One- or two-day intervals in conditioning regimens for allo-HCT affect chronic graft-versus-host disease, but not other clinical outcomes

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Abstract

Background. One- or two-day intervals are generally inserted into scheduled conditioning regimens for allogeneic hematopoietic cell transplantation (HCT), primarily due to various social circumstances, such as unexpected natural adversities, abrupt deterioration of patient health, and delays in graft source arrival. We compared the clinical outcomes of patients with interrupted conditioning to those with ordinarily scheduled conditioning. *Procedure.* We retrospectively analyzed 83 patients (children and adolescents) with oncologic disease who underwent myeloablative conditioning with total body irradiation (TBI). Interruption of conditioning was defined as a regimen in which one or two vacant days (no chemotherapy drug administration or TBI) were added to the initially scheduled regimen. *Results.* Overall and event-free survival were similar between the scheduled conditioning group and the interrupted conditioning groups ($P = 0.955$, $P = 0.908$, respectively). Non-relapse mortality and relapse rates were similar between the groups ($P = 0.923$, $P = 0.946$, respectively). The engraftment rate was not affected by interruption ($P = 1.000$). In contrast, the incidence of grade II–IV acute graft-versus-host disease (GVHD) reached a marginally significant difference between the groups (31% vs. 11%; $P = 0.083$). Conditioning interruption was identified to be an independent risk factor for chronic GVHD by multivariate analysis (odds ratio: 3.72; 95% CI: 1.04–13.3; $P = 0.043$). *Conclusion.* Apart from the incidence of chronic GVHD, clinical outcomes were not affected by one- or two-day intervals during conditioning.

Introduction

Many studies of conditioning regimens for hematopoietic cell transplantation (HCT) have been conducted over the last few decades, and various regimens are now available. Furthermore, conditioning intensity and its effects on transplantation outcomes have been well researched, which has led to decreased transplantation-associated morbidity and mortality [1-4]. Several studies have revealed the equivalence of a reduced intensity regimen, in terms of overall survival (OS) and event-free survival (EFS), in comparison to a conventional myeloablative conditioning (MAC) regimen [5-8]. Additionally, the incidence of graft-versus-host disease (GVHD) is known to be affected by conditioning intensity [9-13]. However, there are no reports concerning the relationship between clinical outcomes and differences in scheduling strategies for conditioning regimens consisting of equivalent doses and types of chemotherapeutic agents and total body irradiation (TBI).

Conditioning regimens for HCT should be performed according to the usual standards and timescales. Nonetheless, one- or two-day intervals are occasionally enacted during the conditioning period because of hospital closure, predetermined dates of unrelated donor HCT, or simultaneous HCTs for multiple patients. Furthermore, unexpected situations requiring HCT postponement can occur. Therefore, it is important to

identify potential negative effects of HCT conditioning interruptions on clinical outcomes. We evaluated this hypothesis in pediatric patients with oncologic diseases undergoing HCT after MAC.

Subjects and Methods

Patient eligibility

A total of 83 children and adolescents with a malignant disease underwent allogeneic hematopoietic cell transplantation (allo-HCT) after MAC with TBI at Sapporo Hokuyu Hospital between October 1994 and July 2018. All of the patients were enrolled in this study, and their clinical data were retrospectively evaluated by December 31st, 2019. All enrolled patients were $<$ 20 years old, and their diagnoses of hematologic malignancies were: acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, juvenile myelomonocytic leukemia, myelodysplastic syndromes, and non-Hodgkin lymphoma. Additionally, the diagnoses for solid tumors included neuroblastoma and hepatoblastoma. Ninety-two percent of the diagnoses were hematologic malignant disease. The enrolled patients received HCT from related or unrelated donors at either complete remission or incomplete remission.

This study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee at Sapporo Hokuyu Hospital, Sapporo, Japan.

Transplant details and GVHD prophylaxis

Both donor types (related or unrelated) contained matched or mismatched grafts. Graft sources were derived from bone marrow, peripheral blood, or cord blood. All conditioning regimens utilized for the eligible patients involved MAC with 12 or 13.2 Gy of TBI. TBI was administered to the patients in six fractions (two fractions per day). Different GVHD prophylaxis was adopted according to the administered graft source. GVHD prophylaxis for cord blood transplantation (CBT) consists of cyclosporin (CSA) and methylprednisolone. Most GVHD prophylaxis for HCT from the graft of a related donor consisted of CSA and methotrexate (MTX). Prophylaxis for HCT from a graft of an unrelated donor consisted of tacrolimus and MTX.

Study endpoints and definitions

The objective of this study was to clarify the impact of conditioning interruptions on clinical outcomes after HCT. Clinical endpoints included OS, EFS, non-relapse mortality (NRM), relapse rate (RR), engraftment, and acute or chronic GVHD incidence. The incidences of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), thrombotic microangiopathy (TMA), and interstitial pneumonia were evaluated as transplantation-associated complications. EFS was defined as survival without death due to any cause, or survival without recurrence of the primary disease. NRM was defined as death for any reason other than primary disease relapse or progression, and RR was estimated by considering death without prior relapse as a competing event. The engraftment definition was attainment of $> 0.5\times10^9$/L absolute neutrophil count for three consecutive days. The diagnosis and grading of acute graft-versus-host disease (aGVHD) were implemented based on the manifestation of skin, intestine, and liver symptoms arising within 100 days after HCT. Other causes for the symptoms were excluded. The aGVHD grading was conducted according to the consensus conference on aGVHD grading in 1994 [14]. The diagnosis of chronic graft-versus-host disease (cGVHD) was also made using the signs and symptoms of cGVHD occurring beyond 100 days after HCT. The distinctive symptoms of cGVHD employed were similar to those specified in the National Institute of Health criteria for cGVHD in 2005 [15].

Interruption of conditioning was defined as a regimen in which one or two vacant days (no chemotherapy drug administration or TBI) were added to the initially scheduled regimen. Examples of interrupted conditioning are shown in Figure 1.

Statistical analysis

Fisher's exact test was used for categorical variables. The Mann-Whitney U test was used for continuous variables such as the baseline characteristics and clinical endpoints of the patients. These tests were used to evaluate differences between the scheduled and interrupted groups. OS and EFS were estimated using

the Kaplan-Meier method and compared with the log-rank test. The comparison of NRM and cumulative incidence of relapse were evaluated using Gray's test.

A multivariate logistic regression model was created to identify the statistically significant clinical variables contributing to the incidence of cGVHD. Categorical variables with P -values< 0.1 in the univariate analysis for the factors causing cGVHD were entered into the model. The categorical variables were sequentially eliminated in a stepwise backward fashion. Factors with a significance level of < 0.05 were retained in the final model. A P -value of [?] 0.05 was considered statistically significant. All statistical analyses were performed with Easy R (EZR), a graphical user interface for R (The R Foundation for Statistical Computing). EZR is a modified version of the T commander designed to add statistical functions frequently used in biostatistics [16].

Results

Patient characteristics

Baseline patient characteristics in the two cohorts are summarized in Table 1. Among the 83 analyzed patients, 64 underwent the ordinarily scheduled conditioning regimen and 19 had their conditioning regimen interrupted. The mean number of interrupted days was 1.4 days, and the interval during TBI was set for eight out of 19 patients with interrupted conditioning. The median age at HCT in the scheduled group was 9.5 years old (a range of 1.5–19.9), and 10.9 years old (range, 3.5–19.5) in the interrupted group.

No significant differences between the groups were detected in the stage at transplantation ($P = 0.721$). TBI combined with etoposide and cyclophosphamide was the most frequently used regimen in this study. The type of conditioning regimen adopted and the drug used in conditioning were also not significantly different between the two groups ($P = 0.537$ and $P = 0.803$, respectively).

Regarding transplantation status, cord blood grafts were occasionally utilized. This procedure was mostly used for unrelated donor grafts and the minority of HLA-matched grafts in this study. The type of graft source was statistically well matched between the two groups ($P = 0.660$). Regarding the drugs used for GVHD prophylaxis, tacrolimus was used more frequently in the interrupted group than in the scheduled group ($P = 0.022$).

Transplantation outcomes

The median administered $CD34^+$ cell dose was the same between the scheduled and interrupted groups ($2.2\text{x}10^6$/kg and $2.0\text{x}10^6$/kg for the scheduled and interrupted groups, respectively; $P = 0.845$). Engraftment was achieved in most enrolled patients (92% and 95% of the scheduled and interrupted groups, respectively; $P = 1.000$). The median days until engraftment was also not significantly different between the two groups (18 days vs. 19 days; $P = 0.976$). The 5-year OS and EFS in the interrupted group were the same as the scheduled group (53% vs. 52%; $P = 0.955$; and 47% vs. 45%;$P = 0.908$, respectively). These results are shown in Figure 2. Additionally, the 5-year NRM and RR were similar between the scheduled and interrupted groups (16% vs. 16%; $P = 0.923$; and 42% vs. 44%; $P = 0.946$, respectively). The incidence of transplantation-associated complications was not different between the two groups (VOD/SOS; 6.3% vs. 5.3%, $P = 1.000$, TMA; 4.7% vs. 0.0%, $P = 1.000$, interstitial pneumonia; 9.4% vs. 5.3%,$P = 1.000$).

The incidences of acute and chronic GVHD in the two cohorts are summarized in Table 2. Overall, aGVHD was more often identified in the scheduled group than in the interrupted group, although the differences were not statistically significant. The incidence of aGVHD in grades I–IV in the scheduled and interrupted groups was 42% and 26%, respectively ($P = 0.286$). Moreover, there was a trend toward a higher incidence of grades II–IV aGVHD in the scheduled group compared to the interrupted group (31% vs. 11%; $P = 0.083$). The incidence of aGVHD in grades III–IV was also higher in the scheduled group than in the interrupted group (19% vs. 5%; $P = 0.280$). Furthermore, the group with interrupted conditioning showed a marginally significant tendency toward a higher incidence of cGVHD than the scheduled conditioning group (42% vs. 19%; $P = 0.063$). The categorical variables entered into the multivariate model were age of [?] 10 years, female, interruption of conditioning, use of cyclosporin, and tacrolimus. Consequently, interrupted

conditioning for allo-HCT was confirmed by the multivariate analysis to be an independent risk factor for cGVHD (odds ratio: 3.72; 95% CI: 1.04–13.3; $P = 0.043$). Additionally, age of [?] 10 years and female gender were also identified as significant risk factors for cGVHD. These results and the results of univariate analysis for cGVHD are shown in Tables 3 and 4.

Discussion

One or two non-treatment days are occasionally added to initial HCT conditioning regimens due to various social circumstances, such as unexpected natural adversities, abrupt deterioration of patient health, and delays in graft source arrival. Consequently, concerns pertaining to the impact of interrupted conditioning on clinical outcomes after HCT have arisen as a consequential issue.

Remarkably, in our cohorts, it was shown that the clinical outcome after HCT was not affected by conditioning interruption. The 5-year OS and EFS were the same between the groups with or without interruption of conditioning. Moreover, the cumulative incidences of relapse and NRM were not significantly different between the groups. We also found that engraftment was not affected by a few-day interruption of conditioning. In contrast, marginal differences were observed in GVHD incidence between the groups. In this study, grade II–IV aGVHD was observed less often in the interrupted conditioning group, with marginal significance. However, a significantly higher incidence of cGVHD was observed in the interrupted conditioning group, as demonstrated by the multivariate model.

Generally, it is presumed that adding one- or two-day intervals into the conditioning regimen leads to the attenuation of conditioning intensity. It is also assumed that the non-treatment days could allow malignant cells to recover from the toxicity caused by chemotherapeutic agents or TBI. However, it is noted that the capacity for toxicity recovery is likely to be decreased more in tumor cells than in normal cells and is expected to be heterogeneous in each type of cancer cell [17-20]. Moreover, it is not known if the repair capacity of tumor cells recovers in a short period of a few days [21-24]. Thus, it is challenging to determine whether the interrupted conditioning decreases anti-tumor effects. Herein, potential negative impacts of conditioning interruption on clinical outcomes, other than the incidence of cGVHD, were assessed.

It is conceivable that normal tissue would benefit from conditioning interruption because of the possibility of recovering from tissue damage and inflammation before HCT [17,25]. However, there were no differences in a transplantation-associated complications between the two groups in the present study.

Regarding aGVHD, differences in tissue damage severity and donor chimerism formation due to interrupted conditioning could be a plausible explanation for the observed lower incidence of aGVHD in the interrupted group [26-30]. It has been reported that patients with mixed chimerism experienced aGVHD less often than patients who attained donor chimerism early after HCT [31-32]. Furthermore, it has been noted that cGVHD development was delayed and of less severity when the state of mixed chimerism was prolonged [33]. Moreover, a study identified reduced-intensity conditioning as a risk factor for cGVHD [34]. In relation to this, it has been reported that a mixed chimerism state was related to high levels of pathogenic IgG autoantibody and the development of cGVHD-like lesions in a murine model. This result was explained by the persistence of host B cells after HCT [35]. Thus, changes in timing or state of donor chimerism caused by interruption of conditioning might affect the present results regarding aGVHD and cGVHD incidences between the scheduled and interrupted conditioning groups.

This study is limited by its retrospective nature and small sample size, especially the small number of patients in the interrupted conditioning group. This limitation did not permit sub-analysis stratified by graft source or donor source. Additionally, the present results would not apply to other conditioning regimens because the narrow study population only contained pediatric patients who received MAC with TBI.

In conclusion, one- or two-day interruptions of HCT conditioning appeared to have no effect on OS and EFS. However, interrupted conditioning could affect the incidence of GVHD and be a risk factor for cGVHD. The relationship between a few-day interval during conditioning and GVHD development and its mechanism requires further elucidation in future studies.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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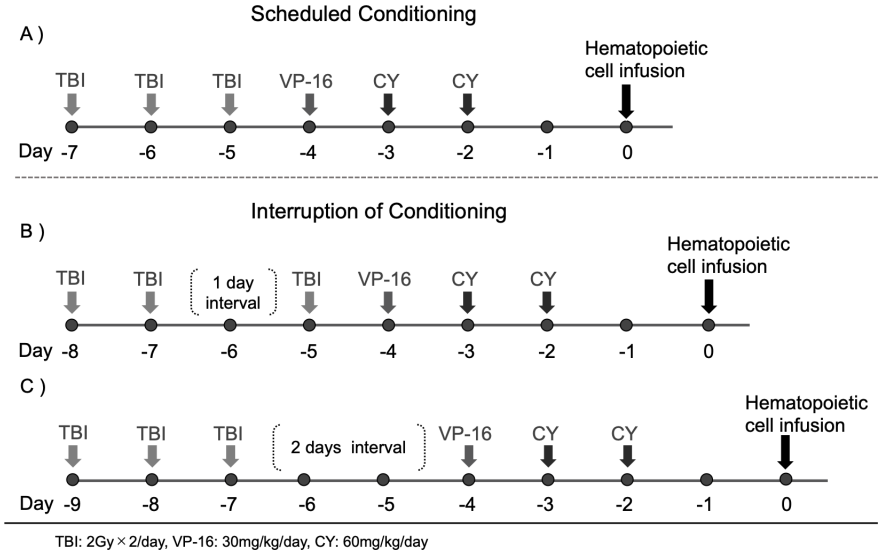
Legends

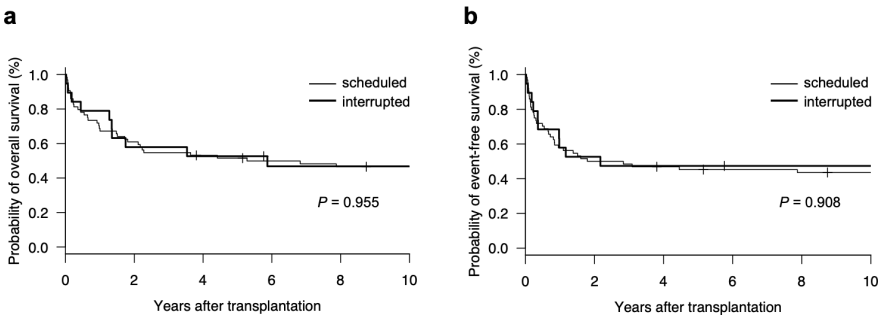
Figure 1.

Examples of interrupted conditioning regimens. Normal conditioning regimen (a). Interrupted conditioning regimens (b, c).

Figure 2.

Comparison of 5-year overall survival (OS) and event-free survival (EFS) between scheduled and interrupted conditioning groups. 5-year OS is 52% in the scheduled conditioning group and 53% in the interrupted conditioning group ($P = 0.955$). 5-year EFS is 45% in the scheduled conditioning group and 47% in the interrupted conditioning group ($P = 0.908$).





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