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%)