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Original article

A multi-center prospective study randomizing the use of fat emulsion in intensive glucose control after allogeneic hematopoietic stem cell transplantation using a myeloablative conditioning regimen

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SUMMARY

Background & aims: Although parenteral nutrition (PN) is often used after allogeneic hematopoietic stem cell transplantation (allo-HSCT), there is controversy regarding PN management, for instance in the use of fat emulsion and glucose control (GC). To clarify these issues, we conducted a multi-center prospective study with intensive GC, randomizing the use of fat emulsion after allo-HSCT using a myeloablative conditioning regimen.

Methods: The primary endpoint was the cumulative incidence of documented infectious disease, namely bacterial and fungal infection, at day 100 after allo-HSCT. Between August 2007 and March 2012, we enrolled 81 patients at 5 centers. Excluding 5 ineligible patients, 76 patients received the protocol treatment. The target fasting glucose level was 80–110 mg/dL.

Results: The median follow-up of surviving patients was 1796 days. The cumulative incidences of documented infectious disease at day 100 were 16% (95% confidence interval [CI] 6–29%) in the no-fat group and 19% (95% CI 8–32%) in the fat group, indicating no significant difference. The mean glucose level at 28 days after allo-HSCT was 107 mg/dL in the no-fat group and 111 mg/dL in the fat group. Grade 3 hyperglycemia (>250 mg/dL) and grade 3 hypoglycemia (<40 mg/dL) occurred in 4 patients each (5.3%). Overall survival and non-relapse mortality rates at 4 years were 75% and 11% in the no-fat group and 69% and 8% in the fat group, respectively.

Conclusions: Irrespective of the use of fat emulsion, the long-term clinical outcomes of the enrolled patients were favorable under intensive GC. To further clarify the benefits of GC after allo-HSCT, a prospective study randomizing the level of GC is warranted.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a standard treatment option in patients with hematological diseases. However, one major obstacle is the high incidence of morbidity and mortality related to infectious diseases, acute and chronic graft-versus-host disease (GVHD), and organ failure. The prospective study BMT-CTN 0201 recently reported that the incidence of bacteremia at day 100 after allo-HSCT was 44.8% (95% confidence interval [CI], 38.5–51.1) in the bone marrow (BM) arm and 35.0% (95% CI, 28.9–41.1) in the peripheral blood stem cell (PBSC) arm, and the incidence of fungal infection at day 100 after allo-HSCT was 8% in the BM arm and 9% in the PBSC arm [1]. These

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findings clearly demonstrate that the infectious diseases caused by bacteria and fungi are still a tremendous burden in allo-HSCT recipients in the modern era. Furthermore, the development of infectious diseases can increase the risk of subsequent GVHD [2,3]. Although intensification of infection prophylaxis might lead to a reduced incidence of infections, it would inevitably be associated with higher cost and the emergence of multidrug-resistant bacteria [4–6].

One possible intervention to decrease the risk of bacterial and fungal infection is intensive glucose control (IGC), as hyperglycemia is a well-known risk factor for both types of infection in the general population and in patients who receive chemotherapy or allo-HSCT [7–14]. Patients with diabetes mellitus (DM) have well-documented defects in neutrophil function, affecting chemotaxis, phagocytosis, and killing, which are attributable to hyperglycemia [8]. Glucose control using continuous insulin infusion was reported to improve the function of neutrophils [15,16]. If IGC can restore neutrophil function, it might reduce the risk of infectious diseases irrespective of the presence of antibiotic resistance.

In addition, several studies reported that the development of posttransplant hyperglycemia was associated with a subsequent inferior clinical outcome after allo-HSCT [17–21]. In a small prospective study designed to assess the feasibility and effectiveness of IGC after allo-HSCT, there were no serious hypoglycemia-related complications and significantly fewer documented infections in patients undergoing IGC compared with the matched-control group [22]. To clarify the feasibility and benefit of IGC after allo-HSCT, a multi-center prospective trial was planned. We focused initially on glucose control during the early phase after allo-HSCT, that is, glucose control in patients receiving insulin-containing parenteral nutrition (PN) for basal insulin coverage, as PN is one of the major causes of hyperglycemia [23,24]. In Japan, the clinical use of PN was not uniform when this study was planned, particularly regarding the use of fat emulsion. Historically, fat emulsion was considered in Japan to be unsafe after allo-HSCT, although it had already been demonstrated to be safe in routine worldwide use [25,26]. Therefore, we randomized patients into a no-fat group and a fat group, incorporating IGC in all enrolled patients. Here, we report the results of this multi-center prospective randomized clinical trial.

2. Patients and methods

2.1. Study design

Patients met all of the following inclusion criteria: age between 18 and 60 years; hematological malignancy; allo-HSCT from an HLA-matched/DRB1-mismatched related/unrelated donor; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; and provision of informed consent. Exclusion criteria were as follows: chemo-refractory aggressive lymphoma; chronic myeloid leukemia in blast crisis; severe cardiac, pulmonary, hepatic, renal, neurologic, or psychiatric disorders; fasting triglyceride level > 350 mg/dL; DM requiring insulin to control hyperglycemia before allo-HSCT; active uncontrolled infections; active malignancy involving the central nervous system; and 2 or more previous allo-HSCTs. In this study, conditions with low disease risk included acute myeloid/lymphoblastic leukemia in first complete remission, chronic myeloid leukemia in chronic phase, follicular lymphoma, myelodysplastic syndrome in refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, and chronic myelofibrosis. Other diseases and disease statuses were all defined as high disease risk. Randomization was performed in a 1:1 ratio stratified according to transplant center, disease risk, age, and the use of total body irradiation (TBI). The primary endpoint was the cumulative incidence of documented bacterial and fungal infection up to day 100 after allo-HSCT. Secondary endpoints included regimen-related toxicity, glucose control, acute GVHD, relapse, non-relapse mortality (NRM), and overall survival (OS). Informed consent was signed before transplantation and the procedures were performed according to each center's protocol. The protocol for each institution was approved by the respective institutional review board. Case report forms were collected at baseline, 100 days, 1 year after allo-HSCT and June 2015 for the last follow up. This study was registered as UMIN000001189.

2.2. Glucose control and nutritional management

The target total caloric intake was set at 1.0–1.3 × basal energy expenditure (BEE), as <1.0 × BEE was previously reported to be obviously associated with weight loss early after allo-HSCT and higher caloric intake could lead to inadequate control of blood glucose level [14,27]. Patients who were assigned to the no-fat group did not receive any fat emulsion during the study period. Those who were assigned to the fat group received fat emulsion to cover 20–30% of calories from total PN (TPN). In this study, we used soybean oil-based fat emulsion (Intralipid). In patients with inadequate glucose control, total caloric intake could be reduced and a higher priority was set on glucose control than caloric intake.

The target blood glucose level was set at 80–110 mg/dL for inpatients receiving PN. Protocol-based glucose control was conducted by adjusting the dose of insulin added to the TPN bag for basal insulin coverage. The addition of prandial insulin, like sliding-scale insulin, was not defined as a treatment protocol and instead followed the institutional protocol.

2.3. Infection prophylaxis

Inpatients were treated in rooms with high-efficiency particulate air filtration systems. Infection prophylaxis was initiated at the beginning of the conditioning regimen. Anti-bacterial prophylaxis was achieved using ciprofloxacin or levofloxacin, and when patients developed febrile neutropenia, broad-spectrum antibacterial drugs were administered. Anti-fungal prophylaxis was accomplished with fluconazole. Acyclovir was used for the prevention of herpes simplex virus and varicella zoster virus infection. Data of infections were prospectively collected and reported.

2.4. Statistical analysis

We calculated that the study would have 80% power to detect a difference of 20% in the incidence of infectious diseases between the 2 study groups (20–25% and 40–45%), with the use of a chi-square test and a two-sided alpha level of 10%. The estimation of the incidence of infectious diseases was based on previous reports [22].

A descriptive statistical analysis was performed to assess the patients' characteristics. Medians and ranges are provided for continuous variables and percentages are given for categorical variables. The probabilities of OS and progression-free survival (PFS) were calculated by the Kaplan–Meier method. A Cox proportional-hazards regression model was used to analyze OS and PFS. The cumulative incidences of NRM, GVHD, and infections were evaluated using the Fine and Grey model for univariate and multivariate analyses of cumulative incidence. In the competing risk models for GVHD and infectious disease, relapse, graft failure, and death before these events were defined as competing risks. In

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