ALLOGENEIC TRANSPLANTS

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Factors Influencing Pulmonary Toxicity in the Setting of Total Body Irradiation-Based Myeloablative Conditioning in Children Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Purpose: To evaluate factors associated with increased risk of pulmonary toxicity in pediatric patients after myeloablative conditioning using total body irradiation (TBI) followed by allogeneic hematopoietic stem cell transplantation (HSCT).

Methods and materials: The records of 129 consecutive pediatric patients (range, 1-21 years) who underwent TBI-based myeloablative conditioning for hematologic malignancies at our institution between January 2003 and May 2014 were reviewed. Although total TBI dose ranged from 10.5 to 14 Gy, lung doses were reduced to 10 Gy with partial transmission blocks. The TBI dose rate ranged from 5.57 to 20.85 Gy/min.

Results: Pulmonary toxicity developed in 70.5% of patients, which proved to be fatal in 38.5% of those patients. Patients with any type of infection at any point during the follow-up period were more likely to develop pulmonary toxicity (p = 0.009), and patients with bacterial infection during the follow-up period had the highest incidence of pulmonary toxicity (p = 0.038). The presence of any grade of acute graft-versus-host-disease (GVHD) was associated with an increased incidence of pulmonary toxicity (p = 0.034), which developed in 94.4% of patients with grade III-IV GVHD (p = 0.001). TBI dose rate was significantly related to the development of pulmonary toxicity (p = 0.0495). Pulmonary toxicity was 3.51 times more likely to develop in patients receiving a TBI dose rate greater than 15 Gy/min (p = 0.017). Overall survival was significantly shorter in patients who developed pulmonary toxicity (p = 0.0053).

Conclusions: A high incidence of pulmonary toxicity was noted in this large series of homogeneously treated pediatric patients undergoing TBI for allogeneic HSCT. The presence of high grade acute GVHD and infection were the most significant factors contributing to the development of pulmonary toxicity. TBI dose rate should be aimed to be kept below 15 Gy/min to decrease the risk of pulmonary injury.

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Encouraging Outcomes of Haploidentical Hematopoietic Stem Cell Transplantation—Single Centre Experience from a Resource Poor Country

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High cost of matched unrelated donor stem cells limits its use in resource poor countries. Haploidential donor is readily available for most of patients and at much lower cost, so can be feasible for poor patients. Here, we are reporting the outcome of 19 patients (16 male, 3 female), median age 37 years (15-63 yrs), who underwent Haplo HSCT using peripheral blood stem cells (n = 16) and marrow (n = 3) during October 2011 to September 2014 at Rajiv Gandhi Cancer Institute & Research Centre (India) using non-myeloablative (NMA) and reduced intensity conditioning regimen (RIC) for hematological disorders (AA = 2, ALL = 4, AML = 5, NHL = 1, HL = 2, MM = 1, CMML = 5) with post-transplant cyclophosphamide for GVHD prophylaxis. Fourteen patients were in remission at the time of transplant. Seven patients received RIC with BuFlu(n = 5) and BuFlu(n = 2), 12 patients received NMA conditioning with FluCyATC(n = 3) and FluCyTB(n = 9). Median CD34 cell dose was 5 X10^6 cells/kg. Fifteen patients (79%) were engrafted, with a median time to neutrophil engraftment of 15 days (range, 9-22) and platelet engraftment of 14 days (range, 10-46). Nine patients had documented bacterial infection in first 100 days whereas none had documented fungal infection. Primary and secondary CMV reactivation occurred in 7 (36.8%) and 2 (10.5%) patients. The estimated day 100 and 1 year overall survival (OS) was 84.2 ± 0.84% & 52.1 ± 0.127 % respectively. The estimated 1 year event free survival (EFS) & non-relapse mortality (NRM) was 48.4 ± 0.123% & 26.3%. Cumulative incidence of aGVHD (II-IV) and (III-IV) was 26.3% & 5.2% whereas cumulative incidence of chronic GVHD at 1 year & 2 year was 15.8% & 10.5% respectively. Graft rejection was seen in 6 patients (31.5%, 5 primary and 1 secondary). These results suggest that this approach is safe & effective, with rapid multilineage engraftment, low rates of both aGVHD & cGVHD and low NRM.

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Plasma IL-7 and IL-15 Levels Vary Greatly after Low-Intensity Conditioning and May be Associated with Clinical Outcome in Recipients of High-Dose Sirolimus GVHD Prophylaxis

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In previous studies using a preparative regimen of fludarabine (Flu) plus high-dose cyclophosphamide (Cy; total dose, 4800 mg/m²) and GVHD prophylaxis of cyclosporine plus methotrexate, it was determined that transplant recipients had quite variable plasma levels of the T cell...
homeostatic cytokines IL-7 (Dean et al; JCO, 2008) and IL-15 (Boyiadzis et al; BBMT, 2008) and cytokine levels were associated with acute GVHD (IL-7) or pattern of immune reconstitution (IL-15). However, it is not known whether recipients of lower-intensity conditioning or sirolimus-based GVHD prophylaxis have variable levels of these cytokines or whether such potential cytokine variability is associated with clinical outcome. To begin to address this, we measured multiple cytokine levels (MesoScale multiplex assay; current analysis restricted to IL-7 and IL-15 levels at day 0 of transplant) in recipients of low-intensity conditioning (Flu/Cy; total Cy dose, 1200 mg/m²; see Table 1). Patients received GVHD prophylaxis consisting of cyclosporine plus short-course sirolimus (d2 through d14 post-SCT) at either standard-dose (n=46; “SD Cohort”) or high-dose (n=20; “HD Cohort”) (target trough level: 5-10 or 20-30 ng/ml, respectively). All patients received pre-emptive DLI consisting of rapamycin-resistant T cells (Fowler et al; Blood, 2013); however, in the current study, T cell manufacturing was reduced from 12 days to 6 days. Clinical outcomes (Table 1) were similar in SD and HD Cohorts, including: donor T cell and myeloid cell chimerism pre-DLI (d14 post-SCT) and post-DLI (d28 post-SCT), and incidence of classical acute GVHD. Remarkably, a wide range of IL-7 and IL-15 values were detected at day 0 of SCT in both SD and HD Cohorts (no difference between cohorts). In the SD Cohort, there was no association of IL-7 or IL-15 values with donor T cell chimerism, myeloid cell chimerism, or acute GVHD. However, in the HD Cohort, IL-7 values were associated with donor T cell chimerism and GVHD; and, IL-15 values were associated with donor T cell chimerism, myeloid cell chimerism, as well as GVHD. In conclusion, these data indicate that: (1) IL-7 and IL-15 values differ widely amongst recipients of low-intensity conditioning; and (2) IL-7 and IL-15 values were potentially associated with allo-engraftment and GVHD in the setting of high-dose sirolimus but not standard-dose sirolimus. This latter result provides a new insight into the pharmacodynamics of mTOR blockade post-transplant, and suggests that a more complete block of cytokine receptor signaling in vivo can unmask relationships between cytokine biology and post-transplant outcome.

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**Table 1**  
Cytokine Levels and Clinical Outcome

<table>
<thead>
<tr>
<th>Cytokine Level</th>
<th>SD Cohort</th>
<th>HD Cohort</th>
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<tbody>
<tr>
<td>IL-7 (day 0; pg/ml)</td>
<td>15.8 (11.4-48.3)</td>
<td>16.4 (11.7-45.2)</td>
</tr>
<tr>
<td>IL-15 (day 0; pg/ml)</td>
<td>19.4 (18.9-45.0)</td>
<td>22.1 (21.1-66.8)</td>
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**Immunogenetic Cross-Talk in Patients Transplanted for AML: CMV Reactivation Is Not a Strong Stimulus for Immune Response Against Leukemia**

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