285
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 ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR HEMATOLOGIC MALIGNENCIES


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 match/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 graft-versus-host disease (68% of patients with at least one case). Factors associated with survival on univariate analysis included CD34+ cell dose greater than the median of $5 \times 10^7$/L (p = 0.0463), age $> 60$ years (p = 0.0016), 1 year survival (p = 0.0494), and full donor chimerism at day +100 (p = 0.0085), and favorable standard versus poor karyotype for myeloid malignancies (p = 0.0149). On multivariable analysis, CD34+ cell dose greater than $5 \times 10^7$/L (RR 0.19, 95% CI 0.0389–0.7222, p = 0.0149) and full donor chimerism at day +100 (RR 0.05, 95% CI 0.0099–0.3237, p = 0.0022) remained an independent prognostic factor. 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.

286
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 to be the 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: 9–110 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.

287
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 (FlBu4) 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 x 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/m2 IV x 5d (days -6 to -2). Pts received demethylasone 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 13–86). 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 hypoinsulin (5/22), hypertension (2/22), and seizure (1/22). Hypersensitivity to clofarabine occurred in one patient however subsequent doses were tolerated with additional desacemabsonse. Also noted were asci (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 readily, 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.