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Comparison of Cyclophosphamide Combined with Total Body Irradiation, Oral Busulfan, or Intravenous Busulfan for Allogeneic Hematopoietic Cell Transplantation in Adults with Acute Lymphoblastic Leukemia

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A B S T R A C T

We conducted a retrospective analysis to compare outcomes in adult patients with acute lymphoblastic leukemia (ALL) who underwent allogeneic hematopoietic cell transplantation (allo-HCT) with conditioning regimens containing cyclophosphamide (CY) in combination with total body irradiation (TBI), oral busulfan (p.o. BU), or intravenous busulfan (i.v. BU). We used data for January 2000 to December 2012 from the Transplant Registry Unified Management Program of the Japan Society of Hematopoietic Cell Transplantation. We identified 2130 patients treated with TBI/CY (n = 2028), p.o. BU/CY (n = 60), or i.v. BU/CY (n = 42). Two-year overall survival (OS) and 2-year relapse-free survival rates were 69.0% and 62.1%, respectively, in the TBI/CY group, 55.9% and 54.2% in the p.o. BU/CY group, and 71.0% and 46.8% in the i.v. BU/CY group. In multivariate analysis, compared with TBI/CY, p.o. BU/CY, but not i.v. BU/CY, was associated with lower OS (hazard ratio [HR], 1.46; $P = .047$) and a higher incidence of sinusoidal obstruction syndrome (HR, 3.36; $P = .030$). No between-group differences were seen in the incidence of nonrelapse mortality, relapse, acute graft-versus-host disease (GVHD), or chronic GVHD. We suggest that i.v. BU/CY might be a possible alternative allo-HCT conditioning regimen for adults with ALL who are not suitable for TBI.

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INTRODUCTION

Adult patients with acute lymphoblastic leukemia (ALL) have poor long-term outcomes with intensive chemotherapy, and allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment option for these patients [1]. Combinations of total body irradiation (TBI) plus

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cyclophosphamide (CY) and oral busulfan (p.o. BU) plus CY have been considered standard myeloablative conditioning regimens for hematologic malignancies. In patients with ALL, TBI/CY has been associated with better outcomes compared with p.o. BU/CY [2-5], and thus TBI/CY has been the most widely used conditioning regimen for allo-HCT in adult patients with ALL.

TBI has the advantage of eradicating resistant leukemic cells in sanctuary sites, such as the central nervous system and the testes [6]; however, TBI toxicity has been associated with serious adverse events, including cataracts, pneumonitis, and secondary malignancies. BU is an alkylating agent that exerts a potent antileukemic effect without the toxicity associated with TBI; however, the absorption and metabolism of p.o. BU have wide intrapatient and interpatient variability. Studies based on BU pharmacokinetics have shown that low BU levels are associated with an increased risk of relapse [7] and rejection [8]. Conversely, high BU levels are associated with adverse effects [9], including sinusoidal obstruction syndrome (SOS; previously known as veno-occlusive disease [VOD]) [10]. To address these issues, i.v. BU has widely replaced p.o. BU in BU-based conditioning regimens for allo-HCT. Previous studies have confirmed that i.v. BU–based regimens reduce the incidence of SOS, the rate of nonrelapse mortality (NRM) [11], and the risk of relapse [12] in patients with hematologic malignancies, and a retrospective study of patients with acute myelogenous leukemia (AML) found that i.v. BU/CY, but not p.o. BU/CY, was associated with superior leukemia-free survival and overall survival (OS) compared with a TBI/CY regimen [13]. Moreover, a prospective cohort analysis in patients with myeloid malignancies showed that i.v. BU–based regimens resulted in superior survival with no increased risk of relapse or transplantation-related mortality (TRM) compared with TBI-based regimens [14]. Another recent retrospective study comparing TBI/CY, p.o. BU/CY, and i.v. BU/CY in patients with chronic myelogenous leukemia (CML) showed that i.v. BU/CY was associated with a lower relapse rate compared with TBI/CY [12].

The data comparing i.v. BU/CY and TBI/CY in adults with ALL are limited. Because ALL carries a high risk of central nervous system involvement, TBI-based regimens may offer an antileukemic advantage over BU-based regimens; however, if i.v. BU/CY has at least equal efficacy as TBI/CY, patients could achieve prolonged survival with i.v. BU/CY while avoiding the toxic effects of TBI. The aim of the present study was to compare outcomes in adults with ALL who underwent allo-HCT following myeloablative conditioning with TBI/CY, p.o. BU/CY, or i.v. BU/CY. We used data from the Transplant Registry Unified Management Program of the Japan Society of Hematopoietic Cell Transplantation (JSHCT).

PATIENTS AND METHODS

Patient Selection and Data Source

This retrospective study enrolled patients aged 16 years and older who underwent first allo-HCT for ALL while in complete remission (CR) following myeloablative conditioning with TBI/CY, p.o. BU/CY, or i.v. BU/CY between January 1, 2000, and December 31, 2012. The patient data were provided by the Transplant Registry Unified Management Program of the JSHCT. Information on transplantation, including survival, disease status, chronic graft-versus-host disease (GVHD), and secondary malignancies, was reviewed annually using follow-up forms. This study was approved by the Data Management Committee of the JSHCT and the Ethics Committee of Tokyo Women's Medical University (approval 3091) and was conducted in accordance with the Declaration of Helsinki.

Study Endpoints and Definitions

The primary endpoint was OS, defined as the interval from the time of transplantation to the time of death from any cause. Secondary endpoints were relapse-free survival (RFS) and nonrelapse mortality (NRM). Relapse was defined by hematologic criteria, and RFS was defined as time to treatment failure (death or relapse). NRM was defined as death without evidence of leukemia relapse. Times to neutrophil and platelet engraftment were calculated as the time from transplantation to the first achievement of 3 consecutive days with an absolute neutrophil count ≥500/μL and a platelet count $\geq 2.0 \times 10^4$/μL 7 days from the last platelet transfusion, respectively. Acute GVHD was graded according to consensus criteria based on the the pattern of severity of abnormalities in skin, gastrointestinal tract, and liver [15]. Chronic GVHD was diagnosed according to established criteria [16]. We defined myeloablative conditioning regimens as having a dosage of p.o. BU ≥9 mg/kg, i.v. BU ≥7.2 mg/kg [17], or TBI ≥8 Gy (fractionated).

Statistical Analysis

We compared characteristics of patients according to conditioning regimen using the chi-square test and Kruskal-Wallis test (for age). OS and RFS were estimated by the Kaplan-Meier method. Rates of relapse, NRM, engraftment, GVHD, and SOS were estimated by the cumulative incidence method to account for competing risks [18]. NRM was the competing event for relapse, and relapse was the competing event for NRM. For engraftment, GVHD, and SOS, death without the event was considered a competing event. Survival and incidence curves were compared using the log-rank test. An adjusted comparison of conditioning regimens for OS, RFS, NRM, GVHD, and SOS was performed by multivariate analysis using the Cox proportional hazards regression model with backward stepwise selection of all variables. The variables considered in addition to conditioning regimen were age at transplantation, sex, disease status, stem cell source (related bone marrow, related peripheral blood, unrelated bone marrow, or cord blood), Philadelphia chromosome positivity, performance status at transplantation, and year of transplantation. Interactions between each selected variable and the main effect were evaluated. A P value <.05 was considered statistically significant. All statistical analyses were performed using Stata version 13 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

A total of 2130 patients underwent first allo-HCT for ALL in CR after myeloablative conditioning using TBI/CY, p.o. BU/CY, or i.v. BU/CY. Characteristics of patients categorized according to conditioning regimen are summarized in Table 1. Among all conditioning regimens, the majority of patients underwent allo-HCT at first CR (83.4% for TBI/CY, 78.3% for p.o. BU/CY, and 78.6% for i.v. BU/CY) with a performance status of 0 or 1 (90.3% for TBI/CY, 80.0% for p.o. BU/CY, and 92.9% for i.v. BU/CY). Patients in the TBI/CY group were younger (61.4% age 16 to 39 years) than patients in the p.o. BU/CY group (43.3% age 16 to 39 years) and or i.v. BU/CY group (52.4% age 16 to 39 years). Unrelated bone marrow was the most common stem cell source in all 3 groups (48.5% for TBI/CY, 36.7% for p.o. BU/CY, and 42.9% for i.v. BU/CY). Cord blood was used more frequently in the TBI/CY group compared with the

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