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ORIGINAL RESEARCH REPORT

Central nervous system infection following allogeneic hematopoietic stem cell transplantation

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Abstract
Objective/background: Here, we described the clinical characteristics and outcomes of central nervous system (CNS) infections occurring after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in a single institution over the previous 6 years.
Methods: Charts of 353 consecutive allogeneic transplant recipients were retrospectively reviewed for CNS infection.
Results: A total of 17 cases of CNS infection were identified at a median of 38 days (range, 10–1028 days) after allo-HSCT. Causative pathogens were human herpesvirus-6 ($n = 6$), enterococcus ($n = 2$), staphylococcus ($n = 2$), streptococcus ($n = 2$), varicella zoster virus ($n = 1$), cytomegalovirus ($n = 1$), John Cunningham virus ($n = 1$), adenovirus ($n = 1$), and *Toxoplasma gondii* ($n = 1$). The cumulative incidence of CNS infection was 4.1% at 1 year and 5.5% at 5 years.
Conclusion: Multivariate analysis revealed that high-risk disease status was a risk factor for developing CNS infection ($p = .02$), and that overall survival at 3 years after allo-HSCT was 33% in patients with CNS infection and 53% in those without CNS infection ($p = .04$).

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients are at a high risk for several central nervous system (CNS) complications [1]. These complications arise either from the primary disease for which the patient is undergoing allo-HSCT or as a consequence of immunosuppressive treatments, infection, or hemorrhage that may develop following allo-HSCT [2—4]. Although CNS infection usually results in a dismal outcome, early diagnosis and immediate treatment intervention may improve prognosis [5,6]. The incidence of CNS infection ranges from 0.8% to 15% [7—14], and various causative pathogens, including bacteria [15], fungi [9,14], viruses [7,16—20], and protozoa [21], have been identified, but the full spectrum of pathogens is not known. Multiple factors, including severe graft-versus-host disease (GVHD) or use of high doses of an immunosuppressive drug, such as alemtuzumab, were identified as risk factors for CNS infection. However, little is known about the precise clinical characteristics of CNS infection, as clinical manifestations may be difficult to distinguish from other conditions that cause neurological symptoms [8,11—13,22,23]. This study described the clinical course of 17 cases of CNS infection among 353 allogeneic transplant recipients over the previous 6 years at a single institution and reviewed their clinical outcomes.

Materials and methods

Patient demographics

We retrospectively reviewed 353 patients (210 men and 143 women; median age, 43 years; range, 16—73 years) with various diseases who underwent allo-HSCT at our institution. Between January 2005 and December 2011, 261 patients underwent bone marrow transplantation (82 related, 179 unrelated), 48 underwent related peripheral-blood stem cell transplantation, and 44 patients underwent unrelated cord-blood stem cell transplantation. Clinical characteristics of patients are summarized in Table 1.

Transplantation procedure

Preparative treatment was performed according to the primary disease and type of transplant. Generally, patients with lymphoid malignancy were conditioned using a total body irradiation (TBI)-containing regimen (12 Gy) that included cyclophosphamide (CY) at 120 mg/kg with or without cytarabine at 8 g/m^2. Conversely, patients with myeloid malignancy were conditioned using a non-TBI-containing regimen that included oral busulfan (BU) at 16 mg/kg or intravenous BU at 12.8 mg/kg and CY at 120 mg/kg. Plasma concentrations of BU were not monitored. Patients with severe aplastic anemia were also conditioned using a total lymphoid irradiation-containing regimen. Reduced-intensity conditioning regimens consisted of fludarabine-based regimens with or without low-dose TBI. Cyclosporine or tacrolimus plus short-term methotrexate were used for prophylaxis. Tacrolimus was used in cases of unrelated or mismatched transplantation. Acute and chronic GVHD were diagnosed and graded according to previously established criteria. Tosufloxacin and fluconazole were orally administered 14 days before allo-HSCT for prophylaxis against bacterial and fungal infection, respectively. For patients with a high risk of invasive fungal infections, voriconazole was administered instead of fluconazole. Trimethoprim and sulfamethoxazole were administered to prevent *Pneumocystis* pneumonia. Acyclovir was administered to prevent herpes simplex virus infection until the end of administration of immunosuppressive drugs. Cytomegalovirus (CMV) disease monitoring using an antigenemia assay for pre-emptive ganciclovir therapy was performed.

Diagnostic procedure for CNS infection and statistical analysis

According to the standard operating procedure at our institution, symptomatic patients with an altered mental status or convulsions, particularly those without any other identified causes of neurological dysfunction, such as hemorrhage [4], metabolic disorder, or drug toxicity, were classified as possibly having CNS infection. These patients immediately underwent cerebrospinal fluid (CSF) examination with standard culturing, staining for bacterial, viral, and protozoan pathogens, and polymerase chain reaction (PCR) testing for human herpesvirus virus 6 (HHV-6), varicella zoster virus (VZV), herpes simplex virus, CMV, and adenovirus. When progressive multifocal leukoencephalopathy was considered, PCR for John Cunningham (JC) virus in the CSF was employed.

Descriptive statistics were provided for patient-baseline characteristics. Patient-, disease-, and transplant-related variables were compared using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The probability of CNS infection was calculated using the cumulative incidence-function method and considering death without CNS infection as a competing event. To evaluate the association between pretransplant clinical factors and CNS infection, a logistic regression model was used. Overall survival (OS) was calculated using the Kaplan-Meier method and compared with the log-rank test. OS was calculated from transplantation to death regardless of cause. Multivariate analyses were performed using the Cox proportional-hazards model. The following covariates were included in the multivariate analysis: age, sex, disease risk, stem cell source, donor type, conditioning regimen, GVHD prophylaxis, and the development of CNS infection. Variables with $p < .10$ in the univariate analyses were subjected to multivariate analysis. Development of CNS infection was treated as a time-dependent covariate. All *p*-values were two-sided, and a $p < .05$ was considered statistically significant.

Results

Clinical features of CNS infection following allo-HSCT

The charts of 353 allo-HSCT recipients were retrospectively reviewed for CNS infection. Table 1 summarizes the charac-

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