Poster Session I

AUTOLOGOUS TRANSPLANTS

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APREPITANT (AP) FOR PREVENTION OF NAUSEA AND VOMITING SECONDARY TO HIGH-DOSE CYCLOPHOSPHAMIDE (CY) ADMINISTERED TO PATIENTS UNDERGOING AUTOLOGOUS (A) PERIPHERAL BLOOD PROGENITOR CELL (PBPC) MOBILIZATION: FINAL RESULTS OF A PHASE II TRIAL

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AP is a neurokinin-1 receptor antagonist with unique antiemetic activity. We conducted a phase II trial evaluating efficacy & safety of AP in combination with 5-HT3 antagonists & adjusted dose of dexamethasone (D) in pts receiving high-dose CY for stem cell mobilization. High-dose CY is associated with significant nausea & vomiting. CY and filgrastim provides a better PBPC yield as compared to filgrastim (failure rate15-20%). Primary endpoint was the control of vomiting without the use of rescue anti-emetics at 24 hours after high dose CY. Secondary objectives were to evaluate side effects, control of nausea & delayed vomiting. Tertiary objective was to estimate the rate of successful $CD34^+$ mobilization (minimum 2 million CD 34^+ cells/kg body weight).

Methods: From May 2005 to June 2009, 40 pts were enrolled, five of whom were not evaluable for response. All received CY 4gm/m^2 and filgrastim (10-16mcg/kg/d). Granisetron 1 mg, (D) 10 mg and AP 125 mg were given orally 1 hour before CY followed by AP 80 mg once daily × 2 days. We used Simons optimal two-stage design constrained to fewer than 40 pts with 10% type I error and 85% statistical power. AP is judged to be of sufficient efficacy for further evaluation if it prevents acute vomiting in > 45% of pts. Under these assumptions, 18 evaluable pts were enrolled in 1st stage. Acute emesis was controlled in 10 pts therefore meeting the goal & enrollment proceeded to stage 2. An additional 17 pts were enrolled in Stage 2. If acute vomiting is controlled in 20 or more of the 35 pts, AP is judged worthy of further study.

Results: Twenty out of 35 response-evaluable patients (57%) did not develop vomiting or require rescue anti-emetics, thus achieving the critical value for success. A total of 22 (63%) of 35 response-evaluable pts met the criterion for the secondary endpoint of control of delayed vomiting defined as no vomiting episodes during days 2 – 5 and no rescue medications; exceeding the critical value for success. Thirty four out of 35 pts had a successful stem cell mobilization, thuse far exceeding the critical value of 23 of 35 pts. Two pts had grade 3 toxicity; 1 had pain (probably AP related) & another reported diarrhea (possibly AP related). Thus the rate of serious toxicity was 6% meeting the criterion for acceptable toxicity.

Conclusion: This final analysis demonstrate that AP has potential to effectively control acute & delayed emesis in pts receiving high-dose Cy and should be evaluated further.

Table 1. Patients Characteristics

Sex: Male/ Female	20/15
Median Age(years)	48 (range: 23-64)
Race	
Caucasians	30
African Americans	4
Native American	1
Diagnosis	
APL	1
HD	4
NHL	11
MM	19
Median CD34 + Cells/kg	7.62 million cells (range: 1.7 -76.15)

APL: Acute Promyelocytic Leukemia, HD: Hodgkin Disease, MM: Multiple Myeloma, NHL: Non- Hodgkin Lymphoma

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A RISK ADAPTED APPROACH UTILIZING PLERIXAFOR IN AUTOLOGOUS PERIPHERAL BLOOD STEM CELL MOBILIZATION

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Introduction: Many patients (pts) who are eligible for ASCT are unable to collect a minimum number of CD34 + stem cells to support high dose chemotherapy and ASCT. Plerixafor, a CXCR4 antagonist, in combination with G-CSF mobilizes more CD34+ stem cells when compared to G-CSF alone. Due to its cost, we commenced a risk adapted approach to the utilization of plerixafor for stem cell mobilization in pts undergoing ASCT. Our goal was to add plerixafor in pts who had ineffective mobilization thereby preventing mobilization failures. Re-mobilization results in added costs, delays with possible disease progression and time lost for the pts.

Methods: The study was restricted to pts mobilized with 10 mcg/kg/day GCSF alone. There were two patient populations: those who had plerixafor added in the evening of day 5 if PB CD 34 < 10/L with apheresis commencing the following morning; and those who during apheresis had a daily collection yield of $< 0.5 \times 10^6$ CD34/kg. Morning administration of G-CSF and evening dosing of plerixafor continued daily until apheresis was complete.

Results: From February to July 2009, 147 mobilization attempts occurred with G-CSF alone (Myeloma 61, NHL 54, Amyloid 17, Hodgkin 10, POEMS 4 and 1 solid tumor). Median CD34 yield: 5.5×10^6 CD34/kg; median apheresis 3. 67 pts (46%) received plerixafor; 37 during mobilization and 30 during collections. Overall, 7 of 147 (5%) failed to achieve a minimum of 2×10^6 CD34/kg compared to a prior 22% failure rate. Day 4 PB CD34 count and day 1 apheresis yield were analyzed to predict who would require plerixafor under these guidelines (Table 1). 72% of pts whose PB CD34 < 10 on day 4 received plerixafor vs 10% if ≥10. 110 pts did not start plerixafor prior to day 1 collection; if day 1 apheresis yield was <1.5, 76% subsequently received plerixafor.

Conclusions: Implementing this risk adapted approach allows poor mobilizers to be identified promptly and for initiation of plerixafor during mobilization and collection, thereby reducing the number of failures. In pts whose PB CD34 < 10 on day 4 of G-CSF or whose day 1 yield is <1.5 x10^6 CD34/kg, earlier addition of plerixafor may result in fewer apheresis days. Based on this data, we are implementing the earlier addition of plerixafor. This risk adapted approach with early implementation of plerixafor may be more cost effective than waiting for failure

to mobilize or utilizing combination G-CSF and plerixafor for all pts as upfront mobilization.

Mobilization and Collection

	All Patients	Plerixafor	No Plerixafor
PB CD34 day 4			
<10	65	47 (72%)	18 (28%)
10-14	11	4 (36%)	7 (64%)
≥15	58	3 (5%)	55 (95%)
not done*	12	12	0
Day 1 Apheresis yield (x10[6] CD34/kg)			
<1	15	14 (93%)	1 (7%)
<1.5	33	25 (76%)	8 (24%)
≥1.5	77	5 (6%)	72 (94%)

*12 patients received Plerixafor on the evening of day 4 due to prior failure to mobilize or high risk of failure

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THE IMPACT OF PRIOR EXPOSURE TO RITUXIMAB ON AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH FOLLICULAR AND TRANSFORMED LYMPHOMA

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Introduction: Addition of rituximab to chemotherapy (CT) for follicular lymphoma (FL) has been shown to improve many outcome parameters. Often, high-dose therapy is followed by autologous stem-cell transplantation (ASCT) after 1, 2 or more relapses. Kang *et al.* (BMT (2007) 40, 973) investigated whether prior exposure to rituximab had any influence on a subsequent ASCT and found no differences in the outcomes analyzed. However, there has been evidence suggesting that that such prior exposure may alter the phenotype of these tumour cells so that they no longer express CD20, and thus potentially altering their behaviour.

Methods: We performed a retrospective review on all patients having received an ASCT at the Ottawa Hospital with an initial diagnosis of FL. They were grouped into four categories according to their prior exposure to or lack of prior exposure to rituximab and according to their pre-ASCT diagnosis, non-transformed FL (FL-NT) vs. transformed (FL-T).

Results: 259 patients who underwent an autoHSCT for FL were divided into 4 groups: 184 FL non-transformed (FL-NT) (31 patients received rituximab and 153 did not), and 75 FL-transformed (FL-T) (24 patients received rituximab and 51 did not). The 5-year progression-free survivals (PFS) were 61.2% and 27.6%, respectively ($p < 0.0001$) and the overall survivals (OS) were 72.5% and 39.3%, respectively, ($p < 0.0001$). In the FL-NT group, no differences existed in PFS or OS between FL-NT rituximab-naïve and rituximab-treated patients (5-year PFS 61% vs. 64%, $p = 0.69$; 5-year OS 73% vs. 68%, $p = 0.80$). Within the FL-T group, the subsequent 5-year PFS of the rituximab-naive vs. pre-treated groups were 22% and 55% ($p = 0.20$), respectively, and the 5-year OS were 36% and 51% ($p = 0.39$), respectively. Prior exposure to R had a positive effect (Hazard Ratio (HR): 0.44, 95% CI 0.20-0.97, $p = 0.04$) on PFS and OS (HR: 0.5, 95% CI 0.21-1.18, $p = 0.11$).

Conclusion: Pre-treatment with rituximab in FL-NT prior to ASCT does not adversely impact ASCT outcomes. There is a suggestion of an increase in the number of patients with FL-T being transplanted in the post-rituximab era and as expected, the FL-T had a poorer outcome than the FL-NT patients. However, prior exposure to rituximab appeared to demonstrate a trend toward an improved OS within the FL-T group. In summary, previous rituximab exposure may be associated with an increased rate of transformation, leading to the poorer outcome of patients originally diagnosed with FL-NT.

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CD34 + ALDH+ PERIPHERAL BLOOD STEM CELLS IN CRYOPRESERVED APHERESIS PRODUCT ARE NON-APOPTOTIC AND PREDICT EARLY AND LATE ENGRAFTMENT FOLLOWING AUTOLOGOUS TRANSPLANTATION

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Methods which permit discrimination between viable and apoptotic peripheral blood stem cells (PBSC) following cryopreservation may be important in assessing the quality and engraftment potential of thawed apheresis product used in autologous transplantation. Previous studies have shown that cryopreservation results in significant apoptosis in CD34+ cells and that estimation of PBSC number based on the expression of the functional stem cell marker, aldehyde dehydrogenase (ALDH) may provide a better estimate of engraftment potential in cryopreserved product than CD34 alone. We assessed whether PBSC subset assessment based upon $DilC_1$, a sensitive marker of mitochondrial membrane potential and apoptosis, together with the viability exclusion dye 7-AAD, ALDH activity and CD34 expression may identify subsets which correlate with short and long term engraftment parameters following cryopreservation of PBSC apheresis product and autologous transplantation. 35 pts (median age 59 ± 9yrs) underwent PBSC collection, high dose chemotherapy and autologous transplantation for haematological malignancy. Most pts had multiple myeloma (42%) or NHL (40%). Post thaw mean infused CD34 × 10^6/kg was 4.10 (0.05-10.5) and ALDH × 10^6/kg 2.28 (0.25-6.5). CD34 viability was 72.3% (11.7-96.0). Most ALDH+ cells were non-apoptotic as assessed by $DilC_1$ staining, 89.9% (55.6-100.0) vs CD34, 34.5% (3.2-84.7), ($p < 0.005$), and most ALDH+ cells expressed CD34 (71.3%, 33.9-97.2). Only the CD34 + ALDH+ subset correlated with time to ANC > 0.5 × 10^9/L, ($p = 0.049$), though a trend was noted for CD34 + $DilC_1$+ ($p = 0.07$). No analysed subset could be significantly correlated to short term platelet recovery (Pl > 20 × 10^9/L). Long term (day 100) erythroid (Hb >100 g/L) and platelet engraftment (Pl > 100 × 10^9/L) was strongly correlated to numbers of CD34 + $DilC_1$+ ($p < 0.005$), CD34 + ALDH+ ($p < 0.005$), and CD34 + ALDH + $DilC_1$+ ($p < 0.005$) in infused product. Assessments of engraftment potential of cryopreserved PBSC's based on viable CD34 counts may be uninformative unless markers of apoptotic activity are included for analysis. In contrast, assessments based on ALDH activity appear to identify a viable and non-apoptotic stem cell subset correlated to both short term neutrophil and long term erythroid and platelet engraftment potential following autologous transplantation. Markers of apoptosis may be redundant when assessing ALDH activity in autologous PBSC product.

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TRANSPLANT UTILIZATION, PROCEDURE PATTERNS AND PATIENT CHARACTERISTICS IN NORTH AMERICAN TRANSPLANT CENTERS FROM 1994-2005

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Autologous (Auto) and allogeneic (Allo) hematopoietic cell transplantation (HCT) have been used to cure malignant and non-malignant conditions for >40 years. Recent advances in HCT techniques and supportive care, new HCT indications, and improvements in survival outcomes may have increased access to and utilization of HCT. We describe the HCT population, utilization and procedure patterns in North American (US and Canada) HCT centers reporting to the CIBMTR from 1994-2005. We divided the population into six 2-year cohorts (Table). All data exclude donor lymphocyte infusions. The number of AutoHCTs increased by >30% from the mid to late 1990s, then