Graft failure (GF) is life-threatening complication of allogeneic transplant (Allo-T). Long-term outcomes of interventions used to treat this complication have not been extensively studied. We retrospectively reviewed the long-term survival after GF occurring at the M.D. Anderson Cancer Center from 1990–2000. Allo-T recipients were included if they had GF for any of the following reasons 1) Primary GF (PGF) if pts failed to achieve an ANC >500/μl for 3 consecutive days by day 28 post transplant if bone marrow (BM) or peripheral blood (PBPCs) were the stem cell source, or 42 days for cord blood (CB); 2) Primary GF with autologous reconstitution (PGF-AR) if patients recovered hematopoiesis without evidence of donor cell engraftment; or 3) Secondary GF (SGF) if there was a decrease in ANC levels to <500/μl for 3 consecutive days after having achieved engraftment without disease progression. 68 pts were identified out of a total of 1750 (4%) allografts performed during that time period. Median age was 37 yrs (range, 4–75); diagnosis included 22 pts with CML or other myeloproliferative disorders, 27 with acute leukemia, 17 with lymphoma or CLL, and 2 with aplastic anemia. 31 pts received cells from a related donor (15 mismatched in at least 1 allele) while 37 received cells from an unrelated donor. 36 pts received BM, 29 received PB, and 3 received CB. 29 pts had PGF, 9 pts had PGF-AR and 30 pts had SGF. The 1 and 5 yr overall survival (OS) for all pts was 31% and 15%. The 1 yr and 5 yr OS for each group were: PGF-29%/18% PGF-AR 55%/11% and SGF 26%/13%. The following Table 1 shows the 1 yr and 5 yr survival rates of pts according to the intervention received. The most common causes of death were GF (18%) and engraftment but death from infection (27%) and recurrent/persistent disease (41%). We conclude that pts who experience GF post allogeneic transplantation can be successfully treated with a variety of interventions, however, death from other causes is common. Our data suggest that harvesting autologous cells for back-up in pts undergoing Allo-T procedures with high risk of GF is warranted.

Outcomes According to Therapy for GF

	None	Growth Factors	Auto Back Up	Retransplant Same Donor	Allo Back Up	Retransplant Different Donor
N	9	19	10	14	9	3
OS @ 1/5 yrs	33%/0%	29%/17%	60%/40%	21%/7%	8%/8%	60%/33%

91

OPPORTUNISTIC INFECTIONS ARE THE MAJOR CAUSE OF MORTALITY AFTER NONMYELOABLATIVE UNRELATED BONE MARROW TRANSPLANTATION WITH ALEMTUZUMAB, FLUDARABINE AND MELPHALAN

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Nonmyeloablative (NM) allogeneic (allo) hematopoietic cell transplantation (HCT) may be effective in patients (pts) at high risk for morbidity and mortality after conventional myeloablative HCT. We report the outcome of NM bone marrow transplantation (BMT) from HLA-matched volunteer unrelated donors (VUDs) in 14 pts (median age 45 yr; range, 19–58) with relapsed and/or refractory hematologic malignancies (1 ALL, 3 AML, 3 MDS/AML, 3 Hodgkin's disease, 2 multiple myeloma, 2 NHL). Thirteen pts had previous autologous (10 pts) or allo (3 pts) HCT. The NM regimen included alemtuzumab (20 mg/day × 5, days −8 through −4), fludarabine (30 mg/m^2/day × 5, days −7 through −3) and melphalan (140 mg/m^2 on day −2), as described by Kottaridis PD et al, Blood 2000;96:2419 and Chakraverty R et al, Blood 2002;99:1071. Two pts had primary graft failure (actuarial probability 16.4%; 95% confidence interval [CI] 0–37.6%). In the 12 evaluable pts, median times to ANC >0.5 × 10^9/L and platelets >20 × 10^9/L were 15 (range, 9–41) and 21 days (range, 15–41), respectively, after NMBMT. Two pts developed grade I or grade II acute graft-versus-host disease (GVHD) at 19 and 76 days, respectively, after NMBMT. The actuarial probability of grade II or greater GVHD is 9.1% (95% CI 0–26.2%). Two pts developed extensive chronic GVHD, and one of these pts died with chronic GVHD-associated pulmonary failure 267 days after NMBMT. Five pts developed cytomegalovirus (CMV) reactivation, and one of these pts died with CMV infection at 122 days after NMBMT. Six pts died with other infections at a median of 74 days (range, 52–209) after NMBMT: 2 adenovirus (1 associated with graft failure), 2 toxoplasmosis, 1 *Aspergillus* (associated with graft failure), and 1 *Pseudomonas* (associated with chronic GVHD). Actuarial nonrelapse mortality (NRM) is 60.0% (95% CI 32.6–87.4%), and infection-associated mortality is 50.0% (95% CI 23.7–76.3%). Three pts relapsed at 181, 182 and 202 days, respectively, after NMBMT; actuarial relapse rate is 37.5% (95% CI 4.0–71.0%). Three pts are alive in remission at 235+, 255+ and 914+ days, respectively, after NMBMT; actuarial event-free survival (EFS) is 14.3% (95% CI 0–37.4%). Opportunistic infection is the major cause of NRM and poor EFS in pts with high-risk hematologic malignancies who undergo VUD NMBMT after alemtuzumab, fludarabine and melphalan. Efforts to improve immune reconstitution and infection prophylaxis after NMBMT with this regimen are warranted.

92

CALCULATING IV BUSULFAN (IVBU) DOSE USING BODY SURFACE AREA PREDICTS MEASURED DRUG EXPOSURE MORE ACCURATELY THAN DOSING IN MG/KG BUT DOES NOT ELIMINATE THE NEED FOR PHARMACOKINETICS (PK) TO OBTAIN DOSING PRECISION

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Bu has been shown to be an effective chemotherapeutic agent against a variety of hematologic diseases when used in high dose preparative regimens for auto and allo hematopoietic stem cell transplantation (HSCT), but variation in area under the curve (AUC) above or below the target range is associated with increased risk of toxicity or relapse. ivBu minimizes intrapatient variability, but interpatient variability remains a significant problem. The initial goal of our study was to determine the ability of a test dose to predict later ivBu levels. Patients are given the first of 16 2-hr infusions of ivBu 48 hours prior to the beginning of the remaining 15 doses given q 6 h. Doses 2–15 are adjusted to achieve a target AUC based on first dose PK. The PK study is performed using a 5-sample limited sampling strategy and a single compartment, first order elimination model in WinNonlin. Using this strategy, more than 80% of patients achieve an AUC within 10% of the target. However, due to the expense and time involved in drawing, processing, and calculating ivBu levels after a test dose, we sought to determine if ivBu doses based on any specific body metric or metric based formula (BSA) could accurately predict ivBu AUC. Fifty-one adult patients (aged 18 to 69) from May 2003 to May 2004 receiving an ivBu containing preparative regimen for allo or auto HSCT for HD, NHL, AML, ALL, or CML were dosed per the above test dose strategy. All were given a test dose equal to 0.8 mg per kg for an average adult weight (70 kg) for a target AUC of 1250 μM · min and proportionately lower doses for lower targets. Using simple linear regression analysis comparing AUC achieved with dose given, we sought to determine whether the fixed dose given recalculated in mg/m^2 (using 3 different formulas), or mg/kg body weight (actual, ideal, or adjusted ideal) was the best predictor of AUC achieved. In this comparison mg/m^2 yielded an R^2 value of 0.58, while the best R^2 value using mg/kg was 0.50. Although BSA predicted for AUC somewhat better than weight alone, neither is adequate to replace busulfan PK levels at present. In the future we will look at other factors, which in conjunction with body metrics may influence ivBu AUC predictability, including race, gender, age, BUN, creatinine, ALT, SGOT, and history of hepatic injury or hepatic risk history. Multivariate linear regression analysis will be used to determine the best dosing algorithm.