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The Sequence of Cyclophosphamide and Myeloablative Total Body Irradiation in Hematopoietic Cell Transplantation for Patients with Acute Leukemia

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A B S T R A C T

Limited clinical data are available to assess whether the sequencing of cyclophosphamide (Cy) and total body irradiation (TBI) changes outcomes. We evaluated the sequence in 1769 (CyTBI, n = 948; TBICy, n = 821) recipients of related or unrelated hematopoietic cell transplantation who received TBI (1200 to 1500 cGY) for acute leukemia from 2003 to 2010. The 2 cohorts were comparable for median age, performance score, type of leukemia, first complete remission, Philadelphia chromosome–positive acute lymphoblastic leukemia, HLA-matched siblings, stem cell source, antithymocyte globulin use, TBI dose, and type of graft-versus-host disease (GVHD) prophylaxis. The sequence of TBI did not significantly affect transplantation-related mortality (24% versus 23% at 3 years, $P = .67$; relative risk, 1.01; $P = .91$), leukemia relapse (27% versus 29% at 3 years, $P = .34$; relative risk, .89, $P = .18$), leukemia-free survival (49% versus 48% at 3 years, $P = .27$; relative risk, .93; $P = .29$), chronic GVHD (45% versus 47% at 1 year, $P = .39$; relative risk, .9; $P = .11$), or overall survival (53% versus 52% at 3 years, $P = .62$; relative risk, .96; $P = .57$) for CyTBI and TBICy, respectively. Corresponding cumulative incidences of sinusoidal obstruction syndrome were 4% and 6% at 100 days ($P = .08$), respectively. This study demonstrates that the sequence of Cy and TBI does not impact transplantation outcomes and complications in patients with acute leukemia undergoing hematopoietic cell transplantation with myeloablative conditioning.

INTRODUCTION

Controversy concerning the optimal conditioning regimen and sequence of modalities for patients with hematologic malignancies still persists. The optimal regimen would maximize tumor cell kill and minimize toxicities. Cyclophosphamide (Cy) and total body irradiation (TBI) have

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been used in combination as a preparative regimen for high-risk hematologic malignancies for several decades. Animal preclinical data in the early 1990s showed that Cy given 24 hours after TBI (TBICy) caused less lung damage but more bone marrow damage in the murine model [1,2]. Lowenthal et al. showed that the reverse, or CyTBI, offers an improved antileukemic effect, compared with TBICy, in mice with B cell leukemia/lymphoma [3]. The optimal sequence of these agents in the preparative regimen and the associated impact on clinical outcomes, such as transplantation-related mortality (TRM) and leukemia relapse, has not been systematically studied to date.

Synergism between chemotherapy and radiation therapy exists. In early studies, TBI was used solely as the conditioning regimen [4]. The goal of TBI is to obliterate the host marrow, deplete residual leukemia, and allow for donor marrow cells to repopulate through immune-ablation. TBI has high efficacy; however, there is controversy over the optimal dose, as higher doses have been related to increased incidence of graft-versus-host disease (GVHD) and mortality, thought to be triggered by radiation-related tissue damage [5]. A TBI-only regimen was less effective at lower doses of TBI and more toxic at higher doses of TBI (1400 to 2000 cGy) [6]. Cy was later added to the regimen, permitting lower TBI doses to be used, thereby decreasing the incidence of pulmonary toxicity while maintaining stable rates of leukemia relapse and immune-ablation [7]. The standard regimen for adults used for disease ablation and immunosuppression in patients with leukemia was established in the early 1970s and is Cy 60 mg/kg/day for 2 days for adults (4 days for children) followed by 3 to 4 days of TBI [7]. A number of modifications to this regimen have been introduced to improve the rates of engraftment and reduce the relapse rate and radiation complications [8,9]. Another rationale for changing the sequence in the conditioning regimens was related to Cy-induced emesis, which could affect the scheduling of subsequent TBI. Despite evidence that CyTBI is a good choice of myeloablative regimen, no overall consensus on timing of TBI and Cy has been investigated in large series.

This is a common clinical question in cases of conflicting schedules of irradiation treatment days and arrival or availability of a stem cell product for transplantation. The goal of this study was to compare CyTBI to TBICy in terms of the incidence of GVHD, leukemia relapse, and incidence of sinusoidal obstruction syndrome (SOS).

METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive hematopoietic cell transplantations to a statistical center located at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. The CIMBTR maintains an extensive database of detailed patient-, transplantation-, and disease-related information, and prospectively collects data longitudinally with yearly follow-ups. Observational studies conducted by the CIBMTR are performed in compliance with Health Insurance Portability and Accountability Act regulations as a public health authority and also in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by a continuous review by the institutional review boards of National Marrow Donor Program and the Medical College of Wisconsin [10].

Patients

Patients were younger than 60 years, received hematopoietic cell transplantation with Cy and TBI with myeloablative doses of 1200 to 1500 cGY for treatment of acute leukemia in first or second complete morphologic remission from 2003 to 2010, and reported to the CIBMTR. Patients who received umbilical cord blood grafts, haploidentical or other HLA-mismatched donors, or ex vivo T cell depletion were excluded. Median follow-up of cohort was 56 months and the completeness index [11] (the observed/the expected follow-up) for a 3-year analysis was 88%. Eligible patients were separated according to the sequence of agents into CyTBI and TBICy groups based on the reported dates of administration of Cy and TBI.

Outcome

The conditioning regimen sequence was compared according to overall survival (OS), leukemia-free survival (LFS), TRM, leukemia relapse, GVHD, and SOS. Events of GVHD and SOS were defined by transplantation centers. GVHD data included date of onset, organ involvement, and maximum grade. SOS data includes differential diagnosis and supporting clinical and diagnostic information. *OS* was defined as death by any cause and patients were censored at time of last follow-up. Leukemia relapse or death was recorded as the event for the LFS outcome. *TRM* was defined as any death in the absence of prior leukemia relapse. GVHD was analyzed as grades III and IV and II to IV acute (aGVHD) according to modified Gluksberg [12] and chronic GVHD (cGVHD).

Statistical Analysis

Eligible patients were separated into 2 cohorts according to the sequence of TBI and Cy (CyTBI and TBICy), defined according to date of initiation of each component of the conditioning regimen. Selected variables were described for both cohorts, continuous variables were compared by Kruskall Wallis test, and categorical variables by chi-square test to assess significant differences (defined as P value $< .05$).

Survival outcomes including OS and LFS were computed using Kaplan-Meier and comparison was done with log rank test. For leukemia relapse, TRM and GVHD outcomes, and SOS incidence, cumulative incidence was used to account for competing risks. Cox proportional hazards regression models for overall mortality, treatment failure (inverse of LFS), relapse and TRM were built using a forward selection approach forcing the main effect covariates (TBICy versus CyTBI) on all outcomes. The covariates analyzed include age, gender, performance score, donor-recipient gender, disease and disease status, cytogenetic risk stratification (for acute myeloid leukemia (AML) according to the Southwest Oncology Group/Eastern Cooperative Oncology Group classification [13]: favorable, intermediate, poor, or unknown; for acute lymphoid leukemia (ALL): presence of Philadelphia chromosome [Ph+], Ph negative and Ph status unknown), year of transplantation, donor type (sibling, well matched, and partially matched unrelated donor) [14], dose of TBI (12 Gy versus 13 Gy), donor recipient cytomegalovirus status, graft source, in vivo T cell depletion. Disease status and cytogenetic assessments were performed at the transplantation center and reported to the CIBMTR. The final model included all covariates significantly associated with the outcome ($P < .05$) and the main effect. Test for proportional hazards was included in case of nonproportional hazards during the study period and test for interactions was done between the main effect covariates and all significant covariates in each model.

RESULTS

Demographics

A total of 948 patients received CyTBI and 821 received TBICy. The 2 cohorts were comparable for patient-, disease-, and transplantation-related characteristics (Table 1) with the exception of age and Cy dose. The median age was 33 in the CyTBI group and 35 in the TBICy group ($P < .01$). The median Cy dose was 108 mg/kg in the CyTBI group and 115 mg/kg in the TBICy group ($P = .01$). The median interval between starting TBI and Cy was 2 and 4 days for CyTBI and TBICy, respectively.

GVHD

Cumulative incidences of grade II to IV aGVHD at day 100 were 39% (95% confidence interval [CI], 35% to 42%) and 45% (95% CI, 41% to 48%; $P = .01$), and of grades III and IV aGVHD were 16% (95% CI, 13% to 18%) and 15% (95% CI, 12% to 17%; $P = .60$) for CyTBI and TBICy, respectively (Figure 1). Multivariate analysis comparing CyTBI to TBICy demonstrated a relative risk for grades II to IV aGVHD of .87 (95% CI, .75 to 1.00; $P = .05$) and for grades III and IV aGVHD of 1.09