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Efficacy and Safety of Micafungin as Prophylaxis for Invasive Fungal Disease in Neutropenic Patients with Hematologic Malignancies

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Abstract: Invasive Fungal Disease (IFD) is a major cause of death in severe neutropenic patients with hematologic malignancies. Micafungin, a new echinocandin antifungal drug, is effective in treating IFD. However, the efficacy and safety of micafungin in preventing IFD in severe neutropenic patients with hematologic malignancies have not been demonstrated. A prospective and multicenter clinical study was conducted to evaluate the efficacy and safety of micafungin as prophylaxis for IFD. Micafungin 50 mg daily was administered intravenously to 117 high-risk patients with hematologic malignancies undergoing intensive chemotherapy or Hematopoietic Stem Cell Transplantation (HSCT), for a median of 24 days. Successful prophylaxis (no proven, probable or possible IFD up to 1 week after the end of prophylactic treatment) was achieved in 88.54% patients. No patient developed proven IFD during treatment and only 2.08% had probable IFD and 9.38% possible IFD. Micafungin potentially accounted for adverse events in 6.84% of patients. No severe adverse events attributable to micafungin were seen. Micafungin 50 mg daily is a promising prophylactic antifungal therapy for neutropenic patients with hematologic malignancies.

Key words: Micafungin, invasive fungal disease, neutropenia, hematologic malignancy, prophylaxis

INTRODUCTION

Patients with hematologic malignancies undergoing intensive chemotherapy or Hematopoietic Stem Cell Transplantation (HSCT) are susceptible to Invasive Fungal Diseases (IFD), especially when they have prolonged (>7 days duration) or profound (absolute neutrophil count $\leq 0.1 \times 10^9$ L^{-1}) neutropenia (Freifeld *et al*., 2011). In a large retrospective cohort study conducted in Italy, the incidence of probable and proven IFD was 4.6% in patients with hematologic malignancies (Pagano *et al*., 2006). It was highest in recipients of allogeneic HSCT (allo-HSCT), in whom the incidence of probable and proven IFD was in the range of 7.8-15.8% (Pagano *et al*., 2007; Goodman *et al*., 1992). The mortality caused by IFD is about 36.8-60% and is much higher than that caused by bacterial infection (Pagano *et al*., 2006; Kurosawa *et al*., 2012; Malagola *et al*., 2008). Due to difficulties in diagnosing IFD and the high mortality rate associated with delayed treatment, prophylactic strategies against fungal infection are very important as they can decrease all causes of mortality, significantly in patients after chemotherapy (Robenshtok *et al*., 2007). Although, triazole antifungal agents have shown good activity in fungal infections, drug-related adverse effects (e.g., liver dysfunction) and drug interactions limit the application of these drugs (Michallet and Ito, 2009).

Micafungin, a potent inhibitor of 1, 3-β-D-glucan synthesis, which is critical to the structure of the cell wall of several common fungal species, has broad antifungal activity against *Candida* and *Aspergillus* species. Fungal cells, that are unable to synthesize this polysaccharide, cannot maintain their shape and lack adequate rigidity to resist osmotic pressure which results in fungal cell lysis.

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Since mammalian cells do not have 1, 3-β-D-glucan, micafungin has markedly less adverse effects than the triazoles. Furthermore, unlike the triazoles, micafungin is not metabolized via the cytochrome P450 pathway and has few interactions with other drugs (Chandrasekar and Sobel, 2006; Fukuoka *et al*., 2010; Inoue *et al*., 2012).

In this prospective, multicenter and open-label study, we evaluated the efficacy and safety of intravenous micafungin as prophylaxis for IFD in high-risk patients with hematologic malignancies.

METHODOLOGY

Inclusion and exclusion criteria: Patients of age 18-60 years with hematologic malignancies were eligible if they were anticipated to have neutropenia with an absolute neutrophil count of 0.5×10^9 L^{-1} or less for 7 days or longer or severe neutropenia with an absolute neutrophil count of 0.1×10^9 L^{-1} resulting from intensive chemotherapy or a conditioning regimen followed by autologous HSCT (auto-HSCT) or allo-HSCT. Exclusion criteria were a history of IFD or antifungal therapy before or at the time of the study; a positive baseline 1, 3-β-D-glucan test; possible, probable or proven IFD at baseline; clinically significant hepatic dysfunction (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥5 times the upper limit of normal and/or total bilirubin ≥2.5 times the upper limit of normal); a history of hypersensitivity to echinocandins and lactation or pregnancy. Before enrollment, written informed consent was obtained from each patient or the patient's legal guardian. The study was registered at www.chictr.org (No. ChiCTR-PNC-11001575) and it was approved by the ethics committee of each participating center.

Study design: A prospective, open-label clinical study was conducted at 7 centers in China. Eligible patients received micafungin (Mycamine Astellas Pharma Inc, China) 50 mg once daily intravenously over 1 h from the first day of chemotherapy or conditioning regimen. Prophylaxis was continued until: (1) Recovery from neutropenia (absolute neutrophil count > 0.5×10^9 L^{-1} for 3 consecutive days); (2) The occurrence of possible, probable or proven IFD; (3) Up to 42 days of prevention had been administered or (4) The patient developed unacceptable adverse effects. Other antifungal agents were not allowed during the study. Patients were followed up 30 days after the last dose of micafungin.

Assessment of efficacy: All patients underwent comprehensive evaluations for the presence of IFD at baseline, then weekly during the prophylaxis and at 7 and 30 days after the conclusion of prophylaxis. In addition to monitoring for symptoms and signs of infection and any adverse effects, complete blood and platelet counts, ALT, AST, alkaline phosphatase, total bilirubin, creatinine, Blood Urea Nitrogen (BUN), electrolyte levels, Urianalysis, serum 1, 3-β-D-glucan test and blood galactomannan test were performed weekly. Chest Computed Tomography (CT) was performed at baseline, the end of prophylaxis and at any time during the study if indicated. Fungi cultures of blood, urine, stool, oropharynx or sputum samples were obtained as clinically indicated by the physician. Types of IFD were defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria (De Pauw *et al*., 2008).

The primary endpoint was the success rate in prevention of systemic fungal infection which was defined as the absence of proven, probable or possible IFD up to the end of micafungin administration. Secondary endpoints included the incidence of possible, probable and proven IFD one week following the end of prophylaxis.

Assessment of safety: All eligible patients, receiving atleast one dose of micafungin, were included in the safety evaluation. All adverse effects, their duration, severity and possible relationship to the study drug were recorded. Decisions to discontinue treatment were made by the investigators. Adverse events were classified according to the common toxicity criteria grading system of the National Cancer Institute, version 2.0. (NCI, 1999).

Statistical analysis: Efficacy analysis was based on per protocol set (all patients who were treated per protocol without major deviation). Adverse effect analysis was based on safety set (all patients who received at least one dose of study drug). The frequency and ratio of category data were determined. Continuous variables were calculated as Mean±Standard deviation. Paired t-test was used to test the differences in biochemical values between baseline and one week after the end of treatment. A value of $p<0.05$ was considered significant. Statistical analyses were performed using SAS V9.0 software.

RESULTS

Patient characteristics: Between June 2011 to September 2012, 122 patients from 7 centers of China were enrolled in the study. However, 5 patients did not meet criteria for the protocol and were excluded from the efficacy and

Table 1: Characteristics of eligible patients

Parameters	All patients (n = 117)	HSCT (n = 43)	Chemotherapy (n = 74)
Median age,	39.14	38.00	39.50
Year range	18-60	21.42-60.00	18-59.97
Male	60 (51.28)	23 (53.49)	37 (50.00)
Weight (kg), Mean±SD	65.28±13.99	63.82±11.14	66.14±15.44
Underlying diseases			
AL	68 (58.12)	12 (27.91)	56 (75.68)
CML	11 (9.40)	9 (20.93)	2 (2.70)
HL	8 (6.84)	8 (18.60)	0 (0.00)
NHL	13 (11.11)	4 (9.30)	9 (12.16)
MM	2 (1.71)	2 (4.65)	0 (0.00)
MDS	6 (5.13)	4 (9.30)	2 (2.70)
Others	9 (7.69)	4 (9.30)	5 (6.76)

HSCT: Hematopoietic stem cell transplantation, AL: Acute leukemia, CML: Chronic myelogenous leukemia, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma, MM: Multiple myeloma, MDS: Myelodysplastic syndrome. Data are presented as n (%) unless otherwise indicated

Table 2: Incidence of possible, probable and proven IFD by per protocol set

Parameters	All patients (n = 96)	HSCT (n = 40)	Chemotherapy (n = 56)
IFD	11 (11.46)	4 (16.67)	7 (12.50)
Possible	9 (9.38)	4 (16.67)	5 (8.93)
Probable	2 (2.08)	0 (0.00)	2 (3.57)
Aspergillosis	2 (2.08)	0 (0.00)	2 (3.57)
Candidiasis	0 (0.00)	0 (0.00)	0 (0.00)
Proven	0 (0.00)	0 (0.00)	0 (0.00)
Time to treatment failure (days), Mean±SD	22.25±6.84	26.00±8.68	20.38±5.40

Data are presented as n (%) unless otherwise indicated

safety analyses (2 were aged > 60 years, 1 had positive 1, 3-β-D-glucan test at baseline, 1 had information only at baseline and the end of the study and 1 had IFD at baseline). Therefore, 117 patients were included in the safety set; 43 underwent allo-HSCT (n = 25) or auto-HSCT (n = 18), 74 received intensive chemotherapy. The median age of the patients was 39.14 years (range 18-60 years). Their clinical characteristics are listed in Table 1. Among the 117 patients included in the safety analysis, 21 were withdrawn from the study; 7 withdrew for personal reasons, 6 discontinued micafungin for safety reasons, in 5 patients, the absolute neutrophil count did not fall to $0.1\times10^9\ L^{-1}$ or $<0.5\times10^9\ L^{-1}$ for 7 days and 3 patients were noncompliant with the study protocol. A total of 40 patients in the HSCT group (24 allo-HSCT and 16 auto-HSCT) and 56 patients in the chemotherapy group completed the study. Thus, 96 patients were evaluated in the efficacy analysis. The median duration of prophylaxis was 24 days for the 96 patients who completed the study (25 days for the HSCT group and 22 days for the chemotherapy group).

Efficacy of prophylactic micafungin therapy: Antifungal prophylaxis was considered successful (i.e., no proven, probable or possible IFD) in 85 of the 96 patients (88.54%), including 36 (90.00%) in the HSCT group, 16 auto-HSCT patients (100%) and 20 allo-HSCT patients (83.33) and 49 (87.50%) in the chemotherapy group. No patient developed proven IFD during the treatment and only 2 (2.08%) were diagnosed with probable IFD, both of whom had newly diagnosed acute myeloid leukemia and received induction chemotherapy and micafungin. One patient had a positive blood galactomannan test with persistent fever and cough and the second patient also had a positive blood galactomannan test and a CT of the chest revealed pneumonia and thoracic effusion. Neither of these patients had positive blood or sputum cultures and they were both diagnosed as having probable *Aspergillus* infection.

Possible IFD occurred in 9 of the 96 (9.38%) patients, including 4 in the HSCT group (all of them underwent allo-HSCT) and 5 in the chemotherapy group. One patient had positive sputum cultures (*Candida glabrata* and *Microsporum fulvum*), 1 had a positive culture for *Candida albus* in a perianal exudate, 2 had positive 1, 3-β-D-glucan tests, 2 had positive blood galactomannan tests and the other 3 patients had minor symptoms but did not have positive blood or sputum cultures. For the 11 patients who developed possible or probable IFD, the median time to failure of fungal prophylaxis was 26.00±8.68 days for HSCT patients and 20.38±5.40 days for chemotherapy patients (Table 2).

Table 3: Adverse events in the safety set

Parameters	All patients (n = 117)	HSCT (n = 43)	Chemotherapy (n = 74)
Adverse events (incidence ≥3%)	56 (47.86)	23 (53.49)	33 (44.59)
Rash	14 (11.97)	7 (16.28)	7 (9.46)
Elevated aminotransferase	13 (11.11)	13 (30.23)	0 (0.00)
Diarrhea	12 (10.26)	11 (25.59)	1 (1.35)
Abnormal liver function test	8 (6.84)	3 (6.98)	5 (6.76)
Elevated bilirubin	6 (5.13)	6 (13.95)	0 (0.00)
Pyrexia	5 (4.27)	1 (2.33)	4 (5.40)
Abdominal pain	5 (4.27)	5 (11.63)	0 (0.00)
Vomiting	5 (4.27)	4 (9.30)	1 (1.35)
Micafungin related adverse events	8 (6.84)	1 (2.33)	7 (9.46)
Rash	7 (5.98)	1 (2.33)	6 (8.11)
Abnormal liver function test	1 (0.85)	0 (0.00)	1 (1.35)

Data are presented as n (%). Safety set included patients who had taken atleast one dose of micafungin

Adverse effects: All 117 eligible patients enrolled in the study were included in the safety analysis. During the study, 56 (47.86%) patients experienced one or more adverse events. Most of the adverse events were mild or moderate in severity and had no influence on usage of the study drug. A total of 8 (6.84%) patients were considered to have adverse events associated with micafungin, including 7 patients with a skin rash and 1 patient with abnormal liver function (Table 3). Two patients with rash were treated with antihistamines, continued using micafungin and experienced rapid resolution of the rash.

The other 6 patients experienced resolution of their rash or abnormal liver function after discontinuing micafungin. There were slight increases in total bilirubin (1.13±8.11), ALT (16.70±71.94), AST (12.71±81.28) and decreases in creatinine (-1.59±5.31) and BUN (-0.21±21.29) between baseline and one week after the end of prophylaxis, only the change in creatinine had significance ($p<0.05$).

DISCUSSION

This multicenter clinical study showed micafungin is effective and safe in preventing IFD in patients with hematologic diseases during neutropenia.

IFD remains a major problem in stem cell transplantation and severely neutropenic patients with hematologic malignancies. As the diagnosis of IFD is often delayed, reducing the risk of fungal infections by an effective prophylactic regimen is recommended for these high-risk patients (Robenshtok *et al*., 2007). In 2010, the Infectious Diseases Society of America provided guidelines for neutropenic patients with cancer recommended antifungal prophylaxis for patients in whom the anticipated duration of neutropenia is more than 7 days. Allo-HSCT recipients and those undergoing intensive chemotherapy for acute leukemia are high-risk patients and therefore, antifungal prophylaxis is recommended for these individuals (Freifeld *et al*., 2011).

Fluconazole has been widely recommended for use in recipients of bone marrow transplant to prevent fungal infection. In a double blind, randomized, controlled trial published in 1992, fluconazole reduced the incidence of superficial and systemic fungal infections from 33.3% to 8.4% and 15.8% to 2.8%, respectively (Goodman *et al*., 1992). However, there is an increased incidence of colonization by *Candida glabrata* and *Candida krusei*, both of which are less susceptible to fluconazole, moreover, fluconazole has no activity against molds (Pfaller *et al*., 2010a, b). Over the last 20 years, an increasing number of infections caused by molds have been reported. *Aspergillus* spp. is the most frequently diagnosed pathogen and it has caused fatal complications in patients with hematologic malignancies (Kurosawa *et al*., 2012). Therefore, new antifungal drugs are required to provide broader and effective prophylaxis.

Echinocandins, such as micafungin, have demonstrated activity against *Candida* and *Aspergillus* spp. In a randomized, double blind, multicenter comparative study that evaluated the efficacy of micafungin versus fluconazole for prophylaxis during the pre-engraftment period of neutropenia in 882 patients undergoing autologous and allogeneic HSCT, the efficacy of micafungin was superior to that of fluconazole (80% vs. 73.5%; $p = 0.03$) (Van Burik *et al*., 2004). However, this study achieved higher treatment success. The present study included patients receiving intensive chemotherapy and all were Asian patients with an average weight of 65.3 kg. In contrast, patients in the previous study were mainly white (91.1%) with an average weight of 75.6 kg. This difference in patient groups may account for the different results.

The recommended dosage of micafungin for *Candida* infection in adults is 100 mg once daily in those weights >40 kg and 2 mg kg^{-1} day^{-1} in those weights <40 kg. In patients with an inadequate response, the dosage may be increased to 200 mg day^{-1} or 4 mg kg^{-1} day^{-} ,^{1} respectively (Scott, 2012). In a pharmacokinetic-pharmacodynamic analysis, dosages of 50 mg once daily and 100 mg once daily demonstrated >95% probability of achieving fungistatic and fungicidal targets against *Candida* spp. (Ikawa *et al*., 2009). The recommended adult dose is 50 mg day^{-1} for antifungal infection (Chandrasekar and Sobel, 2006). Thus, a 50 mg once daily dosage of micafungin was administered in present study for fungal prophylaxis. In a non-randomized retrospective trial, micafungin 150 mg day^{-1} was administered as prophylaxis in neutropenic patients with hematologic malignancies. The incidence of proven and probable IFD in the micafungin group was 1.5%, whereas it was 12.3% ($p = 0.001$) in the control group that did not receive systemic antifungal prophylaxis (Hirata *et al*., 2010). The patient population in the previous study was similar as in present study and the success rate was also similar. However, the dosage of micafungin in present study was only 50 mg day^{-1} which produced a similar effect of 150 mg day^{-1} dosage for prophylaxis of IFD in high-risk patients.

Different from triazole antifungal drugs, micafungin has few adverse effects because its target is unique to fungal cells and is absent in mammalian cells, in addition, micafungin is not metabolized by the CYP450 system. In patients with moderate hepatic dysfunction, severe renal failure or older age, dosage adjustments are unnecessary (Scott, 2012). In a recent multicenter, open-label, randomized study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of IFD in patients undergoing allo-HSCT and auto-HSCT, micafungin 50 mg day^{-1} intravenously was not inferior to itraconazole 5 mg kg^{-1} day^{-1} orally in terms of treatment success (92.6% vs. 94.6%, respectively; $p = 0.48$) but micafungin was associated with a lower incidence of drug-related adverse effects (8% vs. 26.5%; $p = 0.00$) (Huang *et al*., 2012). In present study, although nearly half of the patients experienced one or more adverse events, only 8 out of 117 (6.84%) patients had mild or moderate adverse events which were judged by

investigators as possibly related to micafungin. Unlike the previous study, there was higher incidence of rash in this study. The diverse patient populations may account for this difference. Over 80% of patients in study (Huang *et al*., 2012) were recipients of allo-HSCT versus 25% in this study. Skin rash developing after allo-HSCT was often diagnosed as acute graft versus host disease instead of drug related adverse effects. During the treatment period, there were some changes in total bilirubin, ALT, AST, creatinine and BUN between baseline and one week after the end of treatment which were secondary to the combined effects of all medication including intensive chemotherapy, antibiotics, immunosuppressive agents, growth factors and micafungin, etc., given to patients and also related to the nutrition status in patients during the period.

CONCLUSIONS

Although, this study was not a randomized controlled study, its findings indicate that micafungin 50 mg daily is effective in preventing IFD in neutropenic patients with hematologic malignancies and is well tolerated. Most adverse events occurring with micafungin were mild or moderate in severity and had no influence on its usage.

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