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AN INSTITUTIONAL PERSPECTIVE ON THE EFFICACY OF DONOR LEUKOCYTE INFUSIONS FOR PATIENTS WITH POST-TRANSPLANT RELAPSE

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Patients with post-allogeneic HSCT disease relapse can be treated with salvage chemotherapy but are also candidates for immune suppression withdrawal and/or donor lymphocyte infusion (DLI).

A total of 237 adult patients experienced relapse of disease post-allogeneic transplant at our institution between 1995 and 2010. A retrospective institutional analysis was performed on the 52 patients who received DLI in that timeframe. The DLI product infusion doses ranged from 0.07 to 4.0 x 10^8 CD3+ cells.

CML patients had the most favorable DLI response rates with 78% (n = 7) in remission at 3 years. Patients with relapsed AML/MDS and lymphoid malignancies fared worse with 36% and 21% OS at 3 years respectively. OS was superior in patients in CR prior to DLI (45%) compared to those with active disease (5%) and for patients under the age of 50 (32% vs 21%). Three year OS was observed of 5% for patients who relapsed prior to day +100, 29% for relapse between day +100 and 1 year, and 59% for relapse after 1 year. Patients who developed GvHD prior to relapse had a 3 year OS of 35% vs 9% in patients without GvHD. Patients with post-DLI GvHD had a 39% OS vs 11% for patients without GvHD after DLI. No difference in post-DLI survival was noted with regards to pre-transplant disease status, cell dose or transplant conditioning.

CML patients respond well to DLI however in the TKI era, transplants for these patients are reserved for patients with TKI-resistant disease. In other patients, immune suppression withdrawal and DLI have limited efficacy for those who do not achieve CR post-relapse or who relapse within 3 months of transplant. These patients are in need of alternative treatment strategies.

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PRECONDITIONING WITH RAPAMYCIN AND CTLA4-Ig IN DOGS GIVEN DONOR ANTIGEN AND 1Gy TOTAL BODY IRRADIATION (TBI) BEFORE DOG-LEUKOCYTE-ANTIGEN (DLA)-IDENTICAL MARROW TRANSPLANTATION FAILED TO ASSURE SUSTAINED ENGRAFTMENT

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Stable engraftment of allogeneic, DLA-identical marrow can be achieved by conditioning dogs with a nonmyeloablative dose of 2 Gy TBI followed by a brief course of postgrafting immunosuppression with cyclosporine (CSP) and mycophenolate mofetil (MMF). However, when TBI dose was reduced to 1 Gy, CSP/MMF failed to control host-versus-graft (HVG) reactions, and grafts were uniformly rejected. CTLA4-Ig blocks T-cell costimulation through the B7:CD28 signaling pathway and induces T cell anergy. We used CTLA4-Ig concurrently with infusion of donor peripheral blood mononuclear cells (PMBC) to blunt activated recipient T cells before transplantation (Storb et al., Blood 94, p2523-2529, 1999). The regimen was effective in establishing stable mixed chimerism in ~67% of the animals. Rapamycin mediates immunosuppression by inhibiting both cytokine driven pathways and costimulatory signaling, and has been reported to act in synergy with CTLA4-Ig for tolerance induction in solid organ transplantation. In the current study we asked weather adding rapamycin to CTLA4-Ig before transplantation would improve our earlier results and further aid in sustaining engraftment. Accordingly, six recipient dogs were given CTLA4-Ig on days -7 to -1 and rapamycin on days -6 to -2, with concurrent intravenous administration of 10^6 (n = 2) or 10 x 10^6 (n = 4) PBMC from their respective DLA-identical donors from days -7 to -1 before 1Gy TBI, and CSP/MMF after marrow transplantation. The regimen was well tolerated and all 6 dogs showed initial allogeneic engraftment. Only one dog showed persistent mixed chimerism for more than 34 weeks while 5 dogs rejected their allografts between 8 to 12 weeks followed by autologous marrow recovery, a timing that was comparable to that in control dogs. These findings illustrate the difficulty to achieve uniform sustained engraftment in DLA-identical dogs using pharmacological immunosuppression in combination with 1 Gy TBI.

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EVALUATION OF HCT-CI COMORBIDITY SCORES AND ALLOGENEIC TRANSPLANT OUTCOME OF YOUNG ADULTS AFTER MYELOABLATIVE CONDITIONING WITH FLUDARABINE AND BUSULFAN +/- TBI MALIGNANCIES

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We have previously reported an association between HCT-CI scores 1 and more and increased TRM in allogeneic patients older than 50 years. Now, we have analyzed HST-CI in 411 consecutive younger patients with hematologic malignancy transplanted between 1999 and 2008.

Two hundred and thirty four patients had low-risk disease (AL CR 1 or 2, CML CP), all others were considered high-risk. The myeloablative regimen included fludarabine 250mg/m2 and intravenous busulfan 12.8mg/kg, 203 patients (49.4%) received additional TBI (400cGy). CsA, MTX and Thymoglobulin (4.5mg/kg) were given for GVHD prophylaxis. Donors were matched siblings in 208 cases (50.6%); bone marrow, peripheral and umbilical blood were used in 73 (17.8%), 327 (79.5%) and 11 (2.7%) patients, respectively. Median age was 40 years (range 16-50) and median follow-up was 38 months (1-148 mo).

HCT-CI scores were 0 in 287 (70%), 1 in 68 (16.5%), 2 in 27 (6.5%), 3 in 22 (5.3%) and 4 in 7 (1.7%) patients. TRM of patients with score 0, 1, 2, or 3+ was 13%, 12%, 33% and 10% at 1 year ($p = 0.022$) and 14%, 15%, 33% and 14% at 3 years ($p = 0.074$), respectively.

Multivariate analysis only demonstrated an association of TRM with HCT-CI score 2 (SHR = 2.75; 95%CI: 1.27-5.98; $p = 0.01$). Three other factors were also significant: CMV status (SHR = 2.02; 95%CI 1.1-3.71; $p = 0.024$), alternative donor (SHR = 1.95; 95%CI 1.17-3.25; $p = 0.010$) and age (SHR = 1.03 per year; 95% CI 1.0-1.07; $p = 0.042$).

Conclusions:

1. In contrast to older patients, the TRM of the combined group of patients given a score of 1 and more was no different from those with a score of 0.
2. Patients with score of 2 had significantly higher TRM.
3. Scores of 3 and 4 mostly represented previous malignancies and pulmonary disease and did not seem to influence TRM in these patients.
4. Increasing HCT-CI scores did not accurately reflect increasing TRM in young patients treated with this regimen.

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PLATELET REFRACTORINESS IS ASSOCIATED WITH DELAYED PLATELET ENGRAFTMENT AND INCREASED GRAFT VERSUS HOST DISEASE FOLLOWING PERIPHERAL BLOOD OR BONE MARROW DERIVED STEM CELL TRANSPLANTATION

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Background: Platelets (PLT) play a role in innate and adaptive immunity and possess pro-inflammatory, as well as pro-thrombotic properties. PLT transfusion is associated with transfusion immunomodulation, resulting in alteration of the recipients' immune function. Multiple PLT transfusions may result in alloimmunization leading to refractoriness and greater transfusion requirements. PLT refractoriness is relatively more common in patients undergoing stem cell transplantation (SCT) for hematologic malignancies. We analyzed the clinical outcomes in SCT patients with PLT refractoriness.