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CD34+ CELL DOSE AND FULL DONOR CHIMERISM AT DAY +100 IS ASSOCIATED WITH SURVIVAL IN PATIENTS WHO RECEIVED REDUCED-INTENSITY CONDITIONING (RIC) WITH FLUDARABINE/MELPHALAN PRIOR TO ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR HEMATOLOGIC MALIGNANCIES

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Nonmyeloablative, reduced-intensity conditioning extends allogeneic HSCT as a therapeutic option for elderly or frail patients with relapsed, refractory, or other high-risk hematologic malignancies. We reviewed the medical records of the first 50 patients (34 M, 16 F) at our institution who underwent fludarabine/melphalan RIC from 9/00 to 9/07 to determine factors associated with survival. The median age at transplant was 53.5 years (range 20–67 years). Most patients received HSCT for myeloid malignancies (18 AML, 11 MDS, 8 NHL, 7 MM, 2 each CML and CLL, and 1 each AMM and HL), were in remission at transplant (16 in CR, 9 in PR, 13 relapsed/refractory, and 12 untreated), received stem cells from a matched related versus unrelated donor (37 vs. 13 pts), and were a full 6/6 for sibling donors or 10/10 antigen match for URD (46 versus 4 patients with a single antigen mismatch). Half (25 pts) had received prior HSCT, and 3 had prior chemotherapy for solid tumors. 28% of patients experienced grade 3–4 acute GVHD, and 46% experienced chronic GVHD (38% extensive). 26 of 50 pts have died, 5 from relapsed disease. Only one of the deaths before day +100 was due to relapsed disease, and treatment-related mortality (TRM) at day +100 was 26% (13 pts). 24 patients (48%) are alive after a median of 24 months of follow up. Factors associated with survival on univariate analysis included CD34+ cell dose greater than the median of 5.5×10^6/L ($p = 0.0463$), day +100 disease remission status, ($p<0.0001$), day +100 chimerism status ($p<0.0001$), any chronic GVHD ($p = 0.0005$), and favorable/standard versus poor risk karyotype for myeloid malignancies ($p = 0.0149$). On multivariate analysis, CD34 cell dose greater than 5.5×10^6/L (RR 0.19, 95% CI 0.0389 – 0.7222, $p = 0.0136$) and full donor chimerism at day +100 (RR 0.05, 95% CI 0.0099 – 0.2327, $p = 0.0002$) remained an independent prognostic factors. Achievement of full donor chimerism was not related to CD34 cell dose ($p = 0.46$). In our series, achievement of full donor chimerism at day +100 is associated with 70% 2 year survival, a favorable outcome in this high risk group of patients. While the infused CD34 cell dose can occasionally be a modifiable variable, whether any other host and/or graft factors could be modified to promote the establishment of full chimerism and improve survival remains largely unknown and merits confirmation in larger series.

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CLINICOPATHOLOGICAL MANIFESTATIONS AND TREATMENT OF INTESTINAL TRANSPLANT-ASSOCIATED MICROANGIOPATHY (I-TAM)

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Background: Severe diarrhea is a life-threatening complication after allogeneic hematopoietic stem-cell transplantation. Graft-versus-host disease (GVHD) has been thought as its major cause, but diarrhea is often refractory to treatment even after the resolution of skin GVHD. We previously reported that intestinal transplant-associated microangiopathy (i-TAM) complicated such patients. To clarify more detailed clinicopathological manifestations and treatment of i-TAM, we conducted a retrospective multicenter study.

Design and Methods: From 1997 to 2006, 87 of 886 patients with diarrhea after transplantation received colonoscopic biopsy. I-TAM, GVHD and cytomegalovirus colitis were distinguished histopathologically.

Results: The median duration from transplantation to the onset of diarrhea was 32 days (range: 9–130 days), and that from the onset of diarrhea to biopsy was 12 days (range: 0–74 days). The median maximal amount of diarrhea was 2 L/day (range: 130–5600 ml/day). Histopathological diagnosis included i-TAM (n = 80), GVHD (n = 26), cytomegalovirus colitis (n = 17) and non-specific (n = 2) with overlapping. Among 80 patients with i-TAM, abdominal pain was a major symptom, and only 10 patients fulfilled the proposed criteria for systemic TAM. Nonrelapse mortality (NRM) among patients without resolution of diarrhea was 72% and i-TAM comprised 57% of NRM. NRM was 25% among patients without intensified immunosuppression, but was 52%, 79% and 100% among those with intensified immunosuppression before diarrhea, after diarrhea, and before and after diarrhea, respectively.

Conclusions: I-TAM is a major complication presenting massive refractory diarrhea and abdominal pain, which causes NRM. Avoiding intensified immunosuppression which damages vascular endothelium may improve transplant outcome, and further prospective trials are warranted.

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CONDITIONING WITH CLOFARABINE AND BUSULFAN X 4 (CLOBU4) FOR NON-REMISSION HEMATOLOGIC MALIGNANCIES INCLUDING AML IS WELL TOLERATED, FACILITATES SECURE ENGRAFTMENT, AND EXHIBITS SIGNIFICANT ANTI-TUMOR ACTIVITY

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Background: Combining fludarabine with myeloablative doses of busulfan (FluBu4) has shown reduced toxicity when compared to other myeloablative regimens. We replaced fludarabine with clofarabine, a purine antimetabolite with potent anti-leukemia properties, in a phase I/II trial of Clofarabine-Busulfan × 4 (CloBu4) in pts with refractory hematologic malignancies not in remission at the time of allogeneic hematopoetic stem cell transplant (HSCT).

Methods: Busulfan was administered once daily at 3.2 mg/kg IV x 4d (days -5 to -2) and clofarabine once daily at 20, 30 or 40 mg/m^2 IV x 5d (days -6 to -2). Pts received dexamethasone 12 mg IV on the days of clofarabine. GVHD prophylaxis was tacrolimus/MMF in all but one patient.

Results: Of 23 pts enrolled, 22 were evaluable for toxicity/engraftment, and 21 for response (≥ day 30). One patient withdrew prior to conditioning. Diseases are AML (n = 14), ALL (n = 3), CLL (n = 2), NHL (n = 2), and MM (n = 1). Six pts received prior stem cell transplantation (2 auto; 4 allo). Clofarabine dose levels were: 20 mg/m2 (n = 6), 30 mg/m2 (n = 15) and 40 mg/m2 (n = 1). The median age was 53 years (range 13–68). Donors were related (n = 10) or unrelated volunteers (n = 12). CloBu4 was generally well tolerated. Grade 3–4 toxicities attributable to the conditioning regimen included: transient liver enzyme abnormalities (9/22), transient hypoxia (5/22), hypertension (2/22), and seizure (1/22). Hypersensitivity to clofarabine occurred in one patient however subsequent doses were tolerated with additional dexamethasone. Also noted were ascites (n = 2) in the first post-transplant month with liver biopsy findings in one pt suggestive of veno-occlusive disease (VOD). Both patients were at increased risk for hepatic complications (pre-transplant liver damage, splenomegaly from preceding myelofibrosis). To date, all patients have successfully engrafted. Acute GVHD (≥ grade 2) developed in 2/21 pts (10%) and was fatal in one case. Thusfar, 16/21(76%) pts achieved CR on day 30 (11/13 pts with AML) and the 1 year survival is 68% with a median follow up of 6 months.

Conclusion: Early results show clofarabine is well tolerated when administered with full dose busulfan in high risk HSCT pts. All pts engrafted rapidly, and this combination shows promising anti-tumor activity in very high risk hematologic malignancies. The trial continues to accrue patients and updated results will be presented at the meeting.