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Multicenter, Randomized, Open-Label Study Comparing the Efficacy and Safety of Micafungin versus Itraconazole for Prophylaxis of Invasive Fungal Infections in Patients undergoing Hematopoietic Stem Cell Transplant

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This multicenter, randomized, open-label phase III study compared the efficacy and safety of micafungin and itraconazole in prophylaxis of invasive fungal infections in neutropenic patients undergoing hematopoietic stem cell transplants in China. Micafungin (50 mg/day i.v.) or itraconazole (5 mg/kg/day p.o.) was administered for ≤42 days. The primary endpoint, treatment success, was defined as no proven, probable, or suspected invasive fungal infection through therapy and the absence of proven or probable invasive fungal infection through the end of 4 weeks after therapy. Noninferiority of micafungin against itraconazole was established if the lower boundary of the 95% confidence interval (CI) was >10%. Of 287 patients, 283 were evaluable for efficacy (136 for micafungin, 147 for itraconazole, intent-to-treat population). Treatment success was documented in 92.6% (126 of 136) of micafungin-treated patients and 94.6% (139 of 147) of itraconazole-treated patients (95% CI, −7.562% to 3.482%; $P = .48$), indicating noninferiority of micafungin against itraconazole. Results were similar for patients treated per protocol. Whereas the rates of proven or probable invasive fungal infection were numerically higher with micafungin than itraconazole at 4.4% (6 of 136) and 1.4% (2 of 147), rates of suspected invasive fungal infection were similar at 5.9% (8 of 136) and 7.5% (11 of 147), respectively. More patients treated with micafungin than itraconazole completed the study (82.9% versus 67.3%, respectively). Significant differences in incidence of withdrawal due to an adverse event (4.4% versus 21.1%) and drug-related adverse events (8% versus 26.5%) were shown between micafungin and itraconazole ($P = .00$, chi-square test). Micafungin was as effective as itraconazole in preventing invasive fungal infections in patients with neutropenia. In comparison to itraconazole, treatment tolerance was much better with micafungin.

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INTRODUCTION

Candida and *Aspergillus* species fungal infections occur early in the pre-engraftment phase after hematopoietic stem cell transplant (HSCT). Infection is a primary cause of death in HSCT recipients, with a fatality rate of 50% from invasive aspergillosis in patients with neutropenia alone and 86% in patients who are neutropenic after conditioning for HSCT. Because treatment of an established fungal infection is difficult,

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prophylactic treatment with antifungal agents is commonly used in high-risk patients.

Fluconazole is the most widely used antifungal agent and it is recommended for prophylaxis of *Candida* infections for HSCT recipients during the period of neutropenia until engraftment. *Candida* resistance to fluconazole has emerged and fluconazole lacks activity against molds including *Aspergillus*. In contrast to fluconazole, the broad-spectrum triazole, itraconazole, has shown activity against *Aspergillus* species or other molds in HSCT recipients [1,2].

By comparison, the echinocandin micafungin, which exerts its antifungal activity by inhibiting the production of beta-1,3-glucan, has shown antifungal activity against both *Candida* and *Aspergillus* species. In a randomized, double-blind study, the effectiveness of micafungin in providing prophylaxis against proven, probable, or suspected systemic fungal infection in HSCT recipients was significantly higher than the gold standard, fluconazole (80% versus 74%, respectively; $P = .03$) [3]. The use of micafungin has proven to be effective, safe, and well-tolerated [4] with few known drug interactions [5], which are important considerations when implementing antifungal prophylaxis in HSCT recipients.

Itraconazole is currently the only agent for prophylaxis of invasive fungal infections approved by the State Food and Drug Administration in China. A direct comparison of the efficacy and safety of micafungin against itraconazole for antifungal prophylaxis in HSCT recipients, as reported in a randomized clinical trial, could not be identified before designing this study.

The objective of this randomized, controlled, clinical study was to compare the treatment success of micafungin and itraconazole in preventing invasive fungal infections during prophylactic therapy and up to 4 weeks after discontinuation of prophylaxis antifungal therapy in HSCT recipients. The safety and tolerability of each treatment were assessed.

METHODS

Study Design

This was an open, randomized, phase III, multicenter, parallel group study to evaluate and compare the efficacy and safety of micafungin and itraconazole for prophylaxis of invasive fungal infection in patients undergoing HSCT. The duration of the study was 10 weeks. Study procedures were reviewed and approved by the institutional review boards at each of the 10 study centers in China. Conduct of the study was in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Randomization to the study medication group (micafungin) or to the control group (itraconazole) was 1:1 by block randomization using randomization codes generated by SAS PROC Plan. The randomization table was developed by Excel Pharma Studies, Inc. (Beijing, China). Randomization was stratified by patient age (18-49 and $\geq$50 years) and type of stem cell transplant (SCT).

Patients

Eligible for the study were adult patients, 18 to 70 years old, undergoing allogeneic or autologous HSCT for treatment of a malignancy. Patients were free of liver disease (serum glutamic oxaloacetic or pyruvic transaminase greater than 5 times the normal value, total bilirubin >2.5 times the normal value), the existence of active, deep, or disseminated fungal infection, and known allergy to azoles or echinocandin antifungal agents. Patients were excluded if they had received any antifungal therapy within 72 hours of the first dose of the study drug. Written informed consent was provided before randomization.

Intervention

The study drug, micafungin (Astellas Pharma Inc., Deerfield, IL) was administered i.v. at a dose of 50 mg/day. The control drug, itraconazole (Janssen Pharmaceuticals, Inc., Titusville, NJ) was administered as a solution taken orally at a dose of 5 mg/kg/day (in 2 administrations). Patients were to receive the assigned therapy during the neutropenic (ie, pre-engraftment) phase of HSCT, starting within 48 hours of the beginning of the transplant-related conditioning regimen until the earliest of the following: $\leq$5 days after engraftment (defined as an absolute neutrophil count of $\geq$500 cells/mm^3 after the nadir absolute count); treatment day 42 after HSCT; development of proven, probable, or suspected invasive fungal infection; development of unacceptable drug toxicity; death; withdrawal from study participation (patient's decision); or discontinuation of study treatment (investigator's decision).

Outcomes

Patients were evaluated at baseline, during prophylactic treatment, at the end of treatment, and at 4 weeks after prophylactic treatment, as depicted in the study flow chart (Figure 1). The primary endpoint, treatment success, was defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylactic therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period. Both criteria must have been fulfilled to achieve treatment success.

According to the Chinese criteria for invasive fungal infection diagnosis [6], proven infection was defined as biopsy-proven invasive or disseminated