MINIMAL LATE EFFECTS FOLLOWING REDUCED INTENSITY TRANSPLANT FOR NON-MALIGNANT DISORDERS

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Allogeneic transplant is the only cure for many non-malignant life-threatening disorders. Reduced intensity conditioning regimens are increasingly employed prior to stem cell transplantation, but little is known about the late effects of these regimens. We present here the late effects of a preparative regimen consisting of Campath-1H, Fludarabine, and Melphalan given two years following transplantation. We have found that the regimen itself has very few late effects. Using CTCAE v. 4.03 for criteria to classify the severity of the late effects, out of twenty patients studied, five patients experienced a grade 1, two patients a grade 2, and two patients a grade 3 toxicity; no patients experienced a grade 4 toxicity, and one patient experienced a grade 5 toxicity. The most common regimen-associated toxicity, found in 15% of patients, was an acquired autoimmune disorder affecting red cells and neutrophils. One patient developed extensive, chronic GVHD leading to multi organ system dysfunction, severe linear growth deceleration, and eventual death. 70% of patients fully engrafted, 15% had stable mixed chimerism, and 15% had secondary graft rejection, one of whom required a second, myeloablative transplant. The other two were rescued with donor lymphocyte infusions. There was only one patient with transplant-associated growth failure, and puberty was achieved in the 25% of patients who were of age to pass through puberty during and after transplant, indicating that gonadal function was preserved in this population. We did not observe transplant-associated cognitive impairment. There were two deaths (10%), one (5%) of which was transplant-related, one (5%) was attributable to a complication of his underlying disease. Thus, this non-myeloablative regimen was associated with minimal toxicity two years beyond the transplant procedure, making it an attractive option for patients with, nonmalignant diseases.

LEUKEMIA

UNIVERSAL MINIMAL RESIDUAL DISEASE QUANTIFICATION USING CONSENSUS PRIMERS AND HIGH-THROUGHPUT IGH SEQUENCING PREDICTS POST-TRANSPLANT CLL RELAPSE BETTER THAN PATIENT-SPECIFIC PCR

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Methods for broadening the availability of minimal residual disease (MRD) quantification in chronic lymphocytic leukemia (CLL) are needed to improve patient management. Here, we report the performance of consensus primed PCR to amplify immunoglobulin heavy chain (IGH) loci from polyclonal B cells in peripheral blood, followed by high-throughput sequencing (IGH-HTS) to ascertain CLL burden in patients treated with reduced intensity allogeneic hematopoietic cell transplant (HCT). We achieved 10e-6 MRD sensitivity and found this approach provides better prediction of relapse than allele-specific quantitative PCR (ASO-PCR). We amplified IGH loci from genomic DNA extracted from PBMC (median input 1.4x10e6 cells; range 0.2-23.7x10e6) using consensus V and J segment primers. IGH molecules were sequenced with one million or more dedicated reads using Illumina HiSeq and clonotypes were quantified with Sequenta HTS bioinformatics. 289 samples collected prospectively from 289 patients (84/117 in CR and 19/117 with IGH-HTS compared with ASO-PCR (365 versus 270 days). 80% of patients who achieved ASO-PCR negativity at any time, but who never subsequently achieved negativity by IGH-HTS, relapsed.

IGH-HTS provides heretofore unachievable MRD sensitivity for patients with CLL. The highly prognostic value of achieving MRD negativity with IGH-HTS suggests that IGH-HTS may provide a benchmark for treatment success and a basis for further therapy in patients failing to achieve this status.

FREQUENCY OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION AMONG HIGH-RISK AML PATIENTS IN FIRST COMPLETE REMISSION AT AN ACADEMIC CENTER

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Background: Allogeneic hematopoietic cell transplantation (HCT) likely prolongs survival in high-risk adults with acute myeloid leukemia (AML) in first complete remission (CR1). Prior studies, however, suggest that only about 15% of AML patients age ≥50 with abnormal cytogenetics who entered CR1 at an academic cancer center received a reduced intensity HCT in CR1 (Estey et al., Blood 2007;109:1395-1400). In this study, only HLA-matched siblings were primarily used as donors, raising the question of the frequency with which HCT is performed in adults of all ages entering CR1 if unrelated donors as well as siblings are utilized. Here we address this question and compare high- or intermediate-risk AML patients who did and did not receive HCT while in CR1.

Methods: Between Jan, 1 2008 and March 1, 2011, 244 patients received treatment for newly-diagnosed AML at our Center and who achieved CR or CRi (96/117 (84%) in CR and 19/117 (16%) in CRi). Because HCT is generally not recommended/un undertaken in patients age ≥75 or who have favorable cytogenetic risk [inversion 16, t(8,21), or t(15;17)] or who are NPM1 mutated and FLT3 wild-type, we excluded such patients, leaving 117 with high- or intermediate-risk AML in CR1. Logistic regression was used to distinguish characteristics associated with receiving HCT in CR1.

Results: Seventy-nine AML patients (68%; 95% CI 59-76%) received HCT in CR1 at a median of 5.1 months (range, 1.2-20 months) from their CR1 date. Characteristics of patients who received or did not receive HCT in CR1 are shown in the Table below:

<table>
<thead>
<tr>
<th>Table. HCT vs No HCT in CR1</th>
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<tr>
<td><strong>HCT</strong> (79 pts)</td>
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<tr>
<td><strong>Mean Age (range)</strong></td>
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<tr>
<td>Mean Performance status at CR1 (range)</td>
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<td>Mean HCT-Cl (range)</td>
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