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Efficacy and Safety Assessment of Antifungal Sequential Therapy from Micafungin to Liposomal Amphotericin B for Antibiotics-Refractory Febrile Neutropenia in Patients with Hematologic Malignancies

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Abstract

Invasive fungal infections are a major challenging problem in the management of febrile neutropenia (FN) in patients with hematologic malignancies. Liposomal amphotericin B (L-AmB) or micafungin (MCFG) has been widely used as a first-line empirical antifungal therapy for suspected fungal infection in such patients. However, there are several issues in patients receiving these agents: drug related toxicities for L-AmB and breakthrough fungal infections for MCFG. In order to make the best use of these 2 agents, we conducted a prospective study of sequential therapy from MCFG to L-AmB, and evaluated the efficacy and safety of this strategy in FN patients with hematologic malignancies. A total of 18 patients were enrolled, and 11 patients who fulfilled the protocol defined criteria were evaluated. Underlying diseases consisted of acute leukemia (n = 9), non-Hodgkin lymphoma (n = 1), and myelodysplastic syndrome (n = 1). Treatment success was achieved in 8 patients (72.7%). Drug-related adverse events occurred in 8 patients (72.7%). All of those adverse events except one case were below grade 2. Three patients required discontinuation of L-AmB. Although our empirical antifungal sequential therapy seems to be encouraging for antibiotics-refractory FN in patients with hematologic malignancies, further investigation in large-scale studies is warranted.

Keywords

Empirical Antifungal Therapy, Micafungin, Liposomal Amphotericin B, Febrile Neutropenia, Hematologic Malignancy

1. Introduction

Invasive fungal infections (IFIs) are well recognized to cause significant morbidity and mortality in neutropenic patients with hematologic malignancies receiving intensive chemotherapy [1]. Empirical antifungal therapy is recommended for persistent febrile neutropenia (FN) refractory to broad-spectrum antibacterial therapy in these patients, because an early diagnosis of IFIs remains difficult and a delayed antifungal treatment often increases mortality due to advanced IFIs [2] [3].

Conventional amphotericin B (AmB) or liposomal AmB (L-AmB) has been the standard empirical antifungal agent in reducing IFIs in FN patients with hematologic malignancies [4] [5] [6]. However, L-AmB, a less toxic formulation of AmB, still remains the concern of drug-related adverse events (DAEs) including infusion-related reactions, nephrotoxicity, and electrolyte imbalance [7]. Micafungin (MF), an echinocandin class agent with fewer adverse effects [8], has also been demonstrated to have the high efficacy as an empirical antifungal agent for hematologic patients during the chemotherapy-induced neutropenic period [9] [10]. On the other hand, several reports have described breakthrough fungal infections such as trichosporonosis [11] and zygomycosis [12] in patients receiving a prolonged MF administration. In these regards, there is a critical need for empirical antifungal therapy with less-toxic as well as fewer risk of breakthrough infection.

In order to fulfill such needs, we planned a sequential therapy from MF to L-AmB to cover their drawbacks and effectively utilize their advantages. We hereby report the result of a prospective study evaluating the efficacy and safety of this empirical antifungal sequential therapy setting for persistent FN patients with hematologic malignancies.

2. Patients and Methods

This prospective non-randomized study was conducted at Mie University hospital and its associated 4 hospitals. The purpose of this study was to evaluate the efficacy and safety of empirical antifungal sequential therapy from MF to L-AmB for antibiotics-refractory FN in patients with hematologic malignancies. The primary endpoint was the rate of treatment success, defined as fever resolution during neutropenia, no breakthrough fungal infections during the study period, and no premature discontinuation of the study drug due to adverse events. All patients provided written informed consent prior to registration. The protocol was reviewed and approved by an institutional review board at each hospital.

Patents aged 20 years or older were enrolled in this study if they had received chemotherapy for hematologic malignancies and had antibiotics-refractory FN for 3 days or more. Patients were included irrespective of whether or not they received antifungal agents for prophylaxis or granulocyte colony-stimulating factor (G-CSF). Neutropenia was defined as a neutrophil count below 500/mm^3, or below 1000/mm^3 with the expectation to further decrease to below 500/mm^3 within a few days. Fever was defined as an axillary temperature above 37.5˚C based on a single measurement. Patients were excluded from this study if they had proven or probable fungal infections according to the criteria proposed by European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) [13], beyond grade 3 liver and/or kidney dysfunction based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE Ver. 5.0), or a history of serious allergy to the study drugs. Those who had undergone allogeneic hematopoietic stem cell transplantation were also excluded. Patients were provisionally registered before the administration of MF. Design of the study is indicated in **Figure 1**. When a fever persisted despite the use of MF at 50 to 150 mg per day for 3 to 5 days, the antifungal drug was switched to L-AmB at 2.5 mg per kilogram of body weight daily. Formal registration was made just before the commencement of L-AmB. Therapy was continued until both fever resolution and absolute neutrophil count above 500 per cubic millimeter for more than 3 successive days were achieved. L-AmB treatment was ceased when the drug was considered to be no efficacy, serious DAEs based on the NCI-CTCAE Ver. 5.0 developed, and the cause of fever was found to be due to other than fungal infections.

3. Results

3.1. Patients

A total of 18 patients were initially enrolled in this study. Among them, 7 patients

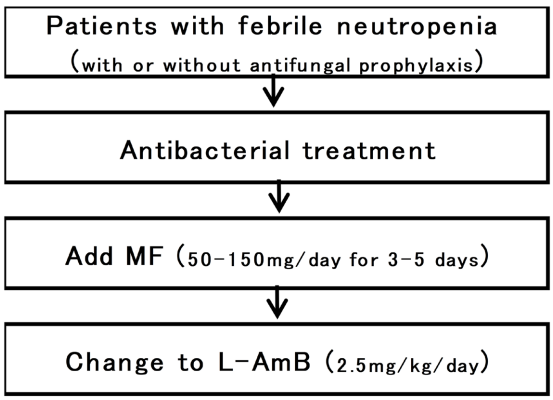

Figure 1. Design of the study. Patients developing FN after chemotherapy received antibacterial treatment. MF was added for those remaining FN for 3 days or more irrespective of antibacterial therapy. When FN persisted despite the use of MF for 3 to 5 days, MF was changed to L-AmB. *FN* febrile neutropenia, *MF* micafungin, *L-AmB* liposomal amphotericin B.

were excluded because of no administration of MF (n = 2), early recovery from neutropenia (n = 2), no neutropenia (n = 1), defervescence during the use of MF (n = 1), and the diagnosis of cytomegalovirus infection (n = 1). The remaining 11 patients who fulfilled the protocol defined criteria were evaluated. Patient characteristics are listed in Table 1. Eight patients were male and 3 were female. The age of patients ranged from 42 to 75 years (median 61 years). Underlying disease of the patients was as follows: 9 as acute leukemia, one as myelodysplastic syndrome, and one as non-Hodgkin lymphoma. Patients were monitored daily for clinical signs and symptoms. Complete blood count, blood chemistry, and c-reactive protein (CRP) were tested regularly every week. Serum (1,3)-β-D-glucan (BDG) and galactomannan antigen (GM), and chest radiography were checked before treatment and in cases of a possible focus of infection. Blood cultures were drawn at any occasion if clinically indicated.

3.2. Efficacy

Treatment success was obtained in 8 of 11 patients (72.7%) (Table 2). None of these patients required discontinuation of L-AmB due to DAEs, lack of efficacy, developed documented breakthrough fungal infection, and died during the study period. The mean duration of treatment was 11.9 (6 - 23) days. Although positive results of BDG in 2 (case 7 and 9) and GM in one patient (case 8), respectively, these abnormalities were all improved during the administration of L-AmB. In chest radiography, no case showed abnormalities of suspected fungal infection during the study.

3.3. Safety

DAEs developed in 8 patients (72.7%) (Table 2, Table 3). All of those except one were below grade 2. Hepatotoxicity was observed in 3 patients (27.3%): elevation of GPT level in case 4 (grade 1), case 5 (grade 1) and case 11 (grade 1). Nephrotoxicity was observed in 2 patients (18.2%): elevation of creatinine level in case 8 (grade 1) and case 10 (grade 2). Hypokalemia occurred in 2 patients (18.2%): case 3 (grade 2) and case 11 (grade 2). Others were observed in 2 patients (18.2%):

Table 1. Patient characteristics.

Characteristic	Total (n = 11)
Gender	**n (%)**
Male	8 (73)
Female	3 (27)
Median age(range), years	61 (42 - 75)
Underlying disease	
Acute leukemia	9
Myelodysplastic syndrome	1
Non-Hodgkin lymphoma	1

Table 2. Clinical characteristics of 11 patients.

Patient no.	Age/Sex	Underlying disease	Prophylactic antimicrobials (0 ral)	BDG level (pg/ml)	GM index	Empirical antibiotics (Drip Infusion)	L-Am B Dose (Duration)	Adverse events	Outcome
1	65/F	Acute leukemia	FLCZ	Negative	Negative	Meropenem + Linezolid	120 mg (7 days)	Nothing	Success
2	78/M	Acute leukemia	LVFX + FLCZ	Negative	Negative	Doripenem → Meropenem	150 mg (22 days)	Nothing	Success
3	69/M	Acute leukemia	VRCZ	Negative	Negative	Meropenem + Vancomycin	135 mg (11 days)	K3.2 mEq/L (G2)	Success
4	50/M	Acute leukemia	NA	Negative	Negative	Doripenem + Arebekacin	150 mg (12 days)	GPT 49 IU/L (G1)	Success
5	67/F	Acute leukemia	ST + ITCZ	Negative	Negative	Meropenem + Arbekacn	112 mg (10 days)	GPT 53 IU/L (G1)	Success
6	42/M	Acute leukemia	FLCZ	Negative	Negative	Meropenem + Vancomycin	185 mg (11 days)	Nothing	Success
7	43/M	Acute leukemia	LVFX + FLCZ	84.2	Negative	Meropenem	200 mg (11 days)	Anal pain (G2)	Success
8	70/F	Acute leukemia	FLCZ	Negative	Negative	Imipenem + Vancomycin	150 mg (11 days)	Creatinine 1.0 mg/dL (G1)	Success
9	64/M	Non-Hodgkin lymphoma	LVFX + ST + ITCZ	43.4	NA	NA	150 mg (8 days)	Physical rigidity (G2)	Failure
10	66/M	Myelodysplastic syndrome	ST	Negative	Negative	Doripenem + Vancomycin	100 mg (3 days) 50 mg (3 days)	Creatinine 2.3 mg/dL (G2)	Failure
11	75/M	Acute leukemia	FLCZ	Negative	Negative	Cefepime + Vancomycin	125 mg (16 days)	GPT 75 IU/L (G1), K 2.2 m Eq/L (G2)	Failure

FLGZ fuconazole, LVFX levofloxacin, VRCZ voriconazole, NA not available, ST sulfamethoxazole-trimethoprim, ITCZ itraconazole, BDG (1,3)-β-D-glucan, GM galactomannan, G2 grade 2, G1 grade 1.

Table 3. Drug-related adverse events.

Events	n
Hepatotoxicity	3 (27.3%)
Nephrotoxicity	2 (18.2%)
Hypokalemia	2 (18.2%)
Others*	2 (18.2%)

All of them except one case were below grade 2 toxicity. *One was anal pan and the other was physical rigidity (grade 3).

anal pain in case 7 (grade 2) and physical rigidity in case 9 (grade 3). L-AmB was discontinued in 3 patients (cases 9 - 11). In case 9, his symptom was relieved after that. In case 10, as the creatinine level increased to 1.67 mg/dL during the

dose of L-AmB at 100 mg, its dose was reduced to 50 mg. But, the creatinine level further up to 2.3 mg/dL. By stopping L-AmB, its level was normalized. In case 11, his hypokalemia further advanced despite discontinuing L-AmB, suggesting that this toxicity seemed to be occurred by L-AmB unrelated cause. The remaining 5 patients (cases 3, 4, 5, 7 and 8) were successfully managed by supportive therapy without withdrawing L-AmB.

4. Discussion

In this study, we prospectively performed an empirical antifungal sequential therapy from MCFG to L-AmB and evaluated the efficacy and safety of this treatment strategy for FN refractory to broad-spectrum antibacterial therapy in patients with hematologic malignancies receiving intensive chemotherapy.

MF is an echinocandin class antifungal agent that inhibits the fungal cell wall synthesis, hence showing a favorable DAE profile [8]. As patients with hematologic malignancies are vulnerable to DAEs right after intensive chemotherapy, we selected MF as the initial antifungal therapy in this study. This agent has potent activity against both *Candida* and *Aspergillus* species *in vitro* as well as *in vivo* [8]. In immunocompromised patients, fungal infection due to both species is more frequently occurred than the other species [1]. Therefore, MF is considered to be useful enough for the treatment of such major fungal infections especially in patients whose conditions are susceptible to DAEs. However, MF has no activity against some fungal species such as *Trichosporon* and *Zycomycetes* [11] [12]. We demonstrated the occurrence of fatal trichosporonemia in hematologic patients receiving MF for more than 5 days [11]. In addition, it was reported that delayed AmB therapy 6 days after the diagnosis of zygomycosis increased mortality in patients with hematologic malignancies [2]. Thus, we limited the MF dosing period to 3 - 5 days. During the use of MCFG, neither case developed any breakthrough fungal infection nor case revealed DAEs in this study. When a fever persisted despite the use of MF, we replaced MF in a timely fashion with L-AmB, looking at the recovery state from the vulnerability of patients. Here, we selected L-AmB as the switching antifungal, because this agent is effective for both *Trichosporon* and *Zycomycetes* species which possibly cause fatal breakthrough infections in patients receiving MCFG [11] [12] [14]. In this situation, if MF is effective, the replacement with L-AmB does not seem necessary, because the possibility of DAEs would increase. Actually, one of the patients who were initially enrolled to this study was restored only with MF administration though such case was not focused on in the current study. This study suggested that the timing of replacement with L-AmB was not too late even in case MF was not effective.

After changing L-AmB, 8 patients (72.7%) developed DAEs. All of those adverse events except one case were below grade 2. The symptoms in the 5 patients improved with supportive therapies without withdrawing L-AmB. Although the other 3 patients needed discontinuation of L-AmB, the DAEs in the 2 patients

improved soon after the stopping L-AmB, and that in the remaining one patient seemed to be caused by L-AmB unrelated factor. Accordingly, L-AmB-associated DAEs were considered relatively mild and tolerable in this study. After all, treatment success rate in our study was 72.7%, indicating that this treatment strategy is effective and safe as an empirical antifungal therapy in FN patients with hematologic malignancies. Since the success rates reported in previous studies stayed at 70% range [9] [10] [15] [16], our result is encouraging. To our knowledge, this is the first report on empirical antifungal sequential therapy from MF to L-AmB in such patients. However, as the main limitation of this study was the small number of cases examined, further investigation in large-scale studies will be needed to determine the usefulness of this sequential antifungal treatment in more detail.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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