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The incidence and risk factors of invasive fungal infection after haploidentical haematopoietic stem cell transplantation without *in vitro* T-cell depletion

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Abstract

In recent years, we have successfully established a novel method of haploidentical haematopoietic stem cell transplantation (HSCT) without *in vitro* T-cell depletion. This study was aimed at analysing the incidence and risk factors of invasive fungal infection (IFI) with this transplantation method. The study comprised 291 patients who had undergone haploidentical HSCT from 1 January 2007 to 31 December 2008. IFI was diagnosed according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group 2002 criteria, and only proven or probable cases of IFI were regarded as true cases. A total of 39 patients were documented as having IFI, including four proven cases and 35 probable cases. The median time of diagnosis was 26 days (range: 6–405 days) after transplantation. The cumulative incidence rates of IFI at 40 days, 1 year, 2 years and 3 years after transplantation were 8.25%, 13.1%, 13.4% and 13.4%, respectively. Multivariate analysis identified platelet engraftment time (>17 days) (p 0.027; hazard ratio (HR) 2.432; 95% CI 1.105–5.355), a high risk of underlying disease (p 0.001; HR 2.916; 95% CI 1.515–5.611) and grade III–IV acute graft-versus-host disease (p 0.019; HR 2.407; 95% CI 1.154–5.022) as risk factors for IFI. The incidence rates of IFI in patients with no, one, two or three risk factors at 3 years after transplantation were 4.48%, 7.86%, 29.6% and 23.1%, respectively. In conclusion, IFI is an important complication following haploidentical HSCT without *in vitro* T-cell depletion.

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Introduction

Haploidentical haematopoietic stem cell transplantation (HSCT) is an effective option for patients with haematological malignancies without human leukocyte antigen (HLA)-matched siblings or unrelated donors. Long-lasting immunosuppression and severe graft-versus-host disease (GVHD), however, lead to high incidence rates of opportunistic infections. Invasive fungal infection (IFI) has been one of the major infectious complications after allogeneic HSCT, with a mortality rate of up to 80% [1]. The incidence of IFI varies in different transplantation models, and data for IFI from haploidentical HSCT cases are scarce.

Recently, we developed a new method for haploidentical allogeneic HSCT from family donors without *in vitro* T-cell depletion (TCD) [2–4]. Long-term outcomes were comparable to that of transplantation with HLA-matched siblings or unrelated persons as donors. Opportunistic infections, however, can occur in up to 39% of patients [4]. The incidence and risk factors related to IFI in the haploidentical HSCT model have not been studied. Our study analysed the incidence and risk factors related to IFI for this transplantation model.

Patients and Methods

Patients

Patients without HLA-matched siblings or unrelated donors were potential candidates for allogeneic HSCT from haploidentical family donors. From 1 January 2007 to 31 December 2008, 291 patients underwent haploidentical HSCT without *in vitro* TCD at the Peking University Institute of Haematology. All patients signed informed consent forms prior to treatment, and the treatment programme was approved by the Ethics Committee of Peking University People's Hospital. The characteristics of all HSCT recipients are summarized in Table 1.

Transplantation procedure

The transplantation procedure has been described in previous reports [2–4]. The modified busulphan/cyclophosphamide + antithymocyte globulin conditioning regimen was used to treat 288 patients. The regimen was as follows: cytosine arabinoside (4 g/m^2/day, days –10 to –9), busulfan (0.8 mg/kg, every 6 h, 12 doses, days –8 to –6), cyclophosphamide (1.8 g/m^2/day, days –5 to –4), simustine (Me-CCNU, 250 mg/m^2, day –3), and thymoglobulin (rabbit antithymocyte globulin (Sangstat-Genzyme, Marcy L'Etoile, France), 2.5 mg/kg, days –5 to –2). The other three patients were treated with fludarabine (30 mg/m^2, days –6 to –2) instead of cyclophosphamide. The patients received cyclosporin A, mycophenolate mofetil and short-term methotrexate for GVHD prophylaxis. Chimerism was determined with at least two of the following three methods: DNA-based HLA typing (for mismatched loci), PCR-based DNA fingerprinting of short tandem repeats, and chromosomal fluorescence *in situ* hybridization (for the Y chromosome). At 30, 60, 90, 180 and 365 days after transplantation, chimerism and peripheral blood lymphocytes (absolute lymphocyte numbers, CD4$^+$ cells) were determined.

TABLE 1. Characteristics of all haematopoietic stem cell transplant recipients (*N* = 291)

Variables	Value
Age (years), median (range)	25 (5–57)
Recipient sex, *n* (%)	
Male	176 (60.5)
Female	115 (39.5)
Underlying diseases, *n*	
AL	217
CML	44
MM	2
MDS	19
SAA	8
NHL	1
Risk, *n* (%)	
Standard risk	234 (80.4)
High risk	57 (19.6)
Number of mismatched HLA loci, *n* (%)	
3	178 (61.2)
2	87 (29.9)
1	26 (8.9)
Donor/recipient blood type, *n*	
Matched	155
Major mismatched	50
Minor mismatched	67
Bidirectional mismatched	19
Donor/recipient sex	
F–M/F–F/M–M/M–F, *n*	88/58/89/56
Previous IFI history, *n* (%)	23 (7.9)
IFI prophylaxis, *n* (%)	
Fluconazole	260 (89.3)
Other	31 (10.7)

AL, acute leukaemia; CML, chronic myelogenous leukaemia; F, female; HLA, human leukocyte antigen; M, male; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anaemia.

IFI prophylaxis

A total of 23 patients had a prior history of IFI: two patients were proven cases, six patients were probable cases, and 15 patients were possible cases. For prophylaxis during the transplantation period, three patients were treated with oral fluconazole, four were treated with amphotericin B, three were treated with voriconazole, two were treated with caspofungin, and 11 were treated with intravenous itraconazole. Of the 268 patients without a previous history of IFI, eight were treated with an itraconazole oral solution, three were treated with micafungin, and the remaining 257 were treated with oral fluconazole (200 mg/day). The prophylaxis lasted until 75 days after transplantation or until empirical/pre-emptive antifungal treatment was given.

Diagnosis of IFI

According to the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group criteria [5], IFI can be categorized as proven, probable or possible cases. In our study, only proven and probable cases were regarded as true cases. For proven cases, the diagnosis time was defined as the time at which histopathological evidence or the results of a sterile tissue culture were acquired. The diagnosis time for probable cases was the time at which positive results for culture/galactomannan (GM) were acquired. A GM index of ≥0.5 for two consecutive instances was regarded as positive. IFI was divided into early IFI (≤40 days) or late IFI (>40 days) according to the time of occurrence.

Definitions

Successful neutrophil engraftment was defined as $\geq 0.5 \times 10^9$/L for three consecutive days, and successful platelet engraftment was defined as $\geq 20 \times 10^9$/L for seven consecutive days without the need for transfusion. The patients were defined as high risk if they were in more than the third complete remission of acute leukaemia; were not in remission; had chronic myelogenous leukaemia beyond the first chronic phase. The other cases were defined as standard risk. The