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TRANSPLANTATION AFTER REDUCED INTENSITY CONDITIONING IN PATIENTS WITH ACUTE MYELOID LEUKAEMIA IN SWEDEN

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Thirty-seven patients, median age 58 yrs (8–69), with AML undergoing allologeneic stem cell transplantation (SCT) after reduced intensity conditioning (RIC) at three Swedish SCT centers were analyzed retrospectively. All except six patients received RIC due to high age or co-morbidity. Twenty-three patients were transplanted in first remission and 14 with more advanced disease. Donors were siblings (n = 22) or matched unrelated donors (MUD, n = 15). Conditioning was fludarabine + busulfan ± anti-thymocyte globulin (n = 32), fludarabine + treosulfan (n = 3) or fludarabine + 2 Gy total body irradiation (n = 2). As stem cell source bone marrow was used in six patients and peripheral blood stem cells in 31. All patients engrafted. At a median follow-up of 15 months (3–63) acute graft-versus-host disease (GVHD) grade 0/1/II/III/IV developed in 22/77/5/0/1 recipients, respectively. Limited chronic GVHD was seen in five and extensive in seven patients among 33 patients at risk. Donor lymphocyte infusions were given to 16 patients during minimal residual disease or relapse. In total 15 patients relapsed and 12 of them died. Only one patient died from a transplant related cause, acute GVHD. Kaplan-Meier probability for survival at 1yr is 79% and for leukemia-free survival (LFS) 68%. Among 23 patients, age 53 yrs (8–69) transplanted in first remission with 16 sibling donors and seven MUD, eight relapsed (35%) and five of them died. There was no transplant-related mortality (TRM). In total 15 patients relapsed and 12 of them died. Only one patient died from a transplant related cause, acute GVHD. Kaplan-Meier probability for survival and LFS at 1yr is 86% and 72%, respectively, for patients receiving transplantation in first remission. Reduced intensity conditioning with a fludarabine containing regimen and transplantation with a sibling or MUD gives a low TRM even in older patients with AML. Survival is encouraging but leukemia relapse remains a major problem. Randomized or controlled prospective trials comparing RIC with conventional conditioning for younger patients and trials comparing RIC to chemotherapy for elderly patients are urgently warranted.

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ABSENCE OF PRIOR INFECTIONS IS STRONGEST PREDICTOR FOR SURVIVAL AFTER ALTERNATE DONOR HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH FANCONI ANEMIA


Alternate donor hematopoietic cell transplantation (HCT) in patients with Fanconi anemia (FA) has been limited by excessive rates of graft failure (GF). In an attempt to improve results, a phase I-II prospective trial was conducted in which fludarabine (FLU, 140 mg/m²) was added to the standard regimen of cyclophosphamide (CY, 40 mg/kg), total body irradiation (TBI, 450 cGy) and ATG (50 mg/kg). Between April 1999 and August 2003, 45 patients with FA (AA [n = 29], early MDS [n = 15], RAEB/AML (n = 3) underwent T cell depleted bone marrow (BM; n = 38) or umbilical cord blood transplantation (UCB; n = 7) from alternate donors (HLA-mismatched related or unrelated), and were followed for a median of 2 years (range, 1.5–3.5 years). Median age was 10 years (range, 1.9–33.5 years). Median BM median CD34+ cells/kg and CD3+ cells/kg infused was 2.23 × 10⁶ and 1.0 × 10⁶. Median UCB CD34+ cells/kg and CD3+ cells/kg infused was 3.3 × 10⁶ and 1.7 × 10⁷. Probability of primary neutrophil engraftment was 98% (95% CI 93–100%), a superior outcome compared to that observed with our previous CY/TBI/ATG regimen (65% [95% CI, 42–82%]; p < .01). Neutrophil engraftment was achieved in 33/35 patients (94%), with a potential median time to neutrophil engraftment in 11 days (range, 9–35 days) in BM recipients and 14 days (range 9–36 days) in UCB recipients. Two patients died from RRT. Probability of grade II–IV acute GVHD was 18% (95% CI 9–33%), and grade III–IV GVHD 13% (95% CI 3–23%). Probability of 1 year survival was 55% (95% CI 41–70%). In univariate analysis, high risk patient characteristics associated with poor survival are age ≥18 years, presence of RAEB/AML, and history of major infection (fungal infection or gram negative sepsis) prior to HCT. In multivariate analysis, patients with a history of severe infections prior to HCT had a 3.2 fold increased risk of mortality (95% CI 1.3–8.0; P = .01). In summary, addition of FLU to CY, TBI and ATG is associated with superior engraftment in FA patients undergoing alternate donor HCT. Rates of GVHD are low which may reduce the risk of late malignancies. On the basis of these results, FLU based preparative therapies should be considered part of the standard of care in FA patients undergoing HCT. In addition, patients should be transplanted earlier, before the development of serious infections.

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INFLUENCE OF KILLER IMMUNOGLOBULIN-LIKE RECEPTOR (KIR) MATCHING ON ACHIEVEMENT OF T-CELL (CD3+) COMPLETE DONOR CHIMERISM (CDC) IN RELATIVELY IMMUNOCOMPROMISED ALLOGENEIC STEM CELL TRANSPLANTATION (NMHSCT)


The interaction of KIRs with target cell HLA class I molecules regulates the reactivity of NK cells and some T cell populations. KIR interactions have been suggested to influence outcomes of haploidentical and HLA-identical allologeneic HSCT. However, in NMHSCT when both donor and recipient hematopoiesis may coexist the effect of KIR interactions on outcomes is not well known. We analyzed 31 patients undergoing related donor NMHSCT at our institution from 5/00–11/03. Diagnoses included 4 AML, 1 CLL, 4 CML, 2 Hodgkin’s lymphoma, 4 MDS, 2 myelo-fibrosis, 5 myeloma, 5 NHL, and 4 renal cell carcinoma. All patients received a preparative regimen of fludarabine 30 mg/m²/day on days −5, −4, −3, and total body irradiation 200 cGy on day −1. The median age was 51 yrs (range, 21–63 yrs). The median CD34+ and CD3+ cell doses infused were 6.64 × 10⁶/kg and 3.92 × 10⁹/kg, respectively. CDC was defined as achievement of >95% DNA of donor origin in the T-cell (CD3+) enriched fractions. Twenty-three (74%) of patients achieved CDC and 15 (65%) of these had a KIR mismatch, suggesting that KIR matching per se did not correlate with CDC achievement. However, when patient inhibitory KIR and donor ligand matches were considered an association with CDC was observed. HLA KIR ligands were categorized as: 1) HLA-Cw groups C1 (+ or −); 2) C2 (+ or −); 3) HLA-Bw4 (+ or −) and 4) HLA-A3 or A11 (+ or −) (as reviewed by Farag et al in Blood 100:1935, 2002). Patient KIR genotype and donor HLA KIR ligands were used to generate an inhibitory KIR score from 1 to 4 for the potential number of inhibitory KIRs engaged. When the patients were analyzed 4 had a score of 1, 16 had a score of 2, 10 had a score of 3 and 1 had a score of 4. The Kaplan-Meier method was used to estimate the achievement of CDC. As compared with those patients with a score of ≥1 the patients with a score of 1 were less likely to achieve CDC (p = .05). Thus, patients with lower inhibitory KIR scores may have more active anti-donor effector cells (NK cells and T cell subsets) that may reduce donor cell chimerism. Conversely, those with higher inhibitory KIR scores may have less active populations and be less likely to achieve CDC. However, further investigation of larger patient populations is clearly warranted.

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REGIMEN RELATED TOXICITY AFTER THIOTEPA, CYCLOPHOSPHAMIDE AND INTRAVENOUS BUSULFAN AS CONDITIONING FOR ALLOGENEIC STEM CELL TRANSPLANTATION

**Objectives:** To evaluate veno-occlusive disease of the liver (VOD) and non-hepatic regimen related toxicity (RRT) in patients receiving variable intensity conditioning (V-ALLOT) after conditioning with BU/C+ plus thiotepa, using an intravenous (IV) formulation of busulfan. **Patients and Methods:** Twenty-six adult patients (20 men and 6 women; median age 32 years) underwent allo-SCT between 2002 and 2004 after conditioning with thiotepa (10 mg/kg), CY (120 mg/kg) and IV BU (9.6 mg/kg). Fourteen patients received anti-thymocyte globulin (ATG). Diagnoses were acute leukemia or myelodysplastic syndrome (20 patients), chronic myeloid leukemia (5 patients) and other diseases (3 patients). Ten patients received grafts from HLA-identical siblings and 16 from alternative donors (cord blood in 12 cases). GVHD prophylaxis consisted of cyclosporin A (CsA) and prednisone in 16 cases, CsA (10 mg/kg), CY (120 mg/kg) and IV BU (9.6 mg/kg). Sixteen patients (62%) developed non-hepatic RRT that were greater than grade 1 in 13 cases (50%). The median maximum levels of AST and total bilirubin were 72 U/L and total bilirubin levels were observed in 19 patients (73%). The median maximum levels of AST and total bilirubin were 72 U/L and 2 mg/dL, respectively. Sixteen patients (62%) developed non-hepatic RRT that was greater than grade 1 in 13 cases (50%). The VOD rate was not significantly different when comparing patients receiving BU/BU and oral BU (15% vs. 6%; P = 0.2). However, non-hepatic RRT was more frequent among patients receiving oral BU (92% vs. 61%; P = 0.05). The use of IV BU seems to reduce non-hepatic toxicity after conditioning with BU/C+ plus thiotepa for allo-SCT.

**LESS TRANSPLANT-RELATED MORTALITY WITH VARIABLE INTENSITY CONDITIONING THAN NON-MYELOABLATIVE CONDITIONING IN UNRELATED AND RELATED ADULT ALLOGENEIC TRANSPLANT RECIPIENTS**

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For the past four years, our adult allogeneic transplant program has implemented an alternative approach to standard regimens conditioning, the use of non-myeloablative “mini” conditioning and variable intensity conditioning. We now report a retrospective comparison of relapse, day +100 and one-year survival, engraftment and grades II-IV and III-IV acute GVHD in unrelated as well as related recipients in these two preparative regimen groups. Patients with a variety of malignancies were not randomized to receive either non-myeloablative (Group 1) or variable intensity (Group 2) conditioning. Twenty patients with a median age of 49 (range 27–64, Group 1) and 18 patients also with a median age of 49 (range 24–58, Group 2) received either marrow or peripheral blood stem cells, usually with a 6/6 match grade. One recipient in Group 2 received a cord blood transplant (4/6 match). Group 1 regimen consisted of four protocols: fludarabine 30 mg/m² × 3 d and TBI 200 cGy; fludarabine × 6 d, busulfan 4 mg/kg × 2 d and ATG 40 mg/kg × 4 d; fludarabine × 5 d and cyclophosphamide 60 mg/kg × 2 d; fludarabine, cyclophosphamide, ATG. Group 2 regimen consisted of Campath 20 mg/d either 5 or 3 days, fludarabine × 5 d and melphalan 140 mg/m² × 1 d. GVHD prophylaxis was the same in both groups (standard dose CsA and MMF). All patients received an adequate CD34+ cell dose and none of the products was manipulated. Relapse rate was 16% in Group 1 and 33% in Group 2. Day +100 survival and one-year survival were 55% and 25%, respectively, in Group 1 vs 69% and 42% in Group 2. Only one patient in Group 2 had acute GVHD grade IV. In Group 1, 6 patients had grades I-II and 7 had grades III-IV (39%). Graft failure occurred in four patients in Group 1, while no patients in Group 2 experienced it. We conclude, first, that in our program the application of variable intensity conditioning has been quite successful in unrelated transplant recipients, as well as in related. Second, significant treatment related mortality in the form of graft failure and acute GVHD occurred less frequently in recipients who received this conditioning than in those receiving non-myeloablative conditioning. This regimen requires some modification to enhance its tumoricidal properties; however, its treatment-related toxicity is minimal and allows us to offer this therapy to patients with co-morbid conditions and older age.

**REPLACEMENT DONOR PROGRAM: MORE THAN PROTECTING STEM CELL DONORS FROM MULTIPLE DONATIONS FOR DIFFERENT PATIENTS**

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Goal of DKMS’ Replacement Donor Program is to provide an alternative donor for search centers in case that a donor has completed a stem cell donation and is reserved for potential further donations for the same patient for 2 years. First intention is to provide a donor as long as possible for “his” patient afterwards the 2 year suspension. This would enable us to provide second or further stem cell donations if required for the one patient. Second intention is to protect the donor from requests for multiple patients. It could be observed several times that post-donation donors were of increased interest for search centers and were requested for confirmatory typing (CT) several times. Providing alternative donors would take off the burden from a single donor. Third intention is to fill up the gap in HLA-phenotypes when a donor is suspended from further donations for 2 years after donation and to increase the number of high resolution typed donors at DKMS. We think that donor centers like the DKMS have the responsibility to protect their donors from excessive demand by search centers. Forth intention is to provide an alternative donor for donors in actual workups in case that the donor in workup is unavailable for unpredictable reasons. As the search for the Replacement Donor starts with initiation of the workup it is very important that the full HLA-phenotype of the patient is available as early as possible. We perform up to 100 DRB1* intermediate resolution or up to 5 DRB/DOB1* high resolution typings with IDMs (CMV) on our own behalf for each donor at initiation of workup per own search to find a Replacement Donor. Own searches are repeated two times. Until October 2004, over 87000 HLA-DRB1* typings on intermediate and 8600 high resolution typings of HLA-DRB* and HLA-DQB1* were performed to provide Replacement Donors for more than 3200 donors. Replacement Donors could be found for 994 donors to date. We could not only find Replacement Donors but also improved the quality of our database. This is shown by the fact that over 3900 further requests (high resolution typing or confirmatory typing) and 340 workups could be observed out of the over 95000 “prospective” typings. Only a few (7) stem cell donors donated again for another patient since start of the project. In 5 cases a Replacement Donor could replace an unavailable donor while the workup was still in process. (DKMS performed over 3900 donations since start of this project in 2001).

**LONG-TERM OUTCOME AFTER MARROW TRANSPLANTATION FROM HLA-IDENTICAL SIBLING DONORS FOR ACQUIRED APLASTIC ANAEMIA USING CYCLOPHOSPHAMIDE AND IN-VIVO ANTI-CD52 MONOCLONAL ANTIBODIES**