Feasibility of Low Dose Azacitidine Post T Cell Depleted Allogeneic Hematopoietic Stem Cell Transplants in Patients with Myeloid Malignancies At High Risk for Relapse
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Background: Post transplant relapse remains a main cause of transplant failure and mortality in patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Azacitidine, a hypomethylating agent, has been reported to reduce post transplant relapse in these patients after unmodified allogeneic hematopoietic stem cell transplantation (HSCT). There have been no reports of azacitidine use in patients undergoing T cell depleted (TCD) HSCT.

Patients: Nine patients; 4 with high risk MDS, 1 with AML evolved from MDS, 2 with therapy-related AML, and 2 with de-novo AML, who had undergone TCD HSCT, were treated with azacitidine post transplant. The dose of azacitidine, as determined in a phase 1 study, was 32mg/m² subcutaneously daily for 5 days monthly. All patients had been conditioned with a myeloablative regimen of busulphan, melphalan, fludarabine and rabbit ATG and had received a peripheral blood stem cell graft from a matched or mismatched related or unrelated donor.

Results: Seven patients were treated in complete remission as a prophylactic measure, one patient was treated in relapse and one patient received, in addition to azacitidine, a dose of DU (0.5x10⁶ CD3 cells/kg) for increasing host chimerism and a new cyrogenetic abnormality. Treatment began at a median of 117 days post transplant (range 80-333) and patients received a median of 3 cycles (range 1-7). At a median of 8 months follow-up, 7 patients were alive and 2 had died; one of pulmonary failure, possibly secondary to busulphan and the other patient of relapsed disease. In one patient, treatment was discontinued after development of an EBV-LPD while receiving budesonide for upper GI GvHD, and in another patient therapy was discontinued because of severe pancytopenia secondary to adenosivirus infection. A third patient had treatment interruption after developing dyspnea secondary to heart failure and chronic obstructive lung disease. The patient with relapsed disease had persistent pancytopenia throughout the treatment. In the 8 remaining patients, there were 4 with grade 1 anemia and/or thrombocytopenia. Only one of the 8 patients required G-CSF and azacitidine dose reduction (20%). However, this patient's neutrophils were noted to decrease prior to initiation of Azacitidine, possibly related to treatment of an EBV-LPD with Rituxan. Two patients had grade 1 skin GvHD and one patient had grade 1 upper GI GvHD. Therapy with azacitidine did not worsen the severity of GvHD.

Conclusions: This review shows that timely administration of low dose azacitidine is feasible after TCD transplant in patients with MDS and AML. The most common toxicity related to azacitidine, myelosuppression, has been reported only in patients who had concomitant viral infections. A phase II trial will be conducted to assess the efficacy of post transplant azacitidine after TCD transplant.

Allograft Leukocyte Content and Post-Allogeneic Hematopoietic Cell Transplant Lymphopenia and Monocytopenia
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Background: We have previously shown that lymphocyte and monocyte recovery by 2-3 months post-allogeneic hematopoietic (HCT) is associated with improved survival in recipients of both myeloablative and reduced intensity conditioning. Here, we test the hypothesis that the allograft lymphocyte and monocyte content correlates with recovery of those hematologic parameters prior to and at day +100.

Methods: We pooled the hematologic recovery data, including absolute lymphocyte and monocyte counts (ALC and AMC, respectively) at day +15, +30, +60, and +100, and outcomes data from our original cohorts of allogeneic HCT recipients undergoing myeloablative or reduced intensity (fludarabine/melphalan). We included only those with peripheral blood stem cell allografts and excluded those with incomplete data regarding allograft leukocyte subset content. 216 consecutive patients from 2000-2010 were included in the analysis.

Results: Neither allograft lymphocyte, monocyte, granulocyte, nor CD34+ content correlated with hematologic recovery parameters or overall survival in this cohort when cell doses were analyzed as continuous variables or divided in quartiles. No overall prognostic or optimal pattern of allograft cellular content as determined by unsupervised hierarchical clustering could be identified. With this pooled data, prognostic factors for overall survival based on multivariate analysis included severity of chronic GVHD (P < .001), development of post-transplant relapse (P = .001), day +60 AMC > 0.3 x 10⁹ cells/L (P = .0015), and day +100 ALC > 0.3 x 10⁹ cells/L (P < .001).

Conclusions: We conclude that, unlike in the autologous HCT setting, post-allogeneic HCT lymphopenia and monocytopenia appear to be related to complications and treatment-related factors, and not related to allograft leukocyte content.
received two alloHSCTs between 1997-2011. Univariate survival analyses (Kaplan Meier log-rank test) were conducted to investigate factors affecting disease-free survival (DFS) and overall survival (OS). Group differences between cases with/without GVHD were examined by t-tests on engraftment lab variables.

The median age was 44 years (20-70). AML/MDS accounted for 71% of the cases. Indications for second alloHSCT were graft failure (16%) and disease relapse (84%). Myeloablative conditioning was used in 62% of the patients. Median time from first to second transplant was 427 days (49-3835) and median time from relapse to second alloHSCT was 142 days (16-2524). 62% of the second alloHSCTs were from an unrelated donor. 36% of second transplants were from the original donor. OS at 1 and 5 years was 41% and 21% respectively [median 229 days (5 – 5320)]. Factors prolonging OS were: GVHD (P = .05), chronic GVHD (cGVHD) (P < .01) and using the same donor for both alloHSCTs (P < .01). Male recipients, transplant from females to males, and transplants from unrelated donors trended towards better survival rates but were not significant (P = .069, 0.09, and 0.059 respectively). Survival was not affected by: age, acute GVHD (aGVHD), diagnosis, risk stratification at diagnosis or second alloHSCT, remission status at second alloHSCT, conditioning intensity, HLA compatibility, donor’s sex, or CMV status of the donor/recipient. The median DFS after the second alloHSCT was 112 days (5-4759). Incidence of aGVHD and cGVHD was 41% and 41% respectively. Patients who developed GVHD or cGVHD had better DFS (P < .01, P = .03 respectively).

Risk of GVHD was higher in patients who received more CD34/kg cells (P = .02) while CD3/kg dose was not statistically significant. Remission status at the time of the second alloHSCT did not affect OS or DFS. 13% of the patients developed CMV viremia. Median time to neutrophil engraftment was 12 days (4-37), and median platelet engraftment >50,000/mcL was 21 days (9-103). Patients who developed GVHD had earlier platelet engraftment (Means: 16 vs. 30 days, P = .04).

This single center experience of second alloHSCT suggests this treatment results in long-term survival in select patients. Survival is improved when the original donor is used as the second donor. Future studies will focus on predictive modeling to help choose patients who may benefit most from a second alloHSCT.

**403**

**Haploidentical Donor Transplantations with TLI, Fludarabine, Cyclophosphamide, and ATG Are Safe and Effective Treatment for Graft Failure**

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Graft failure is a well described complication of allogeneic hematopoietic cell transplantation (HCT). The likelihood of graft failure is greater when an HLA-mismatched donor (such as umbilical cord blood or haploidentical donor) is utilized. Salvage transplantations are associated with high mortality because of common concurrent infections and poor tolerance to reconditioning. We describe the use of a novel reduced-intensity regimen that combines four potent immunosuppressive but well tolerated agents with non-overlapping toxicities.

Patients received 8 Gy TLI divided 2 Gy per fraction (once daily on days -10, -9, and twice daily on day -8). Fludarabine at 40mg/m2/day on the following 3 days (-7, -6, and -5). Cyclophosphamide at 50mg/kg/day over 3 days (-4, -3, -2). Rabbit ATG at 1mg/kg on day -3, and then 3mg/kg/day on days -2 and -1. Patients then received a CliniMacs T-cell depleted peripheral blood stem cell graft from a haploidentical donor. The patients were typically heavily pretreated, had prolonged neutropenia, and many had identified infections.

In total, 7 patients experienced graft failure after haploidentical donor HCT (3 had primary graft failure; 4 had brief engraftment with subsequent rejection). They received salvage HCT at a median of 37 days (range 31 – 78 days) following the first HCT (with the same haploidentical donor in 5 and an alternative haploidentical donor in 2 recipients). Patient 7 required modification of the regimen (no cyclophosphamide given) due to ongoing mechanical ventilation and pressor support. Six of the 7 patients (86%) experienced durable engraftment beginning at a median of 12 days (range 10 – 27 days). All 6 were successfully discharged from the hospital post-engraftment including Patient 7. The remaining patient had rapidly progressive disease and never had signs of engraftment before death at day 101 after the salvage HCT. No other patient has relapsed. Patient 7 ultimately expired due to CMV pneumonitis at 103 days after salvage HCT. The remaining five patients are alive at a median of 846 days after salvage HCT (range 131 to 2569 days). Two patients had acute and 3 had chronic GVHD; all resolved.

Our results indicate that this novel immunosuppressive regimen is tolerable and effective in this heavily pretreated patient population. High success rate in reengraftment was observed despite the use of T-cell depleted haploidentical grafts, including those from the same donor whose graft was previously rejected.

| Table |
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| 1 | 1yr 5mo | AML | Mother | 1 | 78 | Mother | 27 | Alive |
| 2 | 9mo | ALL | Mother | 1 | 65 | Mother | 11 | Alive |
| 3 | 1yr 9mo | ALL | Mother | 1 | 35 | Mother | na | Expired (ALL) |
| 4 | 18yr 2mo | MDS | Mother | 2 | 65 | Mother | 11 | Alive |
| 5 | 10y 10mo | MDS | Father | 2 | 37 | Mother | 14 | Alive |
| 6 | 16yr 7mo | CML | Sister | 2 | 31 | Father | 10 | Alive |
| 7 | 3yr 7mo | SAA | Father | 2 | 34 | Father | 13 | Expired (CMV) |