의학석사 학위논문

소아의 자가 조혈모세포이식에서 진균 감염에 대한 예방적 미카펑긴 투약의 유효성 및 안전성

Efficacy and Safety in Micafungin for Prophylaxis against Invasive Fungal Disease in Pediatric Patients undergoing Autologous Hematopoietic Stem Cell Transplantation

2020년 8월

서울대학교 대학원
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ABSTRACT

Efficacy and Safety in Micafungin for Prophylaxis against Invasive Fungal Disease in Pediatric Patients undergoing Autologous Hematopoietic Stem Cell Transplantation

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Background Invasive fungal infections (IFDs) are important causes of illness and death in patients with neutropenia who receive chemotherapy for cancer or who undergo hematopoietic stem cell transplantation (HSCT). Micafungin is a member of the echinocandin, which has broad spectrum of fungicidal activity and has minimal drug toxicity and a low drug interactions. We perform this study to demonstrate the efficacy and safety of Micafungin for the prophylactic antifungal therapy in patients undergoing autologous HSCT focusing on the pediatric and adolescent patients.

Methods This was a phase II, prospective, single center, open-label, and single-arm study. From November 2011 to February 2017, a total

125 patients were screened from Seoul National University Children's Hospital in Korea, and 112 patients were enrolled. Micafungin was administered intravenous at a dose of 1 mg/kg/day (max. 50mg/day) from the day -8 of the autologous stem cell transplantation until neutrophil engraftment. Treatment success was defined as the absence of proven, probable, or possible IFD through to 4 weeks after therapy.

Results The patients enrolled were 112 and study protocol was achieved without premature interruption in 110 patients (98.2%). The reasons for interrupting micafungin treatment included early death (n = 1), and patients refusal (n = 1). Of the 110 patients in whom micafungin efficacy could be evaluated, treatment success was achieved in 109 patients (99.1%). Only one patient was diagnosed with probable IFD. There were no patients diagnosed with possible or proven IFD. In full analysis group, 21 patients (18.8%) experienced 22 adverse events (AEs) during study protocol, but all AEs were classified with "unlikely" related to micafungin. No patients experienced grade IV AEs. None of patients were discontinued micafungin administration due to adverse events. None of the deaths were related to the study drug.

Conclusion Our study demonstrated that micafungin is a safe and effective option for antifungal prophylaxis in pediatric patients receiving autologous HSCT, with promising efficacy without significant AEs.

Keywords: Micafungin, Invasive Fungal Disease, Autologous Hematopoietic Stem Cell Transplantation

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CONTENTS

Abstract.....i
Contents.....iii
List of tables and figures.....iv
List of Abbreviations.....v

Introduction.....1
Material and methods.....5
Results.....9
Discussion.....15

References.....19
Abstract in Korean.....27

LIST OF TABLES AND FIGURES

Figure 1. Treatment scheme of the study. 11

Figure 2. Flow diagram of the study 12

Table 1. Characteristics of the patients.....13

Table 2. Non-hematologic adverse events during study protocol in 112 patients.....14

LIST OF ABBREVIATIONS

IFD	invasive fungal disease
HSCT	hematopoietic stem cell transplantation
AEs	adverse events
CMV	cytomegalovirus

INTRODUCTION

Invasive fungal disease (IFD) are important causes of illness and death in patients with neutropenia who receive chemotherapy for cancer or who undergo hematopoietic stem cell transplantation (HSCT) [1, 2]. The risk of infection is associated with degree and duration of neutropenia, the disruption of protective skin and mucosal surface barriers, and the use of corticosteroids. A systematic review of the literature calculated a case fatality rate of 86.7% for allogeneic or autologous HSCT recipients with invasive aspergillosis [3]. Studies of pediatric patients undergoing allogeneic or autologous HSCT show an incidence rate of IFD ranging from 3–21% [4-9]. Autologous HSCT patients had known to have a lower risk of IFD than allogeneic HSCT. However, certain autologous recipients have high risk and do merit prophylaxis of IFD [10]. It has been reported that several pediatric patients underwent autologous HSCT could be fatal cases due to invasive fungal disease [11]. To reduce the high mortality rate, antifungal therapy should be initiated early in HSCT patients, but there were not enough study of antifungal agents that were effective and had less drug interaction with HSCT related drugs. The high crude mortality rate associated with these invasive infections stems in part from difficulties to make a timely diagnosis. High-risk patients typically have a decreased inflammatory response and clinical features, although variable and usually nonspecific, which may not manifest before the infection is far advanced [12]. For many years, conventional microbiological, histological, and radiological techniques were the cornerstone of diagnosis, but these techniques have had limited impact on clinical decision making because they

were too insensitive, time consuming, and lacked general accessibility. With the development of the aspergillus-directed galactomannan enzyme immunoassay, the serological kits available for the detection of fungal antigens have inconsistent sensitivity, specificity or both [13].

In view of these findings, a strategy of empirical use of antifungal agents has been advocated since the early 1980s. At the same time, strategy against invasive fungal infection during the neutropenic period was changed from empirical strategy to presumptive strategy, in which anti-aspergillus agents were started based on positive serum test and/or infiltrates or nodules on X-ray or CT-scan associated with persistent febrile neutropenia [14]. In high risk patients, such as patients with leukemia or HSCT recipients, antifungal agent is initiated at a period of high risk of infection to prevent fungal infections.

Fluconazole has been widely used as an antifungal prophylactic agent. On the basis of prior prophylactic trials with in bone marrow transplant recipients, the overall efficacy of fluconazole as antifungal prophylaxis during the neutropenic phase after transplantation was 50-75% [15-17]. Furthermore, routine prophylactic use of fluconazole has been associated with the emergence of fluconazole-resistant candida infections. Additionally, fluconazole is not reliably effective against invasive aspergillosis [18]

Itraconazole which is one of the broad spectrum antifungal agent is efficient in treating both aspergillus and candida not covered with fluconazole and showed good response rate as in controlled study with amphotericin B12. In addition to these stable effect and low side effects, cost effectiveness and enhanced absorption rate of oral

solution has broadened the usage of oral itraconazole in the fungal prophylaxis of hematologic malignancies as well as of HSCT [19-21]. Success rate of oral itraconazole for primary prophylaxis of fungal infection in patients with hematologic malignancy and profound neutropenia was about 60% in previous controlled study [22, 23].

Echinocandins are a novel class of antifungal agents that demonstrate antifungal activity against candida and aspergillus species [24]. Micafungin is a member of the echinocandin, which has broad spectrum of fungicidal activity and is associated with minimal toxicity and a low potential for drug interactions [25]. Mostly, it has been used for treatment of invasive candidiasis in pediatric populations. Micafungin was well tolerated in pediatric patients including neonates, as demonstrated by the lack of documented adverse effects in many studies [19, 26-30].

However, there have been few reports describing its prophylactic use in pediatric patients. An early comparative, double blinded, randomized phase III trial showed promising efficacy and safety findings for prophylaxis in 386 adults, as well as 39 pediatric patients undergoing HSCT [31]. But the sample size of pediatric group in this study was small and enrolled population was heterogenous including autologous and allogeneic HSCT patients. Recently, Japanese study suggested that prophylactic micafungin might prevent IFD pediatric patients receiving allogeneic or autologous HSCT [22]. This study was retrospective, single center study and enrolled only 14 patients. Park et al. [32] demonstrated the efficacy and safety of micafungin for prevention of IFD in allogeneic hematopoietic HSCT in pediatric and adolescent patients.

Based on these findings, we perform this study to demonstrate the

efficacy and safety of micafungin for the prophylactic antifungal therapy in patients undergoing autologous HSCT focusing on the pediatric and adolescent patients.

MATERIALS AND METHODS

Patients

Under 21 year-old, pediatric, adolescent patients with hematological and non-hematological disease undergoing autologous HSCT including second autologous HSCT were eligible for this study. Patients were excluded if they met one of the following: (1) Aspartate transaminase or alanine transaminase level > 5 times the upper limit of normal, (2) bilirubin > 2.5 times the upper limit of normal, (3) history of allergy, sensitivity, or any serious reaction to an echinocandin, (4) invasive fungal disease at the time of enrollment, (5) systemic antifungal therapy within 72 hrs before administration of the first dose of study drug.

Study design

This was a phase II, prospective, single center, open-label, and single-arm study. Eligible patients who provided informed consent form will be administered micafungin (Astellas Pharma US Inc, Deerfiled, Illinois, USA) at 50 mg/day (1mg/kg/day for patients weighting <50kg) as 1 hour infusion. Infusion of micafungin will be started on the day -8 of the autologous stem cell transplantation (Figure 1). This study was approved by the Institutional Review Board of Seoul National University Hospital, and informed consent was obtained from the parents (IRB No. 1102-038-351). This study was registered at Clinicaltrial.gov (#NCT01417169).

Patients received micafungin until the earliest of the following: (1) absolute neutrophil count > 1,000/uL after the nadir absolute count; (2) development of proven, probable, or possible invasive fungal

infections; (3) development of unacceptable drug toxicity; (4) death; (5) withdrawal from study participation (patient's decision); or (6) discontinuation of study treatment (investigator's decision). Serum Galactomannan was sampled weekly (±3 days) from the day of starting micafungin. Patients who terminated micafungin treatment due to the above criteria (3)-(5) were considered as premature interruption

Outcome

Intent-to-treat full analysis set was defined as all patients who received at least 1 dose of micafungin. The primary endpoint was treatment success, which was defined as the absence of proven, probable, or possible IFD during the period of prophylactic therapy and up to 4 weeks after stopping micafungin administration in patients who completed micafungin administration according to study protocol including patients who switched to other antifungal agents due to development IFD or other causes. Primary endpoint efficacy set was defined as patients who completed the treatment according to the protocol without premature interruption. The secondary endpoints were IFD-related mortality and safety profiles in intent-to-treat full analysis group.

Adverse events (AEs) were monitored throughout the course of therapy. Laboratory evaluations were conducted once a week during micafungin therapy. All AEs except for ones which can be generally expected after autologous HSCT. AEs were graded by Common Terminology Criteria for Adverse Events version 4.0 and rated as unassessable, conditional, unlikely, possible, probable and certain according to World Health Organization-Uppsala Monitoring Centre

causality categories [33].

Definition of IFD

Proven, probable, or possible IFD are defined as described by EORTC/MSG group criteria (2008) [34]. Patients are considered to have proven infection if fungal elements are detected in biopsy specimens or cultures of supposedly sterile materials or blood. Probable IFD is defined as the patients' fungal elements were detected directly or indirectly (galactomannan antigen) in conjunction with compatible clinical and radiographic findings. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Possible IFD is defined if sufficient clinical evidence is consistent with IFD but without mycological support. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

If proven, probable, or possible IFD were diagnosed during administration of micafungin prophylaxis, the case will be recorded as treatment failure. Another antifungal can be added to micafungin, or switch to other antifungal agents. Treatment success was defined as the absence of proven, probable, or possible IFD through to 4 weeks after therapy.

Statistical analysis

Treatment success rate was calculated with 2-sided exact 95% confidence intervals. The expected rate with micafungin is 73% compared to the rate of oral itraconazole of 60% [22, 23]. With 5% of one-sided type I error, 80% of power, we needed 102 patients.

Considering exclusion rate of 10%, total 112 patients were needed.

Patients' characteristics and safety were analyzed for intent-to-treat full analysis set. Primary endpoint was analyzed in primary endpoint efficacy set. Engraftment was defined as achieving an ANC > 0.5 x 109/L for 3 consecutive days before day 28. Platelet recovery was defined as achieving a platelet count > 20,000/mL unsupported by platelet transfusions for 7 days.

RESULTS

Enrollment

From November 2011 to February 2017, total 125 patients were screened from Seoul National University Hospital in Korea. Thirteen patients were excluded due to screening failure and 112 patients were enrolled (Figure 2). Patients' characteristic are listed in Table 1.

Treatment outcome

The patients enrolled were 112 and study protocol was achieved without premature interruption in 110 patients (98.2%). The reasons for interrupting micafungin treatment included early death (n = 1), and patients refusal (n = 1). The median duration of micafungin prophylaxis was 16 days (range, 2-26 days). Of 110 patients in the efficacy group, 10 patients were added oral itraconazole due to a positive galactomannan result without evidence of IFD and micafungin was replaced by another antifungal agents in 29 patients with persistent fever despite administration of broad-spectrum antibiotics. Treatment success was achieved in 109 patients (99.1%, 95% exact confidence lower limit: 97.4%). Only one patient was diagnosed with probable IFD. In this patient, consolidative infiltration and nodules in a chest computed tomography were documented in addition to a positive galactomannan result at 27 days after completion of the study protocol. Lung biopsy was done, and there was no evidence of IFD. This patient was administrated intravenous itraconazole and other broad-spectrum antibiotics, and recovered about 2 weeks after administration of other antifungal agents. There were no patients

diagnosed with possible or proven IFD.

Adverse event

In full analysis group, 21 patients (18.8%) experienced 22 AEs during study protocol, but all AEs were classified with "unlikely" related to micafungin. Nine patients (8.0%) experienced grade III AEs and no patients experienced grade IV AEs. None of patients were discontinued micafungin administration due to adverse events (Table 2). None of the deaths were related to the study drug. All patients succeeded in engraftment. The day of neutrophil and platelet engraftment was 11 (range, 9-19) and 18 (range, 10-38) days respectively.

Mortality

There was no IFD-related mortality case. But one patient of premature interruption group had persistent fever during conditioning regimen and died of septic shock at 5 days after HSCT. There were no deaths related to the study drug.

Figure 1. Treatment scheme of the study

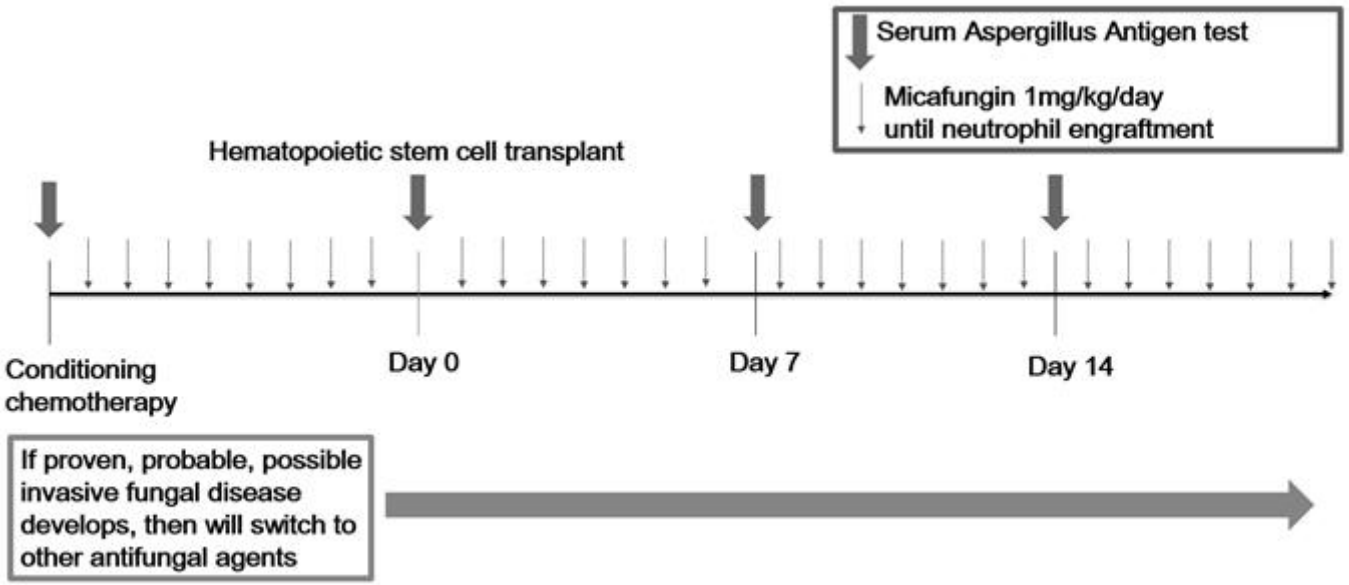

Figure 2. Flow diagram of the study

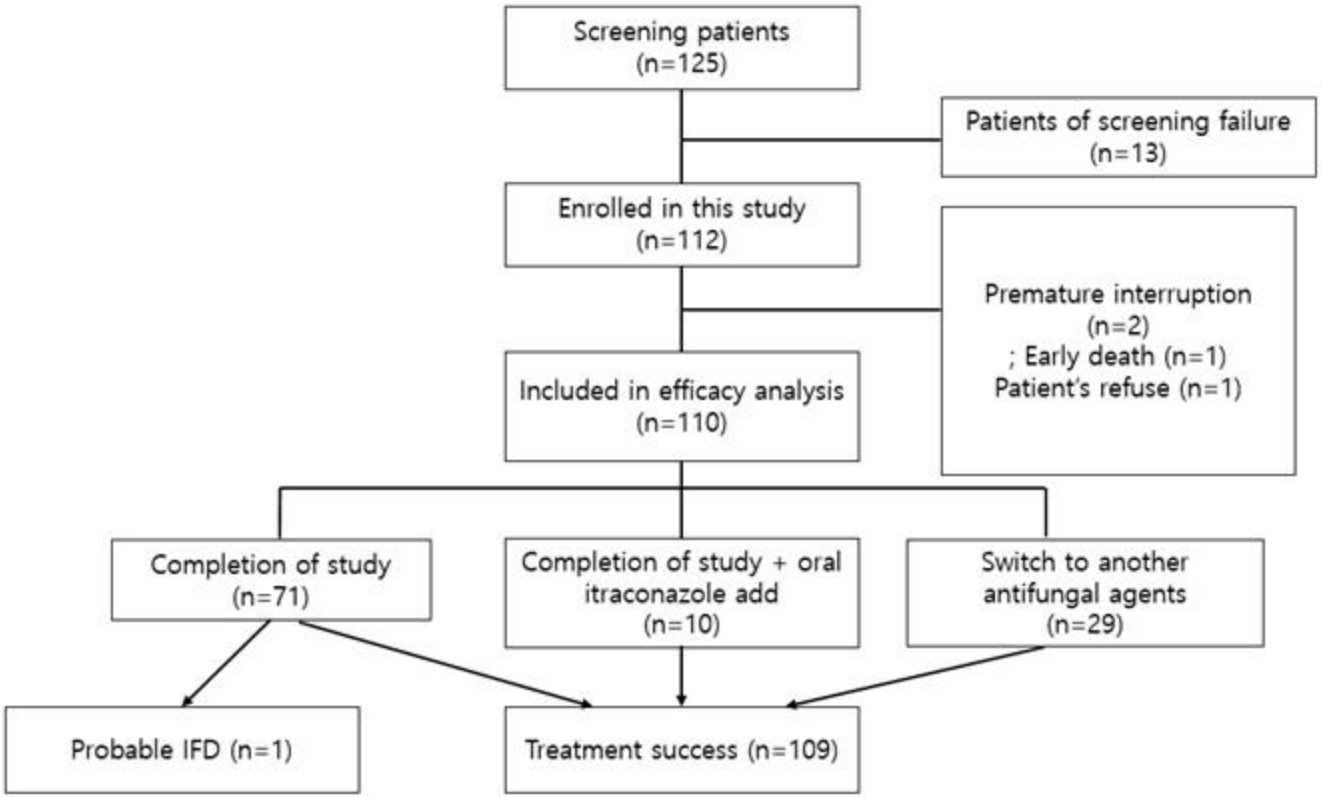

Table 1. Characteristics of the patients

Number of patients	112
Median age, Years (range)	8 (1-19)
Sex, No. (%)	
Male	67
Female	45
Diagnosis, No. (%)	
Non-Hodgkin lymphoma	16
Hodgkin lymphom	4
Medulloblastoma	16
Atypical teratoid rhabdoid tumor	7
Neuroblastoma	15
Primitive neuroectodermal tumor	6
Osteosarcoma	14
Ewing sarcoma	6
Germ cell tumor	6
Others (acute leukemia, retinoblastoma, Wilms tumor, pineoblastoma, rhabdoid tumor of kidney, choroid plexus carcinoma)	21
Neutrophil engraftment, days (range)	11 (7-19)
Platelet engraftment, days (range)	18 (10-38)

Table 2. Non-hematologic adverse events during study protocol in 112 patients

Adverse events	Grade I	Grade II	Grade III
Gastrointestinal			
Abdominal pain	0	0	0
Nausea	2	2	6
Vomiting	2	4	0
Diarrhea	1	0	1
Constipation	0	0	0
Hepatic			
ALP increased	0	0	0
ALT increased	0	3	1
AST increased	0	3	1
Bilirubin increased	0	0	0
Electrolyte imbalance			
Hypocalcemia	1	2	0
Hypokalemia	0	0	1
Hypomagnesemia	0	0	0
Hyponatremia	0	1	0
Total	6	15	10

DISCUSSION

In several study of IFD, the incidence of IFD was reported to be 12% 22.5% among allogeneic [4, 35-38] and 8% 10% among autologous [4, 35, 39-41] HSCT recipients. The risk of IFD is lower in autologous HSCT than allogeneic HSCT, but the incidence of IFD in autologous HSCT has been reported. In recent study published in 2019, Linke et al. analyzed in 95 pediatric patients undergoing autologous HSCT, the cumulative incidence of IFD was 8.7% [11]. IFD is a major cause of morbidity and mortality in patients undergoing pediatric HSCT [42-44]. The reasons for increasing risk include prolonged neutropenia, immunosuppressant therapy, delayed immune reconstitution, the use of indwelling catheters, and broad-spectrum antibiotics [4, 42, 45, 46]. Pagano et al. [44] reported that there could be fatal cases after autologous HSCT recipients in adult patients. For high risk patients, such as HSCT recipients, antifungal agent is initiated at a period of high risk of infection to prevent fungal infections. There are several evidence based guidelines for adults undergoing HSCT [46-49]. However, there are no guidelines in pediatrics and few reports describing its prophylactic use in pediatric patients.

In recent suggested guideline of antifungal prophylaxis in pediatric patients with undergoing allogeneic or autologous HSCT, Michelle et al. [50] recommended that for children 1 month to <19 years of age undergoing allogeneic HSCT or autologous HSCT with anticipated neutropenia for >7 days, administer fluconazole 6 - 12 mg/kg/day (maximum 400 mg/day) intravenous or oral from the start of conditioning (strong recommendation, moderate quality evidence). In

the trial by Van Burik et al. [31], which included allogeneic or autologous HSCT in 39 pediatric and 386 adult patients, a higher proportion of patients receiving micafungin had successful prophylaxis. The overall efficacy of micafungin was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after HSCT (80.0% in the micafungin arm vs. 73.5% in the fluconazole; P = .03). But the sample size of pediatric group in this study was small and enrolled population was heterogenous including autologous and allogeneic HSCT patients. Recently, Japanese study suggested that prophylactic micafungin might prevent IFD pediatric patients receiving allogeneic or autologous HSCT [22]. This study was retrospective, single center study and enrolled only 14 patients.

In patients with fungal infection after allogeneic or autologous HSCT, causative species included candida species (51%) and aspergillus species (25%) [39] and fluconazole's coverage not included aspergillus species. Among other antifungal agents, itraconazole has more extent coverage than fluconazole which includes aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis [51]. Itraconazole undergoes extensive metabolism via the CYP3A4 enzyme system, and also has the ability to increase concentrations of many other medications which includes drugs important to HSCT recipients like cyclosporine, tacrolimus, antineoplastic agents [52]. Huang et al. compared using micafungin to itraconazole in neutropenic patients undergoing allogeneic or autologous HSCT. The patients were 18 to 70 years old, treatment success rate of micafungin was similar to that of itraconazole and significant differences in incidence of drug-related adverse events (8% versus 26.5%) were shown between micafungin and itraconazole (P =

.00, chi-square test).

Amphotericin B is a polyene antifungal agent with activity in vitro against a wide variety of fungal pathogens [53]. However, adverse effects are common, especially with nephrotoxicity being the most serious, occurring early in the course of treatment [54]. And there is few study of amphotericin B as prophylactic antifungal agent during allogeneic or autologous HSCT in children. Roman et al. [55] used liposomal amphotericin B which was a lipid formulation of amphoterincin B for improving toxicity of conventional amphotericin B. It was efficient to prevent IFD, but induced grade 3–4 nephrotoxicity occurred in 7/57 (12%) patients and the dose of liposomal amphotericin B was reduced in 17/57 (30%) secondary to worsening renal function by approximately 30–50% for moderate or severe disturbances and in 6/57 (11%) patients liposomal amphotericin B was discontinued.

Micafungin is a member of the echinocandins and a semisynthetic lipopeptide synthesized by a chemical modification of a fermentation product of Coleophoma which has broad spectrum of fungicidal activity and is associated with minimal toxicity and a low potential for drug interactions [25]. Mostly, it has been used for treatment of invasive candidiasis in pediatric populations and suggested in the 2009 guideline as an alternative therapy to fluconazole in the prophylaxis of patients with standard risk against fungal infections, namely those with allogeneic HSCT or those who with prolonged neutropenia and mucosal damage post autologous HSCT [47]. As for proper dose of micafungin for pediatric patients, there are several studies including Phase I studies [30, 56], initial dose of 1~2mg/kg/day is usually recommended and 1mg/kg/day for under 50kg was effective in a

Phase III study which compared micafungin with fluconazole in pediatric hematopoietic stem cell transplant recipients. Micafungin achieved a treatment success rate of 69.2%, whereas fluconazole at 8 mg/kg/day achieved a treatment success rate of 53.3% [31]. Park et al. [32] demonstrated effectiveness of micafungin as prophylaxis of IFD during neutropenia in children and adolescents undergoing allogeneic hematopoietic HSCT. Of the 132 patients in whom micafungin efficacy could be evaluated, treatment success was achieved in 119 patients (90.2%). There was no proven fungal infection in any patient and no patients experienced grade IV AEs.

The known adverse events of micafungin in children are diarrhea, epistaxis, abdominal pain, headache, nausea, vomiting, fever, chills, elevation of alanine aminotransferase/aspartate aminotransferase values, hypokalemia, thrombocytopenia, mucositis, and rash [57]. Our research also showed similar trends to previous studies. Adverse events included nausea, vomiting, diarrhea, and elevation of alanine aminotransferase/aspartate aminotransferase values and all events were self-limiting and adjustable. However, there was no adverse events related to micafungin and no patient stopped micafungin from adverse events.

There has been no prospective study of the safety and utility of antifungal prophylaxis in children with autologous recipient. It is meaningful that this study is the first prospective study for prophylaxis of IFD using micafungin in autologous HSCT. This study demonstrated that micafungin is a safe and effective option for antifungal prophylaxis in pediatric patients receiving autologous HSCT, with promising efficacy without significant AEs in larger patients than other studies.

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국문초록

서론: 항암 치료를 받거나 조혈모세포이식 시행 후 호중구 감소증이 있는 환자에서 침습 진균 감염은 중요한 질환이며 사망을 초래할 수 있다. Micafungin은 Echonicandin계열의 항진균제로서 광범위한 항진균 효과를 나타내며 부작용이 적고 다른 약들과의 상호작용이 적다. 이에 소아청소년에서 자가 조혈모세포이식을 시행한 환자에서 micafungin을 진균 감염 예방용으로 투약하였을 때의 효용성과 안전성에 대하여 규명하고자 한다.

방법: 이 연구는 단일 기관에서 전향적으로 연구한 2상 연구이다. 2011년 11월부터 2017년 1월까지 서울대학교 어린이병원에서 자가 조혈모세포이식을 시행한 환자 총 125명을 선별하였으며 이중 112명이 연구에 참여하였다. Micafungin은 이식 8일전부터 호중구 생착일까지 1mg/kg/일로 투약하였다. 성공적인 예방은 예방약 투약 이후 4주 동안 '의심되는', '가능한', '거의 틀림없는', 또는 '확진' 진균 감염증이 생기지 않는 것을 기준으로 하였다.

결과: 연구에 참여한 112명의 환자들 중 조기 중단 없이 프로토콜을 마친 환자는 110명(98.2%) 이었다. 조기 중단의 이유로는 사망이 1명, 환자의 거부 1명이 있었다. 110명의 환자들 중 109명(99.1%)의 환자들이 프로토콜에 따라 성공적으로 치료 되었다. 한 명의 환자만이 '가능한' 진균 감염증이 발생하였으며 '의심되는' 혹은 '확진' 진균 감염증이 발생한 환자는 없었다. 연구에 참여한 모든 환자 가운데 21명(18.8%)의 환자에서 Micafungin과 연관되어 있을

수 있는 부작용이 22개 발생하였으며 4단계 이상의 부작용은 나타나지 않았다. 부작용 때문에 micafungin 투약을 중단한 환자는 없었다.

결론: 자가 조혈모세포이식을 받는 소아환자에서 진균 감염증 예방으로 micafungin을 투약하는 것은 안전하고 효용성이 있을 것으로 보인다.

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주요어: Micafungin, 진균 감염증, 자가 조혈모세포이식

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