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Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients

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Summary *Objectives:* Invasive fungal infections (IFIs) cause significant morbidity and mortality among recipients of hematopoietic stem cell transplantation (HSCT). Although fluconazole is used widely as an antifungal prophylactic agent in these patients, it is not reliably effective against mold infection including invasive aspergillosis. Micafungin provides antifungal activity against *Candida* and *Aspergillus* species, and previous studies have demonstrated its efficacy when used as a prophylactic agent for fungal infection in neutropenic patients. Here, we evaluated and compared the incidence of proven or probable IFIs after antifungal prophylaxis using micafungin or fluconazole.
Methods: This was a prospective, single-center, phase II study involving adult patients who received allogeneic or autologous HSCT. Patients were randomly assigned to micafungin or fluconazole arms in a ratio of 2:1, and the treatment was initiated within 24 h of HSCT and maintained for up to 21 days. The primary end point was the incidence of proven or probable IFIs during the 100 days after HSCT. The secondary end points were the incidence rates of possible, proven, or probable IFIs, need to change the antifungal agent before engraftment, IFI-related mortality, and survival within 100 days after transplantation.
Results: Between March 2010 and May 2015, a total of 257 patients were enrolled. After exclusion of seven patients who did not receive at least one dose of a study treatment, 250 patients

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(micafungin, n = 165; fluconazole, n = 85) were included in the analysis of clinical efficacy. The median age was 47 years (range, 20–64). Allogeneic and autologous transplantations were performed in 56.0% (n = 140) and 44.0% (n = 110) of the patients, respectively. Baseline characteristics were well balanced between the two groups. Overall, the incidence of proven and probable IFIs within 100 days of HSCT was 7.6% (n = 19). The percentages of patients who experienced proven or probable IFIs did not differ significantly between the micafungin and fluconazole groups: 7.3% and 8.2%, respectively (p = 0.786). Thirteen patients in the micafungin arm (7.9%) and eight patients in the fluconazole arm (9.4%) needed a change in antifungal agent before engraftment (p = 0.824). Mortality within 100 days after HSCT did not differ significantly between groups: 9.1% vs 12.9% in the micafungin and fluconazole arms, respectively (p = 0.345).

Conclusion: Micafungin is comparable to fluconazole for the prevention of IFIs in HSCT recipients.

Introduction

The reported incidence of invasive fungal infections (IFIs) in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) ranges from 6% to 33% in previous studies.[1–8] Mortality rates associated with documented IFIs are considerable (30%–60%) and may be higher among patients after HSCT.[9–11]

Since randomized studies in the early 1990s established that prophylactic administration of fluconazole in patients undergoing HSCT reduces the incidence of systemic and superficial fungal infections caused by *Candida albicans*,[12,13] it has been the drug of choice for the prophylaxis of invasive candidiasis before engraftment in HSCT recipients.[14,15] However, because of its lack of activity against mold infection, fluconazole cannot protect patients from mold infection. Invasive mold infections have become more important because of a shift in the epidemiology of fungal infection from *Candida* to mold species with the widespread use of azole drugs as prophylaxis during the neutropenic period.[16,17]

Micafungin is an echinocandin antifungal agent that exhibits antifungal activity against *Candida* and *Aspergillus* species.[18–20] Echinocandins inhibit the biosynthesis of β-1,3-glucan linkages, which are essential components of the fungal cell wall. Because glucan polymers are not components of mammalian cells, little toxicity is observed in humans.[21] Poor oral bioavailability is a major weakness of echinocandins, and these drugs require intravenous administration.[22] Given the broader antimicrobial spectrum compared with fluconazole, low toxicity, and less frequent drug interactions in humans, echinocandins might be attractive alternatives to fluconazole in the primary prophylaxis against fungal infection in HSCT recipients.

Based on this idea, a double-blind multicenter trial that assessed the efficacy of micafungin compared with that of standard fluconazole treatment in patients undergoing HSCT was undertaken.[23] In this noninferiority study, micafungin was at least as effective and even superior to fluconazole on the basis of a predefined primary end point that included the absence of suspected, proven, or probable IFIs during the early posttransplant period. There was also a trend toward a reduction in invasive aspergillosis (IA) in favor of patients receiving micafungin. To confirm these findings in Korean patients, we conducted this prospective, randomized trial to compare micafungin with fluconazole for prevention of IFIs during the neutropenic phase in HSCT recipients.

Materials and methods

Study design and patients

This was a prospective, phase II, randomized study conducted at Samsung Medical Center in South Korea, and patient recruitment occurred between March 2010 and May 2015. Patients were eligible if they received allogenic or autologous HSCT and were aged 20 years or older. The exclusion criteria included a previous history of IFI, evidence of active fungal infection before receiving the conditioning regimen, a previous episode of treatment failure of micafungin therapy, history of allergy, sensitivity, or any serious reaction to an echinocandin, and inadequate organ function defined as an aspartate transaminase or alanine transaminase level >2.5 times the upper normal limit (UNL) and bilirubin or alkaline phosphatase level >2.5 times the UNL. Eligible patients were randomly assigned to the micafungin or fluconazole arms in the ratio of 2:1. The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. This study was approved by an independent ethics committee.

Study treatment and definition of IFI

Open-label study drugs were initiated within 24 h of the beginning of hematopoietic stem cell infusion. Micafungin (Astellas Pharma US Inc., Deerfield, IL, USA) was administered intravenously at 50 mg/day (1 mg/kg/day for patients weighing <50 kg) as a 1-h infusion. Patients assigned to the fluconazole arm received a drug orally at a dose of 400 mg/day. If patients were intolerant to oral intake, intravenous administration at the same dose was allowed. The total duration of prophylaxis was planned as per worldwide guidelines[24] with minor modifications and patients received micafungin or fluconazole until the earliest of the following: 1) 2 days after engraftment (defined as an absolute neutrophil count of 500 cells/mm^3 after the nadir absolute count); 2) treatment day 21 after HSCT; 3)