SUPPLEMENTARY APPENDIX

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

Yago Nieto,[1] Stephen Gruschkus,[2] Benigno C. Valdez,[1] Roy B. Jones,[1] Paolo Anderlini,[1] Chitra Hosing,[1] Uday Popat,[1] Muzaffar Qazilbash,[1] Partow Kebriaei,[1] Amin Alousi,[1] Neeraj Saini,[1] Samer Srour,[1] Katayoun Rezvani,[1] Jeremy Ramdial,[1] Melissa Barnett,[1] Alison Gulbis,[3] Terri Lynn Shigle,[3] Sairah Ahmed,[4] Swaminathan Iyer,[4] Hun Lee,[4] Ranjit Nair,[4] Simrit Parmar,[4] Raphael Steiner,[4] Bouthaina Dabaja,[5] Chelsea Pinnix,[5] Jillian Gunther,[5] Branko Cuglievan,[6] Kris Mahadeo,[6] Sajad Khazal,[6] Hubert Chuang,[7] Richard Champlin,[1] Elizabeth J. Shpall[1] and Borje S. Andersson[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center; [2]Biostatistics, University of Texas MD Anderson Cancer Center; [3]Pharmacy, University of Texas MD Anderson Cancer Center; [4]Lymphoma and Myeloma, University of Texas MD Anderson Cancer Center; [5]Radiation Oncology, University of Texas MD Anderson Cancer Center; [6]Pediatrics, University of Texas MD Anderson Cancer Center and [7]Nuclear Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA

 doi:10.3324/haematol.2021.278311

Received: January 5, 2021.

Accepted: April 22, 2021.

Pre-published: May 6, 2021.

Correspondence: *YAGO NIETO* - ynieto@mdanderson.org

Supplemental Methods

We retrospectively analyzed all pts with HRR cHL treated at MD Anderson Cancer Center with HDC and ASCT between 01/01/2005 and 12/31/2019. Same as in our sequential GemBuMel trials,[13,14,16,17] high-risk relapse was defined for this analysis by ≥1 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 (CR) to most recent salvage therapy, or requiring ≥2 salvage lines of therapy.[9] Second or third lines of salvage chemotherapy were defined as different regimens used to treat persistent or progressive disease following a prior line, and did not include additional cycles of a different regimen given with peripheral blood progenitor cell (PBPC) mobilizing purposes following a CR. Patients not meeting any HRR criteria were excluded from this analysis. Bulky lesions at relapse were defined as ≥ 5 cm. All patients' demographic and tumor-related variables were captured prospectively in our departmental database.

During this 15-year period we studied new HDC regimens in sequential trials open to patients with HRR cHL: Phase 2 trial of BuMel (NCT00427765),[12] phase 1 trial of GemBuMel (NCT00410982),[13] phase 2 study of GemBuMel (NCT01200329),[14] phase 1-2 trial of vorinostat/GemBuMel (NCI-2011-02891),[16] and phase 1-2 trial of azacytidine/vorinostat/GemBuMel (NCT01983969).[17] The upper age limit in these studies was 65 and they required patient adequacy for ASCT: Eastern Cooperative Oncology Group performance status 0-2, creatinine clearance $\geq$50 ml/min, diffusion capacity for carbon monoxide corrected for hemoglobin level ≥50%, left ventricular ejection fraction $\geq$40%, and aspartate aminotransferase, alanine aminotransferase, and bilirubin $\leq$3 x upper limit of normal.

BuMel consisted of 4 daily doses of busulfan targeting an average daily busulfan exposure, represented by the area under the plasma concentration curve (AUC) of 4,000 μM/min (days -8 to -5), or total course AUC of 16,000 μM/min, and melphalan at 70 mg/m^2/day x 2 (days -3 and -

2). GemBuMel added 2 doses of gemcitabine at 2,775 mg/m^2/day (75 mg/m^2 bolus followed by 2,700 mg/m^2 at a fixed dose rate of 10 mg/m^2/min over 4.5 hours) on days -8 and -3, preceding busulfan and melphalan, respectively.[13] Vorinostat was added to GemBuMel from days -11 to -2 at 1,000 mg PO daily within 1 hour of start of chemotherapy.[16] Azacytidine was administered up to 15 mg/m^2/day IV from days -11 to -2, immediately preceding all the other chemotherapy drugs.[17] Since azacytidine did not appear to further improve the activity of vorinostat/GemBuMel, we included all patients treated with azacytidine/vorinostat/GemBuMel in the vorinostat/GemBuMel group in the present analysis.

Patients with HRR cHL meeting candidacy for ASCT who were not enrolled on those trials received BEAM as standard of care (SOC) and were prospectively registered in our departmental database. BEAM consisted of carmustine (300 mg/m^2), etoposide (200 mg/m^2 every 12 hours x 8 doses), cytarabine (200 mg/m^2 every 12 hours x 8 doses) and melphalan (140 mg/m^2). In addition, both GemBuMel and vorinostat/Gem/Bu/Mel were adopted as standard regimens at our institution upon publication of their respective trials. Reasons for treating patients off study included their declining trial participation, the requirement by third-party payors that ASCT be done off study, or periods when no clinical trial was open to enrollment. The choice of HDC regimen off study was at the discretion of the treating physician.

Institutional transplant guidelines for antiemetics, antibacterial, antifungal and antiviral prophylaxis, and blood component transfusions were followed in all patients. Infusion of peripheral blood progenitor cells (PBPC) was on day 0. G-CSF was administered at 5 mcg/kg/day subcutaneously beginning on day +5 until neutrophil recovery.

Restaging studies were obtained within 30 days prior to enrollment, and subsequently at 1 month, 3 months, 6 months after SCT, and every 6 months thereafter as feasible. All patients in this analysis had pre-ASCT PET/computed tomography (CT) scans, which were prospectively

interpreted as positive (active tumor) or negative (no active tumor) using mediastinal blood pool activity as the reference background,

[1] and the Deauville score when it became available (a score 1-3 was considered a CR).[2]

Post-transplant consolidative radiotherapy (RT), delivered at a dose between 30 to 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.[8]

Statistical Analyses

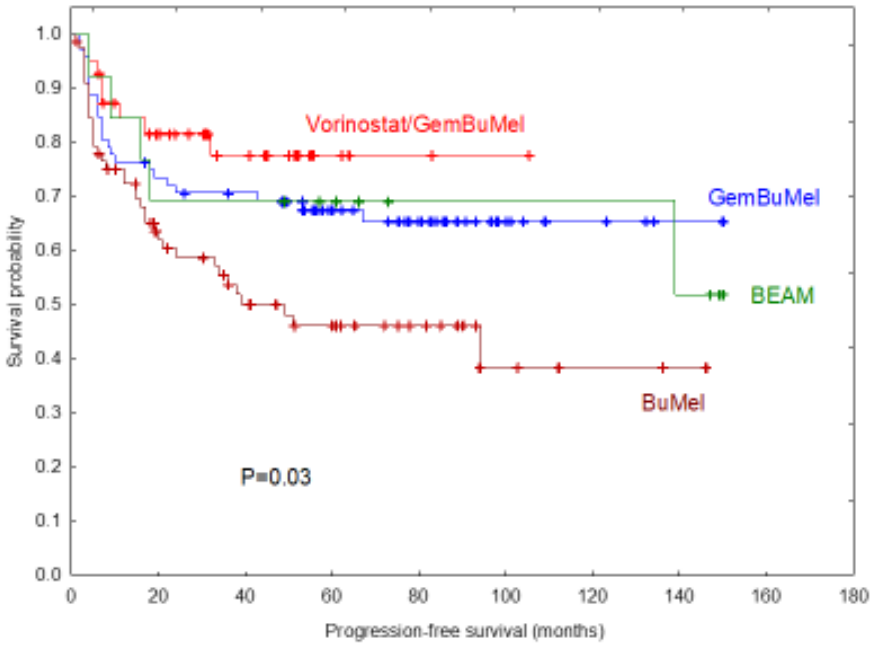
Patients were characterized with respect to age, gender, treatment year, primary induction failure, prior disease-free interval, total number of relapses, total number of prior systemic lines of therapy, bulky relapse (defined as greater lesion >5 cm), extranodal extension at relapse, B symptoms at relapse, PET results at the time of ASCT, and post-ASCT treatment. Mean, median, standard deviation, and minimum/maximum values were described for continuous variables and N (%) were described for categorical/ordinal variables. Differences in demographic and clinical features by regimen cohort were assessed using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.[3] PFS was measured from HDC initiation to disease relapse or death while OS was measured from therapy initiation to death. For both PFS and OS patients not experiencing an outcome were censored at their last follow-up visit. The Kaplan-Meier method was used to estimate 12-, 24-, and 60-month PFS and OS overall and by regimen,[4] and differences in outcomes were assessed using the corresponding log-rank test.[5] Finally, univariable and multivariable Cox regression analysis was employed to identify and evaluate factors associated with PFS and OS.[6] Statistical significance was defined by an $\alpha=0.05$ and all statistical analyses were conducted using SAS version 9.4 (Cary, NC).

Supplemental Table 1. Distribution of the causes of death in the different time periods.

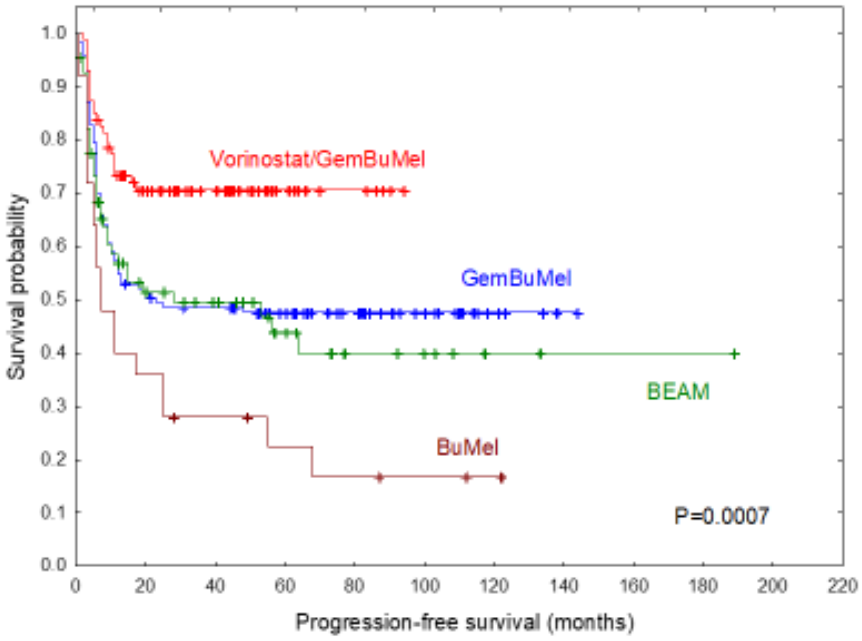
		Time periods			
		2005-2007	**2008-2011**	**2012-2015**	**2016-2019**
PD		41 (88%)	38 (79%)	15 (55%)	2 (66%)
Toxicity from salvage treatments	Allo-SCT	4 (7.7%)	9 (18.75%)	6 (22.2%)	
	BV			2 (7.4%)	
SPM		6 (11.5%)	1 (2%)		1 (33%)
TRM				2 (7.4%)	
MVA				2 (7.4%)	
Unknown		1			
Total		52	48	27	3

PD: progressive disease; BV: brentuximab vedotin; SPM: second primary malignancies; TRM: Transplant-related mortality; MVA: motor vehicle accident.

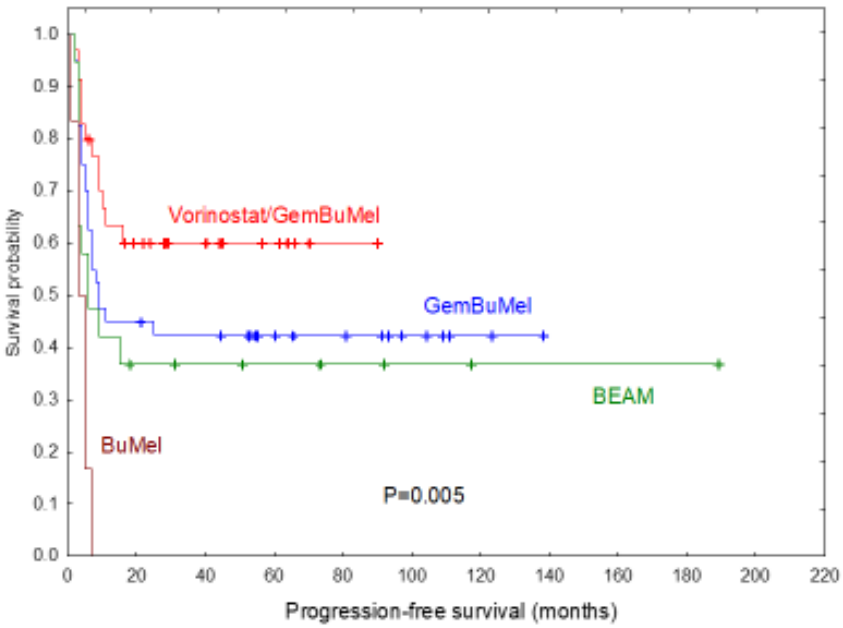
Supplemental Figure 1: Progression-free survival per HDC regimen in patients with 1 high-risk factor.



Supplemental Figure 2: Progression-free survival per HDC regimen in patients with ≥2 high-risk factors.



Supplemental figure 3: Progression-free survival per HDC regimen in patients with ≥3 high-risk factors.



REFERENCES

[1] Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25:571-578.

[2] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano classification. J Clin Oncol. 2014;32:3059-3067.

[3] Fisher R. On the interpretation of x2 from contingency tables, and the calculation of P. J Royal Stat Soc. 1022;85:87-94.

[4] Kaplan EL, Meier P. Nonparametric estimator from incomplete observations. J Amer Stat Assoc. 1958;53:457-481.

[5] Peto R, Peto J. Asymptomatcially efficient rank invariant test procedures. J R Stat Soc A. 1971;135:185-198.

[6] Cox DR. Regression models and life tables. J R Stat Assoc B. 1972;34:187-220.