Original Study

Does Post-Transplant Maintenance Therapy With Tyrosine Kinase Inhibitors Improve Outcomes of Patients With High-Risk Philadelphia Chromosome-Positive Leukemia?

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Abstract

Relapse is the major cause of allogeneic hematopoietic stem cell transplantation failure in high-risk Philadelphia chromosome-positive (Ph^+) leukemia. Post-transplant maintenance therapy is a promising strategy. We found maintenance imatinib and dose-reduced newer generation tyrosine kinase inhibitors to be feasible and generally well tolerated. This approach might reduce the incidence of relapse and improve the outcomes after allogeneic hematopoietic stem cell transplantation for high-risk Ph^+ leukemia.

Introduction: The effect of post-transplant maintenance tyrosine kinase inhibitors (TKIs) on the outcomes of allogeneic hematopoietic stem cell transplantation in high-risk Philadelphia chromosome-positive (Ph^+) leukemia remains unknown. **Patients and Methods:** A retrospective analysis that included allograft recipients with accelerated phase and blast phase chronic myeloid leukemia or Ph^+ acute lymphoblastic leukemia who had received post-transplant maintenance TKI therapy from 2004 to 2014. **Results:** A total of 26 patients, 9 with accelerated phase/blast phase CML and 17 with Ph^+ acute lymphoblastic leukemia, received maintenance post-transplant therapy with imatinib, dasatinib, nilotinib, or ponatinib. The TKI was selected according to the pretransplantation TKI response, anticipated toxicities, and ABL1 domain mutations, when present. Newer generation TKIs were initiated at a $\geq$ 50% dose reduction from the standard pretransplantation dosing to limit the toxicities and avoid therapy interruptions. TKIs were started a median of 100 days (range, 28-238 days) after transplantation and were administered for a median of 16 months (range, 8 days to 105 months). Eight patients discontinued therapy because of adverse events. With a median follow-up of 3.6 years (range, 4 months to 8.7 years), the 5-year relapse-free survival rate was 61%. All 3 patients who developed a relapse underwent successful salvage treatment and remained disease-free. The 5-year overall survival rate was 78%. **Conclusion:** Maintenance TKI therapy after transplantation is feasible and might reduce the incidence of relapses and improve outcomes after allogeneic hematopoietic stem cell transplantation for patients with high-risk Ph^+ leukemia.

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Introduction

Understanding the role of the fusion oncoprotein BCR-ABL1 in the pathogenesis of Philadelphia chromosome-positive (Ph^+) leukemia led to the development of targeted therapy with tyrosine kinase inhibitors (TKIs) and dramatic improvements in the outcomes. For chronic phase (CP) chronic myeloid leukemia (CML),

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the 8-year overall survival (OS) increased from < 20% to 80% to 90%, and the outcomes of TKI-responsive accelerated phase (AP) have been increasingly comparable with those for CP-CML.[1-3] In Ph^+ acute lymphoblastic leukemia (ALL), remission rates of 90% to 95% are commonly achievable when TKIs are combined with chemotherapy, and these remissions can be sustained.[4,5] Allogeneic hematopoietic stem cell transplantation (HSCT) remains the upfront standard-of-care treatment of Ph^+ ALL in first complete remission (CR1) and blast phase (BP) CML and is reserved for TKI failure in CP- and AP-CML. However, the transplant outcomes have not improved, despite greater remissions with the use of pretransplantation TKIs,[6] largely owing to the high incidence of post-transplant relapse.[7,8]

Prophylactic or therapeutic TKIs can be safely administered after transplantation.[9] The administration of post-transplant TKIs as prophylactic maintenance is feasible using imatinib.[10-12] However, given that allografting is increasingly being performed in patients in whom first-line and later TKI therapy has failed, data on the safety and efficacy of newer generation TKIs administered after transplantation would be of great interest, especially if activity is demonstrated before transplantation. We report our single-institution outcomes of allograft recipients transplanted for advanced-phase CML and Ph^+ ALL who received post-transplant maintenance TKI therapy.

Materials and Methods

Patients with AP- and BP-CML or Ph^+ ALL diagnosed and treated at our institution or referred in remission for transplantation who received non−T-cell−depleted allogeneic HSCT at Emory University Hospital from 2004 to 2014 were identified using a computerized database search. The following data were extracted: the baseline disease characteristics, including phase, response to TKI therapy, ABL1 domain mutation, and disease status at transplantation; transplant-specific characteristics, including donor, stem cell source, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, post-transplant complications, acute and chronic GVHD; and post-transplant TKI therapy, disease monitoring, relapses, and survival. The Emory University institutional review board approved the present study.

CP-, AP-, and BP-CML were defined according to the European LeukemiaNet criteria.[13] Ph^+ ALL patients required the presence of metaphases with t(9;22) and/or BCR-ABL1 in the blood or bone marrow. Hematologic, cytogenetic, and molecular responses were defined according to the European LeukemiaNet criteria.[13] A major molecular response (MMR) was defined as a BCR-ABL1/ABL1 ratio of < 0.1%. Undetectable molecular residual disease (UMRD) was defined by undetectable levels of BCR-ABL1 transcripts using quantitative reverse transcription-polymerase chain reaction (PCR) with a sensitivity of ≥ 0.0063% (international scale). The hematologic relapse was defined by the presence of leukocytosis and a hypercellular bone marrow with Ph^+ chromosomes in CML and the morphologic reappearance of blasts in the blood, bone marrow (> 5%), or any extramedullary site in Ph^+ ALL. Cytogenetic relapse was defined by the detection of metaphases with the Ph^+ or BCR-ABL1 by blood or marrow fluorescent in situ hybridization. Molecular relapse was defined by the detection of BCR-ABL1 transcripts by quantitative reverse transcription-PCR in the absence of hematologic or cytogenetic relapse. Minimal residual disease (MRD) in Ph^+ ALL was defined by the presence of lymphoblasts detected by flow cytometry during morphologic remission.

OS was defined as the interval from transplantation to death from any cause. Relapse-free survival (RFS) was defined as the interval from transplantation to relapse, progression, or death. Patients alive without relapse were censored at the date of last contact. OS and RFS were estimated using the Kaplan-Meier method. Acute GVHD was graded according to the Glucksberg criteria, and chronic GVHD was assessed according to the National Institutes of Health GVHD scoring system.[14,15] The SPSS statistical package, version 21.0 (SPSS, Chicago, IL), was used for all data management and statistical analyses.

Results

From 2004 to 2014, 19 patients with advanced-phase CML and 30 with Ph^+ ALL underwent allografting, and 26 received post-transplant maintenance TKI therapy. Another 23 patients (10 with AP- or BP-CML, 13 with Ph^+ ALL) did not receive any post-transplant maintenance owing to early relapse (n = 5), enrollment in a clinical trial (n = 5), physician preference (n = 5), or death (n = 8). These patients were not included in the present analysis.

CML Pretransplant Characteristics

The pretransplant treatments for the 9 patients with advanced-phase CML are depicted in Figure 1. The median age at diagnosis was 49 years (range, 30-56 years), and 4 patients were male (44%). Five had progressed from the CP to the AP (n = 1) or the BP (n = 4), and 4 were diagnosed with de novo AP (n = 1), lymphoid BP (n = 2), or myeloid BP (n = 1). Imatinib was the first-line TKI for the 5 diagnosed with CP, of whom 4 achieved a complete hematologic response (CHR), 1 achieved an MMR, and 2 had undetectable BCR-ABL1 by PCR (UMRD). The response to imatinib was unknown in 1 patient. Progression to AP or BP occurred during imatinib therapy (n = 3) or alternative TKIs (dasatinib in 1; bosutinib in 1) administered for imatinib intolerance. ABL1 kinase domain mutation (F359) was detected in 1 patient. All 5 patients received alternative TKIs at the progression to advanced-phase disease, with 4 receiving TKI combined with hyperfractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone, alternating with high-dose cytarabine and methotrexate (HCVAD; n = 3) or "7+3" (cytarabine and idarubicin; n = 1). The disease status at the initiation of the preparative regimen was second CP (CP2) with MMR in 1 and UMRD in 4. The median time from diagnosis to transplantation was 53 months (range, 44-58 months).

The single patient diagnosed with AP-CML received front-line imatinib. The 2 patients diagnosed with de novo lymphoid BP received imatinib (n = 1) or dasatinib (n = 1) with HCVAD. The 1 patient with de novo myeloid BP received dasatinib monotherapy. All AP and BP patients achieved a CHR; 3 with an MMR and 1 with a UMRD. An ABL1 kinase domain mutation (E255K) was detected in 1 patient. The disease status when the preparative regimen began was CP2 with MMR (n = 3) or UMRD (n = 1). The median time from diagnosis to transplantation was 8.5 months (range, 4-16 months).