Original Study

Risk-Adapted Approach to HLA-Matched Sibling Hematopoietic Cell Allografting: Impact of Adjusting Conditioning Intensity and Integrating Post-Transplant Therapeutic Interventions

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Abstract

Allogeneic hematopoietic cell transplantation is a curative strategy for various hematologic malignancies. However, success is limited by mortality and relapse. We demonstrate the efficacy of a risk-adapted approach to human leukocyte antigen-matched sibling allogeneic hematopoietic cell transplantation by adjusting intensity of busulfan according to age, disease risk, and existing comorbidities, and by implementing appropriate post-transplant prophylactic maintenance therapy. Our findings require validation in a large multicenter study.

Background: Optimizing conditioning and post-transplant intervention may reduce non-relapse mortality and relapse, improving survival after allogeneic hematopoietic cell transplantation (allo-HCT). **Materials and Methods:** We used a risk-adapted intensity of busulfan at 130 mg/m^2/day for either 2, 3, or 4 days, with a fixed dose of fludarabine (30 mg/m^2/day for 5 days), and thymoglobulin (2.5 mg/kg/day for 2 days). Our algorithm was based on age, comorbiditie(s), and disease risk. **Results:** Fifty-three patients with hematological malignancies (median age, 37 years; range, 16-65 years), received an allograft from human leukocyte antigen identical siblings. Post-transplant therapy was initiated between days 30 and 60 after allo-HCT. Twenty-five of 26 patients who were planned for post allo-HCT therapy received it (10 with myeloid malignancies received 5-azacytidine, 5 with FLT-3 ITD acute myeloid leukemia received sorafenib, 4 with Philadelphia-positive acute lymphoblastic leukemia or chronic myelogenous leukemia in blast crisis received dasatinib, or dasatinib followed by imatinib, and 5 with acute lymphoblastic leukemia received intrathecal cytarabine). The remaining 27 patients (51%) did not receive post-transplant therapy because of lack of approval by third-party payers. After a median follow-up of 13 months (range, 2-57 months), 1-year non–relapse-mortality was 2%, and cumulative incidences of grade 2 to 4 acute graft-versus-host disease and all grades chronic graft-versus-host disease were 23% and 9%, respectively. The 2-year overall survival (95% vs. 61%; $P = .04$) and progression-free survival (81% vs. 53%; $P = .05$) were significantly better for patients in the post-transplant therapy group. **Conclusion:** This risk-adapted combined approach of selecting conditioning intensity and integrating post-transplant therapies results in lower non-relapse-mortality and encouraging improvement in survival. Our findings warrant confirmation in a large prospective multicenter trial.

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a well-established treatment for various high-risk hematological malignancies.[1] Standard myeloablative conditioning regimens are associated with significant risks of toxicity, high non–relapse-mortality (NRM), and increased incidence of graft-versus-host disease (GVHD).[2] As a result, reduced-intensity conditioning regimens were developed, especially for elderly, frail, or heavily pre-treated patients,

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and resulted in a less toxicity and lower NRM.[3,4] However, higher relapse rates continue to be a major concern.[5,6] Thus, optimizing the conditioning regimens and incorporating post-transplant therapie(s) aiming at reducing risk of relapse might ultimately improve overall survival after allo-HCT.[7-9] Recently, reduced-toxicity conditioning regimens (RTC) have been introduced. These RTC regimens combine the favorable properties of myeloablative conditioning and reduced-intensity conditioning regimens, by preserving the potent antitumor activity of the former while benefiting from the lower NRM of the latter. Intravenous (IV) administration of busulfan (BU) allows bypassing the unpredictable intestinal absorption and erratic bioavailability when using oral BU.[10-13] IV administration of BU might also allow further increasing the dose, especially for the diseases of more aggressive biology. Despite attempts to identify the optimal dose of BU, by using pharmacokinetically-guided dosing, the ideal dose is still controversial.[14]

Two administration schemes, prescribing either 2 or 4 days of IV BU, have been previously evaluated.[15-17] A recent prospective phase II trial has shown interesting results with an intermediate 3-day administration of BU at a dose of 130 mg/m^2/day.[11] Addition of antithymocyte globulin (ATG) as part of graft-versus-host disease (GVHD) prophylaxis resulted in a decreased incidence of acute and chronic GVHD without an apparent increase in relapse or NRM.

Moreover, the benefit of post allo-HCT therapy has been previously studied. In a recent study from the European Society for Blood and Marrow Transplantation (EBMT), tyrosine kinase inhibitors (TKIs) given in the post-transplant period were associated with improved leukemia-free survival and overall survival (OS); and a lower incidence of relapse incidence in Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) after allo-HCT.[18] Preliminary results using post-transplant 5-azacytidine showed a potential to reduce the risk of relapse in patients with acute myeloid leukemia (AML) who underwent an allo-HCT.[19] We and others have also shown encouraging results using sorafenib in the post allo-HCT setting for FLT3-ITD acute myeloid leukemia.[20,21]

In this analysis, we demonstrate a benefit of using a risk-adapted approach for allogeneic HCT by selecting BU intensity and implementing post-transplant therapeutic intervention. The comparator group, consisting of those who did not receive post-transplant intervention, was not determined a priori but was rather the consequence of lack of approval by some third-party payers.

Patients and Methods

Inclusion Criteria

We conducted a retrospective study at the American University of Beirut Medical Center in Lebanon in patients who had received an allo-HCT and in whom the dose of BU was chosen based on a risk-adapted strategy. This study was approved by the institutional review board of the American University of Beirut, Lebanon. Additional inclusion criteria were a Karnofsky performance score $\geq$ 70% and the availability of an HLA identical sibling donor. Exclusion criteria were refractory acute leukemia, a creatinine clearance $<$ 30 mL/min, bilirubin or aminotransferases $>$ 3 times the upper limit of normal, a cardiac ejection fraction $<$ 40% (by echocardiogram or multi-gated acquisition scan), pulmonary impairment with $<$ 50% lung carbon monoxide diffusing capacity, and evidence of pregnancy. The hematopoietic cell transplantation-specific comorbidity index and the disease risk index were described or retrospectively calculated whenever possible.[22,23]

All patients received granulocyte-colony-stimulating factor-mobilized peripheral blood stem cells from HLA identical siblings. Day 0 was defined as the day of hematopoietic graft infusion. All patients received the procedure in an inpatient unit and remained hospitalized until hematopoietic recovery. Recorded clinical outcomes after transplantation included time to neutrophil recovery (ie, the first of 3 consecutive days with a count exceeding 500/mm^3) and platelet recovery (ie, the first of 3 consecutive days with a count of 20 $\times$ 10^3/mm^3, without requiring platelet transfusion).

Patients' Characteristics

Fifty-three patients with hematological malignancies transplanted between January 2010 and December 2014 were included (median age, 37 years; range, 16-65 years). Patients' characteristics are listed in Table 1. Twenty-six patients had AML including 6 with FLT-3 ITD, 12 had ALL including 3 with Ph+ chromosome, 6 had myelodysplastic syndrome (MDS) including 5 RAEB-2, 4 had chronic myeloid leukemia (CML) including 3 in blast crisis, 2 had chronic lymphocytic leukemia (CLL) including 1 with evidence of Richter transformation, and 3 had myeloproliferative disorders (MPD) including 2 with myelofibrosis.

Conditioning and GVHD Prophylaxis

Conditioning was based on a risk-adapted or personalized dose of BU for 2, 3, or 4 days, a fixed dose of fludarabine (F) at 30 mg/m^2/day for 5 days, and of thymoglobulin (ATG) at 2.5 mg/kg/day for 2 days. Our algorithm was based on age, presence of comorbidity(ies), and disease risk. For instance, for age groups between 16 and 50 years, 51 and 60 years, and 61 and 65 years, we used FB4 + ATG, FB3 + ATG, and FB2 + ATG, respectively. The dose of BU was reduced by 130 mg/m^2 in case of existing associated comorbidity; but was never allowed to drop below FB2 (ie, 260 mg/m^2). Conversely, the BU dose was adjusted upwards by 130 mg/m^2 in the presence of high-risk disease (CR2 or beyond) but never above FB4 (ie, 520 mg/m^2). In the end, 2 (3.8%) patients had FB2-, 14 (26.4%) had FB3-, and 37 (69.8%) had FB4-based conditioning. Five patients with high-risk ALL received total body irradiation (TBI) 4 Gy in addition. For GVHD prophylaxis, all received cyclosporin A (3 mg/kg/day) initiated 3 days prior to stem cell infusion.

Infection Prophylaxis and Supportive Care

Pneumocystis jiroveci prophylaxis included trimethoprim-sulfamethoxazole 20 mL suspension orally twice daily prior to transplantation, discontinued after morning dose on Day (−2) of transplant, and then resumed as soon as the absolute neutrophil count (ANC) exceeded 500/mm^3. Levofloxacin 500 mg orally once daily was started when ANC was less than 1000/mm^3 and discontinued when ANC was more than 1000/mm^3 or fever protocol was activated regardless of ANC level. Doxycycline 100 mg orally twice daily was started from Day 0 after transplant until the removal of central IV catheter as a strategy to reduce central venous catheter infections.[24] Valgancyclovir 900 mg orally twice daily was started with conditioning and discontinued after morning dose on Day (−2) of transplant. Intravenous acyclovir or oral valacyclovir was