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Comparison of Outcomes for Pediatric Patients With Acute Myeloid Leukemia in Remission and Undergoing Allogeneic Hematopoietic Cell Transplantation With Myeloablative Conditioning Regimens Based on Either Intravenous Busulfan or Total Body Irradiation: A Report From the Japanese Society for Hematopoietic Cell Transplantation



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ABSTRACT

Pediatric patients with acute myeloid leukemia (AML) mainly receive myeloablative conditioning regimens based on busulfan (BU) or total body irradiation (TBI) before allogeneic hematopoietic cell transplantation (allo-HCT); however, the optimal conditioning regimen remains unclear. To identify which of these regimens is better for pediatric patients, we performed a retrospective analysis of nationwide registration data collected in Japan between 2006 and 2011 to assess the outcomes of patients receiving these regimens before a first allo-HCT. Myeloablative conditioning regimens based on i.v. BU (i.v. BU-MAC) (n = 69) or TBI (TBI-MAC) (n = 151) were compared in pediatric AML patients in first or second complete remission (CR1/CR2). The incidences of sinusoid obstruction syndrome, acute and chronic graft-versus-host disease, and early non-relapse mortality (NRM) before day 100 were similar for both conditioning groups; however, the incidence of bacterial infection during the acute period was higher in the TBI-MAC group ($P = .008$). Both groups showed a similar incidence of NRM, and there was no significant difference in the incidence of relapse between the groups. Univariate and multivariate analyses revealed no significant differences in the 2-year relapse-free survival rates for the i.v. BU-MAC and TBI-MAC groups in the CR1/CR2 setting (71% versus 67%, $P = .36$;

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hazard ratio, .73; 95% CI, .43 to 1.24, respectively). TBI-MAC was no better than i.v. BU-MAC for pediatric AML patients in remission. Although this retrospective registry-based analysis has several limitations, i.v. BU-MAC warrants further evaluation in a prospective trial.

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INTRODUCTION

Intensive combination chemotherapy results in a 52% to 75% probability of survival for childhood and adolescent patients with acute myeloid leukemia (AML); however, more than 30% of patients relapse [1–4]. Although allogeneic hematopoietic cell transplantation (allo-HCT) is the most promising therapy for intractable disease (eg, cytogenetically unfavorable disease and relapsed disease), the conditioning regimen (as well as effective control of graft-versus-leukemia effects) plays an important role in reducing the incidence of relapse after transplantation [5]. Although pediatric AML patients often receive myeloablative conditioning (MAC) regimens based on total body irradiation (TBI) or busulfan (BU), no optimal regimen has been devised.

Myeloablative TBI conditioning regimens are associated with late complications, which manifest as growth retardation, neurocognitive effects, cataracts, hypothyroidism, gonadal dysfunction, infertility, and a significantly increased risk of a second malignancy [6,7]. Myeloablative BU conditioning regimens can also result in some of these late complications, although the incidence of growth retardation, neurocognitive effects, cataracts, thyroid dysfunction, and second malignancies may be lower [7–10]. Recent studies show treatment of adult AML patients with i.v. BU results in better survival than treatment with TBI [11,12]; however, few reports have examined these regimens in children. Sisler et al. [13] showed conditioning regimens that include TBI have no additional benefit of over those that include BU in pediatric patients beyond first complete remission (CR1). A report by de Berranger et al. [14] demonstrated that disease-free survival was significantly better after BU and cyclophosphamide (CY) than after TBI and CY. However, it should be noted that the patients in these studies received both i.v. and oral BU as a MAC regimen. Also, approximately half of the patients in the latter study received HCT before 2000. On the other hand, another study showed that i.v. BU failed to provide a significant survival advantage in children with acute leukemia when compared with oral BU [15].

The efficacy and adverse events associated with i.v. BU-MAC regimens are unclear, particularly when used to treat pediatric AML patients. Therefore, the present study aimed to compare the outcomes for pediatric AML patients after i.v. BU-MAC or TBI-MAC.

METHODS

Patients and Transplantation

Pediatric patients (aged <18 years) with de novo AML (excluding AML-M3) who underwent a first allo-HCT after either i.v. BU- or TBI-based MAC in CR1 or second CR (CR2) between January 2007 and December 2012 were recruited for the study. Patients were prospectively enrolled in the Japanese Data Center for Hematopoietic Cell Transplantation. Patients with Down's syndrome, Fanconi anemia, or neurofibromatosis type 1 and those who received a graft after ex vivo T cell depletion or CD34⁺ selection or a graft from an HLA-haploidentical donor were excluded. Patients who received combination regimens comprising TBI and BU were also excluded. Finally, data from consecutive patients who received HCT after myeloablative TBI combined with cytotoxic drugs (TBI-MAC) or myeloablative i.v. BU combined with cytotoxic drugs (BU-MAC) were examined. MAC regimens were defined as regimens that included either fractionated TBI >8 Gy or i.v. BU >6.4 mg/kg [16].

Unfavorable cytogenetics/genetics were defined as either 7-/7q-, 5q-, complex karyotype, t(6;11), t(6;9), t(16;21), t(9;22), or as fms-like tyrosine kinase receptor 3 internal tandem duplication. Favorable genetics were defined as either t(8;21) or inv(16). Intermediate genetics were defined as neither unfavorable nor favorable [17,18]. Graft-versus-host disease (GVHD) was graded according to previously published and accepted criteria [19]. Nonrelapse mortality (NRM) was defined as death during continuous remission, and relapse-free survival (RFS) was defined as survival without any relapse of the underlying hematological malignancy or death from any cause.

Statistical Analysis

Pair-wise comparisons of patient, disease, and transplant characteristics (covariates) were performed using Fisher's exact test (for categorical variables). Variables considered in the analysis included year of transplantation (2007 to 2009 versus 2010 to 2012), gender, age at the time of transplantation (<10 versus ≥10), FAB classification (M0, M1, and M2 versus M4 and M5 versus M6 and M7), disease status (CR1 versus CR2), cytogenetics/genetics risk category (favorable versus others), extramedullary/central nervous system involvement (negative versus positive), donor status (matched sibling donor versus others), graft source (bone marrow versus peripheral blood stem cells versus cord blood), donor–recipient HLA-A, -B, and -DR antigen matching (match versus mismatch to GVH direction), donor–recipient ABO group matching (major matching versus major mismatching), donor–recipient gender matching (female-to-male versus other combinations), donor–recipient cytomegalovirus status (negative-to-negative versus other combinations), GVHD prophylaxis (cyclosporine-based prophylaxis versus others), performance status (<2 versus ≥2), comorbidity index (<2 versus ≥2), and conditioning regimen (i.v. BU-MAC versus TBI-MAC). Survival was estimated using the Kaplan-Meier method and log-rank tests, whereas the cumulative incidence between groups was analyzed using Gray's test.

Risk factors associated with relapse, NRM, RFS, and conditioning group were assessed using multivariate Cox and Fine-Gray proportional-hazard models. Parameters with $P < .2$ on univariate analysis were included in the model. NRM was the competing event for relapse, and relapse was the competing event for NRM. Any incidence of death or relapse was the competing event for GVHD onset.

Statistical analyses were performed using STATA 12 (Stata Corp., TX) and EZR data analysis programs [20]. Statistical significance was set at $P < .05$. The present study had 71% power for detecting a 15% difference in the 2-year survival rate between the i.v. BU-MAC and TBI-MAC groups with an error (2-sided) of .05 [20]. The study was approved by the institutional review boards of Matsushita Memorial Hospital and by the Japanese Society for Hematopoietic Cell Transplantation committee.

RESULTS

Patient Characteristics

Data from 220 patients who received either i.v. BU-MAC ($n = 69$) or TBI-MAC ($n = 151$) were analyzed in detail. Intravenous BU-MAC comprised BU plus CY or BU plus melphalan (MEL) either with or without another cytotoxic drug ($n = 13$ and $n = 52$, respectively) or other miscellaneous combinations, including BU ($n = 4$), whereas TBI-MAC comprised TBI plus CY or TBI plus MEL either with or without another cytotoxic drug ($n = 107$ and $n = 42$, respectively) or other miscellaneous combinations, including TBI ($n = 2$). Preliminary analyses revealed that RFS after TBI and CY ± another cytotoxic drug was similar to that after TBI and MEL ± another cytotoxic drug (2-year-RFS: 65% versus 71%, respectively; $P = .51$) and that RFS after i.v. BU and CY ± another cytotoxic drug was similar to that after i.v. BU and MEL ± another cytotoxic drug (2-year-RFS: 71% versus 71%, respectively; $P = .87$). We therefore compared the outcomes after i.v. BU-MAC with those after TBI-MAC.

Table 1 summarizes patient characteristics, comorbidities, and transplant procedures for each conditioning group.

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