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Impacts of graft-versus-host disease on outcomes after allogeneic hematopoietic stem cell transplantation for chronic myelomonocytic leukemia: A nationwide retrospective study

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a therapeutic option that may lead to improved outcomes in patients with chronic myelomonocytic leukemia (CMML). However, few studies have examined the impact of the grade of graft-versus-host disease (GVHD) on post-transplant outcomes for CMML. We retrospectively analyzed the outcomes of 141 patients with CMML who underwent allo-HSCT between 1987 and 2010, and achieved neutrophil engraftment. The effects of acute GVHD (aGVHD) or chronic GVHD (cGVHD) on overall survival (OS), leukemia-associated mortality (LAM), and transplant-related mortality were evaluated by hazards regression models, in which the onset date of aGVHD or cGVHD was treated as a time-dependent covariate. Grade I aGVHD was associated with better OS and lower LAM ($P=0.042$, $P=0.033$, respectively) than no GVHD in univariate analyses, but not in the multivariate analyses. The multivariate analyses demonstrated that extensive cGVHD significantly associated with better OS (Hazard Ratio [HR] 0.35 [95% confidence intervals (CI), 0.16–0.74]; $P=0.007$) and lower LAM (HR 0.36 [95% CI, 0.14–0.92]; $P=0.033$) in patients who were not in complete remission at transplantation. In conclusion, the occurrence of cGVHD may be an important factor affecting the outcomes of CMML patients who received transplantation.

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1. Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder, classified as a myelodysplastic/myeloproliferative neoplasm, and characterized by monocytic proliferation in peripheral blood and less than 20% myeloblasts in bone marrow [1]. CMML is a rare entity, accounting for less than 10% of all cases of MDS [2,3].

Current treatment options for patients with CMML include supportive care, cytoreductive therapies, intensive chemotherapies, and hypomethylating agents (HMA) [4–9]. These therapies have been shown to improve symptoms and control the proliferation of abnormal cells, but are insufficient to achieve long-term survival or a cure. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has emerged as a promising therapeutic option for patients with CMML, with the overall survival (OS) rate at 3 years being approximately 30% [10–17]. Therefore, recent recommendations for the management of CMML state that allo-HSCT should be considered as a therapeutic option for high-risk patients with CMML aged younger than 60 years [18].

Although it has been reported that CMML patients received allo-HSCT showed the better outcomes, which patients are likely to benefit most have not yet been identified. Previous studies have reported the favorable effects of donor lymphocyte infusion on the outcomes of patients, and suggested a potent graft-versus-leukemia (GVL) effect [10,11]. A recent literature review also showed that the occurrence of acute GVHD (aGVHD) was associated with a lower relapse rate and better relapse-free survival [19]. However, few studies have focused on the different effects of GVHD grades on post-transplant outcomes through more detailed analysis in a larger study population. We therefore conducted this study including 141 patients with CMML who achieved neutrophil engraftment after allo-HSCT. The aim of this study was to determine the impact of GVHD on post-transplant outcomes in the patients with CMML. We also discuss the contribution of GVL effect for CMML.

2. Methods

2.1. Data collection

The data source was a network database named the "Transplant Registry Unified Management Program (TRUMP)", which consists of the 3 largest HSCT registries in Japan: the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program, and the Japan Cord Blood Bank Network. Details of the data source have been described previously [20,21]. Data on patients with *de novo* CMML who had received their first allo-HSCT between August 1987 and December 2010 and were followed-up until December 2011, were obtained through JSHCT after the approval of the Data Management Committees of JSHCT (approval no. 8-4), as well as the Institutional Ethics Committee of the Nagasaki University hospital (approval no. 12052896), in which this study was organized.

2.2. Inclusion criteria

The original dataset consisted of 3036 adults who were diagnosed as having myelodysplastic syndromes (MDS), as defined by the FAB classification including CMML, aged 16 years or older at transplantation. Data on 177 patients with CMML were submitted from this dataset. Of these, patients who had a history of prior autologous HSCT, who received anti-thymocyte globulin as a preconditioning regimen ($n = 10$), and who developed primary or secondary graft failure ($n = 26$) were excluded from the analysis. Data included the patient's clinical characteristics such as age at transplantation, sex, disease status at transplantation, date of transplantation, time from diagnosis to transplantation, human leukocyte antigen (HLA) identity determined by serologic or molecular typing for HLA-A, HLA-B, and HLA-DR loci, source of stem cells, preconditioning regimens, date last known alive, date and cause of death, and incidence and severity of aGVHD and cGVHD. Two physicians (H.I and M.I) independently reviewed the quality of the collected data. Finally, a total of 141 patients met these criteria and were included in this study. No patients received HMA prior to allo-HSCT in this cohort, because HMA was not available in Japan as of 2010.

Definitions. Age at transplantation was classified as ≤49 years or >49 years according to the median value. Cytogenetic data at diagnosis were classified into two groups; a low-risk group (Good plus Intermediate) and a high-risk group (Poor), according to the International Prognostic Scoring System (IPSS) for MDS [22]. Disease status at transplantation was divided into complete remission (CR) after chemotherapy or others. The year of transplantation was grouped into two periods, 1987–2000 or 2001–2010.Time from diagnosis to transplantation was classified as ≤7.48 months or >7.48 months according to median value. Donors were classified as HLA-matched-related donor or alternative donor, and the stem cell sources were classified as bone marrow, peripheral blood, or cord blood. Conditioning regimens were classified as either myeloablative or reduced intensity-conditioning according to the established criteria [23]. Neutrophil engraftment was defined by the recovery of absolute neutrophil count of at least 0.5×10^9/L for three consecutive points after HSCT. GVHD prophylaxis was either cyclosporine-based or tacrolimus-based regimen.

Diagnosis and clinical grading of aGVHD and cGVHD were performed according to standard criteria [24,25]. The status of aGVHD was categorized into two groups; no aGVHD and any aGVHD, or into three groups; no aGVHD, grade I aGVHD, and grade II–IV aGVHD. The status of cGVHD was classified as no cGVHD and any cGVHD, or into three groups; no cGVHD, limited cGVHD, and extensive cGVHD.

Three outcome measures, OS, LAM, and TRM, were considered in this study. For the three outcomes, data on patients who were alive at the time of the last follow-up were censored. Causes of death were categorized into LAM or TRM; the former was defined as death after relapse or progression of CMML, and the latter was defined as any death other than LAM.

2.3. Statistical analysis

Continuous variables were compared using the Wilcoxon rank sum test or Kruskal–Wallis test. Categorical variables were compared between groups using the chi-square test or Fisher's exact test. To assess the effects of aGVHD or cGVHD on the three outcomes, the onset date of aGVHD or cGVHD was treated as a time-dependent covariate.

The probability of OS was estimated by the Kaplan–Meier method and group comparisons were performed by the log-rank test, in which semi-landmark analyses were performed as follows: for patients with aGVHD, the individual onset date of aGVHD was termed as the landmark day, whereas, for patients who were disease free and without a diagnosis of aGVHD, day 22 was termed as the landmark day, which was the median day of onset of aGVHD. For patients with cGVHD, the individual onset date of cGVHD was termed as the landmark day, whereas, for patients without cGVHD, day 138 was termed as the landmark day, which was the median day of the onset of cGVHD. In these analyses, patients who died or were censored before the respective landmark day point were excluded. The probabilities of LAM and TRM were estimated using the cumulative incidence method in the competing-risks setting