Poster Session I

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DOSE PRECISION USING A PRETRANSPLANT TEST PK OF INTRAVENOUS BUSULFAN PRIOR TO BuCyVP-16 PREPARATIVE REGIMEN IN LYMPHOMA

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Background: Inter- and intra-subject variability of oral busulfan (Bu) absorption from the gastrointestinal tract may contribute to busulfan overexposure, resulting in unfavorable post-transplant adverse events *i.e.* veno-occlusive disease. Intravenous (IV) Bu helps to circumvent this problem by decreasing variability in drug exposure. However, inter-subject variability of Bu exposure still exists due to differences in Bu clearance. This multi-institutional, prospective Phase 2 study examined if pharmacokinetic (PK) modeling based upon a small test dose prior to the preparative regimen can provide optimized dosing of IV Bu.
Methods: Patients with chemo-sensitive relapsed or primary-refractory lymphoma undergoing a first autologous hematopoietic stem cell transplantation received a test dose of IV Bu (0.8 mg/kg) given as a 2 hour continuous infusion on a day between Days -14 and -11. Bu exposure was determined as area under the concentration-time curve (AUC) using six whole blood samples obtained at defined intervals after the end of the infusion. Based on test PK, the remaining Bu dose was calculated to achieve a total AUC of 20,000 μM·min. One-fourth of this dose was given as a 3 hour infusion on Day -8, during which a second PK analysis was done. The same daily Bu dose was administered on Days -7, -6, and -5 unless Day -8 PK results showed total AUC outside the target ± 20%. Etoposide 1400 mg/m^2 was administered on Day -4, followed by cyclophosphamide 2.5 g/m^2/day on Days -3 and -2.
Results: A total of 145 subjects with non-Hodgkin's (n = 96) and Hodgkin's lymphoma (n = 49) were enrolled from 32 centers in the US and Canada. This analysis includes 137 subjects who had both test PK and Day -8 PK. 52 (38%) patients required dose alteration as a result of test PK. 47 (34.3%) patients required a dose increase, whereas 5 (3.6 %) required a dose decrease. These 52 subjects would have been dosed outside the total target AUC range during conditioning if test PK was not performed. The test PK accurately predicted the Day -8 PK. Based on Day -8 PK, only 5 (3.6%) patients required dose adjustment on Days -6 and -5.

Table. Bu Exposure from Test PK and Day -8 PK

	Patient Number (% and 95% CI)	Patient Number (% and 95% CI)	Patient Number (% and 95% CI)
AUC (μM•min) Test PK from 0.8 mg/kg	< 1000 n = 47 (34.3%, 26.8-42.6)	1000-1500 n = 85 (62.0%, 53.7-69.7)	> 1500 n = 5 (3.6%, 1.3-8.5)
AUC (μM•min) Day -8 PK from Individual doses	< 16, 000 n = 3 (2.18%, 0.7-6.2)	16, 000-24, 000 n = 132 (96.4%, 51.5-98.6)	> 24, 000 n = 2 (1.45%, 0.4-5.2)

Conclusion: A pretransplant test PK of IV Bu is feasible in a multi-institutional setting, provides optimized dosing during the conditioning regimen and prevents the Bu overexposure or underexposure that would have occurred in over a third of patients. Intra-patient changes in Bu clearance between test dose and conditioning dose are minimal.

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BUSULFAN, CYCLOPHOSPHAMIDE, ETOPOSIDE (BUCYVP) OR CARMUSTINE, ETOPOSIDE, CYTARABINE, MELPHELAN (BEAM) FOR CONDITIONING PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH HODGKIN LYMPHOMA (HL)?

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Introduction: Busulfan (Bu) based conditioning regimens were developed for use in ASCT for HL with the goal to reduce the risk of relapse without increasing toxicity in comparison to more conventional regimens such as BEAM. At Ohio State, Bu was combined with cyclophosphamide (CY) and VP-16 (BUCYVP) and became the standard conditioning regimen here for 15 years. In 2005, we switched to the BEAM regimen.
Methods: We retrospectively analyzed 188 patients with HL who underwent ASCT between 1990 and 2010. Cumulative incidence of relapse (CIR) was measured from transplant date until relapse, treating deaths as competing risks using Gray's method. Among patients with adequate follow-up, proportions of early deaths were compared using Fisher's exact test. In relapsed patients, survival was measured from relapse date until death from any cause.
Results: Median age at transplant was 33 years with 60% of patients male. Prior to ASCT, 64% received BUCYVP and 36% received BEAM. Median follow-up among patients relapse-free and alive was 109 and 16 months, respectively for BUCYVP and BEAM patients. Those receiving BUCYVP had higher CIR compared to those receiving BEAM, approaching statistical significance (p = 0.06). When controlling for response status at transplant (p = 0.03) and number of prior chemotherapy lines, conditioning regimen did not predict risk of relapse (p = 0.11; HR = 1.5, 95% CI: 0.9-2.6). However, 5% and 8% of BUCYVP patients suffered from non-relapse mortality at 6 and 12 months, respectively, compared to 0 of 67 and 0 of 48 BEAM patients (p = 0.06 at 12 months). Of 79 relapsed patients, estimated median survival was 16.5 months and was not different between conditioning regimens (p = 0.96).
Conclusion: Although treatment period differed and more BUCYVP patients were refractory (39% versus 16%), our experience in HL does not support that more stringent Bu-based conditioning offers advantages compared with BEAM and in fact may be significantly more toxic.

Table. Cumulative Incidence of Relapse Estimates in Presence of Competing Risks

	All Patients	BUCYVP	BEAM	P crude
CIR	N = 188	N = 120	N = 68	(P adjusted)
Median (months)	Not Reached	50	Not Reached	0.06 (0.11)
% relapsed (95% CI)				
at 12 months	26 (20-33)	29 (21-38)	20 (10-30)	
at 18 months	36 (29-43)	39 (31-48)	28 (15-40)	
at 24 months	39 (31-46)	43 (34-52)	28 (15-40)	

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PHASE I/II STUDY OF VELCADE®-BEAM (V-BEAM) AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (ASCT) FOR RELAPSED INDOLENT NON-HODGKIN'S LYMPHOMA (NHL), TRANSFORMED OR MANTLE CELL LYMPHOMA (MCL)

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A phase I/II trial was designed to evaluate the safety and activity of adding bortezomib to standard BEAM (BCNU, etoposide,