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SALVAGE AND DISEASE CONTROL OF AGGRESSIVE HISTOLOGY NON-HODGKIN'S LYMPHOMA BY ALLOGENEIC STEM CELL TRANSPLANTATION

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Introduction: Allogeneic SCT (Allo-SCT) remains an option for patients (pts) who have failed or are ineligible for autologous SCT (ASCT) or if their long term disease control after ASCT is likely to be suboptimal. Our program employs a strategy using allo-SCT for patients with high risk disease based on clinical characteristics and prior therapy.

Methods: 36 pts with AG-NHL (diffuse large b cell lymphoma [DLBCL] and variants, follicular large cell or follicular grade 3 [FL3], biopsy proven aggressive histology transformation of indolent lymphoma [TRL] or peripheral T cell lymphoma [PTCL]) underwent allo-SCT at our institution between Sept 1989 and Dec 2005. Patients were in a chemosensitive remission at the time of SCT. The conditioning regimen consisted of busulfan (1 mg/kg PO q6h X4 days between 1989-200 and 3.2 mg/kg IV daily X 4days subsequently) and cyclophosphamide 60 mg/kg X 2 days. Cyclophosphamide 60 mg/kg X 2 days and TBI 12 Gy was used for unrelated donor SCT. GVHD prophylaxis was with cyclosporine A and methotrexate.

Results: There were 20 males and 16 females. The median age at the time of transplant was 47 years (range 20 - 62). Histologic subtype was: DLBCL and variants: 13, FL3: 5, TRL: 17, PTCL: 1. The median number of prior chemotherapy regimens was 3 (range 1 - 7) and was unavailable in 5. Prior anthracycline: 36, prior platinum-based: 29, prior mini-BEAM: 14, prior auto-SCT: 5, prior rituximab: 3.The median time from diagnosis to allo-SCT was 29 months (range 7 – 218). One patient underwent RIC SCT. Graft source was: matched related (MRD) bone marrow (BM): 26, MRD peripheral blood stem cells (PBSC): 4, Mismatch related (MMRD) bone marrow (BM): 2, matched unrelated donor (MUD) BM: 2, and syngeneic BM: 2. The five year overall survival of the entire cohort was 50% (95% CI: 33% - 67%). Treatment-related mortality was 12/36 (33%) and the relapse rate was 4/36 (11%). Non-relapse mortality was 1 pt (3%). 2 out of the 4 relapses occurred over 5 years after SCT (1600 and 1828 days post-SCT).

Conclusions: This cohort includes a high proportion of transformed lymphoma and heavy pre-treatment with a median of 3 prior chemotherapy regimens. TRM remains a problem and reduced intensity transplants may improve on these results. However, long-term follow-up of these strategies will be needed to determine their role in the management of aggressive NHL.

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NONMYELOABLATIVE STEM CELL TRANSPLANTATION IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA: POOR EVIDENCE OF AN EFFICACIOUS GRAFT-VERSUS-HODGKIN'S LYMPHOMA EFFECT

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We report the results of reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) and short immunosuppression in 16 patients with advanced Hodgkin lymphoma (HL), 15 of whom (93%) had progression of disease after previous autologous transplantation. Nine patients were males (56%), median age was 27 years (19-43), number of previous treatment courses was 4 (3-6). Donors were HLA-matched siblings (14), matched unrelated volunteers (1) and 4:6 matched cord blood (CB) (1). Source of stem cells was: mobilized peripheral blood (PB) (15) and CB (1). All the patients received an RIC protocol (fludarabine 125 mg/m^2 i.v. plus cyclophosphamide 120 mg/kg i.v.). Unrelated recipients also received rabbit ATG 7.5 mg/kg and 200 cGy TBI. GVHD prophylaxis was done with cyclosporine and "mini-methotrexate" (10+5+5 mg/m^2). Disease status at allo-SCT was refractory relapse (12), sensitive relapse (3) or untreated relapse (1). Four

patients (25%) died from early (< D+100) transplant-related mortality after allo-SCT, two of them before engraftment. The median time to neutrophil recovery (≥ 500/ml) was 14 days, and to platelet recovery (≥ 20,000/ml) was 19 days. All patients who engrafted reached full chimerism without the need for additional donor lymphocyte infusion (DLI). Acute GVHD ≥ grade II was diagnosed in 6/13 patients (46%) and chronic GVHD in 7/12 patients (58%), 5 with extensive cGVHD. Two patients received DLI for treatment of relapse. Five patients (31%) are alive with a median follow-up of 28 months (8-50). Only 1 patient is alive in complete remission with a follow-up of 8 months. Our results suggest that allo-RIC in heavily pretreated HL patients has an acceptable early transplant-related mortality and that extensive cGVHD does not appear to protect from relapse, providing a poor evidence for the existence of a potent graft-versus-Hodgkin lymphoma effect.

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A RANDOMIZED PHASE I TRIAL OF MELPHALAN + BORTEZOMIB AS CONDITIONING FOR AUTOLOGOUS TRANSPLANT FOR MYELOMA: THE EFFECT OF SEQUENCE OF ADMINISTRATION

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Background: High dose therapy and autologous transplant (HDT) clearly benefits most patients with myeloma, but the addition of other chemotherapeutics or TBI to high dose melphalan (M) does not improve outcomes. Bortezomib (B) is a proteasome inhibitor which synergizes with chemotherapy due to its effects on DNA repair enzymes. Recent data has shown that B upregulates the anti-apoptotic protein MCL-1, which would suggest that the sequence of administration may be critical to the combination of B and M. We hypothesize that B followed by M is inferior to M followed by B. To test this hypothesis, we designed a randomized phase I trial combining B and Melphalan 200 mg/m2 (Mel200) in order to determine the toxicity, optimal dose and sequence of administration.

Methods: Patients were randomized to receive either B 24 hours before Mel 200 or B 24 hours after Mel 200. Doses for B range from 1.0mg/m2 up to 1.6mg/m2 as defined using a Basyian phase I design. Standard transplant criteria were used for enrolling patients with the addition of requiring measurable numbers of plasma cells within the marrow at the time of transplant (>5% plasma cells by biopsy or M-protein >1.0). Enrolled patients underwent BM aspirate on day -4 (before B) and day 0 (before PBSC infusion). Bone marrows were tested for annexin V staining, and myeloma cells were sorted for protein analysis. Routine demographics, toxicity, and engraftment data was also collected.

Results: Eleven patients have been enrolled to date, with 10 evaluable. B doses range from 1.0-1.3mg/m2 per current dose escalation. Age range was 48-74 years. No patient had resistant disease at the time of transplant, and only one patient had previously undergone HDT. Time to WBC and Plt engraftment were not different from historical cohorts receiving MEL 200 alone. Six patients have been randomized to the B'before' arm, and 5 in the B 'after' arm. There was no significant difference in myeloma cell annexin V staining on day -4 between the 2 groups, however there was an increase in the percent of Annexin V (+) MM cells for the group randomized to the 'after' arm compared to the 'before' arm (33.3% [after] vs 4.1% [before]). To date there is no difference in bone marrow IL6 levels between the 2 randomized groups. Accrual continues.

Annexin V staining of Myeloma cells in the Marrow

	Day -4	Day 0
'Before' Arm	0.89	4.08
'After' Arm	1.12	33.3

'Before' B before M. 'After' B after M