hematologic recovery was observed in most patients, with values of ANC >500 and platelet >20,000 being reached at 13 and 16 days, respectively. Cardiac toxicity was monitored by echocardiogram. All patients demonstrated a normal left ventricular ejection fraction (LVEF) prior to receiving the conditioning regimen. There were no deaths attributable to heart failure. A significant decline in LVEF developed in only one patient who was over age 60 with underlying diabetes and hypertension. Ninety-four percent of patients survived the first 100 days following transplant. To date, 7 patients are alive and in remission at 2 to 7 years since disease onset, with no patients lost to follow-up. The 3-year failure-free and overall survival are 44% and 55%, respectively. We conclude that high dose mitoxantrone and melphalan is an effective and easily administered conditioning regimen with a low risk of significant cardiac toxicity despite prior treatment with anthracycline based chemotherapy, and thus is a safe regimen for APBSCT in adults with AML.

265

COMPARISON OF FIXED DOSE (6 MG) PEGFILGRASTIM AND DAILY FILGRASTIM TO ACCELERATE HEMOPOIETIC RECOVERY AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

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High dose therapy plus Autologous Stem Cell Transplantation (ASCT) is a milestone treatment program for most hematologic malignancies. ASCO guidelines recommend the use of granulocyte colony stimulating factors (G-CSF) in the post-infusion phase, to shorten the period of severe neutropenia and reduce the related risk of life-threatening infections. Thus, daily subcutaneous injections of G-CSF (filgrastim/lenograstim) at 5 μg/kg dose until ANC > 500/μl are routinely administered from day +1 following ASCT, in order to accelerate hematopoietic recovery and to avoid neutropenic complications. Pegfilgrastim, a novel long-acting recombinant G-CSF, has been shown to have similar efficacy when compared to G-CSF for chemotherapy-induced neutropenia, but little is known about its use in the ASCT setting. We used a 6 mg fixed dose Pegfilgrastim on day +4 following ASCT in 47 patients (23 male/24 female; median age 56 years; range 22–70 years) with multiple myeloma (26 pts) and relapsed or refractory Hodgkin's and non- Hodgkin's lymphoma (21 pts). Patients received peripheral $CD34^+$ stem cells (median number 4.4×10^6/kg; range 1.8–1.8) harvested after mobilizing chemotherapy (cytoxan, vinorelbine/cytoxan, R-IEV, IGEV, R-ICE) and G-CSF. Standard conditioning regimens (HD-Melphalan or BEAM) were used. Engraftment results were compared to those from a historical control group of 182 patients (median age 56 years; range 16–74 years) who had received HD-Melphalan or BEAM and ASCT (median $CD34^+$ cells 7.6×10^6/kg; range 1.8–14.6) supported by G-CSF (5 μg/kg/day from day +1 until ANC > 500/μl). Median number of days to ANC > 500/μl were comparable between the Pegfilgrastim (10, range 8–15) and G-CSF (11, range 7–22) groups, as well as the median number of days to PLT > 20,000/μl (Pegfilgrastim = 12, range 9–20 vs G-CSF = 12, range 7–29). Overall infectious rates, including FUO and documented infections, were of 48% and 39% for Pegfilgrastim and G-CSF groups, respectively (P = NS). Median number of days on iv antibiotics were 0 (range 0–18) and 6 (range 0–13) for the Pegfilgrastim and G-CSF groups, respectively. No significant differences in the incidence of bone pain, intensity of transfusion support, and length of hospital stay were documented between the two groups. These data indicate that a fixed 6 mg single-dose of Pegfilgrastim is safe and effective to accelerate engraftment after ASCT. No significant differences with G-CSF were apparent as to engraftment times and overall infectious complications.

266

PREDICTABILITY OF PRETRANSPLANT INTRAVENOUS BUSULFAN (IVBU) PK DATA IN ACHIEVING TARGETED IVBU AUC'S DURING CONDITIONING IN AUTO BMT

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Eight adult patients with hematological malignancies were enrolled in a phase I IVBU dose-escalation trial in autologous BMT conditioning. All patients received four daily doses of IVBU followed by 2 days of cyclophosphamide (CP) with amifostine cytoprotection. There were 4 planned cohorts of patients with an increasing targeted IVBU AUC of 20% in each subsequent cohort. The targeted average daily AUC range for IVBU in cohort 1 was 4400–5280 uMol*min/dose (mean 4800), the AUC range commonly achieved by single daily doses of 3.2 mg/kg/day. PK data from 6 time points over 5 hours was obtained from an IVBU test dose of 0.4 mg/kg administered to patients 7 to 21 days prior to conditioning. Test dose data was used to achieve the targeted IVBU AUC for conditioning doses 1 and 2. IVBU PK data was also collected around conditioning doses 1 and 3 at 7 points over 20 hours. If the targeted daily AUC range was not achieved based on the IVBU PK data for dose 1, IVBU doses were adjusted to correct the AUC during days 3 and 4 IVBU was measured in plasma samples using a validated gas chromatography method. Acetaminophen and metronidazole were held during all IVBU administration. Fungal prophylaxis was the same during IVBU test and conditioning doses. Patients received phenytoin for seizure prophylaxis. All PK data followed expected pharmacokinetic behavior. In cohort no. 1, test dose PK data resulted in achieving the targeted AUC for 3 of 5 (60%), but in none of the 3 patients in cohort no. #2 based on first IVBU conditioning dose PK results. The test dose PK data resulted in a lower than targeted AUC in 5 patients. Of these 5 patients, 4 achieved the targeted 4-day AUC after dose adjustments. Hepatic veno-occlusive disease was diagnosed in 2 patients in cohort no. 2 after IVBU doses were increased to obtain the targeted mean 4-day AUC. The study was closed. Utilizing PK data based on a small pretransplant IVBU test dose with limited blood sampling of up to 5 hours did not accurately predict conditioning AUCs, especially when higher targeted AUCs were desired. PK data from first dose IVBU conditioning dose was more predictive of later IVBU conditioning AUCs. This suggests that conditions during the test dose as proposed in this study did not accurately reflect those of conditioning and/or that a higher test dose with more comprehensive blood sampling might be more predictive in estimating IVBU dose when single daily busulfan is administered with targeting strategy (Table1).

Table 1. *IVBU PK Data*

Patient no.	Desired IVBU Conditioning AUC Range	Dose 1 AUC	Dose 3 AUC	Ave 4-Day Daily AUC
1	4400–5280	3558	8590	6074
2	4400–5280	4864	4853	4858
3	4400–5280	5152	6232	5692
4	4400–5280	4771	4870	4820
5	4400–5280	4223	5358	4790
6	5281–6340	4034	6858	5446
7	5281–6340	4905	6586	5745
8	5281–6340	4051	6207	5129

267

TANDEM HIGH DOSE THERAPY WITH HEMATOPOIETIC PROGENITOR CELL RESCUE IN CHILDREN WITH HIGH-RISK SOLID TUMORS

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A major advance in the treatment of high-risk patients with solid tumors has been to intensify therapy. We hypothesize that the use of tandem high dose chemotherapy followed by stem cell rescue

will improve survival in children with high-risk solid tumors. Fifteen patients were enrolled from March 2000 to August 2004 with a median age of 6 years (2–19). Each had received at least 2 courses of chemotherapy prior to study enrollment. Patients (Table 1) had the following diagnoses: recurrent Wilms tumor (n = 5), high-risk Ewing's sarcoma (n = 3), recurrent hepatoblastoma (n = 2), recurrent retinoblastoma (n = 2), recurrent germ cell tumor (n = 2), and undifferentiated sarcoma (n = 1). Patients were prepared with etoposide (800 mg/m^2/day on −6, −5, −4), carboplatin (667 mg/m^2/day on −6, −5, −4), and cyclophosphamide (1800 mg/m^2/day on −3, −2) prior to the first transplant, and melphalan (60 mg/m^2/day on −8, −7, −6) and cyclophosphamide (500 mg/m^2/day on −5, −4, −3, −2) prior to the second. Children received a median of 3.86×10^8 TNC/Kg (2.3–9.4) prior to the first transplant, and 4.1×10^8 (2.5–10.5) TNC/Kg prior to the second. Eight patients were in complete remission and 7 were in partial remission at the time of first transplant. One patient received local radiation instead of the second transplant due to parental preference. Following each rescue, patients achieved an ANC > 500 at a median of 13 days (11–34) and 12 days (10–31), respectively. Patients achieved a platelet count >20,000 at a median of 22 days (13–37) and 37 days (15–113), respectively. There was a median of 38 days between rescues (29–49). Five patients received radiation therapy post-transplant to relapse sites. There were no toxic deaths. Toxicity was primarily hematopoietic. Nine of 15 are surviving, 2 with recurrent disease following tandem therapy at a median follow-up of 22 months (11–55). Relapses following transplant occurred at the primary site (n = 3), distant (n = 3), and primary/distant (n = 2). Five have died from progressive disease; 1 from late pulmonary toxicity. We conclude that tandem stem cell transplant used as consolidation in patients with solid tumors is feasible, well tolerated, and offers the potential for cure in some patients with high-risk disease (Table1).

Table 1. *Patient Characteristics*

Patient	Diagnosis	Stage/ Location	Relapse Site Prior to SCT	Relapse Site Following SCT	Follow-up Post Transplant
1	Undifferentiated sarcoma	Pelvis			NED, 55 months
2	Ewing's	Pelvis		Primary site, lungs	PD, died - 39 months
3	Hepatoblastoma	Stage IV		Primary site	Alive, stable disease - 53 months
4	Wilms	Recurrent stage IV	Primary site, lungs		NED, 45 months
5	Ewing's	Pelvis		Primary site, lungs	PD, died - 11 months
6	Wilms	Recurrent stage I	Liver		NED, 49 months
7	Wilms	Recurrent stage III	Lungs	CNS	Alive, stable disease - 38 months
8	Ewing's	Metastatic			NED, 41 months
9	Hepatoblastoma	Recurrent stage IV	Primary site	Lungs	PD, died - 22 months
10	Germ cell tumor	Stage IV			Pulmonary toxicity, died - 19 months
11	Wilms	Recurrent stage II	Primary site	Primary site	NED, 27 months
12	Wilms	Recurrent stage III	Primary site	Primary site	PD, died - 12 months
13	Retinoblastoma	Bilateral	Sinus, orbit		NED, 16 months
14	Retinoblastoma	Bilateral	Pineal	Pineal	PD, died - 11 months
15	Germ cell tumor	Pineal	Primary site		NED, 13 months

268

PHARMACOKINETICS (PK) OF 2 DOSING REGIMENS OF PALIFERMIN IN PATIENTS (Pts) WITH HEMATOLOGIC MALIGNANCIES (HM) UNDERGOING HIGH-DOSE CHEMORADIOTHERAPY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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For patients (pts) with HM undergoing HSCT, oral mucositis (OM) is a frequent and debilitating complication that negatively impacts treatment outcomes, patient quality of life, and healthcare resources. Palifermin reduces the incidence and duration of severe OM in the HSCT setting. This phase 1 open-label study assessed the PK of 2 palifermin dosing regimens. **Methods:** Pts were 18 to 76 years old with HM and a Karnofsky performance score ≥70%. Palifermin was administered intravenously once daily as follows: 60 mcg/kg/day for 3 consecutive days on day −11, day −10, and day −9 before conditioning (total body irradiation [TBI] + etoposide + cyclophosphamide) and following HSCT on days 0, 1, and 2 (part A) and a single dose of 180 mcg/kg (part B) before conditioning on day −11 and after HSCT on d 0. In part A (6 total doses), PK parameters were assessed after the first, third, fourth, and sixth doses. In part B (2 total doses), assessments were made after each dose administration (day −11 and day 0). **Results:** In part A, 13 pts received palifermin; in part B, 12 pts received the single dose on day −11 and 11 pts received the single dose on day 0. For both dosing regimens, palifermin concentrations declined rapidly (≥98% decrease) in the first 30 minutes postdose, followed by a slight increase in mean concentrations between 1 and 4 hours and then a terminal decay phase. Respective mean (SD) PK parameter values for the 2 dosing regimens are shown in Table 1. In part A, mean $AUC_{0\text{-}t}$ values were comparable between doses 1 and 3 (within 15%) and 1 and 4 (within 1%). In part B, mean PK parameter values were similar (within 10% of each other) between doses 1 and 2. The mean AUC after the first 180 mcg/kg dose in part B was approximately 4-fold higher than that after the first 60 mcg/kg dose in part A. Mean half-life values ranged between 3.3 to 5.7 hours in part A and the value was 5.4 hours in part B. **Conclusions:** The PK data in pts receiving HSCT were consistent with approximately dose-linear PK in the dose range of 60 and 180 mcg/kg, with no observed accumulation, based on AUC, after 3 daily doses of 60 mcg/kg in this pt population in the HSCT setting (Table1).

Table 1.

Dosing Regimen (Dosing Day)	n	$AUC_{0\text{-}t}$ (hr × ng/mL) Mean (SD)	Clearance (mL/hr/kg) Mean (SD)	V_{ss} (mL/kg) Mean (SD)
Part A - 60 mcg/kg/day × 3 consecutive days				
1st dose (day −11)	9 to 13	34.3 (15.9)	1730a (497)	5320a (2330)
3rd dose (day −9)	13	39.8 (36.4)	-	-
4th dose (day 0)	11 to 13	34.8 (22.5)	2030a (862)	3870a (2080)
6th dose (day 2)	13	21.2 (15.1)	-	-
Part B - 180 mcg/kg/day × 1 day				
1st dose (day −11)	12	140 (50.9)	1460 (600)	4290 (3270)
2nd dose (day 0)	11	143 (71.8)	1770 (1290)	4270 (4700)

Accurate computations of clearance (CL) and volume of distribution at steady state (V_{ss}) were not possible for some concentration-time profiles.

269

THE FAILURE OF PROGNOSTIC MODELS (PM) FOR HODGKINS DISEASE (HD) TO PREDICT OUTCOMES AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

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PM have been developed for patients with advanced HD in an effort to identify high-risk individuals for and predict outcomes of ASCT. Four PM were evaluated in patients transplanted in our program between 1993 and 2005. One hundred and thirteen patients with relapsed or refractory HD received ASCT. Forty-five patients received a conditioning regimen of busulfan, melphalan, and thiotepa (BuMelTT), whereas 68 patients received other standard conditioning regimens (SCR) including Cy/TBI/VP (23), CBV (39), and other (6). Followup is 113 weeks for BuMelTT