Introduction

The importance of deep-seated fungal infections in Japan is considered to be increasing due to the rise in the number of immunocompromised patients associated with the introduction of advanced medical treatment and the aging of the Japanese population as a whole. *Candida* spp. and *Aspergillus* spp. are the most important causative pathogens in Japan, the same as in other countries [1, 2].

Echinocandins inhibit the biosynthesis of (1,3)-β-D-glucan, the structural component of fungal cell wall, thereby, exhibiting antifungal activity against *Candida* spp. and *Aspergillus* spp. Although caspofungin, micafungin sodium (hereinafter, micafungin), and anidulafungin have been approved and are used worldwide, micafungin is the only approved echinocandin antifungal agent in Japan at the time of this study.

Caspofungin has been shown to be effective as the primary therapy for esophageal candidiasis and invasive candidiasis, as salvage therapy for invasive aspergillosis, and as empirical therapy in patients with persistent fever and neutropenia. To date, caspofungin has been approved for use in over 80 countries worldwide, including the United States and Europe [3–6]. A comparator-controlled study of caspofungin and micafungin conducted in patients with candidemia has been reported by Pappas et al. In this study, micafungin 100 mg or 150 mg once daily was shown to be effective (non-inferior) compared to caspofungin 50 mg daily following a 70-mg loading dose on Day 1 [7]. Additionally, in a cohort analysis, caspofungin and micafungin were compared as empirical therapy in patients with febrile neutropenia, with similar efficacy reported [8]. There are no reports on the comparative study of caspofungin and micafungin for aspergillosis.

Herein, we report the results of a randomized, double-blinded, comparative study of caspofungin versus micafungin conducted in Japanese patients with *Candida* or *Aspergillus* infections. The safety and efficacy profiles of caspofungin and micafungin were compared.

Study patients and study plan

Objective and study design

This is a randomized, multicenter, double-blind, comparative study. The study was conducted in 43 study sites in Japan from August 2008 through July 2010. The protocol was reviewed by the Institutional Review Board of each participating site, and written informed consent was obtained from each patient. The protocol was also registered on clinicaltrials.gov (NCT00717860). In this study, a serious drug-related adverse event or a drug-related adverse event leading to study therapy discontinuation was defined as significant drug-related adverse event(s). Definitions of adverse events and drug relationships, and the determination of seriousness basically complied with the "Definitions and Terminology Associated with Clinical Safety Experience" in the International Conference on Harmonisation (ICH)-E2 [9]. The primary objective of this study was to compare the difference in the proportion of patients who develop significant drug-related adverse events(s) between the caspofungin and micafungin groups. The secondary objective was to evaluate the difference in the overall response by each of esophageal candidiasis, invasive candidiasis, and aspergillosis.

Patient inclusion criteria

Japanese patients aged 20 years and over were enrolled in this study following obtainment of written informed consent. Patients who fulfilled the criteria indicated below were enrolled as probable disease cases. When causative fungi (*Candida* spp. or *Aspergillus* spp.) were identified by culture or relevant organisms with specific morphology (yeast or acutely branching mold with septated hyphae) were observed by microscopic examination in addition to the criteria below, then patients were enrolled as proven disease cases. Both probable and proven disease cases were the target population in this study.

Criteria for probable disease:

- Esophageal candidiasis: patients with clinical symptoms of esophageal candidiasis (i.e., odynophagia, dysphagia, and heartburn) and plaque observed on the esophageal mucosa by endoscopy.
- Candidemia: patients with fever >38 °C observed, or fever of ≥37.5 °C that continues for 1 h or more despite the use of antibiotic therapy and positive results for the (1,3)-β-D-glucan test.
- Other types of invasive candidiasis (except candidemia): fungal infection strongly suspected at screening based on the clinical course and symptoms, typical radiographic imaging findings on X-ray and computed tomography (CT) (based on infection site), and positive results for the (1,3)-β-D-glucan test.
- Invasive aspergillosis: patients with risk factors of fungal infections (e.g., neutropenia, immunosuppressive treatment), clinical symptoms (e.g., fever, generalized malaise, coughing, sputum, bloody sputum, dyspnea), characteristic radiographic imaging findings (e.g., infiltration shadow, nodular shadow, cavitary lesions, or halo sign), and positive results for *Aspergillus* galactomannan antigen (enzyme-linked immunosorbent assay).
- Chronic pulmonary aspergillosis (except pulmonary aspergilloma): patients with clinical symptoms (e.g.,

fever not responding to antibiotic agent, body weight decreased, wet coughing, bloody sputum), characteristic radiographic imaging findings (e.g., pericavity infiltration, increasing size of cavity, or fluid collection in the cavity), and positive results for *Aspergillus* antibody or *Aspergillus* galactomannan antigen.

- Pulmonary aspergilloma: patients who have clinical symptoms (e.g., sputum, bloody sputum, hemoptysis, fever, dyspnea, coughing), characteristic radiographic imaging findings (e.g., coccus image in the cavity, thickened cavity wall, pleural thickening, or fluid collection in the cavity), and positive results for *Aspergillus* antibody.

Of note, patients who received prior antifungal therapies (other than echinocandins) were also allowed to enroll in this study. In such cases, the patients were evaluated on whether they met the criteria of refractoriness (the patient received an antifungal agent within 7 days prior to study therapy administration, but the disease progressed or clinical improvement was not observed) or intolerance (there is a significant problem in tolerance during the administration of prior antifungal agents as judged by the investigators).

Patients who fall under any of the criteria listed below were to be excluded: patients with mycoses due to causes other than *Candida* spp. and *Aspergillus* spp.; patients who had already received caspofungin or micafungin for the current fungal infection within the 7 days prior to initiation of the study; International Normalized Ratio (INR) (prothrombin time) of >2 × ULN (upper limit of normal) for patients not receiving anticoagulants; INR >4 × ULN for patients receiving anticoagulants; total bilirubin of >5 × ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) of >5 × ULN; patients with a history of serious drug-related allergy or sensitivity; patients with moderate or severe hepatic insufficiency (acute hepatitis, hepatic cirrhosis, etc.); patients who received another investigational drug within 1 month prior to study entry; patients who are pregnant, intend to become pregnant during the period up to 2 weeks after study completion, or are lactating.

Treatment plan

The randomization was stratified by infection category [esophageal candidiasis, candidemia, other types of invasive candidiasis (except candidemia), invasive aspergillosis, chronic pulmonary aspergillosis, and pulmonary aspergilloma] using a random permuted block, with the caspofungin group and micafungin group allocated at a ratio of 1:1. Patients, study investigators, and the sponsor remained blinded to the treatment group throughout the study. The pharmacist or preparer of the study therapy at each site was not blinded to the treatment group, but this individual could not be involved with any evaluation or judgment of efficacy and safety in this study.

Each patient received intravenous administration of caspofungin (esophageal candidiasis: 50 mg, invasive candidiasis and aspergillosis: 70/50 mg) once daily or micafungin 150 mg once daily for approximately 1 h in a blinded fashion. The treatment periods were 7–28 days for patients with esophageal candidiasis, 14–56 days for patients with invasive candidiasis, and 14–84 days for patients with aspergillosis. Patients with esophageal candidiasis were treated with study therapy for at least 3 days after the resolution of clinical symptoms and signs. Patients with candidemia were treated for at least 14 days after the last positive culture result for *Candida* spp. Patients with aspergillosis were treated for at least 7 days after the resolution of clinical symptoms/signs and at least 14 days after the resolution of neutropenia (absolute neutrophil count; ANC: >500/μL). The use of other systemic antifungal agents and rifampin was prohibited until the time of the efficacy evaluation.

Safety and efficacy evaluation

With regard to the safety of the study drug, the investigators recorded all adverse events and drug-related adverse events occurring from the initiation of study therapy through 14 days after the last dose of the study drug, based on any abnormal physical findings, vital signs, and laboratory tests, including red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, γ-glutamyl transpeptidase (γ-GTP), ALP, lactate dehydrogenase, blood urea nitrogen, creatinine, Na, K, Cl, Ca, uric acid, blood glucose, C-reactive protein, urinalysis, prothrombin time, and partial thromboplastin time. All safety information pertaining to a significant drug-related adverse event was reviewed by the Independent Safety Assessment Committee (ISAC) under blinded conditions for study therapy. In addition, with regard to hepatic function tests, maximum values from the study period were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3 [10].

The diagnosis of patients enrolled into this study was reviewed by an Independent Efficacy Assessment Committee (IEAC). The efficacy results in this study were based on the overall response, which included the resolution or improvement of clinical symptoms and radiographic imaging findings [or eradication of *Candida* (microbiological response) in patients with candidemia]). All efficacy evaluations made by the investigators were reviewed by the IEAC in a blinded fashion, and the judgment by the IEAC was considered as the final result.

The efficacy evaluation in esophageal candidiasis was conducted 5–7 days after the end of study therapy. The

overall response was determined as "favorable" in patients with esophageal candidiasis if clinical symptoms and signs of *Candida* infections (odynophagia, dysphagia, and heartburn) resolved and follow-up endoscopy results indicated at least a two-grade improvement (or return to Grade 0) in the predefined criteria (Grades 0, 1/2, 1, 2, 3, and 4) [11]. The efficacy evaluation in invasive candidiasis was conducted at the completion of study therapy. The overall response was determined to be "favorable" in patients with invasive candidiasis if the clinical symptoms and signs of *Candida* infections were resolved and follow-up blood culture was negative (for patients with candidemia) or follow-up radiographic imaging findings were "improved" [for patients with other types of invasive candidiasis (except candidemia)]. The efficacy evaluation in aspergillosis was conducted at the completion of study drug. The overall response was determined to be "favorable" in patients with aspergillosis if the clinical symptoms and signs of *Aspergillus* infections were "improved" or "stable", and follow-up radiographic imaging findings were "improved" or "stable". However, if the clinical symptoms and signs and radiographic imaging findings were both "stable" in patients with aspergillosis, the overall response was determined to be "unfavorable".

Identification of fungus and drug sensitivity study

Fungus isolated in the study was sent to Mitsubishi Chemical Medience Corporation and the organism was identified to the species level. The susceptibility of all isolated *Aspergillus* spp. and *Candida* spp. to antifungal agents was measured according to the guidance for microdilution technique M38-A2 (*Aspergillus* spp.) [12] and M27-A3 (*Candida* spp.) [13] of the Clinical and Laboratory Standards Institute (CLSI).

Statistical analysis

The safety analysis population was the all patients as treated (APaT) population (all randomized patients who received at least one dose of study therapy). The incidence and its 95 % confidence interval (CI) by treatment groups were calculated for the primary endpoint, namely, the proportion of patients who developed significant drug-related adverse events (a serious drug-related adverse event or a drug-related adverse event leading to study therapy discontinuation). In addition, 95 % CIs for the difference in the incidence between treatment periods were calculated using the Miettinen and Nurminen method (1985). The study was not powered to show a statistically significant difference between treatment groups.

The primary efficacy analysis population was the per-protocol set (PPS) population. The PPS included any patient who was diagnosed as having *Candida* or *Aspergillus* infections by the IEAC and received an appropriate course of study therapy (at least 5 days for the treatment of esophageal candidiasis or invasive candidiasis or at least 7 days for the treatment of aspergillosis), and in whom the efficacy evaluation was conducted in accordance with the study protocol. For esophageal candidiasis and candidemia, patients were included in the PPS population only when *Candida* spp. was confirmed by culture test. In addition, a secondary efficacy analysis was also performed using the full analysis set (FAS) population to confirm the consistency of the results. The FAS included any patient who received at least one dose of study therapy and was diagnosed as having *Candida* or *Aspergillus* infections by the IEAC.

Patients whose overall response was determined as "unable to be judged" were excluded from the overall response in the PPS analysis. In the FAS analysis, "unable to be judged" patients were treated as "unfavorable". The proportion of patients with a favorable overall response and its 95 % CI were calculated by three disease types (esophageal candidiasis, invasive candidiasis, and chronic pulmonary aspergillosis including aspergilloma), as judged by the IEAC. The analysis methods, handling, and the identification of the patients to be excluded from the PPS population mentioned above were determined before the unblinding.

Results

Study patients and patient background

One hundred and twenty-one patients were randomized. The average age of the randomized patients at the time of enrollment was 69.1 years and the proportion of male patients (79.3 %) was greater than that of female patients (20.7 %). The average weight was 48.8 kg and patients who were refractory to or intolerant of prior antifungal agents accounted for approximately one-quarter of enrollment. There were no patients with human immunodeficiency virus (HIV) infection, allogeneic stem cell transplant, or graft versus host disease. Major risk factors observed in patients with esophageal candidiasis were diabetes mellitus (25.0 %) and malignant tumor (25.0 %). Major risk factors in patients with invasive candidiasis were diabetes mellitus (31.6 %) and malignant tumor (26.3 %). Major risk factors in patients with chronic pulmonary aspergillosis were pulmonary disorder (31.4 %), tuberculosis sequelae (24.3 %), diabetes mellitus (21.4 %), malignant tumor (8.6 %), and use of steroids (5.7 %). There was no statistical difference between the caspofungin group and the micafungin group for any demographic or baseline data (Table 1)

The breakdown of APaT, FAS, PPS and populations in this study and the reasons for the exclusion of patients from

Table 1 Patient demographics and background conditions (all randomized patients)

	Total		Caspofungin		Micafungin		*p*-value[a]
	n	(%)	*n*	(%)	*n*	(%)	
Randomized patients	121		61		60		
Sex							0.472
Male	96	(79.3)	50	(82.0)	46	(76.7)	
Female	25	(20.7)	11	(18.0)	14	(23.3)	
Age (years)							0.815
Mean	69.1		68.9		69.3		
Standard deviation	10.1		11.2		9.0		
Weight (kg)							0.476
Mean	48.80		49.56		48.01		
Standard deviation	11.61		10.75		12.47		
Refractoriness or intolerance to prior antifungal agents							0.884
Refractory	23	(19.0)	12	(19.7)	11	(18.3)	
Intolerant	5	(4.1)	2	(3.3)	3	(5.0)	
Primary therapy	93	(76.9)	47	(77.0)	46	(76.7)	
Underlying risks							0.478[c]
Diabetes mellitus	28	(23.1)	11	(18.0)	17	(28.3)	
Pulmonary disorder[b]	25	(20.7)	13	(21.3)	12	(20.0)	
Malignant tumor	22	(18.2)	13	(21.3)	9	(15.0)	
Tuberculosis sequelae	20	(16.5)	9	(14.8)	11	(18.3)	
Use of immunosuppressive drugs	5	(4.1)	1	(1.6)	4	(6.7)	
Use of steroids	5	(4.1)	2	(3.3)	3	(5.0)	
Neutrophil count <500/mm^3	4	(3.3)	2	(3.3)	2	(3.3)	
Thermal burn	1	(0.8)	1	(1.6)	0	(0.0)	

[a]Chi-square test (*t*-test for age and weight)

[b]Pulmonary disorder includes bronchiectasis, tuberculosis, chronic obstructive pulmonary disease, pulmonary fibrosis, and pulmonary bulla

[c]Based on the comparison of the proportion of patients who have at least one of the underlying risks between two treatment groups

each population is included in Fig. 1. One patient was excluded from the APaT population because blinding was not maintained for this patient. Thirteen patients who were diagnosed as having infections caused by pathogens other than *Aspergillus* spp. and *Candida* spp., based on the determination of the IEAC, were excluded from the FAS population. The most common reason for why patients were excluded from the FAS population and the PPS population was unconfirmed "positive culture" for esophageal candidiasis and invasive candidiasis (15 patients). Most of these excluded patients were with probable candidemia. Candidemia patients were allowed to start study therapy based on the positive (1,3)-β-D-glucan test and clinical symptoms, and, as a result, most of the culture results in these patients were demonstrated as negative. Patients who were not classified into diseases predefined in the study protocol (two patients with aspergillosis not classified) were also excluded from the PPS population. In addition, there were exclusions due to the use of prohibited concomitant drugs (one patient) and insufficient study therapy duration (four patients). There was no notable difference in the number of patients within each treatment group in any of the three analysis populations.

The average dosages in the APaT population were 51.0 mg/day and 149.7 mg/day in the caspofungin and micafungin groups, respectively. The average duration of study drug treatment in the APaT population was 28.7 (range 2–84) days and 33.6 (range 1–84) days in the caspofungin and micafungin groups, respectively. The accounting of patients by disease type is presented in Table 2.

Safety evaluation

The number of patients who reported drug-related adverse events is shown in the APaT population in Table 3. Drug-related adverse events were reported in 38.3 % and 41.7 % of patients in the caspofungin and micafungin groups, respectively. Serious drug-related adverse events were reported in two patients; both were in the micafungin group (AST and ALT increased in one patient and rash in the other patient).

Abnormal values in ALT, AST, and ALP (maximal levels), regardless of the drug relationship, were assessed in an exploratory fashion in accordance with CTCAE Version 3. The numbers of patients who had Grade 2 or higher ALT, AST, or ALP elevations (>2.5 × ULN) were 3, 4, and 5, respectively, in the caspofungin group, and 6, 5,

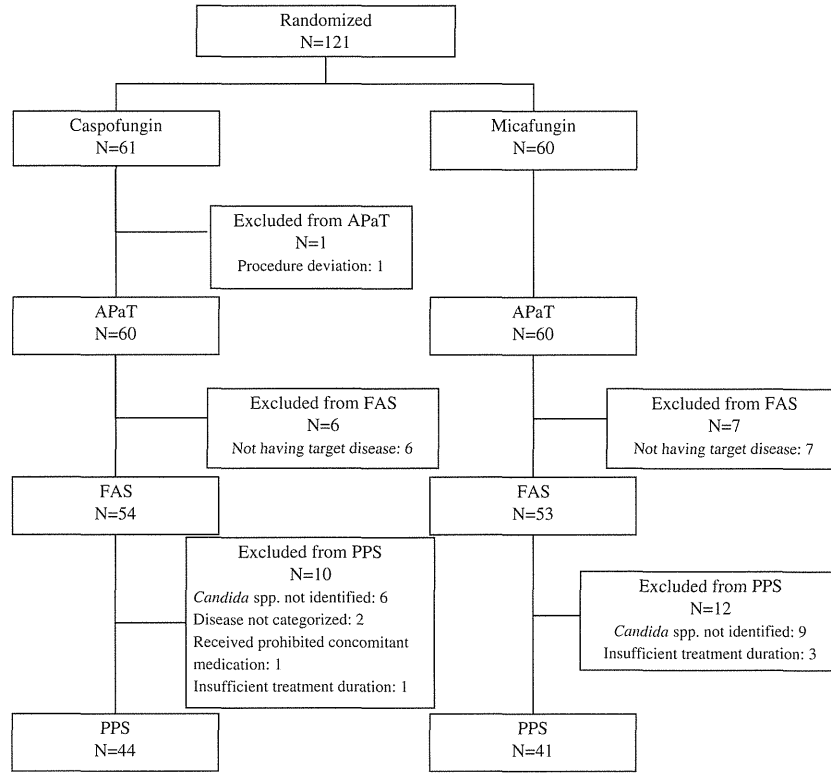

Fig. 1 Analysis populations and reasons for exclusion by treatment group. APaT: all patients as treated, FAS: full analysis set, PPS: per-protocol set

and 2, respectively, in the micafungin group. Of these, the number of patients who had Grade 3 ALT, AST, or ALP elevations (>5.0–20.0 × ULN) was 2, 3, and 1, respectively, in the micafungin group; none of the caspofungin-treated patients had Grade 3 elevations for ALT, AST, or ALP.

The proportion of patients fulfilling the primary endpoint of this study, the presence of one or more significant drug-related adverse events, was 5.0 % (95 % CI: 1.0, 13.9) in the caspofungin group and 10.0 % (95 % CI: 3.8, 20.5) in the micafungin group. The between-treatment difference was −5.0 % (95 % CI: −15.9, 5.2), thereby, showing no significant difference between the two groups. Significant drug-related adverse events were reported in three patients in the caspofungin group (all reported drug-related adverse events leading to study therapy discontinuation) and six patients in the micafungin group (two reported serious drug-related

Table 2 Disposition of patients by disease type

Disease type[a]	APaT		PPS	
	Number of patients [duration of therapy, mean days]		Number of patients	
	Caspofungin	Micafungin	Caspofungin	Micafungin
Esophageal candidiasis	9 [14.7]	7 [13.7]	8	6
Invasive candidiasis	9 [13.2]	9 [13.2]	3	1
Candidemia	6	7	1	0
Invasive candidiasis (excluding candidemia)	3	2	2	1
Aspergillosis	36 [37.1]	37 [42.1]	33	34
Invasive aspergillosis	1	0	1	0
Chronic pulmonary aspergillosis (including pulmonary aspergilloma)	33	37	32	34
Pulmonary aspergillosis (unclassified)	2	0	0	0
Other than mycosis[b]	6 [21.8]	7 [34.9]	0	0
Total	60 [28.7]	60 [33.6]	44	41

APaT all patients as treated, *PPS* per-protocol set

[a]Disease classification is based on the diagnosis by the Independent Efficacy Assessment Committee (IEAC)

[b]Other infectious diseases (not mycosis) diagnosed by the IEAC

Table 3 The number (%) of patients with clinical and laboratory drug-related adverse events (incidence ≥3 % in one or more treatment groups) [all patients as treated (APaT) population]

	Caspofungin[a]		Micafungin[b]	
	n	(%)	*n*	(%)
Patients in population	60		60	
With one or more drug-related adverse events	23	(38.3)	25	(41.7)
With one or more drug-related serious adverse events	0	(0.0)	2	(3.3)
Eye disorders	1	(1.7)	2	(3.3)
Gastrointestinal disorders	3	(5.0)	4	(6.7)
Constipation	0	(0.0)	2	(3.3)
Nausea	2	(3.3)	1	(1.7)
General disorders and administration site conditions	2	(3.3)	3	(5.0)
Injection site reaction	0	(0.0)	2	(3.3)
Hepatobiliary disorders	1	(1.7)	2	(3.3)
Infections and infestations	0	(0.0)	2	(3.3)
Laboratory abnormalities	14	(23.3)	18	(30.0)
Alanine aminotransferase (ALT) increased	5	(8.3)	4	(6.7)
Aspartate aminotransferase (AST) increased	6	(10.0)	3	(5.0)
Blood lactate dehydrogenase (LDH) increased	0	(0.0)	2	(3.3)
Blood potassium decreased	2	(3.3)	1	(1.7)
Blood potassium increased	1	(1.7)	3	(5.0)
Blood pressure increased	0	(0.0)	2	(3.3)
Eosinophil count increased	3	(5.0)	4	(6.7)
Gamma-glutamyl transpeptidase (γ-GTP) increased	2	(3.3)	2	(3.3)
Prothrombin time prolonged	2	(3.3)	0	(0.0)
White blood cell count decreased	1	(1.7)	2	(3.3)
White blood cell count increased	0	(0.0)	2	(3.3)
Platelet count increased	0	(0.0)	2	(3.3)
Blood alkaline phosphatase (ALP) increased	2	(3.3)	2	(3.3)
Nervous system disorders	3	(5.0)	2	(3.3)
Hypoesthesia	0	(0.0)	2	(3.3)
Skin and subcutaneous tissue disorders	1	(1.7)	6	(10.0)
Erythema	0	(0.0)	2	(3.3)
Rash	1	(1.7)	3	(5.0)
Vascular disorders	5	(8.3)	2	(3.3)
Hypertension	2	(3.3)	0	(0.0)
Phlebitis	2	(3.3)	2	(3.3)

[a]Patients with esophageal candidiasis received caspofungin 50 mg once daily. All other patients received caspofungin 50 mg once daily following a 70-mg loading dose on Day 1

[b]All patients received micafungin 150 mg once daily

Every patient is counted once for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted once for that system organ class. A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding

adverse events accompanied by study therapy discontinuation and four reported drug-related adverse events leading to study therapy discontinuation). The significant adverse events of three patients in the caspofungin group were elevation of ALP, AST, and γ-GTP, moderate rash, and elevation of AST and ALT. The significant adverse events in six patients of the micafungin group were elevation of AST and ALT, moderate rash, increased blood pressure level, occurrence of atrial fibrillation, elevation of γ-GTP alone, and elevation of AST, ALT, γ-GTP, ALP, and LDH with the occurrence of nausea. Nine patients in the caspofungin group and 10 patients in the micafungin group died during this study. None of the deaths were considered to be drug-related adverse events.

Efficacy evaluation

Of the 85 patients included in the PPS population, six patients were deemed to be "unable to be judged", and the favorable overall response rate was assessed for 79 patients. Favorable overall response rates in esophageal candidiasis, invasive candidiasis, and chronic pulmonary aspergillosis including aspergilloma are shown in Table 4. Among invasive candidiasis, one patient in the caspofungin group was candidemia and the others (two in caspofungin and one in micafungin) were peritoneal candidiasis patients. The overall response of caspofungin and micafungin in chronic pulmonary aspergillosis (other than aspergilloma) patients were

Table 4 Overall response in the per-protocol set (PPS) excluding patients deemed to be "unable to be judged"[a] from the PPS population

	Caspofungin		Micafungin	
Number of patients in PPS	44		41	
Number of patients determined as "unable to be judged" for overall response	5		1	
Number of patients analyzed for overall response	39		40	
Overall response	Favorable response rate, % (n/m)[b]	(95 % CI)	Favorable response rate, % (n/m)[b]	(95 % CI)
Esophageal candidiasis	100.0 (6/6)	(54.1, 100.0)	83.3 (5/6)	(35.9, 99.6)
Invasive candidiasis	100.0 (3/3)	(29.2, 100.0)	100.0 (1/1)	(2.5, 100.0)
Chronic pulmonary aspergillosis including aspergilloma	46.7 (14/30)	(28.3, 65.7)	42.4 (14/33)	(25.5, 60.8)

CI confidence interval

[a]Patients who were determined as "unable to be judged" were excluded from the PPS analysis for overall response

[b]*n/m* number of patients with favorable overall response/number of patients analyzed

45.0 % (9/20) and 46.7 % (14/30), respectively. The overall response of caspofungin in aspergilloma patients was 50.0 % (5/10), and there were no aspergilloma patients in the micafungin group. In general, the favorable overall responses were similar across the two treatment groups for each disease. Since the efficacy evaluation was independently assessed from an event of death, a listing of patients in the PPS population who died during the study period is shown in Table 5. Three of the four patients in the caspofungin group and one of four patients in the micafungin group died due to the worsening of primary infection (chronic pulmonary aspergillosis in all cases). Three patients deemed to be "unable to be judged" were not included in the calculation of the favorable overall response rate (two patients in the caspofungin group and one patient in the micafungin group).

Additionally, in the FAS population, the favorable overall response rates in the caspofungin group and the micafungin group were 77.8 % (7/9) and 85.7 % (6/7) for patients with esophageal candidiasis, 33.3 % (3/9) and 11.1 % (1/9) for patients with invasive candidiasis, 45.5 % (15/33) and 37.8 % (14/37) for patients with chronic pulmonary aspergillosis including aspergilloma, respectively. The results were generally comparable between the treatment groups, such as those seen in the PPS population.

Duration of therapy and relationships with overall response in aspergillosis patients

Among patients with aspergillosis in the PPS population, an exploratory assessment was performed to compare the number of days on study therapy between the treatment groups

Table 5 Listing of patients who died in the PPS population

Treatment group	Disease	Study therapy duration	Overall response (by the IEAC)	Date of death (relative day after study therapy completion)	Cause of death (by primary investigators)
Caspofungin	Chronic pulmonary aspergillosis	11 days	Unable to judge (due to severe co-infection of bacteria)	Day 1	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	84 days	Unfavorable	Day 11	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	84 days	Unable to judge (due to repeated co-infection of bacteria)	Day 12	(Worsening of) chronic pulmonary aspergillosis
	Candidemia	15 days	Favorable	Day 11	(Worsening of) peritoneal mesothelioma
Micafungin	Chronic pulmonary aspergillosis	8 days	Unable to judge (due to inconsistent imaging data)	Day 2	(Worsening of) lung cancer
	Chronic pulmonary aspergillosis	20 days	Unfavorable	Day 7	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	8 days	Unfavorable	Day 19	(Worsening of) COPD
	Chronic pulmonary aspergillosis	13 days	Unfavorable	Day 8	Death (unknown cause of death)

and by treatment outcome. The mean number (range) of days on study therapy among patients with a favorable response was 36.1 (8 to 84) days for the caspofungin 70/50 mg group (n=14) and 61.5 (22 to 84) days for the micafungin group (n=14). The mean treatment duration was shorter among patients with a favorable response in the caspofungin 70/50 mg group than in the micafungin group. On the other hand, the mean number (range) of days on study therapy among patients with an unfavorable response with aspergillosis was 39.3 (14 to 84) days for the caspofungin 70/50 mg group (n=16) and 35.6 (7 to 84) days for the micafungin group (n=19). The treatment duration was generally comparable between the groups in patients with unfavorable responses.

Susceptibility of fungal isolates to caspofungin

The geometric mean (range) of the caspofungin minimum inhibitory concentration (MIC) of clinical isolates of *Candida* spp. detected at screening (baseline isolates) was 0.25 (0.06–0.5) μg/mL and 0.5 μg/mL for *C. albicans* (19 strains) and *C. glabrata* (one strain), respectively. The geometric mean (range) of the caspofungin minimum effective concentration (MEC) of clinical isolates of *Aspergillus* spp. detected at screening was 0.25 (0.12–0.5) μg/mL, 0.25 (0.25) μg/mL, 0.25 (0.12–0.5) μg/mL, and 0.12 μg/mL for *A. fumigatus* (nine strains), *A. niger* (three strains), *A. flavus* (two strains), and *Aspergillus* spp. (one strain), respectively.

Discussion

This study is a prospective, randomized, double-blind study to evaluate the efficacy and safety of caspofungin versus micafungin in Japanese patients with *Aspergillus* or *Candida* infections. The caspofungin doses investigated in this study were the same as the approved clinical doses outside of Japan. Although the approved standard dose of micafungin for aspergillosis and candidiasis is 50–150 mg once daily and 50 mg once daily, respectively, and the dose can be increased up to 300 mg once daily in Japan, the average daily micafungin dose which has been actually used in a clinical setting is reported to be 110 mg [14]. In addition, in the Japanese "Diagnosis and Treatment Guideline for Deep-Seated Fungal Infections", micafungin doses of 100 to 150 mg daily and 150 to 300 mg daily are recommended for the treatment of candidiasis and aspergillosis, respectively [15]. Based on these data, a micafungin dose of 150 mg daily was determined to be an appropriate comparison to caspofungin (50 mg or 70/50 mg once daily).

Several efficacy findings deserve further attention. The efficacy results from the patients who were in the PPS excluding "unable to be judged" patients (n=79) suggest that the efficacy of caspofungin 50 mg or 70/50 mg once daily was almost comparable to that of micafungin 150 mg once daily. However, it should be noted that two patients in the PPS population receiving caspofungin died due to worsening of the primary disease of chronic pulmonary aspergillosis after 1 and 12 days following the completion of study therapy, respectively, and were assessed as "unable to be judged" by the IEAC because both patients also had bacterial infection and the efficacy of caspofungin could not be evaluated based on their clinical symptoms. Since the ultimate cause of death was the worsening of primary disease, these two patients were highly likely not to respond to caspofungin, and, consequently, the efficacy of caspofungin might be slightly lower in this study. All *Candida* spp. isolates detected at screening in this study showed caspofungin MIC below the current CLSI clinical breakpoint (2 μg/mL) and were deemed to be susceptible. No CLSI clinical breakpoint for *Aspergillus* spp. has been established; however, the MEC values were similar to the data reported to date [16]. Therefore, *Candida* spp. and *Aspergillus* spp. in Japan appear to be susceptible to caspofungin.

Both caspofungin and micafungin demonstrated favorable treatment efficacy against *Candida* infections. This result is similar to that in the fluconazole-controlled comparative studies of caspofungin and micafungin in patients with esophageal candidiasis [3, 17] and to that in the direct comparative study between caspofungin and micafungin in patients with invasive candidiasis [7].

On the other hand, the favorable response rate was slightly below 50 % in aspergillosis. In this study, no patients in the primary efficacy analysis group were confirmed by the IEAC to have invasive aspergillosis, and, thus, all patients who were categorized into the aspergillosis population had subacute to chronic stage of aspergillosis. As for the study evaluating the efficacy against chronic pulmonary aspergillosis, a study has been conducted comparing micafungin with voriconazole. In this study, the favorable overall response rates at the completion of study therapy with micafungin (average dose 167.4 mg/day) or voriconazole (6 mg/kg twice daily on Day 1, followed by 4 mg/kg twice daily on Day 2 onwards) were 60.0 % and 53.2 %, respectively [18]. Although a direct comparative assessment is difficult due to the different enrollment and efficacy evaluation criteria, based on this previous report and the results from the current study (favorable overall response rate of 46.7 % in the caspofungin group and 42.4 % in the micafungin group), it can be considered that both agents are effective to some extent against chronic pulmonary aspergillosis. Additionally, among the chronic pulmonary aspergillosis patients who showed favorable efficacy response, we found that the duration of therapy in the caspofungin group was numerically shorter than that in the micafungin group. Since the number of patients was very limited (n=14 in each group) and any adjustment based on the

medical history or concomitant diseases including risk factors for fungal infection was not considered, it is difficult to conclude that the difference in periods show antifungal responses. However, it might be interesting to investigate the difference of echinocandins, and, thus, further investigation in the patients with more controlled status is needed.

Taken together, the overall efficacy results seem consistent to those of other previous reports, although there is a limitation to comparing the efficacy to each candidiasis and aspergillosis between caspofungin and micafungin due to the small number of patients in each subset of infection.

Amongst the proportion of patients with significant drug-related adverse events, the primary endpoint of this study was 5.0 % in the caspofungin group and 10.0 % in the micafungin group. The 95 % CI for the treatment difference in the incidence was −15.9 % to 5.2 %, thereby, showing no significant difference. Furthermore, no apparent difference between the treatment groups was observed in the incidence of specific adverse events or drug-related adverse events. In addition, relatively common drug-related adverse event categories were similar to those previously reported in association with caspofungin [3–5]. Drug-related adverse events relating to liver function enzymes have been commonly reported in association with echinocandins. Since these events were also frequently reported compared to other drug-related adverse events in this study, these events were further assessed. When maximal levels of AST, ALT, and ALP were graded in accordance with CTCAE Version 3 criteria, all abnormal changes observed in the caspofungin group were Grade 2 (>2.5–5 × ULN), but some patients in the micafungin group had Grade 3 levels (>5.0–20.0 × ULN). Since multiple types of drugs were concomitantly used with the study therapy in this trial, a discussion of the drug association with elevation of these enzymes is difficult to make. However, the monitoring of liver function enzymes is generally recommended for patients receiving echinocandins.

Conclusion

In Japanese patients with *Aspergillus* or *Candida* infections, the safety of the treatment with caspofungin 50 mg or 70/50 mg once daily was similar to that of micafungin 150 mg daily. Consistent to other data on these two agents, caspofungin treatment showed similar efficacy to micafungin.

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Conflict of interest Shigeru Kohno received honorarium, consultation fee, and research grant from both Astellas Pharma, Inc. and MSD K.K. Koichi Izumikawa received honorarium from both Astellas Pharma, Inc. and MSD K.K. Yoshihito Niki received honorarium, consultation fee, and research grant from both Astellas Pharma, Inc. and MSD K.K. Shinichi Oka received a research grant from MSD K.K. Minoru Yoshida, Yoshio Takesue, Katsuhiko Kamei, and Yoshitsugu Miyazaki received per diem stipends from MSD K.K. for attending the committee meeting. Tomoko Yoshinari is an employee of MSD K.K., a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA, and Nicholas Kartsonis is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

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References

1. Kriengkauykiat J, Ito JI, Dadwal SS (2011) Epidemiology and treatment approaches in management of invasive fungal infections. Clin Epidemiol 3:175–191

2. Kume H, Yamazaki T, Togano T, Abe M, Tanuma H, Kawana S et al (2011) Epidemiology of visceral mycoses in autopsy cases in Japan: comparison of the data from 1989, 1993, 1997, 2001, 2005 and 2007 in annual of pathological autopsy cases in Japan. Med Mycol J 52:117–127
3. Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ et al (2002) A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med 113:294–299
4. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J et al (2002) Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 347:2020–2029
5. Maertens J, Raad I, Petrikkos G, Boogaerts M, Selleslag D, Petersen FB et al (2004) Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis 39:1563–1571
6. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A et al (2004) Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351:1391–1402
7. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ et al (2007) Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 45:883–893
8. Kubiak DW, Bryar JM, McDonnell AM, Delgado-Flores JO, Mui E, Baden LR et al (2010) Evaluation of caspofungin or micafungin as empiric antifungal therapy in adult patients with persistent febrile neutropenia: a retrospective, observational, sequential cohort analysis. Clin Ther 32:637–648
9. ICH Harmonized Tripartite Guideline (1994) Clinical safety data management: definitions and standards for expedited reporting. Recommended for Adoption at Step 4 of the ICH Process on 27 October 1994 by the ICH Steering Committee. Available online at: http://www.pmda.go.jp/ich/e/e2a_95_3_20e.pdf
10. DCTD, NCI, NIH, DHHS (2003) Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. Available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed 9 August 2006
11. Villanueva A, Arathoon EG, Gotuzzo E, Berman RS, DiNubile MJ, Sable CA (2001) A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clin Infect Dis 33:1529–1535
12. Rex JH, Alexander BD, Andes D, Arthington-Skaggs B, Brown SD, Chaturveli V et al (2008) Reference method for broth dilution antifungal susceptibility testing of filamentous fungi; Approved standard—second edition (M38-A2). Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, vol. 28, no. 16
13. Rex JH, Alexander BD, Andes D, Arthington-Skaggs B, Brown SD, Chaturveli V et al (2008) Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved standard—third edition (M27-A3). Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, vol. 28, no. 14
14. Hanadate T, Wakasugi M, Sogabe K, Kobayashi T, Horita H, Kawamura I et al (2011) Evaluation of the safety and efficacy of micafungin in Japanese patients with deep mycosis: a post-marketing survey report. J Infect Chemother 17:622–632
15. The Japanese Mycology Study Group (ed) (2007) Guidelines for management of deep-seated mycoses 2007. Kyowa Kikaku, Tokyo
16. Pfaller MA, Castanheira M, Messer SA, Moet GJ, Jones RN (2011) Echinocandin and triazole antifungal susceptibility profiles for *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus fumigatus*: application of new CLSI clinical breakpoints and epidemiologic cutoff values to characterize resistance in the SENTRY Antimicrobial Surveillance Program (2009). Diagn Microbiol Infect Dis 69:45–50
17. de Wet N, Llanos-Cuentas A, Suleiman J, Baraldi E, Krantz EF, Della Negra M et al (2004) A randomized, double-blind, parallel-group, dose–response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 39:842–849
18. Kohno S, Izumikawa K, Ogawa K, Kurashima A, Okimoto N, Amitani R et al (2010) Intravenous micafungin versus voriconazole for chronic pulmonary aspergillosis: a multicenter trial in Japan. J Infect 61:410–418

INTERNAL MEDICINE

CASE REPORT

Infectious Endocarditis Caused by *Lactobacillus acidophilus* in a Patient with Mistreated Dental Caries

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Abstract

We present a rare case of infectious endocarditis caused by *Lactobacillus acidophilus* in a patient on long-term steroid use for autoimmune hepatitis. *In vitro* susceptibility-guided antibiotics with benzylpenicillin plus clindamycin and successive mitral annuloplasty resulted in a favorable outcome. Infectious endocarditis was suspected to be a complication of mistreated periodontal infection. Maintenance of oral hygiene is important in immunocompromised patients.

Key words: infectious endocarditis, lactobacillus species, immunocompromised, dental infection

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Introduction

Lactobacilli are commensal bacteria in the human oral cavity, gastrointestinal tract, and female genital tract. Lactobacilli are widely used in food and as probiotics, and are effective in the treatment of infantile and adult diarrhea and antibiotic-associated diarrhea (1, 2). However, rare cases of lactobacilli-induced bacteremia, meningitis, or endocarditis have been reported particularly in immunocompromised patients (3, 4). Here we report a case of infectious endocarditis caused by *Lactobacillus acidophilus* in a patient with autoimmune hepatitis.

Case Report

A 28-year-old female of East Asian origin was hospitalized in our clinic with a 3-month history of fever and pain in the right foot. She had a history of autoimmune hepatitis and had been taking prednisolone (2.5 mg/day) for more than one year. She had also been treated for dental caries, but she stopped seeing the dentist six months before admission. There was no history of cardiac disease, intravenous drug use or intake of probiotics. Since the appearance of fever, the patient was treated with levofloxacin (500 mg/day).

On admission, the patient was alert and oriented. The body temperature was 38.3℃. Physical examination showed a painful nodule in the 5th toe of the right foot. Oral examination showed multiple caries. Cardiac auscultation revealed grade 3/6 systolic murmur loudest over the apex, which was not evident during hospitalization 3 years earlier. Blood test showed leukocytosis (8,910/μL, neutrophil 87.4 %), microcytic anemia with hemoglobin of 9.9 g/dL, thrombocytopenia (platelet count: 102,000/μL), and elevated C reactive protein of 3.91 mg/dL. Liver function was relatively maintained with serum albumin 3.9 g/dL, total bilirubin 1.1 mg/dL, and prothrombin activity 75.1%. Liver transaminase and lactate dehydrogenase were within the normal ranges. Rheumatoid factor was positive, and anti-phospholipid antibody, anti-nucleus antibody, and anti-neutrophil cytoplasmic antibody were negative. Erythrocyte segmentation rate was 51 mm/hr.

Computed tomography of the abdomen showed a hypodense, wedge-shaped splenic lesion, suggestive of splenic infarction. There were heterogeneous hypoattenuating areas in the liver, but no ascites. Whole-body fluorodeoxyglucose positron emission tomography revealed high uptake in the 5th toe of the right foot, but no uptake in the splenic infarct

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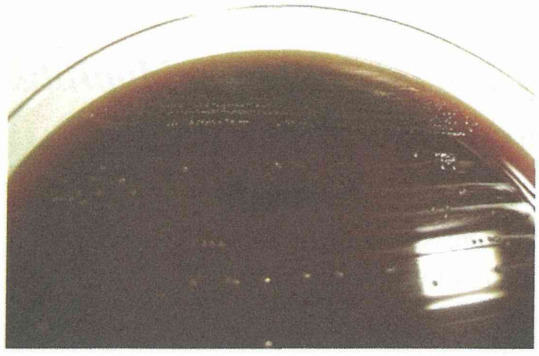

Figure 1. ***Lactobacillus acidophilus*** **cultured on ABHK agar.**

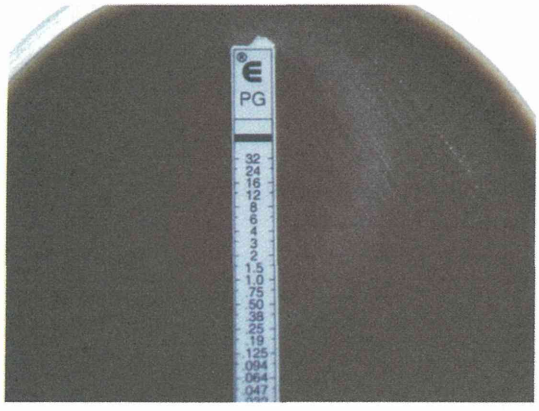

Figure 2. **Susceptibility testing of benzylpenicillin with Etest for** ***Lactobacillus acidophilus*****.**

area. Transesophageal echocardiography showed mitral prolapse with third-degree mitral regurgitation but no valvular vegetation was found. Dental consultation indicated multiple apical periodontitis and dental treatment was commenced.

All four culture bottles of two sets of blood samples drawn the day before admission showed Gram positive rods (GPR) on day 3. The patient was treated with intravenous antibiotics (meropenem 2 g plus clindamycin 2,400 mg). Another set of four culture bottles of two blood samples taken on day 3 also revealed GPR. *L. acidophilus* was identified on day 8, and the isolate was susceptible to benzylpenicillin (minimum inhibitory concentration [MIC] 0.12 μg/mL), ampicillin (MIC 0.25 μg/mL), imipenem (MIC ≤ 0.25 μg/mL) and clindamycin (MIC ≤0.12 μg/mL) (Fig. 1). MIC was measured with Etest® for penicillin according to the Clinical and Laboratory Standards Institute guidelines, and others with the microbroth dilution method [(5); Fig. 2]. On day 9, the antibiotics were replaced with benzylpenicillin (24 million units) plus clindamycin (2,400 mg). The final diagnosis was infectious endocarditis caused by *L. acidophilus* with Osler's node in the right foot and splenic infarction.

One anaerobic culture bottle of two sets of blood samples taken on day 6 revealed *L. acidophilus*, but no growth was observed in blood cultures prepared on day 14 and thereafter. Computed tomography on day 32 confirmed the disappearance of the nodule in 5th toe of the right foot. She was discharged on day 42 after 6 weeks of intravenous antibiotics treatment, and continued to take clindamycin 1,800 mg orally for 6 more weeks. Mitral annuloplasty was performed one year later, and no relapse has been observed for 2 years.

Discussion

We reported a rare case of infectious endocarditis caused by *L. acidophilus* in a patient on long-term steroid use for autoimmune hepatitis. To our knowledge, only 28 cases (3 cases in Japan), including this case, of infectious endocarditis caused by lactobacilli have been reported since 1992 after the publication of Duke's criteria (4, 6-9).

Endocarditis was diagnosed based on modified Duke's criteria (9). This patient fulfilled one major criterion: new valvular regurgitation, and four minor criteria: fever, major arterial embolus (splenic infarction), immunologic phenomenon (Osler's node in one toe), and microbiological evidence (positive blood culture).

Since the data for treatment and susceptibility of lactobacillus is scarce, there is no recommended empiric therapy (4). Salminen et al. indicated that the choice of antibiotics should depend on the susceptibility testing of lactobacilli, and that therapy guided by *in vitro* susceptibility tests significantly reduced mortality (10). Accordingly, we chose the combination therapy of intravenous benzylpenicillin plus clindamycin for 6 weeks and thereafter, clindamycin orally for 6 weeks. Mitral annuloplasty was conducted for severe mitral regurgitation, and no relapse was observed during the 2-year post-discharge period.

Maintenance of oral hygiene is important in immunocompromised patients in order to prevent systemic infection (11). Cannon et al. reported that dental procedures or oral diseases are the predisposing condition in almost half of the patients with lactobacillus-induced endocarditis (3). The present patient developed endocarditis caused by *L. acidophilus* after she discontinued dental treatment. Thus, dental infection was highly likely the predisposing factor for endocarditis.

In summary, we presented a case of infectious endocarditis caused by *L. acidophilus* in a patient with autoimmune hepatitis. Long-term use of *in vitro* susceptibility-guided antibiotics and mitral annuloplasty led to a favorable outcome. Maintenance of oral hygiene is important in immunocompromised patients.

The authors state that they have no Conflict of Interest (COI).

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References

1. Alvarez-Olmos MI, Oberhelman RA. Probiotic agents and infec-

tious diseases: a modern perspective on a traditional therapy. Clin Infect Dis **32**: 1567-1576, 2001.
2. Bezkorovainy A. Probiotics: determinants of survival and growth in the gut. Am J Clin Nutr **73**: 399S-405S, 2001.
3. Cannon JP, Lee TA, Bolanos JT, Danziger LH. Pathogenic relevance of Lactobacillus: a retrospective review of over 200 cases. Eur J Clin Microbiol Infect Dis **24**: 31-40, 2005.
4. Salvana EM, Frank M. Lactobacillus endocarditis: case report and review of cases reported since 1992. J Infect **53**: e5-e10, 2006.
5. Clinical and Laboratory Standards Institute (CLSI). Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria; approved guideline—second edition. In: CLSI document. CLSI, Wayne, PA, 2011: M45-A 2.
6. Yagi S, Akaike M, Fujimura M, et al. Infective endocarditis caused by lactobacillus. Intern Med **47**: 1113-1116, 2008.
7. Suárez-García I, Sánchez-García A, Soler L, Malmierca E, Gómez-Cerezo J. *Lactobacillus jensenii* bacteremia and endocarditis after dilatation and curettage: case report and literature review. Infection, 2011 Aug 25 [Epub ahead of print].
8. Makaryus AN, Yang R, Hahn RT, Kort S. A rare case of *Lactobacillus acidophilus* presenting as mitral valve bacterial endocarditis. Echocardiography **22**: 421-425, 2005.
9. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **30**: 633-638, 2000.
10. Salminen MK, Rautelin H, Tynkkynen S, et al. *Lactobacillus* bacteremia, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG. Clin Infect Dis **38**: 62-69, 2004.
11. Slots J. Update on general health risk of periodontal disease. Int Dent J **53** (Suppl 3): 200-207, 2003.

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CASE REPORT

Chemotherapy for thymic carcinoma in an adult patient with HIV infection

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Abstract A 69-year-old man was referred to our hospital in June 2010 after the diagnosis of an anterior mediastinal tumor and HIV infection. Histopathological examination of a CT-guided needle biopsy specimen showed undifferentiated thymic carcinoma. Chest CT revealed pleural dissemination, bone invasion, and left lung metastases. The final diagnosis was Masaoka stage IVb. Surgery was considered inappropriate. Instead, the patient first underwent highly active antiretroviral therapy for HIV infection, followed by four courses of cisplatin, doxorubicin, vincristine, and cyclophosphamide chemotherapy for thymic carcinoma. A partial response was achieved. To our knowledge, this is the first report of thymic carcinoma in an adult patient with HIV infection.

Keywords Thymic carcinoma · ADOC chemotherapy · HIV infection · HAART · Cytochrome

Introduction

Although the number of HIV-infected patients is increasing, the development of highly active antiretroviral therapy (HAART) has made it possible to control the disease. HIV infection has thus become a chronic disease, and the incidence of malignant tumors other than AIDS-defining malignancies has been increasing [1, 2].

Thymic epithelial tumors are reported to comprise approximately 25–46.1 % of all mediastinal tumors in adults and are classified as thymomas or thymic carcinomas [3, 4]. The incidence of thymic carcinoma is low, but this malignancy is associated with poor prognosis, with a 5-year survival rate of 35–50.5 % [3–5].

We report here a case of HIV infection complicated with thymic carcinoma. The patient was successfully treated with raltegravir (RAL)-containing HAART and cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) chemotherapy.

Case report

A 69-year-old man visited his local physician for cough and exertional dyspnea since April 2010, and was found to have an anterior mediastinal tumor on a chest radiograph. Subsequent follow-up and laboratory tests identified HIV infection in June 2010, and he was referred to our hospital for further management. In mid-July 2010, a CT-guided needle biopsy of the mediastinal tumor was performed due to pleural dissemination and infiltration of the left seventh rib. Histopathological examination of the biopsy material showed undifferentiated carcinoma of the thymus. In addition, diagnostic imaging showed pleural dissemination, bone invasion, and metastases in the left lung. The final

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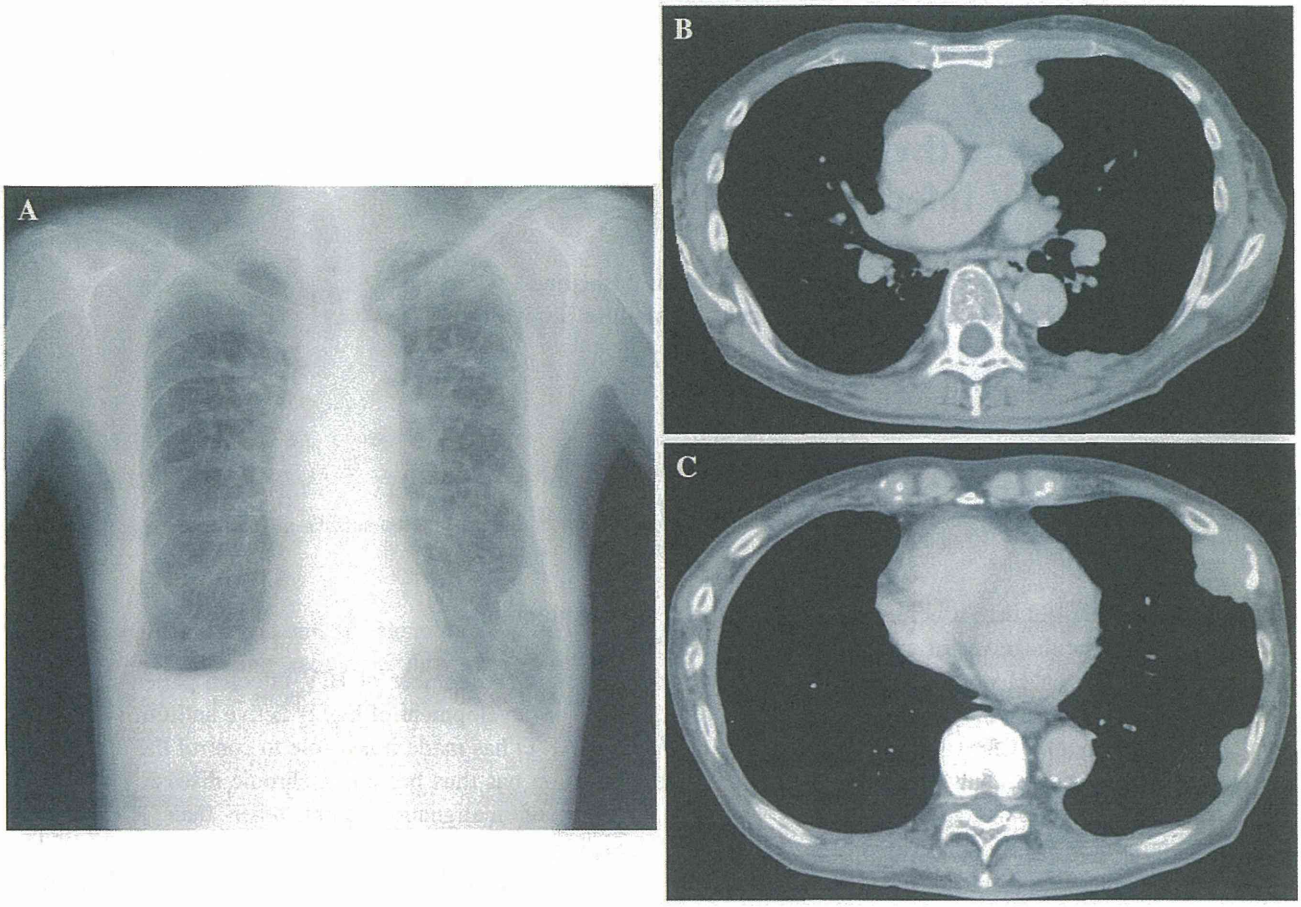

Fig. 1 **a** Chest radiograph on admission shows a mass protruding from the mediastinum into the left hilar region. **b**, **c** Enhanced chest CT scans on admission show the mediastinal mass and pleural dissemination

diagnosis was Masaoka stage IVb. The case was considered unsuitable for surgery. In late July 2010, the CD4 count was 379 cells/μL and viral load (VL) was 6.0×10^5 copies/mL. He received HAART, consisting of the combination of abacavir and lamivudine (ABC/3TC) and RAL for treatment of HIV infection. The patient was hospitalized for chemotherapy in late-August 2010. The medical history included hypertension, diabetes mellitus, and pulmonary tuberculosis (in 2006). He was a smoker of three packs of cigarettes per day for the preceding 45 years. On admission, physical examination showed no abnormal respiratory sounds and laboratory tests showed slightly reduced hemoglobin (11.7 g/dL), C-reactive protein 3.50 mg/dL, and elevated hemoglobin A1c (6.7 %). Analysis of various tumor markers showed high levels of CYFRA 21-1 (15.3 ng/mL) and 1-CTP (5.5 ng/mL). The CD4 count was 419 cells/μL and VL was 54 copies/mL. Chest radiography (Fig. 1a) showed a mass protruding from the mediastinum into the left hilar region, a nodular shadow and a granular shadow in the left upper and middle lung fields, respectively, and a nodular shadow in the lower left lung field. Enhanced chest CT scan (Fig. 1b, c) revealed a 7.3 × 5.2 × 8.5 cm tumor with an irregular border and heterogeneous internal contrast that was slightly to the left and superior to the anterior mediastinum. The mass had extensive contact with the aorta, pulmonary artery, epicardium, and left lung. Pleural dissemination and bone invasion of the left seventh rib were noted. Multiple shadows of small nodules were seen in the left lung field, and metastases in the left lung were suspected. A pathologic specimen revealed medullary proliferation of large atypical cells with fibrous stroma. Hassall corpuscle-like structure was observed, but no apparent keratinization was identified. Mucin production was not evident. Immunohistochemically, CD5 and c-kit were positive for tumor cells, and the MIB-1 index of tumor cells was 10–20 %. No TdT-positive T lymphocytes were observed. The lesion was diagnosed as thymic carcinoma (undifferentiated carcinoma) (Fig. 2).

The patient was started on ADOC chemotherapy consisting of drip infusion of doxorubicin 40 mg/m^2 and cisplatin 50 mg/m^2 on day 1, vincristine 0.6 mg/m^2 on day 3, and cyclophosphamide 700 mg/m^2 on day 4. Four courses of this ADOC chemotherapy were administered, at roughly

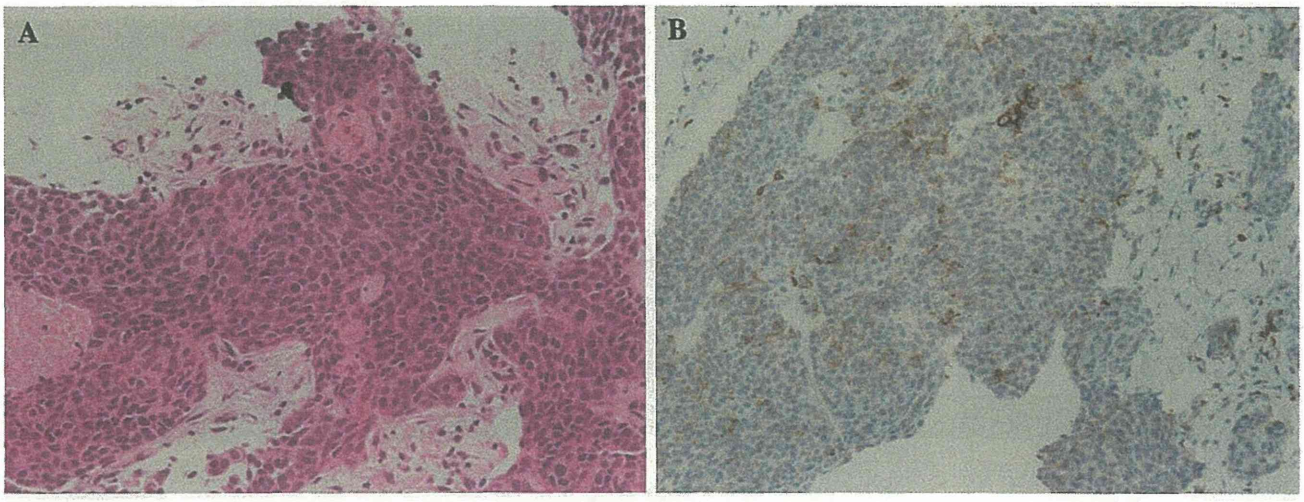

Fig. 2 **a** Microscopic findings of the CT-guided needle biopsy specimen diagnosed as undifferentiated thymic carcinoma (H&E stain). **b** Positive immunohistochemical staining for CD5 is seen in the cell membrane of tumor cells

4-week intervals, to allow for recovery of myelosuppression. Chest CT scan after chemotherapy showed a 5.1 × 3.7 × 6.0 cm tumor. The therapeutic efficacy was evaluated using Response Evaluation Criteria in Solid Tumors, and the evaluation was a partial response (Fig. 3). Hematological toxicity included grade 4 neutropenia and febrile neutropenia, while non-hematological toxicity included grade 1 anorexia, hiccups, and alopecia, but no hepatic or renal toxicity. The CD4 count was maintained at more than 300 cells/μL, and VL was suppressed to undetectable levels. Thus, disease control was achieved for both the thymic carcinoma and HIV infection. On the basis of the patient's history of pulmonary tuberculosis, acid-fast staining and sputum cultures were performed repeatedly, but results were negative. In the last outpatient visit, 9 months after diagnosis, the patient was in good general condition and no signs of recurrence or metastasis were noted.

Discussion

Thymic carcinomas, together with thymomas, are thymic epithelial tumors, and comprise approximately 14.1 % of thymic epithelial tumors [5]. Thymic carcinomas display clear cytological atypia and histological features and have the capacity to invade and metastasize both locally and to distant organs. At diagnosis, the thymic carcinoma is at an advanced stage in approximately 90 % of patients (at least Masaoka stage III, with invasion of surrounding organs) [5]. The indications for surgical treatment are limited compared with thymomas [3–5]. Our patient was diagnosed as Masaoka stage IVb [6] and was not considered a suitable candidate for surgery.

Thymic carcinomas do not show the high degree of sensitivity seen with thymomas, but some patients respond well to chemotherapeutic regimens that include cisplatin or carboplatin and anthracycline [7–12]. Koizumi et al. [9] described 8 patients with advanced thymic carcinoma who received ADOC chemotherapy, and reported a response rate of 75 % with a median survival time of 19 months. Yoh et al. [10] treated 12 patients with unresectable advanced thymic carcinoma by the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen and reported a response rate of 41.7 % and median survival time of 46 months. Igawa et al. [11] administered carboplatin and paclitaxel to 11 treatment-naïve patients with unresectable thymic carcinoma, and reported a response rate of 36 % with a median survival time of 22.7 months. Lemma et al. [12] used the same combination of carboplatin plus paclitaxel for 23 treatment-naïve patients with advanced thymic carcinoma in a prospective phase II study, and reported a response rate of 21.7 % and median survival time of 20.0 months. On the other hand, a large percentage of thymic tumors are reported to express c-kit protein [13–15]. Strobel et al. [16] reported an objective response to imatinib, an inhibitor of c-kit protein, in a patient with thymic carcinoma, but results were negative in a later phase II study [17]. Thus, there are several reports on thymic tumors but the number of treated cases has always been small, and there is still no standard chemotherapy regimen for thymic carcinoma.

Following the development of HAART, which improved disease control, HIV infection began to be considered a chronic disease. Furthermore, an increased incidence of malignant tumors other than the AIDS-defining malignancies in HIV-infected individuals has been reported [1, 2]. However, although one case of both HIV

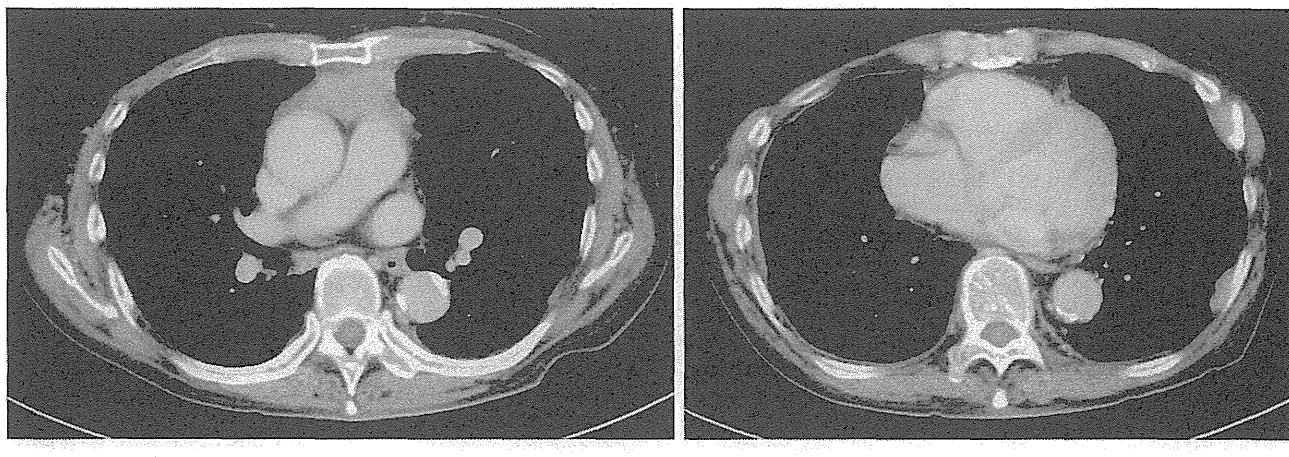

Fig. 3 **a**, **b** Chest CT scans after four cycles of ADOC chemotherapy show a decrease in both the mediastinal mass and pleural dissemination

infection and thymic carcinoma has been reported in a child [18], to our knowledge, there have been no such reports in adults, and the present case appears to be the first in the literature.

Decreased hemopoietic function in HIV patients [19] results in susceptibility to chemotherapy-induced myelosuppression, and therapy often cannot be completed due to treatment-related toxicities [20]. In addition, exacerbation of HIV and opportunistic infections associated with such myelosuppression is a concern. The present case is significant because a treatment regimen comprising the coadministration of HAART and antineoplastic drugs was used. Although there are no previous studies regarding coadministration of HAART and antineoplastic drugs for cases of HIV complicated by thymic carcinoma, the utility of this treatment regimen has been reported for HIV patients with lung cancer, Kaposi's sarcoma, and malignant lymphoma [20–23]. HAART offers the following advantages during anticancer treatment: (1) improved immune function by decreasing CD4-positive lymphocyte counts; (2) reduced myelosuppression by inhibition of HIV; and (3) reduced incidence of HIV infection-related conditions (chronic inflammation, tumorigenicity, renal impairment, arteriosclerosis, etc.) [24].

Some anti-HIV drugs either interact with antineoplastic drugs or cause similar toxicities, making it necessary to exercise caution when these drugs are administered at the same time. In particular, ritonavir (RTV), a protease inhibitor, is a very potent inhibitor of the cytochrome P (CYP) 450 3A4 drug-metabolizing enzyme in the liver. RTV can cause the blood concentrations of coadministered antineoplastic drugs to increase and may cause serious toxicities [25]. Potential cumulative toxicities between HAART and antineoplastic drugs are primarily related to nucleoside reverse transcriptase inhibitors (NRTIs) [26, 27]. Zidovudine causes myelosuppression (especially anemia and neutropenia), tenofovir is nephrotoxic, and stavudine and didanosine cause peripheral neuropathy. If these anti-HIV drugs are coadministered with antineoplastic drugs that can cause the same types of toxicities, there is a strong possibility that the toxicities will become even more severe [26, 27]. Thus, such coadministration should be avoided whenever possible. In the patient reported here, ABC/3TC, a combination of abacavir and lamivudine, which are NRTIs, and RAL, which is an integrase strand transfer inhibitor, was used, and these drugs did not alter the blood concentrations of antineoplastic drugs because they are not metabolized by CYP [27].

Coadministration of platinum-containing and anthracycline antineoplastic drugs, which constitute key agents in systemic chemotherapy for thymic carcinoma, can be expected to deliver a marked antineoplastic effect, despite the risk of myelosuppression [7–12]. In the present case, we selected ADOC chemotherapy on the basis of treatment outcome in the previous study [9] and the low incidence of drug interactions with ABC/3TC and RAL [27]. During chemotherapy, white blood cells, neutrophils, CD4 counts, and HIV viral load were monitored as closely as possible, and neutropenia and febrile neutropenia were rapidly treated, enabling completion of four courses of ADOC therapy.

In conclusion, we reported an HIV-infected patient with thymic carcinoma, who responded well to ADOC chemotherapy and HAART. For HIV-positive patients with malignant tumors, care should be exercised in selecting anti-HIV drugs to optimize therapeutic efficacy and reduce potential antineoplastic drug toxicities.

Conflict of interest No author has any conflict of interest.

References

1. Engels EA, Pfeiffer RM, Goedert JJ et al (2006) Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 20:1645–1654

2. Engels EA, Brock MV, Chen J et al (2006) Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol 24:1383–1388
3. Travis WD, Brambillia E, Muller-Hermelink HK et al (2004) Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC, Lyon
4. Ueda Y, Fujii Y, Kuwano H, et al. Thoracic and cardiovascular surgery in Japan during 2007. Annual report by the Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg. 2009;57:488–513
5. Kondo K, Monden Y (2003) Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 76:878–884
6. Masaoka A, Monden Y, Nakahara K et al (1981) Follow-up studies of thymomas with special reference to their clinical stages. Cancer 48:2485–2492
7. Loehrer PJ Sr, Jiroutek M, Aisner S et al (2001) Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 91:2010–2015
8. Lucchi M, Mussi A, Ambrogi M et al (2001) Thymic carcinoma: a report of 13 cases. Eur J Surg Oncol 27:636–640
9. Koizumi T, Takabayashi Y, Yamagishi S et al (2002) Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC chemotherapy). Am J Clin Oncol 25:266–268
10. Yoh K, Goto K, Ishii G et al (2003) Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. Cancer 98:926–931
11. Igawa S, Murakami H, Takahashi T et al (2010) Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. Lung Cancer 67:194–197
12. Lemma GL, Lee JW, Aisner SC et al (2011) Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol 29:2060–2065
13. Pan CC, Chen PC, Chiang H et al (2004) KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. J Pathol 202:375–381
14. Nakagawa K, Matsuno Y, Kunitoh H et al (2005) Immunohistochemical KIT (CD117) expression in thymic epithelial tumors. Chest 128:140–144
15. Petrini I, Zucali PA, Lee HS et al (2010) Expression and mutational status of c-kit in thymic epithelial tumors. J Thorac Oncol 5:1447–1453
16. Strobel P, Hartmann M, Jacob A et al (2004) Thymic carcinoma with overexpression of mutated KIT and the response to imatinib. N Engl J Med 350:2625–2626
17. Salter JT, Lewis D, Yiannoutsos C et al (2008) Imatinib for the treatment of thymic carcinoma. J Clin Oncol 26(Suppl):8116 (ASCO [abstract])
18. McDonald M, McLean T, Belhorn T et al (2005) Thymic carcinoma in a child with HIV infection. Pediatr Blood Cancer 49(7):1004–1007
19. Moses AV, Williams S, Heneveld ML et al (1996) Human immunodeficiency virus infection of bone marrow endothelium reduces induction of stromal hematopoietic growth factors. Blood 87:919–925
20. Kato T, Ieki R, Saito E et al (2005) A long-term survival case of small cell lung cancer in an HIV-infected patient. Jpn J Clin Oncol 35:349–352
21. Cadranel J, Garfield D, Lavole A et al (2006) Lung cancer in HIV infected patients: facts, questions and challenges. Thorax 61:1000–1008
22. Holkova B, Takeshita K, Cheng DM et al (2001) Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. J Clin Oncol 19:3848–3851
23. Sparano JA, Lee S, Chen MG et al (2004) Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol 22:1491–1500
24. Marin B, Thiebaut R, Bucher HC et al (2009) Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. AIDS 23:1743–1753
25. von Moltke LL, Greenblatt DJ, Grassi JM et al (1998) Protease inhibitors of human cytochrome P450: high risk associated with ritonavir. J Clin Pharmacol 38:106–111
26. Bower M, Collins S, Cottrill C et al (2008) British HIV Association guidelines for HIV-associated malignancies 2008. HIV Med 9:336–388
27. Makinson A, Pujol J, Moing VL et al (2010) Interactions between cytotoxic chemotherapy and antiretroviral treatment in human immunodeficiency virus-infected patients with lung cancer. J Thorac Oncol 5:562–571

Research Letter

AIDS 2012, **24**:000–000

Once-daily darunavir/ritonavir plus abacavir/lamivudine versus tenofovir/emtricitabine for treatment-naïve patients with baseline viral load >100,000 copies/mL

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The efficacy and safety of fixed-dose abacavir/lamivudine against tenofovir/emtricitabine, both with once-daily darunavir/ritonavir, was examined in 80 treatment-naïve patients with baseline HIV-1 viral load >100,000 copies/ml. The time to virologic failure by 48 weeks was not different between the two groups. The percentage of patients with viral suppression was not significantly different with per protocol population. Tenofovir/emtricitabine showed better tolerability; more patients on abacavir/lamivudine changed regimen than those on tenofovir/emtricitabine. A randomized trial to elucidate the efficacy and safety of these two regimens is warranted.

Little information is available on the efficacy and safety of antiretroviral therapy (ART) of ritonavir-boosted darunavir (DRV/r) plus fixed-dose abacavir/lamivudine (ABC/3TC) [1,2]. DRV/r is a protease inhibitor with proven efficacy and safety, and with high barrier to drug resistance [3,4]. ABC/3TC is an alternative choice of nucleoside reverse transcriptase inhibitors (NRTI) in the American Department of Health and Human Services Guidelines [5]. Here we conducted a single-center, observational pilot study to compare the efficacy and safety of DRV/r plus ABC/3TC versus TDF/FTC in patients with baseline HIV-1 viral load (VL) >100,000 copies/ml. Subjects with such VL were chosen because ACTG 5202 demonstrated that the time to virologic failure (VF) was significantly shorter with ABC/3TC than with TDF/FTC in patients with VL >100,000 copies/ml on efavirenz or ritonavir-boosted atazanavir [6]. All subjects were treatment-naïve who commenced once-daily DRV/r plus either fixed-dose ABC/3TC or TDF/FTC from November 2009 to August 2011 at the AIDS Clinical Center, Tokyo. Baseline data (basic demographics, CD4 count, and VL) were collected. VL was measured by Cobas TaqMan HIV-1 real-time PCR version 1.0 assay (Roche Diagnostics, NJ) to the end of November 2011, and later by Cobas TaqMan version 2.0 assay. It was the decision of the attending physician to start ART with either TDF/FTC or ABC/3TC, because the Japanese guidelines consider both TDF/FTC and ABC/3TC the preferred NRTIs [7].

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The efficacy outcomes were the time from commencing ART to VF (defined as VL >1,000 copies/ml at or after 16 weeks and before 24 weeks, or >200 copies/ml at or after 24 weeks) [6], and the proportion of patients with VL < 50 copies/ml at 48 weeks regardless of previous VF. The tolerability outcome was the time to any regimen modification. Intent-to-treat (ITT) population, comprising all subjects, was used for all efficacy and tolerability analyses, while per protocol population was used in the efficacy analysis of the suppressed VL. Censored cases represented those who dropped out, referred to other facilities, or reached 48 weeks. Time-to-event distributions were estimated using the Kaplan-Meier method. Uni- and multivariate Cox hazards models estimated the impact of ABC/3TC use over TDF/FTC on the incidence of VF.

The study included 80 patients [ABC/3TC: 21, TDF/FTC: 59, median age: 37.9 years, males: 74 (92.5%), East Asian origin: 72 (90%)], of whom 66 (82.5%) were infected with HIV-1 through homosexual contact. Patients on ABC/3TC had lower baseline CD4 count (46/μl versus 100, $P=0.031$), higher VL (5.75 log10/ml versus 5.58, $P=0.044$), and more likely to have history of AIDS (71.4% versus 37.3, $P=0.010$), than patients with TDF/FTC. All subjects were HLA-B*5701-negative, and all underwent HIV-1 drug-resistance tests before commencement of ART and none had resistant mutations.

The time to VF with ABC/3TC [3 patients (14.3%)] was not significantly different from that with TDF/FTC [4 (6.8%)] by 48 weeks (Fig. 1a), by univariate and multivariate analyses adjusted by CD4 count and VL (HR, 2.651; 95% CI, 0.592–11.88; $P=0.203$, adjusted HR, 1.589; 95% CI, 0.341–7.401; $P=0.555$). At week 48, ITT analysis showed more patients with TDF/FTC had VL of <50 copies/ml (ABC/3TC: 38.1%, TDF/FTC: 64.4%, $P=0.043$) (Fig. 1c), whereas with per protocol analysis, no difference was noted (ABC/3TC: 57.1%, TDF/FTC: 73.1%, $P=0.328$) (Fig. 1d).

Among the seven patients with VF, three (ABC/3TC: 1, TDF/FTC: 2) achieved sustained VL suppression after week 60 of the initial regimen. The other four underwent drug-resistance tests. One on ABC/3TC was switched to TDF/FTC at week 41; however, viral suppression was not achieved until raltegravir was added at week 74. The

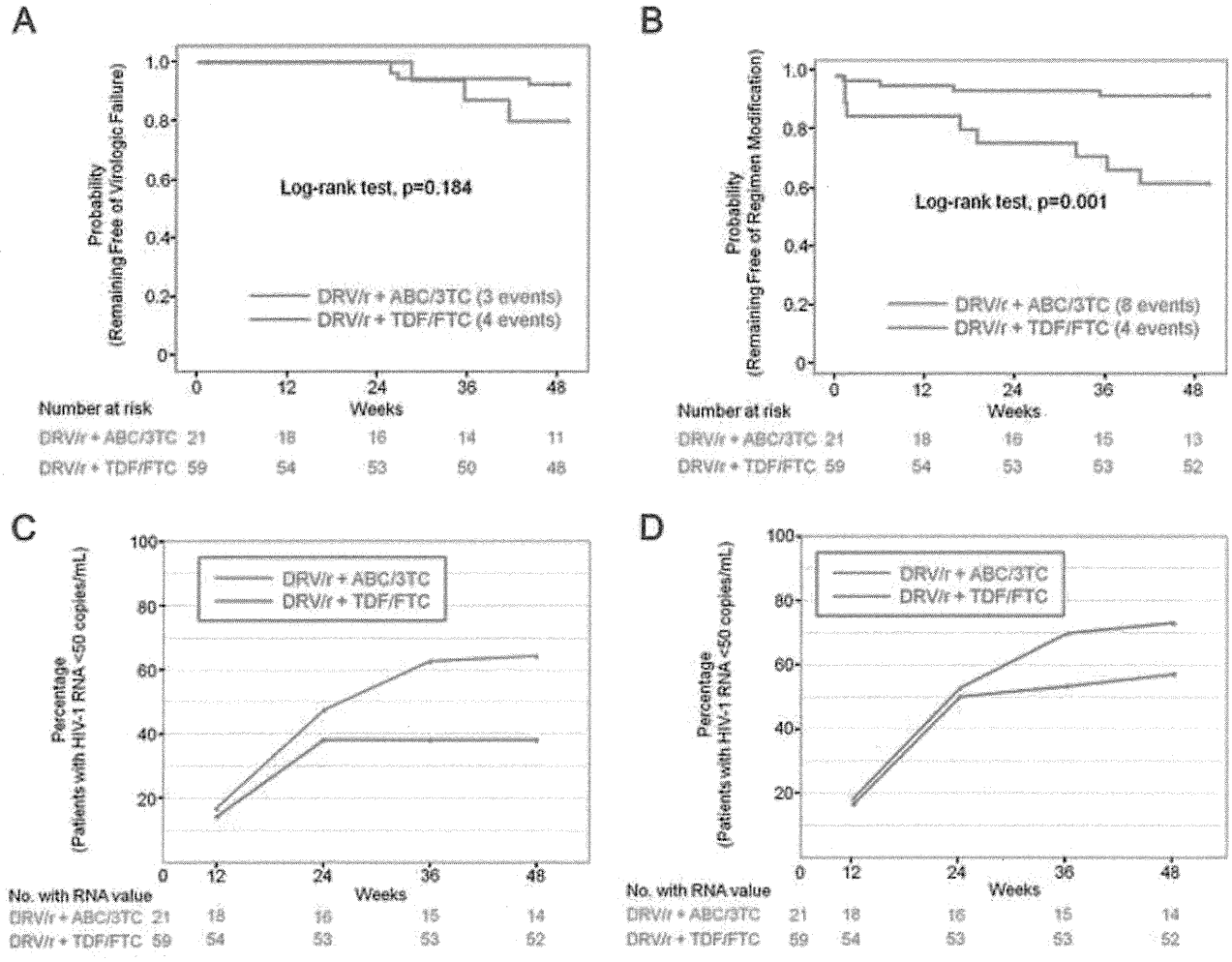

Fig. 1. Efficacy and tolerability results over 48 weeks. (a) Time to protocol-defined virologic failure. (b) Time to tolerability endpoint, defined as first change in treatment regimen. Percent of patients with HIV-1 RNA <50 copies/ml at week 12, 24, 36, and 48, regardless of previous virologic failure, with (c) intention-to-treat population, and with (d) per protocol population.

other with ABC/3TC was switched to TDF/FTC at week 49 and achieved viral suppression despite emergence of protease mutation M46I. Another patient on TDF/FTC had persistent viremia (100–200 copies/ml) without mutation. Another patient on TDF/FTC showed emergence of reverse transcriptase mutation V75L and viremia persisted with 200–500 copies/ml. Reverse transcriptase mutation M184I/T/V did not emerge in any patients.

More patients on ABC/3TC changed or discontinued the initial regimen during the research period [ABC/3TC: 8 (38.1%), TDF/FTC: 4 (6.8%), $P=0.001$] (Fig. 1b). Six [ABC/3TC: 4 (19%), TDF/FTC: 2 (3.4%)] changed ART due to adverse events or VF [ABC/3TC: VF ($n=1$), limb paresthesia ($n=1$), and nausea ($n=2$); TDF/FTC: tenofovir nephrotoxicity ($n=2$)]. None developed ABC-associated hypersensitivity.

This is the first comparison report of the efficacy and safety of ABC/3TC against TDF/FTC with DRV/r in treatment-naïve patients with VL >100,000 copies/ml. The time to VF by 48 weeks was not different between the two groups. Although a higher percentage of patients on TDF/FTC showed viral suppression than those on ABC/3TC at week 48 with ITT population, the difference was not significant with per protocol population. TDF/FTC showed better tolerability, as more patients on ABC/3TC changed regimen than those on TDF/FTC.

These results need to be interpreted with caution, because the baseline characteristics of patients of the two groups were not well-matched due to the nature of the observational study, and this study did not have sufficient power due to the small number of enrolled patients. Because our patients had small stature with median body weight of 58.1 kg, a risk factor for TDF nephrotoxicity, it