Efficacy and safety of micafungin in empiric and D-index-guided early antifungal therapy for febrile neutropenia; A subgroup analysis of the CEDMIC trial

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ABSTRACT

Objectives: The D-index is defined as the area over the neutrophil curve during neutropenia. The CEDMIC trial confirmed the noninferiority of D-index-guided early antifungal therapy (DET) using micafungin to empirical antifungal therapy (EAT). In this study, we evaluated the efficacy and safety of micafungin in these settings.
Methods: From the CEDMIC trial, we extracted 67 and 113 patients who received micafungin in the DET and EAT groups, respectively. Treatment success was defined as the fulfilment of all components of a five-part composite end point. Fever resolution was evaluated at seven days after the completion of therapy.
Results: The proportion of high-risk treatments including induction chemotherapy for acute leukemia and allogeneic hematopoietic stem cell transplantation was significantly higher in the DET group than in the EAT group (82.1% vs. 52.2%). The efficacy of micafungin was 68.7% (95%CI: 56.2–79.4) and 79.6% (71.0–86.6) in the DET and EAT groups, respectively. When we focused on high-risk treatments, the efficacy was 69.1% (55.2–80.9%) and 78.0% (65.3–87.7%), respectively (P = 0.30). There was no significant difference in any of the 5 components between the two groups.
Conclusions: The efficacy of micafungin in patients undergoing high-risk treatment was not strongly impaired in DET compared to that in EAT.

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Introduction

Micafungin has been widely used as empiric or preemptive antifungal therapy during neutropenia in Japan (Kimura et al., 2020). This is partly because micafungin was the only available echinocandin agent until caspofungin was launched in 2012. Previous randomized controlled trials and prospective single-arm studies showed that the use of micafungin in empiric antifungal therapy offered comparable efficacy and better safety compared with other classes of mold active agents (Jeong et al., 2016; Oyake et al., 2016; Park et al., 2010; Tamura et al., 2009; Yamaguchi et al., 2011; Yoshida et al., 2012). Lately, preemptive or diagnostic-driven antifungal therapy triggered by fungal biomarkers or imaging study findings has been replacing empiric therapy (Cordonnier et al., 2009; Morrissey et al., 2013). However, data on the efficacy and optimal selection of antifungal agents in this setting are still scarce.

Recently, we conducted a randomized controlled trial comparing classic empiric antifungal therapy (EAT) and D-index-guided early antifungal therapy (DET) using micafungin for persistent or recurrent febrile neutropenia in patients undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) in the CEDMIC trial (Kanda et al., 2020). In the DET group, the administration of micafungin 150 mg/day was postponed until the cumulative D-index (c-D-index), which is a neutropenia index reflecting both the depth and duration of neutropenia simultaneously (Kimura et al., 2010; Portugal et al., 2009), exceeded 5500, unless there were abnormal findings in fungal biomarkers or imaging studies. In other words, DET is basically preemptive antifungal therapy and is combined with empiric therapy in particularly high-risk situations. We reported that DET successfully reduced the usage of antifungal agents by approximately 50% compared to EAT, without increasing the incidence of invasive fungal infection or mortality.

In this subgroup analysis of the CEDMIC trial, we focused on the efficacy and safety of micafungin in the EAT and DET groups. Especially, the data in the DET group will provide useful information on antifungal treatment in D-index-guided and preemptive antifungal treatment settings.

Methods

Summary of the eligibility criteria and treatment of the EAT and DET groups

Patients with hematological malignancies aged between 16 and 79 years, who had planned to undergo chemotherapy or HSCT that was expected to cause neutropenia for at least seven days, were enrolled (Kanda et al., 2020). Allogeneic HSCT and induction chemotherapy for acute leukemia were defined as high-risk treatments, while others were low-risk. Antifungal prophylaxis with fluconazole or itraconazole was allowed, while prophylactic use of polyenes, echinocandins, voriconazole, or posaconazole was not. In the EAT group, micafungin at 150 mg/day was started for persistent or recurrent febrile neutropenia. In the DET group, micafungin at 150 mg/day was started only when positive findings were observed in monitoring or diagnostic tests such as the *Aspergillus* galactomannan test, beta-D-glucan test, chest X-ray and chest computed tomography (CT) scan until the c-D-index reached 5,500. Once the c-D-index exceeded 5500, micafungin was started for persistent or recurrent febrile neutropenia regardless of the results of these tests. The c-D-index was calculated as the area surrounded by the neutrophil curve, the horizontal line at a neutrophil count of 500/μL, and the vertical line at the day of latest measurement of the neutrophil count. The chest CT scan was obtained if febrile neutropenia persisted for 4 days or if relapse of

fever occurred after the initial onset of febrile neutropenia which once achieved defervescence. The CT scan from the paranasal cavity to the chest was additionally obtained if the results of beta-D-glucan test or *Aspergillus* galactomannan test turned positive. Additional imaging tests were performed if attending physicians considered them necessary. The details were described in the original CEDMIC trial report (Kanda et al., 2020). The trial was approved by the institutional review board or independent ethics committee at each institution and was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided their written informed consent. Astellas Pharma Inc. sponsored this study, but was not involved in the design of the study or analyses or interpretation of the results. This trial was registered in UMIN-CTR [UMIN000010411].

Patients

In the original CEDMIC trial, 423 patients were enrolled from June 2013 through April 2017 and 413 patients were included in the intent-to-treat (ITT) analyses. Two-hundred twelve and 201 patients were assigned to the DET and EAT groups, respectively. Among these patients, 69 patients in the DET group and 121 in the EAT group received micafungin. For this efficacy and safety analysis, we extracted 67 and 113 patients from the DET and EAT groups after excluding 10 patients in whom data on efficacy were not reported.

Patient characteristics are shown in Table 1. The proportion of allogeneic HSCT recipients was higher in the DET group, while that of autologous HSCT was higher in the EAT group, leading to a significantly higher proportion of high-risk treatment in the DET group. This was also associated with the difference in the underlying diseases, which meant that acute leukemia accounted for more than half of the patients in the DET group while malignant lymphoma and multiple myeloma accounted for approximately 45% of those in the EAT group. The difference in median durations of micafungin administration between DET and EAT groups was 1

Table 1
Patient characteristics.

	DET		EAT		P value
	n = 67		n = 113		
Age, years [range]	53.0	[20.0–73.0]	60.0	[20.0–77.0]	0.08
Gender Female	31	(46.3 %)	44	(38.9 %)	0.35
Male	36	(53.7%)	69	(61.1%)	
ECOG-PS0	44	(65.7%)	83	(73.5%)	0.36
1	19	(28.4%)	27	(23.9%)	
2	4	(6.0%)	3	(2.7%)	
DiseaseALL	12	(17.9%)	14	(12.4%)	0.009
AML	29	(43.3%)	35	(31.0%)	
ML	13	(19.4%)	36	(31.9%)	
MDS	5	(7.5%)	6	(5.3%)	
MM	1	(1.5%)	16	(14.2%)	
Others	7	(10.4%)	6	(5.3%)	
Antifungal prophylaxis	4	(6.0%)	16	(14.2%)	0.16
None	47	(70.1%)	78	(69.0%)	
FLCZ	16	(23.9%)	19	(16.8%)	
ITCZ					
Treatment	35	(52.2%)	33	(29.2%)	< 0.001
Allogeneic HSCT	8	(11.9%)	41	(36.3%)	
Autologous HSCT	20	(29.9%)	26	(23.0%)	
Induction therapy	4	(6.0%)	13	(11.5%)	
Other treatments					
Risk* High-risk Low-risk	55	(82.1%)	59	(52.2%)	< 0.001
	12	(17.9%)	54	(47.8%)	

DET, D-index-guided early therapy; EAT, empiric antifungal therapy; PS, performance status; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ML, malignant lymphoma; MM, multiple myeloma; FLCZ, fluconazole; ITCZ, itraconazole; HSCT, hematopoietic stem cell transplantation.
* Allogeneic HSCT and induction chemotherapy for acute leukemia were defined as high-risk treatments, while others were low-risk treatments.

day but there was a statistically significant difference (median 13 days vs. 12 days, *P* = 0.022). Because of the difference in patient background between the two groups, we focused on high-risk patients in the comparison of the efficacy of micafungin.

Efficacy of micafungin

Treatment success was defined as the fulfillment of all components of a five-part composite end point: 1) successful treatment of any baseline fungal infection, 2) absence of any breakthrough fungal infection during therapy or within seven days after the completion of therapy, 3) survival for seven days after the completion of therapy, 4) no premature discontinuation of study therapy because of drug-related toxicity or lack of efficacy, and 5) resolution of fever (defined as an axillary temperature below 37.5 °C for at least two days) at seven days after the completion of therapy. Baseline fungal infection was defined as the development of proven or probable invasive fungal infection within 2 days after the start of micafungin administration, and breakthrough fungal infection was defined as the development of proven or probable invasive fungal infection 3 or more days after the start of micafungin administration. We adopted the definition of fever resolution in accordance with the proposal by de Pauw et al. (2006), which is fever resolution at seven days after the completion of therapy instead of that during neutropenia, which had been used in previous clinical trials of empirical antifungal therapy (Walsh et al., 1999; Walsh et al., 2002; Walsh et al., 2004). Overall survival after the completion of micafungin administration was also assessed.

Adverse events

Patients were monitored for any clinical adverse events from the initiation of micafungin administration until seven days after completion. The severity of adverse events was evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The relationship between each adverse event and micafungin administration was judged by each investigator and principal investigator. Adverse events associated with micafungin administration were reported as drug-related adverse events.

Statistical considerations

Fisher's exact test was used to compare categorical variables and the Mann-Whitney *U*-test was used to compare continuous variables. Time-to-event data were analyzed using the Kaplan-Meier method and compared among groups with the log-rank test.

Survival was calculated from the completion of micafungin administration. All statistical analyses were performed with EZR (Jichi Medical University Saitama Medical Center, at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda, 2013).

Results

Efficacy of micafungin

The efficacy of micafungin as evaluated by a five-part composite end point was 68.7% (95% confidence interval (95%CI): 56.2–79.4%) in the DET group and 79.6% (95%CI: 71.0–86.6%) in the EAT group (Table 2). Since baseline fungal infection was observed only in the EAT group, which consisted of three cases of invasive pulmonary aspergillosis, its effects on successful treatment of baseline fungal infection could not be assessed. All these baseline fungal infections were successfully treated. The proportion of patients who did not achieve fever resolution was 29.9% in the DET group and 15.9% in the EAT group. Premature discontinuation of micafungin was observed in 16.4% of the patients in the DET group and 14.2% in the EAT group. The reasons for premature discontinuation were as follows: lack of efficacy in seven and other reasons in four in the DET group, and lack of efficacy in 10, adverse events in two and other reasons in four in the EAT group. Breakthrough proven or probable fungal infection during MCFG administration was seen in one patient with fusariosis in the DET group and two patients with probable invasive pulmonary aspergillosis in the EAT group. Breakthrough possible IMI during MCFG administration was seen in one patient in the DET group and three patients in the EAT group.

We evaluated the efficacy of micafungin depending on antifungal prophylaxis. In the DET group, the efficacy of micafungin was 50.0% in patients without antifungal prophylaxis (n = 4), 68.1% in those with fluconazole prophylaxis (n = 47) and 75.0% in those with itraconazole prophylaxis (n = 16), which were not significantly different (*P* = 0.66). In the EAT group, the efficacy of micafungin was 93.8% in patients without antifungal prophylaxis (n=16), 76.9% in those with fluconazole prophylaxis (n=78) and 78.9% in those with itraconazole prophylaxis (n=19), which were not significantly different (*P* = 0.35).

We performed a comparison analysis among the high-risk groups (DET n = 55, EAT n = 59). The efficacy of micafungin was 69.1% (95%CI: 55.2–80.9%) in the DET group and 78.0% (95%CI: 65.3–87.7%) in the EAT group, which was not significantly different (*P* = 0.30) (Table 2). There was also no significant difference in any of the five components. We did not perform a similar analysis in

Table 2
Efficacy of micafungin evaluated by a five-part composite end point.

	Total patients				High-risk group[*]				
	DET n = 67		EAT n = 113		DET n = 55		EAT n = 59		*P* value[**]
Efficacy	46	(68.7%)	90	(79.6%)	38	(69.1%)	46	(78.0%)	0.30
Occurrence of baseline fungal infection	0		3[#]		0		3[#]		
Absence of breakthrough fungal infection within seven days after the completion of therapy	64	(95.5%)	107	(94.7%)	52	(94.5%)	55	(93.2%)	1.00
Survival for seven days after the completion of therapy	63	(94.0%)	111	(98.2%)	52	(94.5%)	57	(96.6%)	0.67
No premature discontinuation of study therapy	56	(83.6%)	97	(85.8%)	45	(81.8%)	51	(86.4%)	0.61
Lack of efficacy	7	(10.4%)	10	(8.8%)	6	(10.9%)	5	(8.5%)	
Adverse events	0		2	(1.8%)	0		0		
Other reasons	4	(6.0%)	4	(3.5%)	4	(7.3%)	3	(5.1%)	
Resolution of fever at seven days after the completion of therapy.	47	(70.1%)	95	(84.1%)	39	(70.9%)	47	(79.7%)	0.38

DET, D-index-guided early therapy; EAT, empiric antifungal therapy.
[*] Patients undergoing allogeneic hematopoietic stem cell transplantation and induction chemotherapy for acute leukemia.
[**] Comparison in high-risk group.
[#] All baseline fungal infections were successfully treated.

low-risk patients because of the small number of patients in the DET group (n = 12).

Survival analysis

There was no significant difference in overall survival after the completion of micafungin administration between the DET and EAT groups as analyzed by the log-rank test (P = 0.75) (Figure 1A). Overall survival in the DET and EAT groups was 90.9% and 96.4% at 42 days, and 90.9% and 91.0% at 84 days after the completion of micafungin administration, respectively. When we analyzed the high-risk group, there was also no significant difference in overall survival (P = 0.19) (Figure 1B). Overall survival in the DET and EAT groups was 90.8% and 94.9% at 42 days, and 90.8% and 83.3% at 84 days, respectively (Figure 1B). Fungal-related death was observed in one allogeneic HSCT recipient in the DET group who developed systemic fusariosis. Other causes of death included progression of underlying diseases in 13 patients, infectious complication other than fungal infection in two and others in six.

Triggers to initiate micafungin in the DET group

Among 67 patients in the DET group, micafungin was started based on the value of the c-D-index in 42 (62.7%) patients, a diagnosis of possible invasive mold infection (IMI) in three (4.5%), abnormal findings in imaging studies that did not fulfill the diagnosis of possible IMI in 13 (19.4%) and suspected fungemia based on septic shock in one (1.5%). In the remaining eight (11.9%) patients, micafungin was started at the discretion of the attending physician based on persistent fever without any other findings when the c-D-index was still less than 5500. In total, 16 (23.9%) patients received micafungin based on abnormal findings in imaging studies. The efficacy of micafungin was 76.2% (95%CI: 60.5–87.9%) in patients who received micafungin triggered by the c-D-index and 50.0% (95%CI: 24.7–75.3%) in those who received micafungin based on imaging studies. Among 16 patients who had abnormal findings in imaging studies, seven (43.8%) and five (31.3%) patients did not fulfill the criteria of no premature discontinuation and fever resolution, respectively. In three patients who received MCFG for possible IMI based on specific pulmonary lesion with negative biomarkers, treatment failures were seen in two patients in terms of progression of pulmonary nodules or appearance.

Adverse events

Twenty-one adverse events associated with micafungin were reported in 15 patients, consisting of five (7.5%) patients in the DET group and 10 (8.8%) in the EAT group (Table 3). Hepatic impairment was the most common adverse event. Six instances of hepatic impairment were seen including one grade 3, two grade 2 and three grade 1. Other relatively common adverse events were drug eruption (two grade 2 and one grade 1) and oral mucositis (three grade 2). Grade 4 drug-related adverse events were not observed in this study.
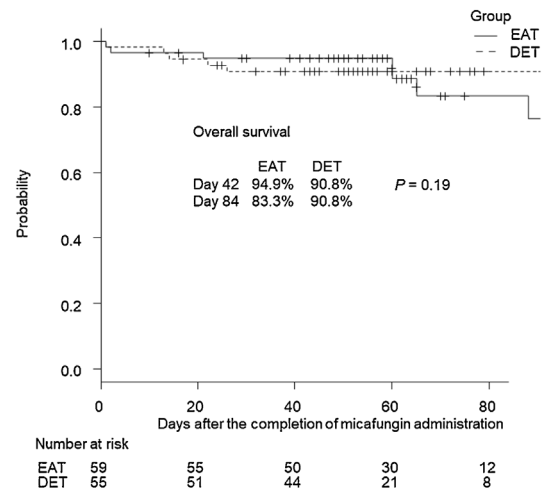
Discussion

This study confirmed the preferable efficacy and safety of micafungin in EAT for febrile neutropenia, similar to the results of previous clinical trials (Jeong et al., 2016; Oyake et al., 2016; Park et al., 2010; Tamura et al., 2009; Yamaguchi et al., 2011; Yoshida et al., 2012). The efficacy of micafungin in the EAT group was 79.6% (95%CI: 71.0–86.6%) in the total patients and 78.0% (95%CI: 65.3–87.7%) in high-risk patients in this study. A previous randomized controlled trial conducted by Walsh et al. showed that the efficacy
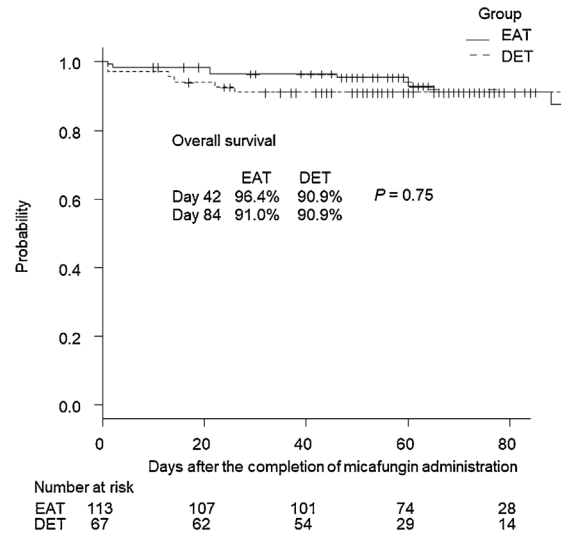
Figure 1. **A.** Overall survival after the completion of micafungin administration. There was no significant difference in overall survival after the completion of micafungin administration between the D-index-guided early antifungal therapy (DET) and classic empirical antifungal therapy (EAT) groups (P = 0.75). Overall survival in the DET and EAT groups was 90.9% and 96.4% at 42 days, and 90.9% and 91.0% at 84 days after the completion of micafungin administration, respectively. **B.** Overall survival after the completion of micafungin administration in high-risk patients

There was no significant difference in overall survival in high-risk patients between the DET and EAT groups (P = 0.19). Overall survival in the DET and EAT groups was 90.8% and 94.9% at 42 days, and 90.8% and 83.3% at 84 days after the completion of micafungin administration, respectively.

of caspofungin in EAT was 33.9% (Walsh et al., 2004). The reason for this considerable difference in success rate between antifungal agents in the same class was the different criteria for fever resolution. Walsh et al. adopted a definition of fever resolution that was achieved during neutropenia, which was fulfilled in only 41.2% of the study patients. On the other hand, we used a definition of fever resolution at seven days after the completion of therapy, which was met in 84.1% of the patients. We adopted this alternative definition proposed by de Pauw et al. (2006) because fever resolution during neutropenia was considered to be too strict to reflect the actual efficacy of antifungal agents and can mask other clinically relevant outcomes. Yamaguchi et al. also reported that the overall response rate for micafungin in empirical therapy was

Table 3
Drug-related adverse events.

	DET (n = 67)			EAT (n = 113)		
	Total	Grade1−2	Grade3	Total	Grade1−2	Grade3
Hepatic impairments	2	1	1	4	4	
AST elevation	1	2	1	3	3	
ALT elevation	1		1	1	1	
ALP elevation	2					
Not specifically reported						
Skin rash	1	1		2	2	
Oral mucositis / Oral pain				3	3	
Diarrhea	1	1		1	1	
Loss of appetite				1	1	
Hypotension				1	1	
Alveolar pneumonia				1		1
Cervical lymphadenopathy				1	1	
Dyspnea				1		1
Hypoxemia	1	1				
Weight gain	1	1				

DET, D-index-guided early therapy; EAT, empiric antifungal therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

79.0% when they used a four-part composite end point without resolution of fever in a single-arm prospective study (Yamaguchi et al., 2011). However, the response rate dropped to 39.5% when they added resolution of fever during neutropenia and applied the resulting five-part composite end point. Similarly, only 45.1% of the patients in the EAT group in our study exhibited fever resolution during neutropenia and the response rate dropped to 41.6% if we adopted this definition. Regarding the components other than fever resolution, the results seem to be comparable among previous studies and our study (Oyake et al., 2016; Walsh et al., 2004; Yamaguchi et al., 2011). If we take these results into consideration, the definition of fever resolution strongly affects the success rate. We should interpret the results with caution in this respect.

In this study, we evaluated the efficacy of micafungin in DET. In the DET group, micafungin was administered mostly in high-risk patients. The success rate as evaluated by a five-part composite end point in the DET group seemed to be slightly lower than that in the EAT group even when we analyzed it among high-risk patients (69.1% vs 78.0%), although there was no statistically significant difference. The success rate was greatly affected by the rate of achieving fever resolution, which was 70.9% in the DET group and 79.7% in the EAT group. When we analyzed the entire cohort, there was a statistically significant difference in the proportion of patients who achieved fever resolution at 7 days after completion of the treatment among total patients (70.1% vs 84.1%, P = 0.037). However, whether fever resolution really reflected the efficacy of antifungal therapy was unclear because there were many possible causes of fever aside from fungal infection such as bacterial or viral infection, tumor fever, drug fever and immune reaction after allogeneic HSCT. Since the DET group included a greater proportion of allogeneic HSCT recipients, the significant difference in fever resolution between the DET and EAT groups among total patients might be because of causes other than fungal infection. Indeed, there was no significant difference in other components such as breakthrough fungal infection, survival at seven days after the completion of therapy and premature discontinuation of micafungin between the DET and EAT groups. In addition, there was no significant difference in overall survival after the completion of micafungin. Causes of death consisted mostly of those other than fungal infection. According to these results, it was thought that the efficacy of micafungin in DET was basically similar to that in EAT and at least not strongly impaired in terms of fever resolution.

We also analyzed the efficacy of micafungin in the DET group, dividing the patients into subgroups depending on the trigger used to start antifungal therapy. In this analysis, the efficacy of micafungin was 50.0% (95%CI: 24.7–75.3%) in 16 patients who started micafungin based on a diagnosis of possible IMI or abnormal findings in imaging studies. Premature discontinuation mainly due to lack of efficacy was observed in seven (43.8%) patients. We could not draw a definitive conclusion from this data because of the small number of patients evaluated and no comparison to other antifungal agents in a similar situation. However, the efficacy of micafungin might be impaired in a situation with some findings associated with fungal infection compared to febrile neutropenia without any other findings. In these settings, antifungal drug selection considering invasive aspergillosis such as voriconazole or liposomal amphotericin B might be an alternative option, but further evaluation is required.

Regarding adverse events, micafungin basically had a preferable safety profile. Drug-related adverse events occurred in 8.3% of the patients. Hepatic impairment and drug eruption were common adverse events as in previous studies (Oyake et al., 2016; Tamura et al., 2009; Yamaguchi et al., 2011; Yoshida et al., 2012). Most of them were manageable and discontinuation due to adverse events was observed in only two patients in the EAT group (1.8%).

There are some important limitations in this study. First, there were differences in background and condition at the initiation of micafungin between the DET and EAT groups. While we focused on high-risk treatments in the comparison analysis, the DET group still included more patients who had a longer period of neutropenia until the initiation of micafungin and those who had abnormal findings on imaging studies. Therefore, the comparison of efficacy should be interpreted with caution. Second, the efficacy of micafungin was not compared to that of other antifungal agents in this study. In particular, there are no data regarding other antifungal agents in the DET setting. Therefore, we could not decide which antifungal agent was appropriate in DET or preemptive antifungal therapy settings from this study. However, we believe that micafungin is an acceptable choice in these settings based on the results of this study. Third, the efficacy of micafungin could be different depending on antifungal prophylaxis. Although there was no significant difference in the efficacy of micafungin among patients with no fluconazole and itraconazole prophylaxis in this study, it could be different under posaconazole or voriconazole prophylaxis.

In conclusion, micafungin had preferable efficacy and safety in EAT and DET settings. The efficacy of micafungin was not strongly impaired in DET compared to that in EAT. Further studies and discussions are warranted to determine an appropriate choice of antifungal agents in DET and preemptive antifungal therapy.

Authorship contributions

Funding

Ethical approval

The trial was approved by the institutional review board or independent ethics committee at each institution and was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided their written informed consent. Astellas Pharma Inc. sponsored this study, but was not involved in the design of the study or analyses or interpretation of the results. This trial was registered in UMIN-CTR [UMIN000010411].

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