Biol Blood Marrow Transplant 23 (2017) 1158–1164

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Supportive Care

A Retrospective Study of Central Nervous System Invasive Fungal Disease after Allogeneic Stem Cell Transplantation: Risk Factors, Clinical Characteristics, and Outcomes

Yu-Qian Sun [1,2], Zhao-Yu Liu [1,3], Xiao-Jun Huang [1,2,4,*], Chen-Hua Yan [1,2], Lan-Ping Xu [1,2], Xiao-Hui Zhang [1,2], Kai-Yan Liu [1,2], Yu Wang [1,2]

[1] *Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China*
[2] *Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation for the Treatment of Hematological Diseases, Beijing, China*
[3] *The Second Hospital of Shanxi Medical University, Taiyuan, China*
[4] *Peking-Tsinghua Center for Life Sciences, Beijing, China*

Article history:
Received 9 January 2017
Accepted 17 March 2017

Key Words:
Invasive fungal disease
Allogeneic stem cell transplantation
Central nervous system
Aspergillus
Voriconazole

A B S T R A C T

There are limited reports of central nervous system (CNS) invasive fungal disease (IFD) in allogeneic stem cell transplantation (HSCT) recipients. We aimed to describe the clinical characteristics of and the risk factors for CNS-IFD. We retrospectively reviewed consecutive HSCT patients at Peking University Institute of Hematology during a 10-year period. A total of 29 patients were diagnosed with CNS-IFD. The median onset of CNS-IFD was 173 (range, 24 to 972) days after HSCT. The most frequent pathogen was *Aspergillus*, and the most common clinical symptoms and signs were space-occupying presentations. We found that prior pulmonary IFD ($P < .001$; hazard ratio, 62.746; 95% confidence interval, 14.28 to 275.27) was the only risk factor associated with occurrence of CNS-IFD. Poor response at 6 weeks after treatment ($P = .045$; hazard ratio, 2.574; 95% confidence interval, 1.021 to 6.487) was the only risk factor predicting the involvement of the CNS in pulmonary IFD. Overall survival was 24.2% at the last follow-up, with a median of 289 (range, 27 to 3341) days after transplantation. We conclude that patients with pulmonary IFD had higher risk of CNS-IFD, especially in those with poor response after 6 weeks of treatment. The prognosis of CNS-IFD was very poor after HSCT.

INTRODUCTION

Invasive fungal disease (IFD) is an important complication after allogeneic stem cell transplantation (HSCT). The incidence rate ranges from 3% to 23% [1-3]. *Aspergillus* is the most common pathogen, accounting for more than 90% of pathogens [4]. The mortality of IFD after HSCT ranges from 30% to 100%, depending on the involved organ. Lung and sinus are the most common sites involved directly, follow by other sites such as central nervous system (CNS) via dissemination. Localized IFD has lower mortality than disseminated infection [2]. CNS-IFD is rare (incidence <1% after HSCT); however, the prognosis is very poor, with the mortality up to 90% to 100% [5]. Several studies have reported CNS-IFD in a heterogeneous population with different underlying diseases [6]. However, there are relatively limited up-to-date reports of CNS-IFD specifically related to HSCT. The risk factors of CNS-IFD with HSCT are also not well documented. In this retrospective study, we aim to review cases in a single center to describe the clinical characteristics and the treatment outcomes of CNS-IFD in transplant recipients, and we also aim to identify the risk factors by using a matched-pair method.

PATIENTS AND METHODS

Patient Cohort

During the period of January 2007 to June 2016, 3855 consecutive patients received their first allogeneic stem cell transplantation at the Peking University Institute of Hematology. All patients signed informed consent forms before treatment. Based on the revised European Organization for Research and Treatment of Cancer/Mycosis Study Group criterion [7], 29 patients were diagnosed with CNS-IFD. In this report, we review and analyze the medical data of these patients.

Transplantation Procedure

The method of transplantation was described in previous reports [8]. The conditioning treatment regimen included a modified busulfan and cyclophosphamide regimen in most matched sibling donor transplantations.

Financial disclosure: See Acknowledgments on page 1163.

* Correspondence and reprint requests: Prof. Xiao-Jun Huang, MD, Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation for the Treatment of Hematological Diseases, 11 Xizhimen South Street, Beijing 100044, PR China.

E-mail addresses: pk200608@126.com, xiaojunhuang1@126.com (X.-J. Huang).

http://dx.doi.org/10.1016/j.bbmt.2017.03.026
1083-8791/

For haploidentical donor transplantations, most patients received a regimen of the busulfan and cyclophosphamide plus antithymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA) at 2.5 mg/kg per day for 4 days. Cyclosporine (CSP) plus short-term methotrexate (MTX) and mycophenolate mofetil (MMF) were administered to prevent the graft-host immune rejection. MTX (15 mg/m^2) was administered intravenously at day 1, followed by 10 mg/m^2 on days 3, 6, and 11 after transplantation. Four doses of MTX were given in haploidentical donor transplantations, whereas only the first 3 doses were given in matched sibling donor transplantations. CSP (2.5 mg/kg twice a day) started at day 9 intravenously and continued until patients were able to tolerate oral medication. Thereafter, CSP was given orally twice daily with target trough levels of 150 ng/mL to 250 ng/mL. MMF (7.5 mg/kg twice daily) treatment began at day 9 and discontinued at day 14 in HLA-matched patients. However, in mismatched patients, MMF was discontinued between days 30 to 60, depending on the presence or absence of graft-versus-host disease (GVHD).

Diagnosis of CNS-IFD

Patients suspected of having IFD were evaluated with high-resolution computed tomography (CT) of chest; cultures with clinical specimens; detection of galactomannan and 1,3-β-D-glucan; and biopsy when necessary. When CNS or sinus involvement were suspected, magnetic resonance imaging (MRI) or CT were used for screening lesions. When patients were eligible based on their performance, additional invasive examination (such as lumbar puncture or stereotactic brain biopsy) were performed.

We used the diagnostic criteria proposed by the European Organization for Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group and by the National Institute of Allergy and Infectious Diseases Mycoses Study Group [7] to categorize IFD outside the CNS.

Cultural or histologic (fungal elements with typical morphologic characteristics) evidence for fungi in cerebrospinal fluid (CSF) or brain biopsy specimens was considered *proven CNS-IFD*. Patients with *probable CNS-IFD* had CNS symptoms/signs plus radiologic signs of CNS infection in CT or MRI scans plus evidence of fungal infection as follows: (1) elevated galactomannan or glucan from CSF or (2) a proven/probable/possible fungal infection at body sites outside the CNS. Patients with CNS symptoms/signs plus imaging evidence without microbiological findings were regarded as having *possible CNS-IFD*.

Definitions and Statistical Analysis

The response to therapy was based on the previously published report [9]. *Complete response* (CR) was defined as the resolution of all attributed symptoms and signs of disease and radiological abnormalities and mycological evidence of eradication of disease. *Partial response* (PR) was defined as improvement in attributed symptoms and signs of disease and radiological abnormalities and evidence of clearance of cultures or reduction of fungal burden. CR and PR were considered successful responses. *Poor response* was defined as stable disease status, disease progression, and death. IFD was the attributed cause of death when the patient died of progressive organ failure in the absence of other comorbidity-related death.

Overall survival curves were plotted by the Kaplan-Meier method. The 2-tailed log-rank test was used for statistical comparison. All *P* values were 2-sided *t*-tests for the comparison of indicated treatments. The significant difference was at $P < .05$ unless otherwise stated. Ninety-five percent confidence intervals were calculated.

We selected the control group using the matched-pair method to analyze the risk factors of CNS-IFD. Among those patients without CNS-IFD (3826 patients), CNS-IFD were matched in a 1:3 ratio using the variates of age, sex, and underlying disease. As such, 87 patients were matched as the control group for analysis. In univariate analysis, factors included disease status, prior HSCT, transplantation type, prior IFD history, prophylactic drugs (voriconazole plus amphotericin versus others), delayed neutrophil engraftment time (> median), delayed platelet engraftment time (> median), acute GHVD, chronic GVHD, cytomegalovirus reactivation, relapse of underlying disease, diagnosis grade of IFD (proven, probable, possible), onset time of IFD, antifungal drugs (voriconazole plus amphotericin versus others), and response at 6 weeks after initiation of antifungal treatment (CR + PR versus others). Categorical variates were compared using the kappa square test, whereas continuous variates were compared using the independent sample *t*-test. The Cox proportional model was used for identifying risk factors associated with CNS-IFD.

RESULTS

Characteristics of Patients with CNS-IFD

During the study period, 3855 patients received HSCT in Peking University Institute of Hematology. A total of 29 (.8%) patients were diagnosed with CNS-IFD (Figure 1). The basic clinical characteristics of the 29 patients were listed in Table 1. The median age of patients was 24 (range, 9 to 49) years. Among these patients, only 1 (3.4%) patient received a transplant from an HLA-matched sibling. All the other patients underwent haploidentical transplantation. Thirteen (44.8%) patients had previous IFD history with prior HSCT. Most patients had acute GVHD (79.3%) and chronic GVHD (55.2%) before onset of CNS-IFD. Cytomegalovirus reactivation occurred in 24 (82.8%) patients.

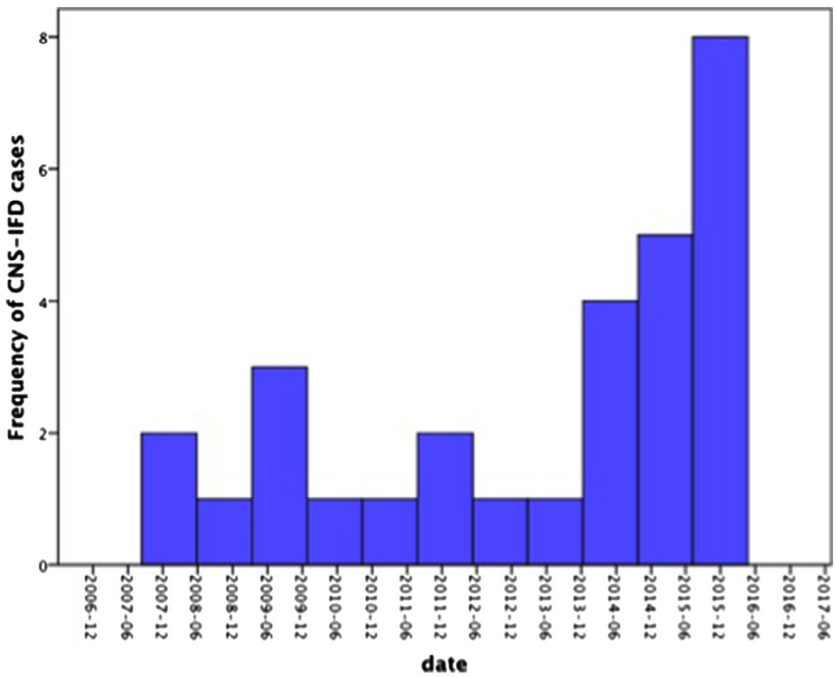

Figure 1. The histogram of CNS-IFD cases (y-axis) diagnosed by half-year intervals (x-axis).