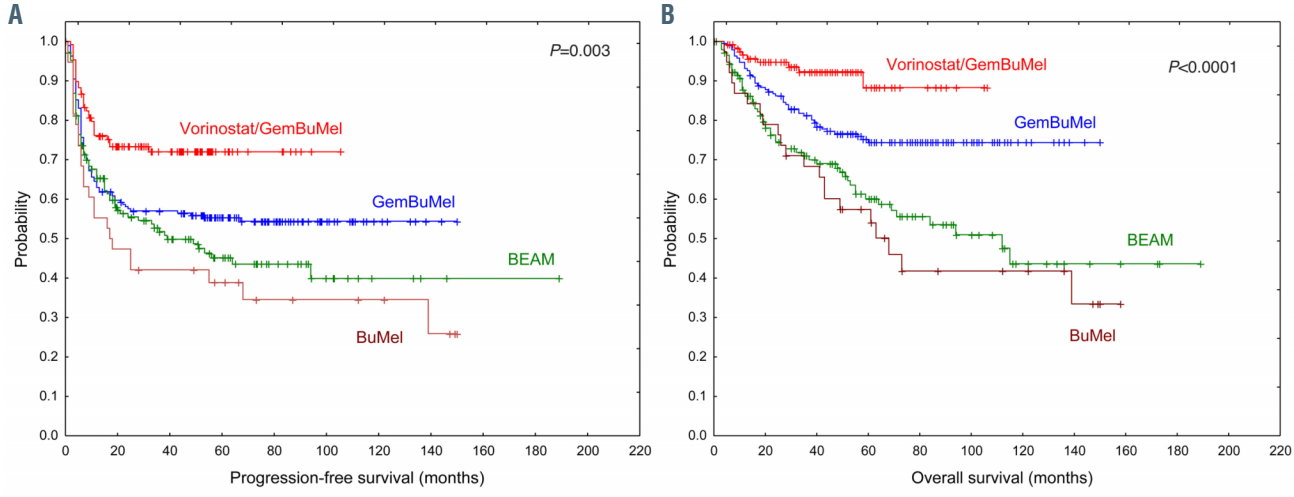

Figure 3. Outcomes by high-dose chemotherapy regimen. (A) Progression-free survival, (B) overall survival. GemBuMel: gemcitabine/busulphan/melphalan; BEAM: carmustine/etoposide /cytarabine/melphalan; BuMel: busulphan/melphalan.

Table 4. Cox regression univariable and multivariable analyses of overall survival of the matched cohorts of patients.

	Univariable				Multivariable			
		95% CI				95% CI		
	HR	LL	UL	P	HR	LL	UL	P
Age >35 years	1.63	1.15	2.32	0.006	1.80	1.24	2.60	0.002
Female gender	0.99	0.69	1.42	0.96	1.18	0.81	1.73	0.39
Treatment year								
2005-2007	11.87	3.69	38.23	<0.0001	–	–	–	–
2008-2011	7.21	2.23	23.31	0.001	–	–	–	–
2012-2015	3.41	1.03	11.31	0.04	–	–	–	–
2016-2019	1 (ref)							
Primary refractory disease	1.38	0.97	1.97	0.07	1.27	0.82	1.96	0.28
Prior disease-free interval <1 year	0.70	0.42	1.15	0.15	0.78	0.44	1.39	0.39
N. of prior relapses >1	2.03	1.42	2.89	0.0001	1.25	0.74	2.13	0.40
N. of prior lines of therapy >2	2.07	1.45	2.96	<0.0001	2.11	1.26	3.53	0.004
PS ≥1 at relapse	1.37	1.21	1.98	0.002	1.21	0.79	1.85	0.44
Bulky relapse	1.22	0.84	1.77	0.29	1.51	1.00	2.29	0.05
Extranodal extension at relapse	1.00	0.70	1.42	0.98	1.08	0.74	1.57	0.69
B symptoms at relapse	1.86	1.22	2.84	0.004	1.74	1.13	2.68	0.01
Positive PET at ASCT	2.80	1.96	4.00	<0.0001	1.88	1.16	3.04	0.01
Progressive disease at ASCT	3.38	2.14	5.32	<0.0001	1.92	1.02	3.58	0.04
Prior BV	0.52	0.30	0.90	0.01	0.46	0.23	0.90	0.02
Prior anti-PD1	0.34	0.05	2.42	0.28	0.72	0.09	5.64	0.75
HDC regimen				global				global
			P<0.0001				P<0.0001	
Vorinostat/GemBuMel	1 (ref)				1 (ref)			
GemBuMel	2.27	1.14	4.51	0.01	1.63	0.75	3.57	0.22
BEAM	4.24	2.14	8.39	<0.0001	5.06	2.30	11.10	<0.0001
BuMel	5.53	2.59	11.80	<0.0001	5.17	2.13	12.54	0.0003
Post-ASCT BV	0.21	0.03	1.54	0.12	0.41	0.06	3.05	0.38
Post-ASCT radiotherapy	1.18	0.74	1.89	0.48	1.06	0.62	1.82	0.83

HR: hazard ratio. 95% CI: 95% confidence interval. LL: lower limit. UL: upper limit; ref: reference; PS: performance status; PET: positron emission tomography; ASCT: autologous stem-cell transplant. BV: brentuximab vedotin; HDC: high-dose chemotherapy; GemBuMel: gemcitabine/busulphan/melphalan; BEAM: carmustine/etoposide/cytarabine/melphalan; BuMel: busulphan/ melphalan.

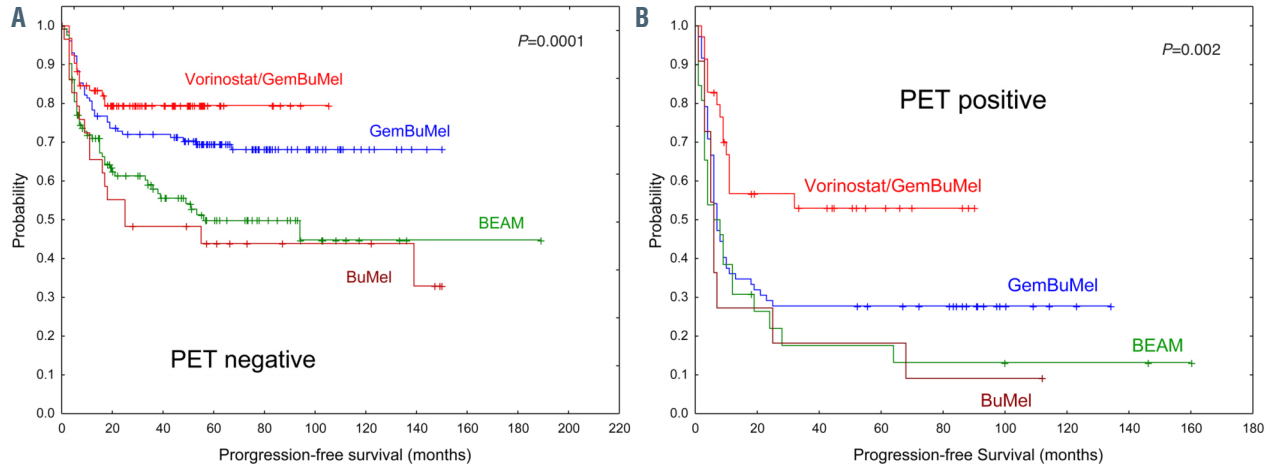

Figure 4. Progression-free survival by high-dose chemotherapy regimen according to positron emission tomography status. (A) Progression-free survival in patients with (A) positron emission tomography (PET)-negative disease and with (B) PET-positive disease.

five patients developed therapy-related acute myeloblastic leukemia: seven after BEAM (4.8%), three after GemBuMel (1.5%), two after BuMel (5.2%) and one after vorinostat/GemBuMel (0.07%), at a median 31 months (range, 5-133) after ASCT. The incidence of therapy-related myelodysplastic syndrome/acute myeloid leukemia did not vary significantly among the cohorts (P=0.13). Cytogenetic findings in these patients included complex abnormalities with -7/del(7q) ± -5/del(5q) (n=7), -7 alone (n=3), 11q+ (n=1), and other abnormalities (n=2). These patients were older (median age 54, range 22-72) than all other patients (n=493) who did not develop therapy-related myelodysplastic syndrome/acute myeloid leukemia (median age 32; range, 8-71) (P=0.0005).

Other second primary malignancies were renal-cell carcinoma (2 BEAM patients), Müllerian adenocarcinoma and epithelioid hemangioendothelioma (1 GemBuMel patient each), and diffuse large B-cell lymphoma (1 BuMel patient, 1 vorinostat/GemBuMel patient).

Discussion

Our analysis of patients with HRR cHL treated with HDC and ASCT shows a gradual and significant improvement of outcomes over the last 15 years. Improved tumor control with BV before ASCT and the use of more active HDC regimens, particularly vorinostat/GemBuMel, emerged independently as favorable prognostic factors in multivariable analysis.

The clinical development of vorinostat/GemBuMel was based on two important preclinical observations. The first one was the synergistic inhibition by gemcitabine of the repair of DNA damage caused by busulfan and melphalan.[15] The use of ASCT enables the infusion of gemcitabine at its optimal rate of 10 mg/m^2/min, previously shown to avoid saturation of its intracellular enzymatic activation,[25] which results in greater activity and myelotoxicity than shorter infusions of this drug,[26,27] and in turn optimizes the synergy with the bifunctional DNA-alkylating agents.[28] Our second major *in vitro* observation was that relaxation of chromatin after increased histone acetylation with vorinostat facilitated access of gemcitabine, busulfan and melphalan, to DNA, which increased DNA damage, apoptosis and cytotoxicity in refractory lymphoma cell lines.[17] Those preclinical observations, tested in subsequent clinical trials, are confirmed in the present analysis, and notably did not increase the risk of treatment-related mortality.

The other major favorable factor was the use of BV before ASCT. BV has revolutionized the treatment of cHL in the last decade. Following its favorable results and approval in 2011 for post-ASCT relapses,[29] BV was moved up to the first or second line of salvage therapy before ASCT,[8,30] which allows more patients to receive HDC in a PET-negative complete remission. Lastly, BV was successfully tested in the post-ASCT maintenance setting, in which the randomized AETHERA trial compared 16 cycles of BV with placebo in 329 patients with HRR cHL, defined by the same criteria as in our analysis. The use of BV resulted in improved 2-year PFS (63% *vs.* 51%) and 5-year PFS (59% *vs.* 41%), albeit with no OS benefit.[9,10] In contrast to our population, this trial did not allow prior BV and more than 60% of patients received BEAM. Despite these differences, we also saw a correlation of maintenance BV with improvement of PFS but not OS in our univariate analyses. Maintenance BV was restricted to patients we treated in later years, which likely resulted in a loss of power and significance in the multivariable analysis.

We saw that the pre-ASCT use of the anti-PD1 antibodies nivolumab and pembrolizumab was associated with improved PFS, although this did not hold significance in multivariable analysis, probably due to the small number of patients who received them. This class of drugs has produced another breakthrough in the treatment of Hodgkin lymphoma. Besides their efficacy in post-ASCT relapses,[31,32] these drugs can serve as a successful bridge to ASCT by inducing responses in refractory relapses.[33] In addition, anti-PD1 might chemosensitize refractory tumors and improve results of HDC.[34]

The strengths of our analysis include the homogeneity of the population of patients and of the treatments administered in the four cohorts and the large sample size, which allowed us to independently dissect the prognostic value of the patient-, tumor-, and treatment-related variables. On the other hand, our study has several limita-

tions. First, we only intended to analyze those patients who ultimately received HDC and ASCT after HDC, and our analyses exclude patients who failed to successfully undergo salvage chemotherapy, e.g., due to morbidity or highly refractory disease. Thus, our population does not represent an unselected real-world cohort of HRR cHL patients. Second, the comparison of the different HDC regimens is nonrandomized. While all of our HRR patients met the eligibility criteria of the prospective trials, physician biases in assigning patients with more aggressive tumors who were perceived to be fitter to a clinical trial instead of standard HDC likely played a role, as was reflected in the higher proportion of patients with positive PET at ASCT or other HRR criteria in the cohorts treatment with GemBuMel with or without vorinostat, compared with the BEAM group. Third, while all patients' data were captured prospectively, this study is retrospective in nature, and thus, fraught with the usual limitations of these analyses, including the possibility of reporting biases or underreporting of second primary malignancies and other long-term events. Fourth, our analysis, which encompasses a 15-year period, is subject to the changes in ASCT supportive care during this time span. However, refinement of supportive measures does not appear to be the cause of the improvement in results over time, as the treatment-related mortality was minimal. Fifth, the weight in our analysis of some major new treatments of Hodgkin lymphoma incorporated more recently, such as post-ASCT maintenance or the pre-ASCT use of anti-PD1, is limited by smaller numbers of patients. Lastly, since patients in the vorinostat/GemBuMel cohort had worse prognostic features and since this was the HDC regimen most used in the last period (2016-2019), this cohort had the highest use of pre-ASCT and post-ASCT BV, which likely contributed to its better results. Nevertheless, this regimen clearly stands out as an independent favorable factor for both PFS and OS after adjusting for all other variables. However, definite proof of superiority of vorinostat/GemBuMel over BEAM will require a randomized trial.

Other novel strategies developed to improve the outcome of HRR cHL patients undergoing ASCT include new maintenance therapies, such as anti-PD-1 alone[35] or anti-PD-1 plus BV,[36] which have shown very promising results. Anti-PD-1 can be easily used after ASCT with vorinostat/GemBuMel. Tandem ASCT based on BEAM has been studied,[11-13] but it is unclear, in the absence of a prospective randomized trial, how this approach might compare to a single ASCT using vorinostat/GemBuMel.

In conclusion, the outcome of HRR cHL patients treated with HDC and ASCT has improved substantially over the last 15 years. The incorporation of BV into pre-ASCT salvage therapy and the use of pharmacologically optimized, more active HDC regimens, particularly vorinostat/GemBuMel, were associated with these improved results.

Disclosures

YN has provided consultancy services for Affimed and Novo Nordisk; and has received research funding from Affimed, Novartis, Takeda, Astra-Zeneca, and Biosecura. BA holds a patent for intravenous busulfan. None of the other authors has any conflicts of interest to disclose.

Contributions

YN designed research, collected data, treated patients, and wrote the manuscript; SG and HC: analyzed the data and wrote the manuscript; BCV, RBJ, PA, CH, UP, MQ, PK, AA, NS, SS, KR, JR, MB, AG, TLS, SA, SI, HL, RN, SP, RS, BD, CP, JG, BC, KM, SK, RC, EJS and BSA treated patients and reviewed the manuscript.

Data sharing statement

All clinical trial protocols (NCT00427765, NCT00410982, NCT01200329, NCI-2011-02891, NCT01983969) and treatment orders will be made available upon request.

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