

Effectiveness of posaconazole as primary prophylaxis in allogeneic hematopoietic stem cell transplantation

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Abstract

We retrospectively analyzed the effectiveness of posaconazole (tablet and infusion formulations) and its correlation with blood concentration in preventing invasive fungal infections (IFIs) in 360 patients who underwent allogeneic hematopoietic stem cell transplant (allo-HSCT) between 2010 and 2023. A total of 61 patients received posaconazole, 102 received micafungin, and 197 received fluconazole for primary prophylaxis. By day 100 post-transplant, the cumulative incidence of IFIs was significantly lower with posaconazole (5.0%) compared with fluconazole (14.4%) or micafungin (16.9%). Multivariate analysis showed that the risk of IFIs was significantly higher with fluconazole/micafungin than with posaconazole (hazard ratio 4.04, 95% CI 1.17-13.94, $P = 0.027$). This difference was most notable among patients with lymphoid malignancies ($P = 0.053$) and those undergoing repeat transplantation ($P = 0.024$). There were no significant differences in overall survival, non-relapse mortality, or mortality from IFI. Mean blood levels of posaconazole dropped to 0.57 $\mu\text{g/mL}$ two weeks after allo-HSCT, coinciding with the observation of most IFIs in the posaconazole group shortly after transplant. Posaconazole appears to be more effective than fluconazole or micafungin as primary prophylaxis against IFIs in allo-HSCT recipients.

Abbreviations: GVHD, graft-versus-host disease; IFIs, invasive fungal infections; allo-HSCT, allogeneic hematopoietic stem cell transplant; IQR, interquartile range; MRD, matched related donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; ATG, antithymocyte globulin; CR, complete response; HLA, human leukocyte antigen; PSCZ, posaconazole; MCFG, micafungin; FLCZ, fluconazole; HR, hazard ratio; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; IPA, invasive pulmonary aspergillosis; PTCy, post-transplant cyclophosphamide; CMV, cytomegalovirus; G-CSF, Granulocyte Colony-Stimulating Factor

Introduction

Invasive fungal infection (IFI) is recognized as one of the leading causes of death in patients undergoing hematopoietic stem cell transplantation (HSCT)[1–4]. Consequently, experts and clinical guidelines strongly recommend primary prophylaxis with antifungal agents to prevent life-threatening IFIs in these patients[5–11]. Historically, fluconazole has been the standard drug for antifungal prophylaxis in HSCT due to its effectiveness in reducing the incidence of invasive *Candida* infections and improving the prognosis of allo-HSCT patients[5,11–13].

However, the epidemiology of IFIs has shifted with the widespread use of fluconazole. Invasive aspergillosis has now become the most prevalent fungal infection among allo-HSCT recipients[14,15]. Identifying safe antifungal agents that can prevent these infections and reduce fungal-related mortality remains a critical challenge. Unlike fluconazole, micafungin is effective against both *Candida* and *Aspergillus* species[16–19]. Furthermore, compared to other antifungal agents, micafungin has fewer drug interactions, including cytochrome P450 (CYP450) interactions, making it safer for use in HSCT recipients[20,21]. Nevertheless, cases of breakthrough IFIs have been reported in HSCT recipients treated with micafungin[22,23].

Posaconazole is a new-generation triazole with a broad antifungal spectrum that includes *Candida*, *Aspergillus*, *Zygomycota*, and *Fusarium* spp[24]. It is approved for antifungal prophylaxis in patients receiving chemotherapy for acute myeloid leukemia and myelodysplastic syndromes, as well as preventing IFI in patients with GVHD following allo-HSCT[25,26]. Due to the variable bioavailability of posaconazole in its oral suspension form, many patients have experienced subtherapeutic blood concentrations[27,28], leading to the development of delayed-release tablets and infusion formulations, which offer higher and more consistent exposure[29–35]. There are several studies on the association between primary prophylaxis without GVHD and the blood concentrations of posaconazole in its oral suspension form[36–38]. However, data on the tablet or infusion formulations are still limited[39]. It has been suggested that patients who have undergone allo-HSCT may have impaired absorption of the posaconazole tablet due to mucosal damage in the early post-transplant period, potentially resulting in lower blood concentrations, but the data are currently insufficient to confirm this. Therefore, this study aims to analyze the association between blood concentrations of posaconazole in tablet and infusion forms and IFIs in allo-HSCT recipients during the early post-transplant period. We measured weekly blood concentrations of posaconazole and assessed overall survival, non-relapse mortality, and mortality due to IFIs.

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3 1 **Methods**
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7 2 **Data collection**
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11 3 This retrospective study was conducted at Kyoto University Hospital, an 1141-bed
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14 4 acute care hospital in Kyoto, Japan. We included a total of 374 patients who underwent
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17 5 allo-HSCT and received prophylactic posaconazole, fluconazole, or micafungin in our
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20 6 HSCT unit between September 2010 and April 2023. Regarding the transplant cases,
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23 7 informed consent was obtained from all patients for the retrospective analysis, and
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26 8 separate consent was obtained at the time of transplantation for the use of posaconazole
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29 9 and the measurement of its blood concentrations. The study adhered to the Declaration
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33 10 of Helsinki and was approved by the Institutional Review Board of Kyoto University.
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36 11 We excluded patients with active IFI at the time of HSCT, those receiving secondary
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39 12 prophylaxis with antifungal agents on the day of transplantation, and those receiving
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42 13 prophylaxis with agents other than posaconazole, fluconazole, or micafungin.
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45 14 Specifically, one patient in the posaconazole group was excluded due to treatment for
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49 15 active IFI at the time of transplantation. In the fluconazole or micafungin group, 5
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52 16 patients were excluded for treatment of active IFIs and 8 for secondary prevention.
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3 **1 Patients care**
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7 2 All patients were treated in wards equipped with laminar airflow (LAF) systems.
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10 3 Antifungal prophylaxis prior to HSCT included oral or intravenous fluconazole (100-
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13 4 400 mg/day), intravenous micafungin (50-150 mg/day), or posaconazole (300 mg/day,
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16 5 with a double dose on the first day), administered orally or intravenously. Patients
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19 6 transplanted prior to October 27, 2020 had fluconazole used at the time of transplant
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22 7 unless there was a history of IFI. In patients with a history of IFI prior to transplantation
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25 8 during the same time period, use of voriconazole or itraconazole was considered. These
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28 9 patients who used fluconazole continued to receive it after discharge unless there were
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31 10 clinical findings suggesting IFI due to strains not covered by it. However, they were
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34 11 switched from fluconazole to micafungin if they had difficulty taking the drug, but were
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37 12 returned to fluconazole as soon as they were able to take it. Patients transplanted after
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40 13 October 27, 2020 received posaconazole at the time of transplant unless there was a
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43 14 specific reason not to. In those patients, posaconazole was either continued after
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46 15 discharge or switched to fluconazole at the discretion of the outpatient physician. In
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49 16 addition, fluconazole and micafungin were changed to voriconazole when middle to
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52 17 high dose of systemic steroids became necessary for grade II-IV GVHD, but not for
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55 18 posaconazole. These antifungal agents were continued until the onset of neutropenic
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fever necessitated a switch to another broad-spectrum antifungal agent. For some patients, the dosage of posaconazole was adjusted from 100 to 400 mg per dose based on the serum drug concentration. Galactomannan antigen and beta-D-glucan were measured weekly whenever possible. Prophylaxis against *Pneumocystis jirovecii* was initiated with inhaled pentamidine, Trimethoprim/sulfamethoxazole, or atovaquone after neutrophil engraftment was confirmed. Regarding Granulocyte Colony-Stimulating Factor (G-CSF) administration, in cord blood transplantation, filgrastim at 300 µg/m² or lenograstim at 5 µg/kg was intravenously administered once daily after transplantation. In cases of peripheral blood stem cell transplantation or bone marrow transplantation, G-CSF was administered intravenously once daily either regularly or in the event of infectious complications or delayed engraftment, at the discretion of the attending physician.

Endpoints and definitions

Subjects were grouped based on the antifungal agent used on the day of transplantation. The assigned group remained unchanged even if the medication was switched to another drug. The primary endpoint of the study was the incidence of breakthrough IFI

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6 based on the European Organization for Research and Treatment of Cancer (EORTC)
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10 2020 criteria, suspected IFIs were defined as cases where clinical features suggestive of
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13 such infections necessitated the initiation of broad-spectrum antifungal therapy[40].
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16 Other assessed endpoints included overall survival, non-relapse mortality, and mortality
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19 from IFI. During the transplant period, blood trough levels of posaconazole were
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22 measured weekly in the hospital laboratory until discharge in many patients. To assess
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25 posaconazole concentrations at a steady state, blood samples were drawn at least 5 days
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28 after the start of administration. Detailed information is described in a previous
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31 report[41]. We analyzed the association between posaconazole blood concentrations
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35 post-transplantation and the timing of the onset of IFIs.
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43 **Statistical analysis**

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47 Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as
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50 appropriate. Continuous variables were evaluated using the Kruskal-Wallis test.
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53 Categorical data are presented as frequencies, while continuous variables are expressed
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56 as medians and interquartile ranges (IQR). Overall survival was estimated using the
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1 Kaplan-Meier curve, with comparisons between groups made via the log-rank test.

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1 Cumulative incidences of IFI at 100 days post-transplantation, non-relapse mortality, and

2 mortality from IFI were estimated using cumulative incidence curves. Competing events

3 included death without IFI for estimating the incidence of IFIs, relapse for non-relapse

4 mortality, and death without IFI for mortality from IFI. These were compared using

5 Gray's test. The Fine-Gray subdistribution hazard model was employed for endpoints

6 associated with competing risks. Potential confounding variables included recipient age

7 at transplantation, recipient sex (female or male), type of malignancy (myeloid or

8 lymphoid), disease status prior to transplantation (complete response or non-complete

9 response), conditioning regimen (myeloablative or reduced-intensity), number of

10 transplants (first transplant or re-transplant), stem cell source (bone marrow, peripheral

11 blood, or umbilical cord blood), HLA-locus mismatch (matched or mismatched), and the

12 relationship between donor and recipient (related or unrelated). Factors with a P-value <

13 0.05 in the univariate analysis were included in the multivariate analysis. The paired t-

14 test was used to compare mean trough values of blood concentrations between two weeks

15 post-transplant and one week pre-transplant where both data points were available (n=12).

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17 A P-value < 0.05 was considered statistically significant. All statistical analyses were

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1 performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama,
2 Japan)[42].
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1 **Results**

2 **Patient and transplant characteristics**

3 During the study period, data from 360 patients who received HSCT were collected. All
4 demographic characteristics of the patients at baseline are summarized in **Table 1**.
5 Sixty-one patients (16.9%) received oral or intravenous posaconazole, 102 patients
6 (28.3%) received intravenous micafungin, and 197 patients (54.7%) received oral
7 fluconazole for primary prophylaxis. The median age (1st and 3rd quartiles) was 51
8 years (40-61), with no significant difference between the three groups ($P = 0.52$). The
9 most common underlying diseases were acute myeloid leukemia ($n = 137$), acute
10 lymphoblastic leukemia ($n = 60$), and myelodysplastic syndromes ($n = 59$). Sources of
11 stem cells included bone marrow ($n = 174$), peripheral blood stem cells ($n = 48$), and
12 umbilical cord blood ($n = 138$). Bone marrow was used less frequently, and cord blood
13 was used more frequently in the micafungin group ($P = 0.026$). Cyclosporine-based
14 GVHD prophylaxis was more common in the fluconazole group (8.1%) compared to the
15 posaconazole (0.0%) and micafungin groups (2.9%) ($P = 0.021$). Post-transplant
16 cyclophosphamide (PTCy) for the prevention of GVHD was more commonly
17 administered in the micafungin group ($n = 4$, 3.9%) compared to the posaconazole

group (n = 1, 1.6%) and the fluconazole group (0.0%) (P = 0.023). A history of prior allo-HSCT was less common in the fluconazole group (12.7%) compared to the posaconazole (23.0%) and micafungin groups (26.5%) (P = 0.008). The median transplant year was 2021 for the posaconazole group, 2015 for the micafungin group, and 2016 for the fluconazole group (P < 0.001). Grade III-IV acute GVHD occurred more frequently in the micafungin group (P = 0.031). The frequency of corticosteroid use for the treatment of acute GVHD was lower in the posaconazole group (27.9%) than the micafungin (47.1%) and the fluconazole group (42.1%), although it was not statistically significant (P = 0.05). The proportion of patients with cytomegalovirus (CMV) reactivation requiring treatment was lower in the posaconazole group (6.6%) compared to the micafungin (36.3%) and fluconazole groups (41.1%) (P < 0.001). Fluconazole was administered at doses of 100 mg in 22 patients (11.2%), 200 mg in 171 patients (86.8%), and 400 mg in 4 patients (2.0%), while micafungin was administered at doses of 50 mg in 36 patients (35.3%), 100 mg in 49 patients (48.0%), and 150 mg in 17 patients (16.7%). The median duration of the main antifungal agent used in each group was 88 days (IQR 52-100) in the fluconazole group, 31 days (IQR 24-42) in the micafungin group, and 75 days (IQR 38-100) in the posaconazole group. The shorter duration in the micafungin group is due to frequent switching to fluconazole.

Invasive fungal infection

The cumulative incidence of IFI at 100 days after allo-HSCT was 5.0% (95% CI 1.3-12.8) in the posaconazole group, 14.4% (95% CI 9.9-19.7) in the fluconazole group, and 16.9% (95% CI 10.3-24.9) in the micafungin group (Gray's test, $P = 0.094$) (**Fig. 1a**).

Due to the large number of switches between fluconazole and micafungin, we found it difficult to separate them and decided to integrate them for analysis. To be sure, we analyzed the data separately for the fluconazole ($P = 0.057$) and micafungin ($P = 0.029$) groups, but the results were not significantly different from the integrated results that will now be presented below. This analysis revealed a higher cumulative incidence of IFI at 100 days post-transplant in the combined fluconazole and micafungin group ($P = 0.038$) (**Fig. 1b**). An additional analysis, censoring cases at the time of antifungal drug change, yielded similar results ($P = 0.044$) (**Fig. 1c**).

Among the 28 patients who developed IFIs in the fluconazole group, 4 patients had suspected fungal infections of undetermined species, and one patient was suspected of having disseminated trichosporonosis after switching from fluconazole to micafungin (**Table 2**). Seventeen patients had possible fungal infections of undetermined species, and

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3 6 had probable invasive pulmonary aspergillosis (IPA). In the micafungin group, among
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6 the 17 patients with IFIs, one had a suspected IPA, 13 had possible fungal infections of
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9 undetermined species, two had probable IPA, and one had a proven fungal infection as
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12 schizophyllum. By contrast, in the posaconazole group, only two cases developed
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15 possible fungal infections of undetermined species, and one patient had a probable IPA.
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18 Notably, the latter patient developed this probable fungal infection after switching from
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21 posaconazole to fluconazole.
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26 Subgroup analysis revealed that the posaconazole group had a comparable cumulative
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29 incidence of IFI to the fluconazole and micafungin group for myeloid malignancy at
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32 100 days after allo-HSCT (Gray's test, $P = 0.33$) (**Fig. 2a**). However, there was a
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35 decreasing trend in the incidence of IFIs in the lymphoid malignancy subgroup within
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38 the posaconazole group ($P = 0.053$) (**Fig. 2b**). There was no significant difference in the
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41 cumulative incidence of IFI between patients who did not receive PTCy and those who
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44 did ($P = 0.375$). There was no significant difference in the cumulative incidence of IFI
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47 among those who developed acute GVHD Grade II-IV compared to those who did not
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50 develop acute GVHD Grade I or acute GVHD itself ($P = 0.191$). There was no
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53 significant difference in the cumulative incidence of IFI between patients who received
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56 corticosteroids for acute GVHD and those who did not ($P = 0.10$). Patients with CMV
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3 reactivation requiring treatment showed no significant difference in the cumulative
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6 incidence of IFI compared to those without such reactivation ($P = 0.64$). Additionally,
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9 there was no significant difference in the first transplant subgroup ($P = 0.27$) (**Fig. 3a**),
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12 but there was a significant decrease in the re-transplant subgroup for the posaconazole
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15 group ($P = 0.024$) (**Fig. 3b**).

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19 In the multivariate analysis, the risk of IFI at 100 days after allo-HSCT was higher in the
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22 fluconazole and micafungin group than in the posaconazole group, with a hazard ratio
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25 (HR) of 4.04 (95% CI 1.17-13.94, $P = 0.027$) (**Table 3**).

34 35 **Overall survival, Non-relapse mortality, and Mortality from IFI**

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39 There was no significant difference in overall survival, non-relapse mortality, and
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42 mortality from IFI between the groups receiving posaconazole and those receiving
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45 fluconazole or micafungin ($P = 0.28$, $P = 0.72$, and $P = 0.40$, respectively) (**Fig. 4a-c**).

54 55 **Association between trough values of posaconazole blood concentration and IFI**

The mean blood concentration of posaconazole decreased to a low of 0.57 µg/mL two weeks after allo-HSCT. In 50% of the cases, the concentration fell below 0.7 µg/mL, which is considered effective for prevention (**Fig. 5**) [43,44]. The mean trough values of blood concentrations were significantly lower in the second week after transplantation compared to one week before transplantation (paired t-test, P = 0.0027). Among the three patients in the posaconazole group who developed IFIs, two had low blood concentrations at the onset of their infections. One patient developed an IFI on day 8 post-transplant, with a PSCZ blood concentration of 0.3 µg/mL on day 7; at that time, posaconazole was being administered orally. Another patient developed an IFI on day 21 post-transplant, when the PSCZ blood concentration was 0.5 µg/mL on day 17; in this case, posaconazole was being administered intravenously. In both cases, the fungal species was undetermined and classified as a possible IFI. The third patient did not develop an IFI while hospitalized and on posaconazole. However, he developed probable IPA on day 92 after being switched to fluconazole on day 29 post-transplant by his outpatient attending physician after discharge.

Discussion

In this study, we demonstrated that posaconazole may be more effective than fluconazole or micafungin as primary prophylaxis prior to transplantation in allo-HSCT. This efficacy was particularly notable in patients with lymphoid malignancies and those undergoing re-transplantation. Additionally, we observed that blood concentrations of posaconazole tend to fall below the effective range early in the post-transplant period, increasing the likelihood of developing IFIs during this time.

The role of primary prophylaxis with posaconazole (tablet and infusion) prior to transplantation in allo-HSCT remains somewhat unclear. Cornely et al. demonstrated that oral suspension posaconazole significantly reduces the incidence of IFI during remission induction and rescue therapy for AML and MDS compared to fluconazole and itraconazole[25]. Moreover, Ullmann et al. found that oral suspension posaconazole is noninferior to fluconazole in preventing the development of IFIs in patients with GVHD after allo-HSCT[26]. However, these studies did not specifically address the efficacy of posaconazole as primary prophylaxis for IFI in allo-HSCT prior to transplantation. Ortega et al. demonstrated the efficacy of posaconazole for primary prophylaxis in the early post-transplant period, but their study differed from ours as it

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3 used itraconazole as a comparator, involved an oral suspension rather than tablet or
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6 infusion, and included only a limited number of patients with lymphoid
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9 malignancy[38]. Similarly, Takpradit et al. showed that posaconazole was non-inferior
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12 to fluconazole for primary prophylaxis in the early post-transplant period, but their
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15 study used posaconazole in oral suspension, focused on children, and primarily
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18 involved non-hematological malignancies[45]. Maurer et al. studied the incidence of IFI
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21 in patients undergoing re-transplantation in allo-HSCT and suggested that re-
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24 transplantation may be a risk factor for IFI; however, their study differs from ours in
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27 that they did not actually compare with the initial transplantation group[46]. Harrison et
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30 al. identified malignant lymphoma as a risk factor for invasive aspergillosis in allo-
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33 HSCT[47]. Considering that posaconazole has greater efficacy against *Aspergillus*
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36 species compared to fluconazole and micafungin, its effectiveness is thought to be
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39 especially pronounced in lymphoid malignancies, where the risk of invasive
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42 aspergillosis is higher. Our findings suggest that posaconazole, when used as primary
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45 prophylaxis in allo-HSCT, may reduce the risk of fungal infections, with a particularly
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48 strong effect observed in patients with lymphoid malignancies and those undergoing re-
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3 Overall survival, non-relapse mortality, and mortality from IFI did not significantly differ
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6 between the groups treated with posaconazole and those treated with micafungin or
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9 fluconazole when used for primary prevention of IFI. The lack of significant differences
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12 in overall survival and non-relapse mortality rates, despite a significant difference in the
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15 cumulative incidence of IFI, may be attributed to the effective rescue of many patients in
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18 the micafungin or fluconazole groups with voriconazole or amphotericin B.
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23 Several studies have measured the blood concentration of posaconazole using oral
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26 suspensions in the early post-transplant period, but data on delayed-release tablets or
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29 infusions are limited[37,39]. It was observed that the blood concentration of posaconazole
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32 tended to decrease below the effective range during the early post-transplant period
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35 (between the first and third weeks after transplantation). In fact, of the three cases of IFI
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38 in the posaconazole group, two occurred when blood concentrations dropped during this
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41 period, aside from one case that happened after switching to fluconazole. Sugimoto et al.,
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44 through a population pharmacokinetics (Pop PK) analysis, identified factors within the
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47 first year after HSCT, such as diarrhea occurring more than five times per day and
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50 elevated aspartate aminotransferase levels, as covariates affecting the apparent clearance
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53 (CL/F) of posaconazole. This early post-transplant decrease in blood concentration may
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58 be linked to malabsorption caused by mucosal damage[41]. Therefore, increasing the
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dosage or switching from oral administration to infusion could be considered to maintain adequate blood concentration levels.

This study has several limitations. First, it was retrospective, and the heterogeneity of patient backgrounds could have introduced statistical bias, although we tried to mitigate this by adjusting for effects in a multivariate analysis. Second, the relatively small sample size for each group may have led to an underestimation of the differences between groups. Third, patients were grouped based on the antifungal drug used on the day of transplantation, and group affiliations were not changed even if the drug was subsequently changed. Therefore, we conducted an additional analysis censoring the case at the time of the drug change and found that the results were similar. Fourth, fluconazole has no antifungal activity against *Aspergillus*, whereas micafungin has only fungistatic activity against *Aspergillus*, and the dosage used in this study may have been insufficient to effectively control *Aspergillus* infections. In contrast, with posaconazole, it was possible to adjust the dosage and formulation based on blood concentration levels. These differences may have contributed to the variation in IFI incidence between the two groups. Fifth, reasons for switching antifungal agents included difficulty with oral administration and drug-induced organ damage such as hepatic dysfunction; however, it was difficult to identify all specific reasons for the changes. Sixth, the

majority of IFI cases in this study were classified as "possible"; therefore, the inclusion of non-fungal infections cannot be ruled out.

In conclusion, we demonstrated that posaconazole may be more effective than fluconazole or micafungin as primary prophylaxis prior to transplantation in allo-HSCT.

This efficacy was particularly significant in patients with lymphoid malignancies and those undergoing re-transplantation. Additionally, we observed that blood concentrations of posaconazole tend to fall below the effective range early in the post-transplant period, increasing the likelihood of developing IFIs during this time.

Therefore, if possible, careful monitoring of trough concentrations is recommended.

However, in facilities where this is not feasible, switching to intravenous administration of posaconazole based on clinical indicators such as frequent diarrhea or severe mucositis can be an effective alternative strategy.

Acknowledgments

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Author Contributions

Y.H. designed the research, performed the statistical analysis, analyzed the data, and interpreted the data; J.K. organized the project, designed the research, performed the statistical analysis, and interpreted the data; M.S. gathered the data; Y.H. wrote the first draft and all other authors interpreted the data and contributed to the final version.

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2
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4
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10 11 12 13 14 **Data Availability Statement** 15

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18 The data that support the findings of this study are available from the corresponding
19
20
21 author on reasonable request. The data are not publicly available due to privacy or
22
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24 ethical restrictions.
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Figure Legends

Fig. 1 Cumulative Incidence of invasive fungal infection after allo-HSCT

(a) comparison between PSCZ, MCFG, and FLCZ, (b) comparison between PSCZ and MCFG/FLCZ combination groups, analyzed without considering changes in post-transplant antifungal medication, (c) comparison between PSCZ and MCFG/FLCZ combination groups, censored at the time of medication change.

Fig. 2 Cumulative Incidence of invasive fungal infection after allo-HSCT in patients with myeloid malignancy (a) and lymphoid malignancy (b), comparing PSCZ and MCFG/FLCZ combination groups

Fig. 3 Cumulative incidence of invasive fungal infection in PSCZ vs. MCFG/FLCZ after allo-HSCT in the first transplant group (a) and the re-transplant group (b)

Fig. 4 Overall survival (a), non-relapse mortality (b), and mortality from invasive fungal infection (c) in PSCZ or MCFG/FLCZ combination groups after allo-HSCT

Fig. 5 Time course from week -2 to week 8 for the mean trough concentration of posaconazole after allo-HSCT

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Table 1

Table 1. Patient and transplant characteristics

Variables	Posaconazole (n=61)	Micafungin (n=102)	Fluconazole (n=197)	P value
Age in y, median (IQR)	53 (40-61)	50 (39-59)	52 (40-60)	0.52
Gender				0.42
Male	32 (52.5)	60 (58.8)	122 (61.9)	
Female	29 (47.5)	42 (41.2)	75 (38.1)	
Underlying disease				0.23
Acute myeloid leukemia	26 (42.6)	45 (44.1)	66 (33.5)	
Acute lymphoblastic leukemia	9 (14.8)	20 (19.6)	31 (15.7)	
Myelodysplastic syndrome	9 (14.8)	11 (10.8)	39 (19.8)	
Myeloproliferative neoplasia	6 (9.8)	4 (3.9)	8 (4.1)	
Lymphoma	6 (9.8)	16 (15.7)	34 (17.3)	
Multiple myeloma	0 (0.0)	0 (0.0)	4 (2.0)	
Adult T-cell leukemia/lymphoma	2 (3.3)	5 (4.9)	8 (4.1)	
Others	3 (4.9)	1 (1.0)	7 (3.6)	
Conditioning regimen				0.99
Myeloablative	29 (47.5)	48 (47.1)	94 (47.7)	
Reduced-intensity	32 (52.5)	54 (52.9)	103 (52.3)	
Stem cell source				0.026
Bone marrow	30 (49.2)	38 (37.3)	106 (53.8)	
Peripheral blood	11 (18.0)	19 (18.6)	18 (9.1)	
Umbilical cord blood	20 (32.8)	45 (44.1)	73 (37.1)	
Donor type				0.47
MRD	5 (8.2)	13 (12.7)	25 (12.7)	
MMRD	4 (6.6)	10 (9.8)	8 (4.1)	
MUD	18 (29.5)	25 (24.5)	47 (23.9)	
MMUD	34 (55.7)	54 (52.9)	117 (59.4)	
GVHD prophylaxis				0.021
Tacrolimus-based	61 (100)	99 (97.1)	181 (91.9)	
Cyclosporin-based	0 (0.0)	3 (2.9)	16 (8.1)	
ATG combination therapy				0.4
No ATG combined use	55 (90.2)	96 (94.1)	187 (94.9)	

ATG combination	6 (9.8)	6 (5.9)	10 (5.1)	
PTCy combination therapy				0.023
No PTCy combined use	60 (98.4)	98 (96.1)	197 (100.0)	
PTCy combination	1 (1.6)	4 (3.9)	0 (0.0)	
Number of transplantation				0.008
First transplantation	47 (77.0)	75 (73.5)	172 (87.3)	
Re-transplantation	14 (23.0)	27 (26.5)	25 (12.7)	
Disease status				0.23
CR	49 (80.3)	70 (68.6)	138 (70.1)	
Non-CR	12 (19.7)	32 (31.4)	59 (29.9)	
Transplantation year, median (IQR)	2021 (2021-2022)	2015 (2013-2018)	2016 (2012-2018)	<0.001
2010-2014	0 (0.0)	41 (40.2)	81 (41.1)	
2015-2019	0 (0.0)	43 (42.2)	96 (48.7)	
2020-2023	61 (100)	18 (17.6)	20 (10.2)	
Acute GVHD				0.031
No Grade	36 (59.0)	32 (31.4)	76 (38.6)	
Grade I	8 (13.1)	20 (19.6)	33 (16.8)	
Grade II	13 (21.3)	38 (37.3)	73 (37.1)	
Grade III-IV	4 (6.6)	12 (11.8)	15 (7.6)	
Treatment of acute GVHD				0.05
Corticosteroid-free	44 (72.1)	54 (52.9)	114 (57.9)	
Corticosteroid-treated	17 (27.9)	48 (47.1)	83 (42.1)	
CMV reactivation				<0.001
Not requiring treatment	57 (93.4)	65 (63.7)	116 (58.9)	
Requiring treatment	4 (6.6)	37 (36.3)	81 (41.1)	

IQR interquartile range, *MRD* matched related donor, *MMRD* mismatched related donor

MUD matched unrelated donor, *MMUD* mismatched unrelated donor

GVHD graft versus host disease, *ATG* antithymocyte globulin, *CR* complete response *PTCy* post-transplant cyclophosphamide, *CMV* cytomegalovirus

Table 2. Characteristics of invasive fungal infection after allo-HSCT

Variables	Posaconazole (n=61)	Micafungin (n=102)	Fluconazole (n=197)	P value
Invasive fungal infection	3 (4.9)	17 (16.7)	28 (14.2)	0.088
Type of IFI				
Suspected	0 (0.0)	1 (1.0)	5 (2.5)	
Possible	2 (3.3)	13 (12.7)	17 (8.6)	
Probable	1 (1.6)	2 (2.0)	6 (3.0)	
Proven	0 (0.0)	1 (1.0)	0 (0.0)	
Mold				
Aspergillus	1 (1.6)	3 (2.9)	6 (3.0)	
Schizophyllum	0 (0.0)	1 (1.0)	0 (0.0)	
Undetermined	2 (3.3)	13 (12.7)	21 (10.7)	
Yeast				
Candida	0 (0.0)	0 (0.0)	0 (0.0)	
Trichosporon	0 (0.0)	0 (0.0)	1 (0.5)	

IFI invasive fungal infection, *allo-HSCT* allogenic hematopoietic stem cell transplant

Table 3

Table 3. Univariate and multivariate analysis of the cumulative incidence of invasive fungal infection at 100 days after allo-HSCT

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age (continuous)	1.03	1.00-1.05	0.019	1.04	1.01-1.06	0.0061
Sex						
Female	1		reference			
Male	0.61	0.35-1.07	0.086			
Conditioning regimen						
Myeloablative	1		reference			
Reduced intensity	1.41	0.79-2.50	0.25			
Stem cell source						
Bone marrow	1		reference			
Peripheral blood	0.57	0.20-1.58	0.28			
Umbilical cord blood	1.28	0.72-2.25	0.4			
Underlying disease						
Myeloid malignancy	1		reference			
Lymphoid malignancy	1.5	0.86-2.64	0.16			
Others	- †	-	-			
Relationship between donor and recipients						
Related donor	1		reference			
Unrelated donor	1.3	0.58-2.91	0.53			
HLA-locus mismatch						
Matched	1		reference			
Mismatched	0.88	0.49-1.56	0.66			
Disease status						
CR	1		reference			
Non-CR	1.56	0.87-2.80	0.13			
Number of transplantation						
First transplantation	1		reference	1		reference
Re-transplantation	2.17	1.18-3.99	0.013	2.96	1.50-5.85	0.0017

Treatment of acute GVHD						
Corticosteroid-free	1		reference			
Corticosteroid-treated	0.60	0.33-1.10	0.10			
Antifungal agent						
PSCZ	1		reference	1		reference
MCFG/FLCZ	3.14	0.98-10.23	0.053	4.04	1.17-13.94	0.027

HLA human leukocyte antigen, *CR* complete response, *PSCZ* posaconazole

MCFG micafungin, *FLCZ* fluconazole

† None of the patients whose underlying disease was included in the others

Fig. 1

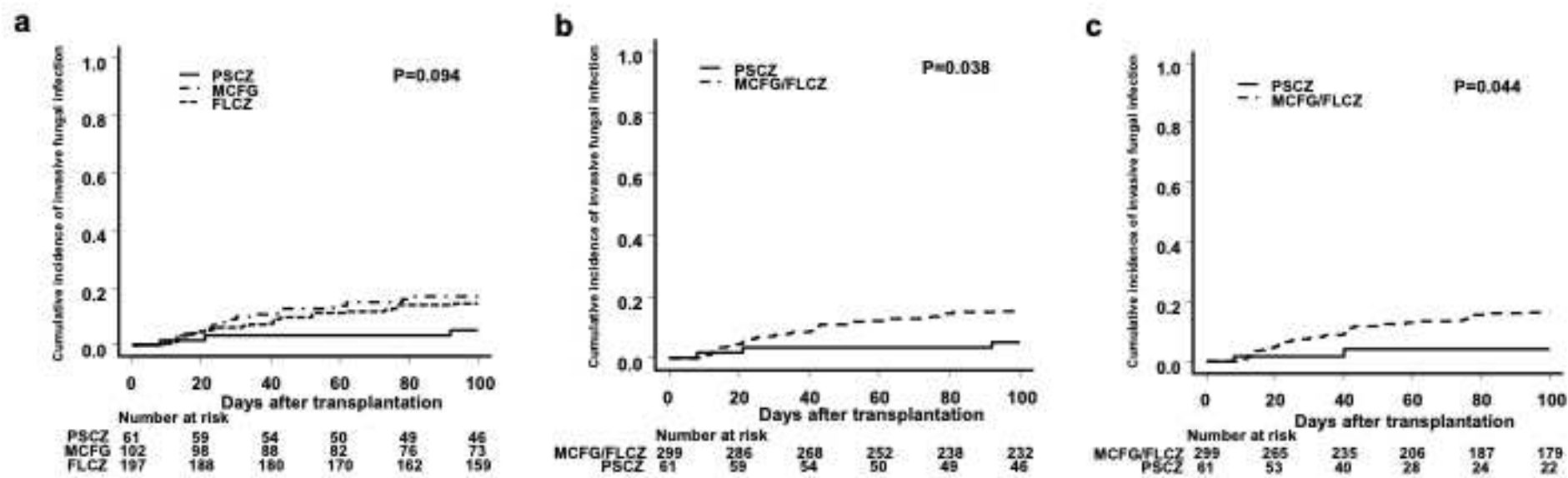


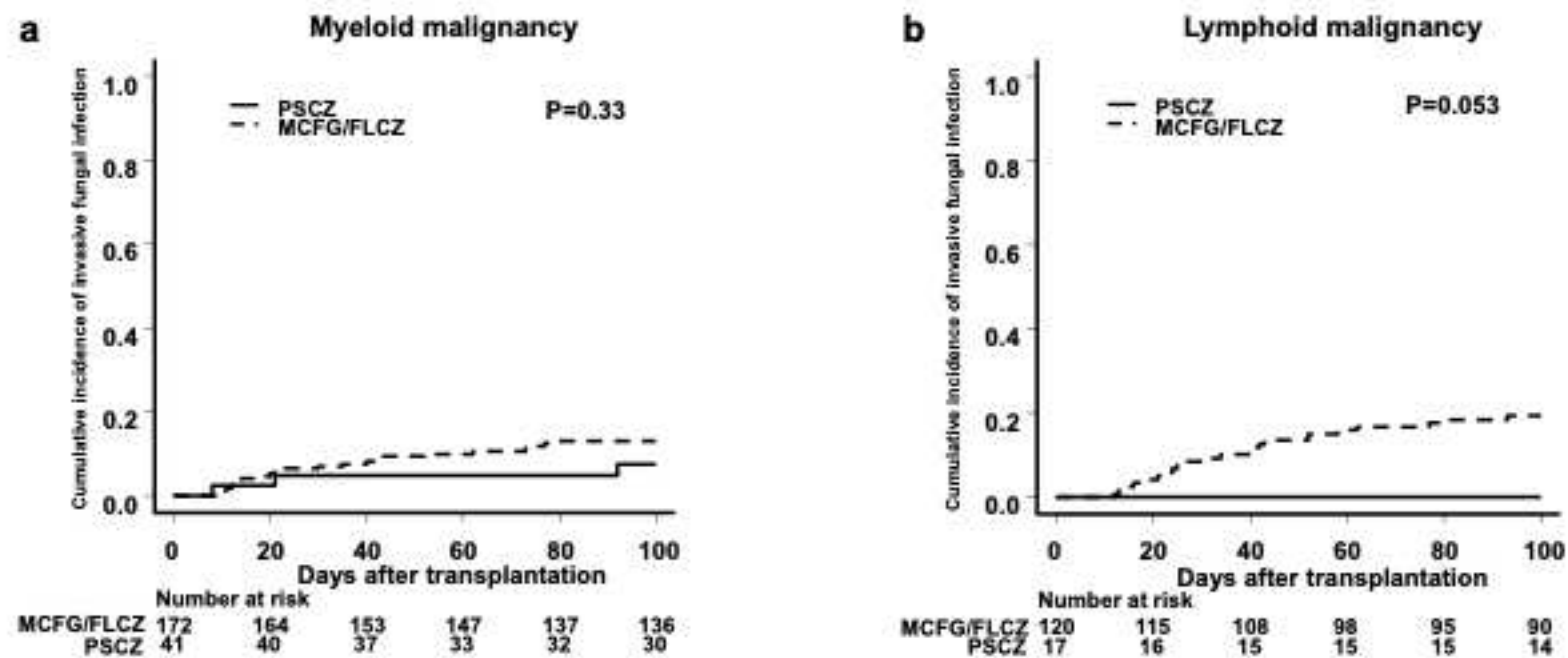
Fig. 2

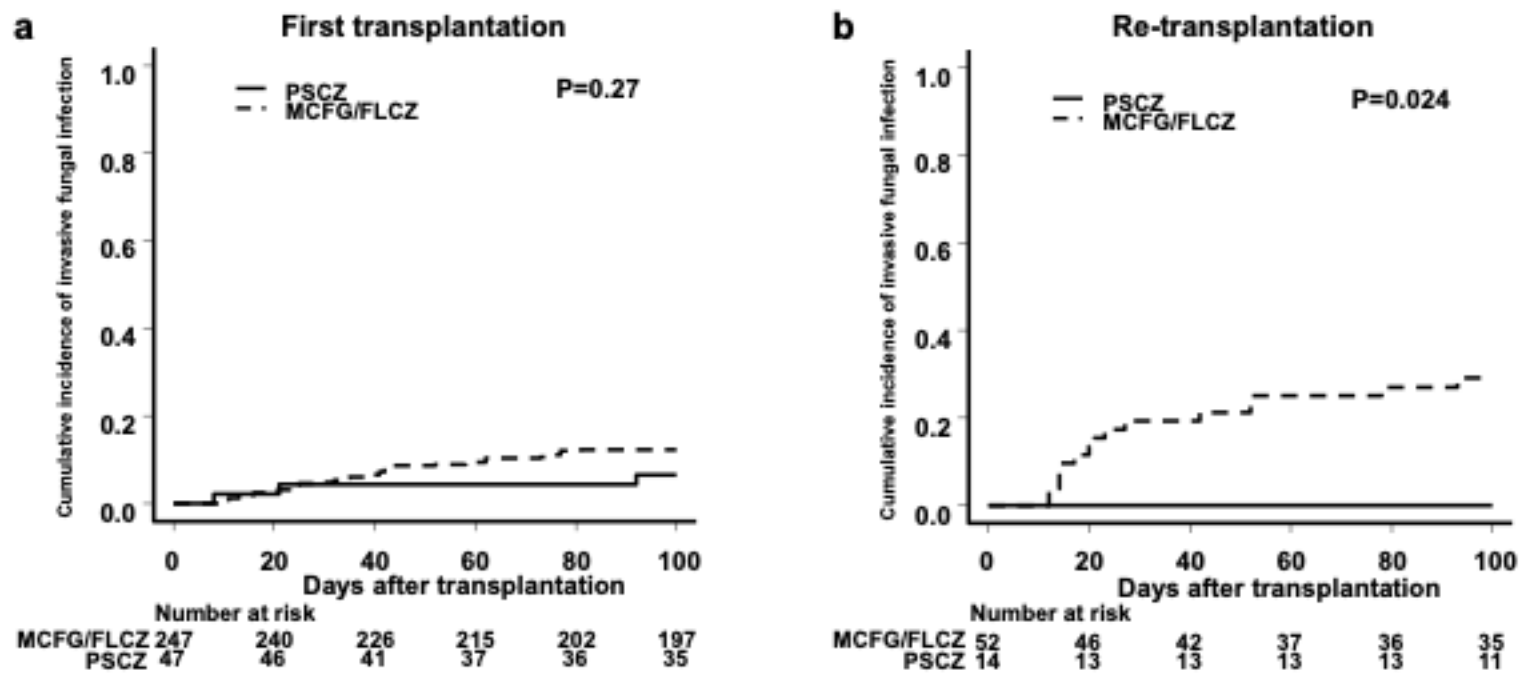
Fig. 3

Fig. 4

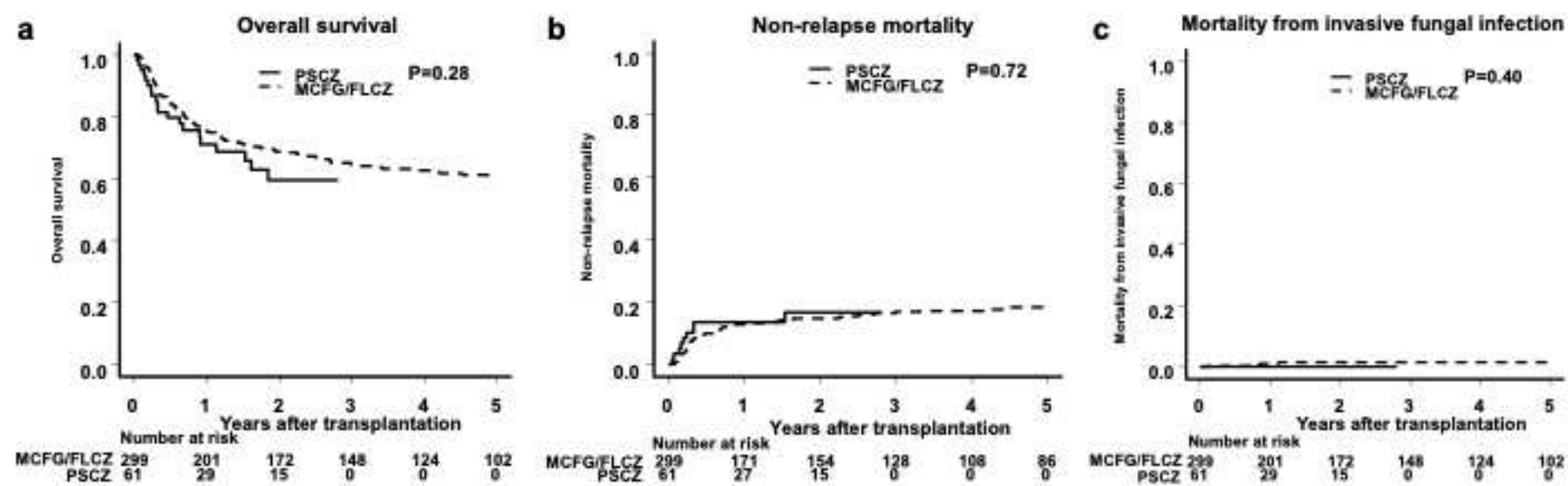


Fig. 5

