Conclusions: P has permitted safe dose escalation of M up to 180 mg/m^2 with acceptable toxicity in AbRF pts.

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URINARY EXCRETION OF EPINEPHRINE AND DOPAMINE CORRELATES WITH EFFICIENCY OF G-CSF MOBILIZED STEM CELLS IN PATIENTS WITH AL AMYLOIDOSIS

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Introduction: Hematopoietic stem cell (HSC) migration is essential for peripheral blood HSC collection. Sympathetic signaling regulates HSC egress from bone marrow. Ablation of adrenergic transmission in animal models indicates that norepinephrine (NE) controls G-CSF-induced HSC mobilization (Cell 2006). β adrenergic agonists and antagonists enhance and reduce HSC mobilization, respectively. We prospectively studied catecholamines and the efficiency of HSC collection in patients (pts) with AL amyloidosis undergoing G-CSF mobilization prior to high dose melphalan and HSC rescue on a phase II study.
Methods: 24h urine samples were analyzed for epinephrine (EPI), NE and dopamine (DA) excretion before G-CSF administration and after HSC collection was completed. Statistics included Spearman rank coefficient (r), Wilcoxon rank sum and Signed rank tests.
Results: In 39 pts median (med) CD34 cells collected was 8.3 x 10^6/kg (IQR 5,12.3) in a med of 2 (IQR 2,3) collections. The med CD34 cells infused on day 0 was 4.7 x 10^6/kg (IQR 3.8, 6) and time to neutrophil engraftment (ANC> 500 x 2 days) was 9 days (IQR 9, 11). Baseline urinary excretion of EPI and DA correlated with total CD34 cells collected (r = 0.33, P = 0.005; r = 0.47, P = 0.05, respectively). An optimal collection defined as 5 x 10^6 CD34 cells/kg in 2 collections was achieved by 25/39 pts and was associated with higher baseline EPI (7 vs 4mcg/24h, P = 0.02) and DA (220 vs 156mcg/24h, P = 0.05) but not NE. Only DA significantly changed from baseline to after HSC collection ($P \leq 0.0001$).
Conclusion: Sympathetic signals regulate HSC egress from their niche, and we found baseline EPI and DA excretion are associated with greater and more efficiently collected HSCs following G-CSF in pts with AL amyloidosis. In mouse models G-CSF mobilization requires peripheral adrenergic signals and reduces NE in bone (Cell 2006). Reduced DA excretion following G-CSF in our study may indicate that circulating catecholamines serve as markers for overall sympathetic tone and could possibly predict mobilization efficiency in humans. These data support other evidence that DA plays a role in progenitor migration (Nat Immunol. 2007) and indicates that DA is important in G-CSF mobilization in pts with AL amyloidosis. Modulation of the sympathetic system to enhance HSC mobilization and the use of catecholamine values to guide clinicians with respect to the need for plerixafor or chemo-mobilization should be explored.

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PHARMACOKINETICS AND SAFETY OF ONCE-DAILY INTRAVENOUS BUSULFAN WITH BORTEZOMIB IN PATIENTS WITH RELAPSED MULTIPLE MYELOMA UNDERGOING A SECOND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Limited therapeutic options exist for patients with multiple myeloma (MM) relapsing after initial autologous hematopoietic stem cell transplantation (HSCT). A second autologous HSCT using a different conditioning regimen may provide long-term disease control. We report the pharmacokinetics and safety of daily intravenous (IV) busulfan (Bu) conditioning given with bortezomib for autologous HSCT from a multicenter, prospective Phase 2 study.
Methods: 30 patients with relapsed MM who had a first autologous HSCT ≥1 year prior to the planned HSCT were enrolled from eleven centers in the US and Canada. Patients received a test dose of IV Bu (0.8 mg/kg) over 2 hours between Days -12 and -9 prior to HSCT. Blood samples were drawn for pharmacokinetic (PK) analysis and Bu exposure was determined as area under the concentration-time curve (AUC). Individualized Bu PK-directed dosing for the conditioning regimen was recommended to achieve a total regimen AUC of 20,000 μM·min. IV Bu was administered over 3 hours once daily from Day -5 to Day -2. Confirmatory PK analysis was conducted in all patients on Day -5. Bu doses were adjusted on Days -3 and -2, if needed. Bortezomib (1.3 mg/m^2 QD) was administered as an IV bolus injection on Day -1.
Results: PK testing with 0.8 mg/kg of IV Bu dose revealed that 40.0% (n = 12/30) of patients had doses outside the expected range (1,250 μM·min +/- 20%). PK-directed daily Bu dose on the first day of conditioning (Day -5) ranged between 1.99 and 4.73 mg/kg (94.6 and 213.4 mg/m^2). Subsequent dosing based on test PK resulted in 93.3% of patients (n = 28/30) falling within the target range (AUC, 20,000 μM·min +/-20%), underscoring the utility of test PK in achieving optimal dosing during conditioning. Mean Bu clearance for test dose and on Day -5 were comparable, 3.03 and 2.93 ml/min/kg, respectively. Two patients (6.7%) needed dose reduction on Days -3 and -2. No instances of VOD, seizure, or worsening neuropathy have been reported to date. Grade 3 or higher stomatitis was observed in 23% of patients (n = 7/30). One death occurred on Day 30 after transplant in a patient with Parkinsonism who died of pulmonary complications.
Conclusion: Pre-transplant test dose PK analysis allows accurate targeting of IV busulfan dosing in more than 90% of patients. The conditioning regimen of bortezomib and IV busulfan with PK-directed dose optimization is well-tolerated in patients with relapsed MM who undergo second autologous HSCT.

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STEM CELL MOBILIZATION FAILURES SALVAGED WITH PLERIXAFOR: LONG TERM FOLLOW UP OF ENGRAFTMENT AND OUTCOMES

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We enrolled 49 pts in a compassionate use protocol to mobilize stem cells(SC) for pts who failed a mobilization attempt. Pts received 0.24 mg/kg of Plerixafor (P) sq 9 -11 hrs prior to apheresis in addition to BID GCSF. Table 1 shows pt demographics. Using P and GCSF, ≥ 2.5 x 10^6 CD34+ cells/Kg were collected in 33 pts (67%).

Table.

Patient Demographics	Results
Median Age	64 (23-74) years
Diagnosis	
Non Hodgkin Lymphoma	27 Pts (55%)
Multiple Myeloma	17 Pts (35%)
Hodgkin Lymphoma	5 Pts (10%)
# of Previous mobilization Attempts	
1	37 Pts (76%)
≥ 2	12 Pts (24%)

The median days for pheresis was 1 day (range, 1-3). The median SC dose collected was 4 x 10^6 CD34+ cells/ Kg (range, 2.5 – 14.3). The median CD-34+ peripheral blood count on the 1st day collection with P was 22.4/uL. In contrast the median peripheral blood CD-34+ cell count on the day of failed collection was 6.2 /uL. The average increase using P was 14.9 CD-34+ cells/uL. We collected $\geq$ 2.5 x 10^6 CD34+ cells/Kg on 4/5 pts with HD, 13/17 pts with MM and 16/27 pts with NHL. 16 pts (33%) collected < 2.5 x 10^6 CD34+ cells/Kg, with median cell dose of 1.4 x 10^6 CD34+ cells/ Kg (range, 0.4-2.2). The median number of days of pheresis was 2 days (range, 1-4). For these16 pts the median CD-34+ count on the day of unsuccessful collection was11.2 /uL, compared to 8.3/ uL with use of P and GCSF. The common side effects attributed to P were diarrhea, fatigue, thrombocytopenia and bone pain; observed in 12%, 8%, 8% and 6% pts, respectively. 43/ 49 pts proceeded to an autologus SC transplant, 34 pts received $\geq$ 2.5 x 10^6 CD34+ cells/Kg. Thirty two of these pts used the P collection as the only source of SC. Two pts had their P mobilized SC combined with a previous suboptimal SC collection. Nine pts received < 2.5 x 10^6 CD34 + cells/Kg; 4 pts received P mobilized SC alone, 5 pts received P mobilized SC combined with their previously mobilized SC. All pts received GCSF from day +6 till WBC engraftment. The median days of WBC and platelet engraftment were day +11 (range, 9-13 days) and day +16 (range, 11-77 days), respectively. With a median follow up of 13.7 months, long term engraftment data is available on 27 pts. The median white cell count, hemoglobin and platelet count 1 year after transplant was 4.7 x 10^9/L, 12.2 g/dL and 109 x10^9/L, respectively. To date 15 pts have evidence of disease progression. Two patients have developed MDS/AML post transplant. Failure to increase peripheral CD34 count after P when compared to previous attempts may predict unsuccessful mobilization. P is well tolerated with minimal side effects, acceptable time to engraftment and acceptable peripheral blood counts at 1 yr after the transplant.

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OUTCOMES FOLLOWING SALVAGE AUTOLOGOUS STEM CELL TRANSPLANT (SCT) FOR MULTIPLE MYELOMA

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Background: High-dose therapy and SCT has improved the progression-free (PFS) and overall survival (OS) of patients with multiple myeloma (MM). However all patients eventually develop disease recurrence. In the era of effective novel agents (such as bortezomib, lenalidomide and thalidomide), the optimal salvage strategy is undefined.

Methods: We retrospectively analyzed the outcomes of patients who underwent salvage melphalan-based SCT for relapsed MM at Memorial Sloan-Kettering Cancer Center.

Results: Between 1995 and 2011, 60 patients with MM received an initial SCT and then second autograft for relapsed disease at our center. Conditioning regimen consisted of melphalan 100 (N = 9), 140 (N = 20) or 200mg/m2 (N = 31). The median age at 2nd SCT was 59 years (range 36-75) and 58% (N = 35) were male. At the time of 1st and 2nd transplant, 14% (5/36) and 36% (14/39) of patients who were assessed with either karyotype or FISH had high risk cytogenetics (including t (4;14), +1q, p53 loss, or del 13q by karyotype), respectively. Median interval between first and salvage SCT was 32 mos (range 7.1-88.7). Of evaluable patients, 78% (46/59) had chemotherapy sensitive disease prior to salvage SCT and 22% were chemoresistant. Twenty-eight patients received maintenance following salvage SCT, most often IMID-based, while 11 went on to receive an allogeneic SCT, 3/11 patients were received maintenance prior to allogeneic SCT. Response was assessed at 2-3 mos post-SCT and 77% of evaluable patients achieved > = partial response (PR), 16% had stable disease (SD), and 7% progressed despite salvage SCT. Following salvage SCT, 23 patients received maintenance therapy and 11 went on to allogeneic SCT. The median PFS following second autograft was 11.2 mos (95% CI: 7.6-14.5); the median OS was 24 mos (95% CI: 19-42). Although the numbers were small, high-risk cytogenetics, the interval from first to second SCT, chemosensitivity, response and whether patients received maintenance therapy or allogeneic SCT following salvage autologous SCT did not significantly impact PFS or OS in this data set.

Conclusions: Salvage SCT is an effective strategy for relapsed MM following initial autograft and results in responses in the majority of patients. Although OS and PFS following salvage SCT is similar to other salvage strategies, novel conditioning regimens and/or effective maintenance strategies may improve this approach.

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THE ROLE OF HEMATOPOIETIC CELL TRANSPLANTATION COMORBIDITY INDEX (HCT-CI) IN AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

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Both autologous stem cell transplantation (ASCT) and novel agents have improved outcomes for patients (pts) with multiple myeloma (MM). ASCT is often restricted to fitter pts due to concerns of excessive treatment-related morbidity and mortality. Pre-transplant risk-stratification based on comorbidity index (CI) has been recognized as an important decision-making tool in pts with lymphoma and MM. Although Charlson and hematopoietic cell transplantation CI (HCT-CI) were previously correlated with post-ASCT toxicities and length of hospital stay in pts with MM, the groups with higher scores included fewer pts, limiting study interpretation. We evaluated the prognostic significance of HCT-CI on treatment-related morbidity (as determined by changes in pulmonary function, length of hospital stay, and 100-day readmission rate), overall (OS), and progression-free survival (PFS). Our analysis included 85 consecutive pts (median age, 57 yrs; 68% males) with MM who underwent ASCT at our institution from 01/2009 to 12/2010. 59% of pts were in first complete or partial remission prior to ASCT. 65% of pts had received>1 prior therapy. Median time from diagnosis to ASCT was 13.4 months. Melphalan-based preparative regimen was used in 61 pts, whereas others received Bu/Cy on a clinical trial. 24.7% had HCT-CI of 0; 37.6% pts had scores of 1-2; 37.6% pts had scores≥3. Incremental HCT-CI groups were associated with worse performance status (p<0.001), lower absolute and % predicted pre-transplant FEV1 (98% vs. 90% vs. 86%, p = 0.01), lower absolute and % predicted pre-transplant DLCO (91% vs. 78% vs. 66%, p<0.001), lower % predicted post-transplant DLCO (82% vs. 60% vs. 75%, p<0.001), longer hospital stay (15 vs. 16 vs. 18 days, p = 0.03), and faster platelet recovery (17 vs. 12 vs. 12 days, p = 0.007). With median follow up of 12 months, 12 pts were readmitted within 100-days of discharge, 12 pts died (9 relapses, 1 heart failure, 1 sepsis, 1 subdural hematoma) with 2 deaths within 100-days from ASCT, and 12 pts progressed. None of the 3 non-relapse deaths occurred in the lowest HCT-CI group (two in HCT-CI≥3). HCT-CI groups did not differ by pt readmissions, OS, PFS, and % changes in Pulmonary Function Tests pre- and post-ASCT (all p>0.3). With over a third of our study pts having HCT-CI≥3, we detected no association between higher HCT-CI scores and major clinical outcomes. Our data demonstrate the safety of ASCT in pts with MM who have higher pre-transplant HCT-CI.

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VINORELBINE-CYCLOPHOSPHAMIDE COMPARED TO CYCLOPHOSPHAMIDE IN PERIPHERAL BLOOD STEM CELL MOBILIZATION

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Background: High dose therapy followed by autologous stem cell rescue is the standard of care for transplant eligible patients with plasma cell myeloma. High dose cyclophosphamide (Cy) at 4-7mg/m^2 with granulocyte colony stimulating factor (GCSF) has been shown to be an effective regimen for stem cell mobilization despite associated haematologic toxicity. Vinorelbine 25mg/m^2 in