regimens produce encouraging long term survival, with a low incidence of GvHD and low toxicity especially in patients with early disease. The addition of MEL or TBI reduces RRD, but increases significantly TRM and does not improve survival. Disease phase remains a major predictor of outcome.

225 KEPIVANCE USE IN ALLOGENEIC STEM CELL TRANSPLANTATION
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KEPIVANCE (palifermin) is a human keratinocyte growth factor produced by recombinant DNA technology. KEPIVANCE is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelo-toxic therapy requiring hematopoietic stem cell support. Graft vs. host disease remains as one of the major obstacles in allogeneic stem cell transplantation. The role inflammatory cytokines play in GVHD is well known. It has been postulated that if mucositis can be lessened, cytokine storm will be less and hopefully GVHD. When looking at the allogeneic stem cell transplant patients during 2005 and 2006 at our institution a trend for a decrease in severity of acute GVHD was noted in patients treated with KEPIVANCE (66 mcg/kg/day) compared to patients treated with no treatment. Median dose of KEPIVANCE was 60 mcg/kg/day. The addition of MEL or TBI reduces RRD, but increases incidence of GvHD and low toxicity, especially in patients with refractory disease. The other 31 patients had 6/6 or better antigen matches at A, B or DR. The other 31 patients were 6/6 or better antigen matches at A, B or DR. These RIC regimens were used: fludarabine 30 mg/m 2 x 5 days and melphalan 140 mg/m 2 x 1 day in all groups, and Alemtuzumab 20 mg/d x 5 days (protocol 1), x 3 days (protocol 2), and x 2 days (protocol 3). Twenty-three patients received MUD products and 17 received MRD products; cell source was bone marrow (17), PBSC (19), cord blood (one) and combination products (3). All patients received an adequate CD34+ cell dose or TNC dose (cord blood transplant). GVHD prophylaxis was tacrolimus tapering after day +30. Determination of the optimal dose of Alemtuzumab was a goal of this study. All patients except one achieved a WBC graft. Relapse or disease progression occurred in only 37% of protocol 3, 40% of protocol 2 and 67% of protocol 1. Although Alemtuzumab dose was given in a standard fashion not adjusted for body weight or surface area it was found that lack of consideration of patient size did not represent the intent of the given protocols. Weight-based Alemtuzumab dose adjustment showed that a much broader dose range than expected had occurred. Those receiving protocol 1 were in a dose range of 1.01-1.90 mg/kg; for protocol 2 the range was 0.36-1.08 mg/kg; for protocol 3 the range was 0.36-0.70, overlapping the previous group. The median dose of Alemtuzumab for the cohort was 0.68 mg/kg. A clustering of acute GVHD grades I-II appeared below the median dose at approximately 0.55 mg/kg; only one patient had grade IV acute GVHD. In summary, formulation of a conditioning protocol that balances engraftment and recurrence of primary disease on the backdrop of a newly reconstituted immune system is problematic. These data indicate that using the patient’s body weight in the determination of an optimal Alemtuzumab dose is a more reasonable approach to developing and standardizing RIC protocols with this drug.

226 DIFFERENTIAL REQUIREMENT FOR NKGD2 IN THE REJECTION OF HAPLOMISMATCHED AND MHC-I DEFICIENT BONE MARROW
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Mouse Natural Killer (NK) cells mediate rejection of MHC-mismatched or MHC-deficient bone marrow allografts. Counteracting activating and inhibitory signals regulate NK cell activity. The ability of F1 mice to reject parental bone marrow (BM) cells (hybrid resistance) has been attributed to the presence in the recipient of a subset of NK cells that lack inhibitory receptors for the MHC class I antigens expressed by the donor cells. Evidence supporting the “missing self” hypothesis of hybrid resistance was provided by demonstration that MHC class-I deficient donor BM is rejected by otherwise syngeneic recipients. We have previously demonstrated a role for NKGD2, an activating NK cell receptor, in rejection of Balb/c (H-2d) parental BM by (Balb/c x C57Bl/6; H-2b/d) F1 (CB6F1) recipient mice. NKGD2 ligands are expressed on the regenerating C57Bl/6 BM cells. Moreover, the rejection of Balb/c BM by CB6F1 recipients was blocked by neutralizing anti-NKG2D monoclonal antibody. The purpose of this study was to determine whether NKGD2 blockade was sufficient to prevent rejection of MHC-I deficient BM. Beta-2 microglobulin deficient (B2M−/−) Balb/c or NOD bone marrow was transplanted into irradiated CB6F1 mice that had been pretreated with neutralizing antibodies to NKGD2. In contrast to results with wild-type Balb/c or NOD BM whose rejection was prevented by anti-NKG2D, B2M−/− cells were rejected despite NKG2D blockade. Furthermore, syngeneic MHC class I+ Balb/c recipients were able to reject B2M−/− Balb/c donors despite NKGD2 blockade. These results suggest that rejection of MHC class I-bearing BM requires activation via NKGD2, whereas MHC class I-deficient BM elicit a sufficiently strong NK response that augmentation by NKG2D signaling is not essential for the rejection. Therefore, the hybrid resistance model in which MHC class I-bearing BM are used for transplantation may better reflect the situation in human hematopoietic stem cell transplantation.

227 DETERMINATION OF ALEMTUZUMAB DOSE FOR REDUCED INTENSITY CONDITIONING IN ALLOGENEIC TRANSPLANTATION
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From June, 2002, to August, 2006, our institution utilized reduced intensity conditioning (RIC) regimens for 40 adult at-risk older patients or those with comorbid conditions. Malignancies included multiple myeloma, AML, CML, NHL, MDS, CLL and one renal cell carcinoma. Thirteen (32%) were in CR at time of transplant while 27 (68%) had relapsed or refractory disease. Median age was 50 years (range 24-66) and median follow-up was eight months (1-36 months). Nine patients were single antigen or allele mismatches at either A, B or DR. The other 31 patients were 6/6 or better antigen matches at A, B and DR. Three RIC regimens were used: fludarabine 30 mg/m 2 x 5 days and melphalan 140 mg/m 2 x 1 day in all groups, and Alemtuzumab 20 mg/d x 5 days (protocol 1), x 3 days (protocol 2), and x 2 days (protocol 3). Twenty-three patients received MUD products and 17 received MRD products; cell source was bone marrow (17), PBSC (19), cord blood (one) and combination products (3). All patients received an adequate CD34+ cell dose or TNC dose (cord blood transplant). GVHD prophylaxis was tacrolimus tapering after day +30. Determination of the optimal dose of Alemtuzumab was a goal of this study. All patients except one achieved a WBC graft. Relapse or disease progression occurred in only 37% of protocol 3, 40% of protocol 2 and 67% of protocol 1. Although Alemtuzumab dose was given in a standard fashion not adjusted for body weight or surface area it was found that lack of consideration of patient size did not represent the intent of the given protocols. Weight-based Alemtuzumab dose adjustment showed that a much broader dose range than expected had occurred. Those receiving protocol 1 were in a dose range of 1.01-1.90 mg/kg; for protocol 2 the range was 0.36-1.08 mg/kg; for protocol 3 the range was 0.36-0.70, overlapping the previous group. The median dose of Alemtuzumab for the cohort was 0.68 mg/kg. A clustering of acute GVHD grades I-II appeared below the median dose at approximately 0.55 mg/kg; only one patient had grade IV acute GVHD. In summary, formulation of a conditioning protocol that balances engraftment and recurrence of primary disease on the backdrop of a newly reconstituted immune system is problematic. These data indicate that using the patient’s body weight in the determination of an optimal Alemtuzumab dose is a more reasonable approach to developing and standardizing RIC protocols with this drug.
Patients and Methods: Between 10/04 and 6/06, 24 patients (pts) with high risk AML or refractory hematologic malignancies underwent NST using a modification of our original Pt-TBI regimen. The median age was 60 years. The median number of prior therapies was 2 (range 0-6). Diseases transplanted included acute lymphoblastic leukemia (n=3), myelodysplastic syndrome (n=2), acute myelogenous leukemia (n=8), chronic lymphocytic leukemia (n=3), indolent non-Hodgkin’s lymphoma (n=2), mantle cell lymphoma (n=1). Conditioning consisted of Pentostatin 4 mg/m2 daily on day -10, -9, and -8, followed by 200 cGy TBI on day -1. Post-grafting immunosuppression consisted of cyclosporine/mycophenolate mofetil. Results: Transplantation was performed using mobilized progenitor cells from matched related (n=8) or unrelated (n=16) donors. Death prior to 100 days post transplant occurred in 4 unrelated donor transplants. The median nadir values for hemoglobin, neutrophil count and platelet count were 8.9 g/dl (range 7.6-13.7), 300/mm3 (range 0-1900), and 63/mm3 (range 9-165) respectively. Primary graft failure/autologous recovery occurred in one patient with mantle cell lymphoma. The median values for CD3+ cells and WBC at day 28 were 85% and 90% donor cells respectively. The analogous median values at day 70 were 85% and 100% respectively. One pt with a myeloproliferative disorder and thalidomide as his only prior therapy experienced late graft failure despite donor lymphocyte infusions. The cumulative incidence of grade II-IV acute graft-versus-host disease was approximately 54% (14% in related versus 68% in unrelated donors, P=0.08). The probability of extensive chronic graft-versus-host disease in patients surviving beyond 100 days is 38%. The cumulative incidence of relapse at one year post transplant is 43%. The one year probabilities of event-free and overall survival are 41% and 61% respectively. Conclusions: This modification of our original Pt-TBI regimen continues to demonstrate fairly minimal regimen related toxicity, although as expected hematologic toxicity appears to be more significant than with our prior day -21 Pentostatin regimen. Graft versus host disease continues to be a major cause of morbidity/mortality, particularly in unrelated donor transplants. Further studies will concentrate on attempting to decrease the incidence of acute and chronic graft versus host disease through the use of T-cell depletion with in vitro alemtuzumab.

229 UMIBLICAL CORD BLOOD TRANSPLANTATION FOR ADULT PATIENTS WITH CHRONIC MYELOID LEUKAEMIA

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Chronic myelogenous leukemia (CML) is primarily treated with HSCT until imatinib mesylate was shown to be effective and safe for patients with chronic phase CML. However, patients who fail imatinib therapy due to disease progression or drug intolerance still require HSCT. UMBilical cord blood (UCB) has been an increasingly used source of hematopoietic stem cells for transplantation (HCT) of patients with hematologic malignancies who lack a suitable sibling donor. We report here on 20 adult patients who underwent UCB transplantation (UCBT) for Ph+ CML at the University of Minnesota between 1998 and 2005. Patient received myeloablative (MA, n=12) or nonmyeloablative (NMA, n=8) conditioning. The median age was 46 y (r: 18-58), 12 (60%) were male, and median weight was 78 kg (r: 57-103), and 13 (65%) were CMV positive. The MA conditioning was Bu/Cy (n=2) Cy/TBI z ATG (n=4), or Cy/Fludarabine(Flu)/TBI (n=6). The NMA conditioning was Bu/ Flu/TBI (n=2) or Cy/Flu/TBI: ATG (n=6). Posttransplantation immunosuppression was CsA alone (n=1), CsA/methylprednisolone (MP) (n=5), or CsA/MMF (n=14). Eleven patients (55%) receive a double UCB graft. The highest HLA disparity of UCB units was 4/6 (r: 0-13), 5/6 (n=5), and 6/6 (n=2). Six patients (30%) were in first chronic phase (CP1) and 14 (70%) were in accelerated phase (AP) CML. The median TNC dose infused was 2.9 x 10^7/kg (r:1.2-5.3) and median CD3 dose infused was 1.0 x 10^7/kg (r: 0.5-7.6). The median time from diagnosis to transplant was 24.5 months (r: 6.7-118.8), and the median follow-up of surviving patients was 2.9 yrs (r: 0.7-7.0). There were no failures of neutrophil engraftment.

In the MA setting median time to neutrophil engraftment was 21d (r:13-33), grade II-IV acute GVHD was 58% (95%CI, 28-88%), 1-yr transplant related mortality (TRM) 41% (95%CI, 6-71), 2-yr relapse rate 10% (95%CI, 0-26), and overall survival 58% (95%CI, 30-86). In the NMA setting median time to neutrophil engraftment was 13d (r:5-32), grade II-IV acute GVHD was 63% (95%CI, 28-98%), 1-yr transplant related mortality (TRM) 38% (95%CI, 6-70), 2-yr relapse rate 13% (95%CI, 0-34), and overall survival 50% (95%CI, 15-85). There was no statistically significant difference between MA and NMA conditioning regimens on all outcomes. In this report we show that UCB appears to be a safe and effective HSC for transplantation of patients with CML.

230 FLUDARABINE/FULL DOSE I.V. BUSULFAN CONDITIONING REGIMEN IN ALLOGENEIC PBSC TRANSPLANTATION FOR HIGH RISK PATIENTS

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Fludarabine/ full dose busulfan (FluBu) conditioning regimen causes moderate extrahematologic toxicity and low rates of acute graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplantation (HSCT).

In this study we utilized this regimen in 21 adult patients with hematologic malignancies, including 15 patients (71%) at high risk of relapse (8 acute leukemia in relapse, 3 NHL in relapse, 1 NHL in CR2, 1 myelodysplasia in transformation, 2 CML-AP resistant to imatinib) and 6 patients at standard risk (3 AML in CR1, 2 CML-CP resistant to imatinib). All patients were prepared with fludarabine (30 or mg/m2/day) for 4 days from d-9 to d-6 and i.v. busulfan (3.2 mg/kg/day) for 4 days from d-5 to d-2, and received an HLA matched related (n=14) or unrelated (n=7) peripheral blood stem cell (PBSC) transplant. Mean number of CD34+ cells infused was 7.3±4.0 x 10^6/kg. Thymoglobulin was added to the preparative regimen on d -3 to d-1 in 9 patients, including those receiving an unrelated HSCT. Acute GVHD prophylaxis included standard tacrolimus and methylprednisolone on d1, d3, d6 and d11. All patients fully engrafted but one ALL patient transplanted in relapse who recovered with leukemic blasts. Median times to ANC 0.5 x 10^9/L and platelet 20 x 10^9/L were 15d (range: 18-24) and 134 (range: 20-24), respectively. Acute GVHD grade II-IV was observed in 24% of the patients (grade III-IV 18%) and chronic GVHD in 9 of 14 evaluable patients (64%). Of 21 patients, 8 died in full relapse with bacterial or fungal infection and 2 for acute GVHD grade III and fungal infection. Median time to relapse after HSCT was 72d (range: 18-328). At a median follow-up of 447 d (range: 120-1196) for patients who are alive, the overall survival (OS) and event-free survival (EFS) are 52% and 48%, respectively. In the group at high risk the OS and EFS are both 33% at 447 d median follow-up (range: 147-834).

FluBu conditioning regimen, besides causing low transplant-related morbidity and mortality, is also effective in high risk patients receiving an allogeneic PBSC transplant from related or unrelated donors.

231 HAPLOIDENTICAL NON-MYOELoblATIVE HEMATOPOIETIC TRANSPLANTATION WITH SIROLIMUS BASED IMMUNOSUPPRESSION YIELDS RELIABLE ENGRAFTMENT AND MAY RESULT IN LONG TERM SURVIVAL

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Timely availability of matched donors limits allo-hematopoietic transplant (HCT) options for many otherwise suitable patients. We have explored sirolimus (rapamycin) based immuno-