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A PILOT STUDY EVALUATING THE SAFETY AND EFFICACY OF AMD3100 FOR THE MOBILIZATION AND TRANSPLANTATION OF HLA-MATCHED SIBLING DONOR HEMATOPOIETIC STEM CELLS IN PATIENTS WITH ADVANCED HEMATOLOGICAL MALIGNANCIES

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We are studying an antagonist of the SDF-1/CXCR4 interaction, AMD3100, as a single agent to procure mobilized blood from allogeneic donors. Eleven HLA identical siblings received one or two doses of AMD3100 at 240 μg/kg subcutaneously followed in four hours by leukapheresis (LP). After successful collection and a one week washout period, the same donors were remobilized using a standard G-CSF dose and schedule. AMD3100 administration resulted in a median 7-fold increase in peripheral CD34+ cell count from baseline within 4-6 hours compared to 21-fold after five days of G-CSF. Nine of eleven donors mobilized following AMD3100 collected at least 1.9×10^6 CD34+ cells/kg recipient weight following 1 (n = 5) or 2 (n = 4) LP procedures. Allografts mobilized following AMD3100 contained less CD34+ cells but proportionately greater numbers of T-,B-, and NK-cells compared to G-CSF allografts. AMD3100 was well tolerated and no donors experienced any greater than grade 1 toxicity. One donor could not tolerate apheresis and was taken off study. Eight patients have been transplanted using the AMD3100 mobilized allografts. Two patients did not receive allografts due to progressive disease. The median age of the recipients was 45 years (range 32-53). Three had AML, one ALL, one CLL, one accelerated CML, and two non-Hodgkin's lymphoma. With a median follow-up of 290 days (range 75 to 486 days), all eight evaluable pts have engrafted neutrophils >500/μl at a median of 10 days (range 8-13) and platelets >20000/μl at a median of 19 days (range 15-25). Acute GVHD prophylaxis employed single agent cyclosporine only. One of eight patients to date has experienced grade 2-4 acute GVHD, and that pt expired due to refractory GVHD. Two of five evaluable patients have experienced extensive chronic GVHD requiring immunosuppressive therapy. All pts achieved early full donor chimerism of peripheral T- and myeloid cell compartments which has been sustained. Seven of the eight pts currently survive progression free with full trilineage hematopoiesis. In summary, grafts mobilized following AMD3100 differ from G-CSF mobilized allografts in the content of CD34+ and immune effector cells yet appear to reconstitute hematopoiesis similarly. The risk of acute GVHD does not seem to be increased despite the transplantation of higher T-cell doses. It appears that a chemokine antagonist given alone can safely and rapidly induce the mobilization of a functionally competent hematopoietic allograft.

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PHASE 2 STUDY OF TARGETED INTRAVENOUS BUSULFAN (IV BU) COMBINED WITH FRACTIONATED TOTAL BODY IRRADIATION (FTBI) AND ETOPOSIDE (VP-16) AS PREPARATIVE REGIMEN FOR ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANT (PBSCT) FOR PATIENTS WITH POOR RISK LEUKEMIA

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Between 3/2000 and 11/2004 30 patients with high risk of relapse post myeloablative SCT received an augmented conditioning regimen consisting of IVBU followed by FTBI 1200 cGy in 10 fractions over 4 days and VP-16 30 mg/kg. BU was administered at 18 mg/m^2 targeted for an AUC of 700-900 μM · min every 6 hours × 16 doses. Based on pharmacokinetics, doses for each patient could be adjusted up to a maximum of 32 mg/m^2 to achieved targeted AUC. 24 patients had active leukemia (AML 9 induction failure (IF), 7 relapse, 1 untreated MDS evolved to AML, ALL 4 IF and 3 relapse) while 6 patients had remission marrows at time of SCT (3 AML with poor risk cytogenetics and 3 with prior MDS evolved to AML). All patients received PBSC from HLA matched sibling donors. GVHD prophylaxis was CSA and MMF. With a median follow-up of 35 months (3.3, 55.3), the 2 year probabilities of overall and event free survival were 63% (95% CI 38-82%) and 64% (95% CI 39-83%) for patients with active AML and 50% (95% CI 17-83%) and 33% (95% CI 8-73%), respectively, for ALL. The probability of relapse for AML and ALL with active disease was 13% (95% CI 3-40%) and 58% (95% CI 19-89%) respectively. The 2 year probability of both overall and event free survival was 83% (95% CI 37-98%) for patients with AML in remission at time of SCT with no relapses to date. The 100 day non relapse mortality was 7% (95% CI 2-23%) and overall non relapse mortality assessed at date of analysis was 30%. Grade 2-4 acute GVHD occurred in 60%; limited chronic GVHD was present in 36% and extensive in 56% of eligible patients. This regimen was very effective in reducing relapse in patients both with high risk myeloid malignancy in remission and relapse at time of SCT. It was less effective in reducing relapse in patients with ALL transplanted with active disease.

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PENTOSTATIN IN REFRACTORY ACUTE AND CHRONIC GVHD. A SINGLE CENTER EXPERIENCE

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Graft-versus-host disease (GVHD) is a major complication of allogeneic bone marrow transplantation. In refractory acute (aGVHD) and chronic (cGVHD) GVHD, mortality is very high. Pentostatin, a potent inhibitor of adenosine deaminase, induces lymphocyte apoptosis and may be useful in the treatment of this condition. **Patients and Methods:** We have conducted a prospective study of pentostatin in patients with refractory acute and cGVHD. Ten patients were enrolled in the analysis, 7 with refractory aGVHD (2 skin, 5 gut and 2 liver aGVHD with a grade 2 and 3 in 2 and 5 patients, respectively) and 3 with refractory extensive cGVHD (2 skin, 1 gut and 1 sinew as organs involved). Pentostatin dose was 1.5-2.5 mg/m^2/d by intravenous injection for 3 days among seven patients diagnosed of refractory aGVHD (one patient required an additional dose on day +14 and +28) and 2.5 mg/m^2/week during 4 weeks and them 4 mg/m^2/2 weeks regarding 3 refractory chronic GVHD patients. **Results:** Regarding refractory aGVHD, response rate was 79%, with 2 (28.5%) out of 7 patients in complete response (CR) and 3 (43%) out of 7 patients in partial response (PR). Two (28.5%) out of 7 aGVHD patients did not respond. Regarding refractory cGVHD all patients included reached responses to pentostatin, all of them PR. Only 2 out of 10 patients receiving pentostatin as refractory GVHD treatment died due to GVHD complications. No more incidence of late infections and other complications were observed in this subgroup of patients, the drug was well tolerated. **Conclusion:** Pentostatin has activity in patients with refractory acute and chronic GVHD without important side effects.

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RENAL DYSFUNCTION AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: RISK FACTORS AND OUTCOME

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Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can potentially cure various malignant and non-malignant hematological disorders. However, allo-HSCT is associated with a high risk of treatment-related mortality. Renal dysfunction is one of frequent, life-threatening treatment-related toxicities. In this study, we evaluated the incidence and risk factors