Biol Blood Marrow Transplant 21 (2015) 1117–1126

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Supportive Care

Epidemiology, Management, and Outcome of Invasive Fungal Disease in Patients Undergoing Hematopoietic Stem Cell Transplantation in China: A Multicenter Prospective Observational Study

Yuqian Sun [1], Fanyi Meng [2], Mingzhe Han [3], Xi Zhang [4], Li Yu [5], He Huang [6], Depei Wu [7], Hanyun Ren [8], Chun Wang [9], Zhixiang Shen [10], Yu Ji [1], Xiaojun Huang [1,*]

[1] *Peking University Institute of Hematology, Peking University People's Hospital, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China*
[2] *Nanfang Hospital, Nanfang Medical University, Guangzhou, China*
[3] *Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China*
[4] *Xinqiao Hospital, The Second Affiliated Hospital of Third Military Medical University, Chongqing, China*
[5] *Chinese PLA General Hospital (301 Hospital), Beijing, China*
[6] *The First Affiliated Hospital of Medical School of Zhejiang University, Hangzhou, China*
[7] *The First Affiliated Hospital of Soochow University, Suzhou, China*
[8] *The First Hospital of Peking University, Beijing, China*
[9] *The First People's Hospital of Shanghai, Shanghai, China*
[10] *Rui Jin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Article history:
Received 15 October 2014
Accepted 20 March 2015

Key Words:
Allogeneic
Autologous
China
Fungal infection
Stem cells
Transplant

A B S T R A C T

The China Assessment of Antifungal Therapy in Hematological Disease study, the first large-scale observational study of invasive fungal disease (IFD) in China, enrolled 1401 patients undergoing hematopoietic stem cell transplantation (HSCT) (75.2% allogeneic and 24.8% autologous) at 31 hospitals across China. The overall incidence of proven or probable IFD was 7.7% (108 of 1401); another 266 cases (19.0%) were possible IFD. After allogeneic or autologous HSCT, the incidence of proven/probable IFD was 8.9% (94 of 1053) and 4.0% (14 of 348), respectively. Some cases (14 of 108) developed during conditioning before transplantation. The cumulative incidence of proven/probable IFD increased steeply in the first month after transplantation and after 6 months, the incidence was significantly higher in allogeneic than it was in autologous transplant recipients (9.2% versus 3.5%; $P = .001$) and when stem cells were derived from cord blood or bone marrow and peripheral blood ($P = .02$ versus other sources). Independent risk factors for proven/probable IFD in allogeneic HSCT were diabetes, HLA-matched unrelated donor, prolonged severe neutropenia (absolute neutrophil count $> 500/mm^3$ for >14 days), and immunosuppressants (odds ratio, 2.0 to 3.4 for all). Antifungal prophylaxis was independently protective ($P = .01$). Previous IFD and prolonged severe neutropenia were significant independent risk factors among autologous transplantation patients ($P < .01$, $P = .04$, respectively). In total, 1175 (83.9%) patients received antifungal prophylaxis (91.6% triazoles) and 514 (36.7%) were treated in the hospital with therapeutic antifungals (89.1% triazoles; median 27 days). Empirical, pre-emptive, and targeted antifungals were used in 82.3%, 13.6%, and 4.1% of cases, respectively. Overall mortality (13.4%; 188 deaths) was markedly higher in patients with proven (5 of 16; 31.3%), probable (20 of 92; 21.7%), or possible (61 of 266; 22.9%) IFD; allogeneic (171 of 1053; 16.2%) rather than autologous (17 of 348; 4.9%) HSCT and was significantly higher in patients receiving pre-emptive (18.6%) rather than empirical (6.1%) or targeted (9.5%) antifungal therapy ($P = .002$). Improvements in the selection and timing of prophylactic antifungals would be welcome. Health care providers should remain alert to the increased risk of IFD and associated mortality in allogeneic HSCT recipients and the ongoing risk of IFD even after discharge from the hospital.

Financial disclosure: See Acknowledgments on page 1125.

* Correspondence and reprint requests: Professor Xiaojun Huang, Peking University Institute of Hematology, Peking University People's Hospital, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, No. 11 Xizhimen South Street, Beijing, People's Republic of China.
E-mail address: xjhrm@medmail.com.cn (X. Huang).

http://dx.doi.org/10.1016/j.bbmt.2015.03.018
1083-8791/

INTRODUCTION

Invasive fungal disease (IFD) is a common complication after hematopoietic stem cell transplantation (HSCT) and is associated with significant morbidity and mortality [1]. Until recently, the epidemiology of IFD in HSCT was gleaned primarily from single-center and retrospective studies. However, the publication of large, prospective observational studies in recent years has improved understanding of the epidemiological landscape in geographical areas including the United States and parts of Europe [2-4]. These data suggest that, despite reductions in IFD-related deaths in the past decade [5], IFD-related mortality after HSCT still approaches 50% [2,3], with higher rates among recipients of allogeneic compared with autologous transplants, particularly in the presence of *Aspergillus* infection [2,4]. As a result, HSCT recipients with suspected IFD often receive early empirical therapy or pre-emptive treatment.

Treatment guidelines for IFD, including some that are specific to HSCT patients, have been developed by academic societies in different world regions [6-9]. Notwithstanding this guidance, and despite advances in the diagnosis and prophylaxis of IFD, as well as new dose forms of amphotericin B and antifungal agents, treatment is often delayed because of nonspecific disease presentation and a lack of reliable diagnostic techniques, leading to poor clinical outcomes.

Data on the epidemiology and real-world management of IFD in high-risk patients in China are limited to a small number of single-center retrospective studies. Here, we report findings from the China Assessment of Antifungal Therapy in Hematological Disease (CAESAR) study, the first large-scale observational study of the epidemiology, risk factors, management and prognosis of IFD among adults and children undergoing HSCT in China.

METHODS

Study Design

The CAESAR study was a multicenter, prospective, observational study in 35 hematology centers across China, including 2 children's hospitals. Subjects were consecutive patients of any age with hematological malignancy who were hospitalized during the study period either after allogeneic or autologous HSCT or to receive intravenous chemotherapy. Overall study methods have been described previously [10]. This report focuses on patients who underwent HSCT in 31 HSCT centers; data from patients receiving chemotherapy have been published [10].

All patients in each study center who were hospitalized and underwent HSCT between January 1, 2011 and October 30, 2011 were eligible for inclusion. A single case report form was used for each subject to record the following data: demographic characteristics, type of HSCT and pre-transplantation conditioning, IFD risk factors, clinical features suggestive of IFD, results of mycological testing if available, antifungal prophylaxis and treatment, and survival at discharge. Physicians diagnosed and treated cases of IFD according to their usual practice, using their own judgment. In patients who received antifungal treatment (at investigator discretion), the case report form was also used to record initial treatment strategy against protocol definitions of prophylaxis and treatment scenarios (*empirical*, administered to patients with immune deficiency, prolonged corticosteroid use, persistent fever of unknown cause, or unresponsive to broad-spectrum antibiotics for 7 days; *pre-emptive*, administered to patients with indirect microbiological evidence of infection [antigen test]; or *targeted*, administered to patients with proven IFD [11]), treatment adjustment, and treatment course. IFD was categorized as proven, probable, or possible according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) 2008 criteria [12]. Patients were diagnosed as having suspected IFD if they had IFD risk factors; were observed to have symptoms, radiological abnormalities, or indirect microbiological evidence of fungal infection; and were treated empirically with antifungal agents but could not be diagnosed with proven, probable, or possible IFD according to EORTC/MSG 2008 criteria. Documentation continued until termination of antifungal treatment, completion of observation, or death. Patients were followed for 6 months ± 7 days after the date of transplantation; follow-up was completed on April 30, 2012. In all, 30 patients were lost to follow-up.

This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, and nationally mandated ethical requirements. The study protocol and informed consent document were reviewed and approved by the ethics committee of Peking University People's Hospital. All other participating institutions obtained ethical approval separately before initiation of the study. All study participants provided informed consent.

Data Analysis

Sample size calculation was based on the proportion of patients expected to develop IFD based on published data. Assuming an overall incidence of IFD of 8% with a ±5% margin of error [13,14] at least 707 patients were required.

In accordance with common practice, and to maximize diagnostic accuracy, incidence of IFD was calculated based on proven and probable cases combined. Cumulative incidence was calculated as the incidence of proven plus probable IFD for the first 187 days after transplantation, divided by the number of cases at risk. Unless stated otherwise, IFD data in this manuscript refer to proven and probable cases combined. Data were grouped according to transplantation type (autologous or allogeneic).

Statistics were primarily descriptive and were compared using analysis of variance, Wilcoxon rank-sum test, or chi-squared test, as appropriate. Risk factors for IFD were analyzed using univariate analysis followed by multivariate logistic regression. Each risk factor with a P value $< .15$ on univariate analysis was examined further using multivariate logistic regression, in which clinical significance and interaction between variables were taken into account. Overall survival status was estimated from the engraftment to 6 months using the Kaplan-Meier method and subgroups were compared statistically using the log-rank test. Risk factors for death were analyzed by univariate analysis. Each risk factor with a P value $< .10$ was included as a covariate in multivariate analysis using the Cox proportional hazard regression model. Factors with $P \leq .05$ in the final analysis were considered statistically significant.

RESULTS

Patient Characteristics

A total of 1401 patients undergoing HSCT were enrolled from 31 HSCT centers across China (n ≤ 10 at 7 centers; n = 10 to 50 at 16 centers; n = 51 to 100 at 7 centers; n > 100 at 1 center). Table 1 shows baseline patient demographic and clinical characteristics at the time of admission for transplantation.

In the overall population, the mean age was 31.1 years (range, 1 to 66 years) and 252 patients (18%) were children (age < 18 years). Over 90% of patients had profound neutropenia with an absolute neutrophil count (ANC) < 500/mm^3 for a median of 14 days. Eastern Cooperative Oncology Group scores indicated that most patients were able to undertake routine activities of daily living with few limitations.

Three quarters of the patients (n = 1053; 75.2%) received allogeneic transplants and one quarter (n = 348; 24.8%) received autologous transplants. A total of 504 (47.9%) allogeneic HSCT patients developed graft-versus-host disease (GVHD) within 6 months of transplantation (39.8% acute GVHD [19.6% grade III or IV] and 13.8% chronic GVHD [71.7% local lesions]). Median time from transplantation to onset of acute and chronic GVHD was 23 and 135 days, respectively.

In the overall population, incidence of oral or intestinal mucositis was 48.5% (679 of 1401), primarily grade 1 (40.9%) or grade II (35.8%); 8.4% had grade IV severity. The median time from transplantation to onset of inflammation was 6 days (interquartile range [IQR], 3 to 8).

Incidence of IFD and Associated Risk Factors

Incidence

In all, 374 patients were diagnosed with IFD: the incidences of proven, probable, and possible IFD were 1.1% (16 of 1401), 6.6% (92 of 1401), and 19.0% (266 of 1401),