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Introduction: Busulfan (BU) and etoposide (VP) have been employed as preparative therapy for autologous stem cell transplantation (autoSCT) in adults with acute myeloid leukemia (AML) for over 20 years. Toxicity and safety significantly improved with the transition from oral to intravenous (IV) BU and the use of pharmacokinetic (PK)-based dosing. In an attempt to enhance outcomes following autoSCT, we designed a Phase I study with the following objectives: 1) to determine the maximum tolerated dose (MTD) of targeted, dose-escalated IV BU in combination with VP- 60mg/kg and 2) to achieve BU levels within +/- 10% of goal in >80% of patients (pts) after dose-adjustment (DA).

Methods: Patients with AML in CR1 meeting all eligibility criteria including, ECOG 0-1, age 18-69, good organ function, and adequate stem cells stored (>3 x 10e6 CD34 following consolidation chemotherapy (HDAC+VP)) were prospectively enrolled. Three cohorts (targeted AUC 1250, 1400 and 1550 mMol*min were planned with Cohort 1 (C1) receiving IV BU at 0.9mg/kg, Cohort 2 (C2) at 1 mg/kg and Cohort 3 (C3) at BU 1.1mg/kg. PK studies were performed after doses 1 (day -10), 4, and 12, with DA occurring with doses 2 and 11 of 16 total doses. VP was given IV on day -3 with autoSCT on day 0. Palifermin and standard antimicrobial prophylaxis were used.

Results: To date, 12 pts have undergone autoSCT with targeted, dose-escalated IV BU. Median age 50 (range 24-61). Cytogenetics were diploid in 5 (1 FLT3+, 2 FLT3 WT, 2 FLT3 unknown). The remaining 7 pts had t(9;11) (2), +21 (2), t(8;21), 9q-, and 1 failed. TRM was 0% and engraftment robust; mean ANC >500/uL and platelets >20,000/uL was 11 (range 10-13) and 30 days (range 13-124), respectively.

All pts received a DA after dose #1 and 7 (58.3%) prior to dose #11. The mean final AUC was 1243 (range 1151-1361) for C1 and 1464 (range 1401-1558) for C2. All pts in C1 were within 10% of the target AUC in C1 (range -2.8 to +8.2%) versus 83% in C2 (range +0.1 to +10.1%). PK studies revealed BU accumulation at dose 12, with the final AUC exceeding goal by a mean of 14.9% (range 1-35%). Grade 3-4 mucositis occurred in 50% in C1 and in 66% in C2. Grade 3 hepatic dysfunction was observed in 33% in C1 and in none in C2.

As of October 2013, 50% of pts are alive and relapse-free. Median relapse-free survival (RFS) for the entire study group is 12.6 months (range 2.2-28.9). In C1, RFS is 33% (median13.1 months; range 3.0-28.9) vs. 66% in C2 (median 12.2 months; range 2.2-20.6). Non-relapse mortality (NRM) was 0% at 100 days post-autoSCT.

Conclusions: Targeted, dose-escalated IV BU in combination with VP as preparative therapy for autoSCT in AML is safe, with mucositis being the most significant toxicity, limiting escalation to C3. An AUC target of 1400 was deemed the maximum acceptable dose. Serum BU levels accumulate, with higher-than-expected final AUC despite interval DA based on PK studies. Increased BU AUC target is associated with improved RFS at one year.

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The Aethera Trial: An Ongoing Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at High Risk of Residual Hodgkin Lymphoma Following Autologous Stem Cell Transplant

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Background: Although autologous stem cell transplant (ASCT) can be curative for patients (pts) with relapsed/refractory Hodgkin lymphoma (HL), those with high-risk disease have long-term progression-free survival (PFS) of approximately 25% and could benefit from novel therapeutic approaches (Majhail 2006). Brentuximab vedotin (ADCETRIS®) comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). In a pivotal phase 2 study in pts with relapsed or refractory HL following ASCT, the objective response rate was 75%, with complete remissions (CR) in 33% of pts. A phase 3 study was initiated to evaluate the potential of brentuximab vedotin to prevent relapse post-ASCT in pts at high risk of lymphoma progression (ClinicalTrials.gov #NCT01100502).

Methods: The AETHERA trial is a phase 3, randomized, double-blind, placebo-controlled, multicenter study. After ASCT, pts received brentuximab vedotin 1.8 mg/kg q3wk and best supportive care (BSC) or placebo and BSC for up to 16 cycles (approximately 12 months). The primary endpoint is PFS per independent review; additional endpoints include overall survival and safety/tolerability. A planned interim safety and futility analysis was performed in Q4 2012; at that time 1214/1251 (97%) of the expected CT scans had been received for central independent review.

Patient Characteristics/Results: Protocol enrollment occurred from April 2010 through September 2012. A total of 329 pts were enrolled and randomized; of these, 327 received study treatment. Of the 327 pts, 133 (40%) were enrolled from the United States, 48 (15%) from Western Europe, and 146 (45%) from Central/Eastern Europe and Russia. The median age was 32 years (range 18–76) and 52.6% were male. Pts were enrolled in 1 of 3 high-risk categories: refractory to frontline therapy: 195 pts (59.6%), relapse <12 months after frontline therapy: 107 pts (32.7%), and relapse ≥12 months after frontline therapy with extranodal disease: 25 pts (7.6%). Response to salvage pre-ASCT was CR: 122 pts (37.3%), PR: 112 pts (34.3%), and SD: 93 pts (28.4%). Overall, 33% of pts were known to be PET-negative prior to ASCT. ASCT conditioning regimens were carmustine, etoposide, cytarabine, and melphalan (BEAM; 61%), cyclophosphamide, carmustine, and etoposide (CBV; 11%), or other (28%) and included radiation in 6% of pts. All pts were off treatment as of August 2013. The median number of

treatment cycles was 15 (range, 1-16) and 159 pts (49%) received 16 cycles. A total of 61 pts (19%) discontinued treatment due to adverse events. Thirty-five pts (11%) are known to have died; 31 deaths occurred after disease progression. One death occurred within 30 days of last dose and was considered disease-related.

Conclusions: Based upon a planned interim safety and futility analysis, the IDMC recommended that the AETHERA trial continue per protocol.

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Characterizing Melphalan Efficacy and Toxicity in Multiple Myeloma Patients with Renal Insufficiency

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High Dose melphalan (200 mg/m2, Mel200) is the standard conditioning for autologous stem-cell transplant (ASCT) in multiple myeloma (MM) patients. Forty percent of MM patients experience some degree of renal insufficiency. Although common practice, there is no standard for dose reduction in melphalan due to renal impairment. In addition, there is no clear correlation between melphalan pharmacokinetics in renal failure and outcome in these patients. Here we report the impact of renal impairment on response and toxicity outcomes in patients receiving Mel200 as part of ASCT.

We identified 111 patients who received Mel200 and ASCT between 2001 and 2012 at the University of Illinois. Overall, the majority of patients were African American (60%). Patients were stratified by renal function (n=35 CrCl $<$60 ml/min and n=76 CrCl $\geq$ 60 ml/min). Baseline characteristics were equal between the 2 groups aside from age (63.2 years $\pm$ 8.8 vs. 56.8 $\pm$ 8.8. P=.0004). Patients with renal failure experienced a significantly longer time to engraftment (12.2 days $\pm$ 3.51 vs. 10.6 days $\pm$ 1.7, P=.0025) and duration of diarrhea (6.6 days $\pm$ 6.3 vs. 4 days $\pm$ 3.7. P=.007). Length of hospital stay was similar between the two groups (17.6 days $\pm$ 4.5 vs. 16.25 days $\pm$ 5.2. P=.21). Patients with renal failure spent an average of 10.6 days on total parenteral nutrition, compared to 7.27 days in patients with normal renal function (P=ns). There were no deaths related to transplant related mortality in either group. . There was no difference in response rates between the 2 groups in terms of complete response (50% in CrCl$<$60ml/min vs. 40% in Cr Cl $>$ 60ml/min,P=ns) or overall response rate at day +90 (75% in CrCl$<$60ml/min vs. 100% in Cr Cl $>$ 60ml/min,P=ns).

This data demonstrates an increase in drug-related toxicities of diarrhea, and time on TPN in patients with renal impairment conditioned with HD Mel. We hypothesize that this is due to reduced renal drug clearance. In addition, longer time to engraftment in the renal failure group may be a result of greater overall melphalan exposure. In light of the large numbers of patients impacted by this data, we suggest that this would be an ideal patient group for the development of pharmacokinetic based strategies for individual patient dosing.

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Routine Prophylaxis of Pneumocystis Jirovecii Pneumonia in Recipients of Autologous Hematopoietic Stem Cell Transplantation

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Background: Pneumocystis jirovecii pneumonia (PJP) is a potentially life-threatening disease in immunocompromised patients. The at-risk population includes patients with HIV infection and low CD4 counts, hematological malignancies, hematopoietic stem cell (HSC) and solid organ transplant recipients, and patients receiving glucocorticoids or other immunomodulatory agents. The highest-risk group of immunocompromised patients tends to be those with HIV (human immunodeficiency virus) infection, where PJ follows an indolent course. However, in non-HIV immunocompromised patients, such as HSC transplant recipients, the infection tends to present with respiratory failure. The incidence of PJP in autologous BMT (bone marrow transplant) has not been clearly determined, and the indication for prophylaxis in this setting remains unclear. In this study we evaluate the incidence of PJP over a 10-year period in recipients of autologous transplants.

Methods: A retrospective analysis of 1191 consecutive autologous HSC transplants (1-75 years) performed between 1/1/2000 and 6/30/2011 at the University of Michigan BMT Program. The data was obtained from BMT Program Database at The University of Michigan Comprehensive Cancer Center. The diagnosis of PJP was established by bronchoscopy with brochoaveolar lavage (BAL) with polymerase chain reaction (PCR). We analyzed the following risk factors for the development of PJP: diabetes, glucocorticoids, infections, cutaneous T-cell lymphoma, hypertension, and seizure disorder.

Results: A total number of 5 PJ infections were diagnosed during study period, resulting in a cumulative incidence of 0.42% (95%CI [0.136449%–0.976969%]) over 10 year period. All cases occurred between 2001 and 2006, and 3 months or later following transplantation. Most patients (n=4) were older than 50 years old, and all of them were on steroids. Diagnoses included non-Hodgkin's lymphoma (n=3), Hodgkin's lymphoma (n=1) and multiple myeloma (n=1). Conditioning regimen was BEAM (BCNU, etoposide, cytarabine, melphalan, n=4) and high dose melphalan (n=1). Only 2/5 patients were neutropenic at the time of the pneumonia, and this did not correlate with the CD34+ cell infused, which was $\geq$2.2x10E6/kg for all patients. Four patients were on corticosteroids for relapsed lymphoma (n=2), ITP (n=1), BCNU pneumonitis (n=1). The remainder patient was on florinef and was coinfected with candida and herpes virus. There were no particular comorbidities associated with the diagnosis of PJ pneumonia. One patient died of PJ, the remainder were treated successfully.

Conclusions: Our retrospective analysis of a large cohort of autologous transplant recipients reveals an extremely low