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ORIGINAL ARTICLE

Incidence and risk factors of probable and proven invasive fungal infection in adult patients receiving allogeneic hematopoietic stem cell transplantation

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Background: To investigate the incidence and risk factors for the occurrence of proven or probable invasive fungal infection (IFI) in adult patients receiving allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: We retrospectively analyzed 421 patients undergoing HSCT between 2002 and 2013 in our hospital. The risk factors for the occurrence of IFI were analyzed using Cox regression models.
Results: Thirty-one patients with the median age of 42 years (range, 19–60 years) developed IFI after HSCT. The post-HSCT IFI incidence was 7.4% and median time from HSCT to the diagnosis of IFI was 139 days (range, 2–1809 days). Of the pretransplant factors, European Group for Blood and Marrow Transplantation (EBMT) risk score > 2 ($p = 0.001$) and prior history of IFI ($p = 0.006$) or type 2 diabetes mellitus (DM; $p = 0.042$) were the significant predictors for

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post-HSCT IFI in univariate analyses. In multivariate analysis, EBMT risk score > 2 ($p = 0.015$) and prior history of IFI ($p = 0.006$) retained significance. Of the post-transplant factors, acute graft-versus-disease (GVHD) overall Grade III–IV ($p < 0.001$), extensive chronic GVHD ($p = 0.002$), development of post-transplant lymphoproliferative disorders ($p = 0.005$), and the use of high-dose steroids ($p < 0.001$) were statistically significant in univariate analyses. After multivariate analysis, high-dose steroids ($p < 0.001$) and acute GVHD overall Grade III–IV ($p = 0.045$) retained significance.

Conclusion: These results suggest that risk group stratification prior to HSCT and monitoring of IFI in patients with severe GVHD receiving high-dose steroids is mandatory to reduce the mortality and morbidity of post-HSCT IFI, especially in those with prior history of IFI.

Introduction

Invasive fungal infection (IFI), especially aspergillosis, is a serious complication following hematopoietic stem cell transplant (HSCT) and can cause significant morbidity and mortality in recipients of the procedure.[1,2] Recent studies have demonstrated that routine prophylactic use of fluconazole during HSCT decreased the risk of invasive candidiasis to a low incidence of 1.1–5%.[2–6] On the contrary, increasing incidence of invasive mold infection has been reported in recent series.[7,8] Analyses of The Transplant-Associated Infection Surveillance Network (TRANSNET) database showed that the cumulative annual incidence of IFIs were 7.7, 8.1, 5.8, and 1.7 in every 100 transplants for matched-unrelated allogeneic, mismatch-related allogeneic, matched-related allogeneic, and autologous HSCT, respectively.[2] In the TRANSNET database, the estimated post-HSCT 1-year survivals of invasive candidiasis and invasive aspergillosis are only 33% and 25%, respectively.[2] In the other prospective study, high post-HSCT mortality in invasive candidiasis, about 49% at 12 weeks, was also noted.[9]

IFI may occur during the pre-engraftment neutropenic period, the early postengraftment period or in the late postengraftment period after Day +100.[10,11] The reported risk factors for IFI after HSCT include transplant type, use of antifungal prophylaxis, conditioning regimen, compatibility of human leukocyte antigen between donor and recipient, cytotoxic conditioning therapy-related intestinal mucosal damage, stem cell source, and disease status.[7,11–13] In addition, other important recipient-related factors were age at HSCT, duration of pre-engraftment neutropenia, graft failure or rejection, the severity of acute and chronic graft-versus-host disease (GVHD), use of steroids, the presence of cytomegalovirus (CMV) infection, and geoclimatic factor.[5,7,11–14] Taiwan is located in Southeastern Asia with generally hot and wet climatic condition. It is presumed that patients receiving HSCT here may have an increased incidence of IFI. Our study attempts to look at the incidence of IFI after HSCT in a single medical center of Taiwan and to explore the associated risk factors and the final outcome after the infection.

Materials and methods

Study patient population

We retrospectively reviewed the medical records of 421 adult patients (age ≥ 18 years) who received allogeneic HSCT between January 1, 2002 and December 31, 2013 in the Blood and Marrow Transplant Center of Taipei Veterans General Hospital in Taipei, Taiwan. Transplant-related clinical data including age, gender, disease diagnosis, type of transplant, human leukocyte antigen (HLA) matching, conditioning regimen, GVHD, and other clinical complications were all retrospectively collected. For those undergoing multiple transplants, only the data pertinent to the last procedure were included. The retrospective review of medical records was approved by the Institutional Ethical Committee in agreement with the Helsinki Declaration of 1975, revised in 2008.

Transplant details and conditioning regimens

HLA-typing tests of low to intermediate resolution for six or eight alleles (HLA-A, -B, -DR, or -C) were performed to select donors for allogeneic HSCT. Donor's types included sibling donor, matched unrelated marrow, haploidentical donor (father or mother) or umbilical cord blood. Accordingly, patients were categorized into the fully matched group or mismatched group. Myeloablative conditioning regimens including busulfan combined with cyclophosphamide, or total body irradiation of 1200 cGy combined with cyclophosphamide. Fludarabine-based nonmyeloablative conditioning regimens were administered to elderly patients or those with comorbidities.

Antifungal prophylaxis, monitoring, and treatment

Standard antifungal prophylaxis with fluconazole was started on initiation of conditioning till the end of neutropenia. From 2010 onwards, echinocandin, such as micafungin or caspofungin, was given to patients with history of pre-transplant fungal infection, intolerance to fluconazole toxicity, high EBMT risk score, or as the clinical physician's option.