The Effect of Peritransplant Minimal Residual Disease in Adults With Acute Lymphoblastic Leukemia Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Patients with acute lymphoblastic leukemia (ALL) with minimal residual disease (MRD) present at the time of allogeneic hematopoietic stem cell transplant (HSCT) showed a trend for greater risk of relapse after transplant in this retrospective, single-center study.

Background: Allogeneic HSCT is highly effective for treating ALL. However, many ALL patients relapse after HSCT. There has been a continuing effort to improve identification of patients at high risk of relapse, with the goal of early intervention to improve outcome. **Patients and Methods:** In this retrospective analysis, we examined the effect of MRD on the risk of hematologic relapse in 149 adult patients with ALL in morphologic remission undergoing allogeneic HSCT. MRD was assessed at the time of HSCT and after HSCT. **Results:** Patients with pretransplant MRD had a trend for shorter progression-free survival (PFS) at 2 years compared with patients without MRD, nearing statistical significance; 28% versus 47%, $P = .08$, on univariate analysis. This trend remained on multivariate analysis with better PFS in patients without MRD at the time of HSCT, hazard ratio (HR), 0.62 (95% confidence interval, 0.37-1.04); $P = .07$. Additionally, emergence of MRD after HSCT was a strong predictor for overt hematologic relapse (HR, 4; $P < .001$) with a median latency interval of 3.8 months. **Conclusion:** These findings demonstrate the predictive value of monitoring for MRD around the time of transplant in adult patients with ALL.

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only effective therapy for patients with high-risk or relapsed acute lymphoblastic leukemia (ALL). Select patients with ALL who have received allogeneic HSCT have a significant survival advantage over patients without HSCT.[1-6] However, substantial numbers of ALL patients still relapse after HSCT, mostly occurring within the first 2 years after transplant. There has been a continuing effort to improve the identification of patients at high risk for relapse after HSCT,[7-11] with the goal of early therapeutic intervention to improve outcome.

Minimal residual disease (MRD) at the end of induction or induction/consolidation therapy is one of the most significant risk factors for subsequent disease relapse in ALL patients.[12-20] Persistent MRD has become a significant indicator for HSCT or intensified chemotherapy.[17,21] The presence of MRD before HSCT is also a predictor for relapse, but has been less well studied in adults compared with children.[22,23] In pediatric patients, the presence of MRD before HSCT is highly predictive for relapse after transplant.[24-28] The frequency of disease progression in children with

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MRD before HSCT is approximately 3-fold the frequency in children without MRD. However, the effect of MRD at the time of HSCT in adults with ALL is less clear, with conflicting results. In reports by Bassan et al[21] and Spinelli and colleagues,[29] MRD was assessed at the time of transplant using polymerase chain reaction (PCR) amplification and patient leukemia-specific probes, and was found to be a predictor for relapse. In contrast, in the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 study using similar methods to assess for MRD in 161 patients with B-lineage Philadelphia chromosome-negative ALL, the presence of MRD was not associated with a higher rate for relapse.[21,23] Interestingly, MRD at the time of autologous HSCT was associated with a higher rate of relapse suggesting that the graft versus leukemia (GVL) effect was protective against MRD in the allogeneic HSCT setting.

Furthermore, there are only limited studies of the risk, or tempo, of progression in patients who demonstrate positive MRD soon after HSCT.[30,31] Using immunoglobulin and T-cell receptor rearrangements as clonal markers, Uzunel and colleagues showed that detectable MRD preceded relapse in 8 of 14 patients, with a median time of 5 months between first MRD detection and relapse.[30] Regular MRD monitoring after transplant might offer an opportunity to detect emerging hematological relapse before overt hematological relapse, and thus provide a window for therapeutic intervention.

In this retrospective study, we investigated whether MRD before and after transplant had an association with patient outcomes, including overall (OS) and progression-free survival (PFS).

Patients and Methods

Patients

Uniform assessment of MRD using flow cytometric immunophenotyping (FCI) was established at our hospital in 2004. Therefore, our study cohort was limited to patients who received a first allogeneic HSCT at M.D. Anderson Cancer Center (MDACC) from February 2004 through October 2012. Patients needed to be in complete remission and have available FCI MRD assessment within 30 days before HSCT. A total of 149 patients met these criteria and were included in the current study. The first assessment of MRD after HSCT was done approximately 30 days after the procedure, and 135 patients had post-HSCT MRD assessments. Patients were treated in clinical trials that were approved by the institutional review board, and written informed consent was obtained in accordance with the Declaration of Helsinki.

Donors

Human leukocyte antigen (HLA) typing for class I antigens was performed using standard serologic or low resolution molecular techniques, followed by confirmatory typing with high-resolution molecular typing using PCR for class I and II antigens for sibling donors; high-resolution molecular typing of class I and II antigens was performed for all unrelated donors. Peripheral blood stem cells were obtained from donors using standard mobilization protocols and apheresis techniques, with a target progenitor cell dose of 4×10^6 $CD34^+$ cells per kilogram and minimal acceptable dose of 2×10^6 $CD34^+$ cells per kilogram; bone marrow was used if peripheral blood could not be used. Stem cells from all related donors were collected at MDACC. Peripheral blood progenitor cells or bone marrow harvests from unrelated donors were obtained through the National Marrow Donor Program. All grafts were T lymphocyte replete.

Conditioning Regimens

Patients received a variety of myeloablative transplant preparative regimens, based on available existing protocols at the time of treatment. Conditioning intensity was defined according to the Center for International Blood and Marrow Transplant Research criteria.[32] Myeloablative, radiation-based regimens were largely considered for patients younger than 50 years of age, and included cyclophosphamide (Cy) 60 mg/kg intravenously for 2 days, followed by 12 Gy of total body irradiation (TBI).[33,34] Additionally, Cy TBI was combined with rituximab 375 mg/m^2 weekly for 4 doses,[35] or alemtuzumab 10 mg for 5 doses, or TBI was combined with a single dose of etoposide at 60 mg/kg with or without rituximab. Non-TBI, myeloablative regimens included intravenous busulfan (Bu) at 130 mg/m^2 infused daily for 4 days, either as a fixed dose per body surface area, or based on pharmacokinetic data derived from a Bu test dose followed by melphalan (Mel) 70 mg/m^2 for 2 doses[36] or followed by clofarabine 40 mg/m^2 for 4 doses.[37] Additionally, fludarabine was administered at 25 mg/m^2 daily for 5 doses followed by 2 daily doses of Mel 70 mg/m^2.

Supportive Care

Graft versus host disease (GVHD) prophylaxis consisted of a combination of tacrolimus and mini-dose methotrexate in all patients. Patients with matched unrelated donors additionally received antithymocyte globulin for total dose of 4 mg/kg infused over 3 days. Central nervous system (CNS) prophylaxis after HSCT was recommended for patients with a history of CNS disease. Tyrosine kinase inhibitor (TKI) maintenance after HSCT was physician-based, and administered as feasible for patients with Philadelphia chromosome-positive (Ph^+) ALL with adequate cell count recovery after HSCT. Institutional transplant guidelines for antimicrobial prophylaxis and blood transfusions were followed.

Minimal Residual Disease Assessment Using FCI

Minimal residual disease was assessed using multiparameter FCI with a sensitivity of 0.01%. Bone marrow aspirate specimens were analyzed using a panel of 10 to 21 markers, including in most cases, CD10, CD13, CD15, CD19, CD20, CD22, CD33, CD34, CD38, CD45, CD58, and CD66c for B-lineage ALL,[38] and CD1a, CD2, cytoplasmic CD3, surface CD3, CD4, CD5, CD7, CD8, CD10, CD13, CD33, CD34, CD45, CD56, HLA-DR, and Terminal deoxynucleotidyl transferase for T-lineage ALL. Data were collected on 200,000 nucleated bone marrow cells. At the beginning of the study, samples were stained with 8 to 10 four-color tubes, and later samples were stained with 4 six-color tubes for B-lineage ALL and 5 seven-color tubes for T-lineage ALL. CD19 was included in each tube for gating in B-lineage ALL, along with CD34 to delineate the immature subset. Cytoplasmic CD3 staining was used for gating in T-lineage ALL, with surface CD3 also included in each tube to identify immature (surface CD3-negative) cells. MRD was scored as positive based on a distinct cluster of at least 20 cells on bivariate dot plots, showing a significant difference in the level of