J Infect Chemother
DOI 10.1007/s10156-012-0412-9

ORIGINAL ARTICLE

Fatal candidemia caused by azole-resistant *Candida tropicalis* in patients with hematological malignancies

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Received: 12 December 2011 / Accepted: 21 March 2012

Abstract *Candida tropicalis* is one of the most important *Candida* species causative of candidemia that is isolated from the blood of patients with hematological malignancies. Candidemia caused by *C. tropicalis* is known to be highly virulent in neutropenic patients. *C. tropicalis* has been shown to be favorably sensitive to azole agents in general. Here we discuss 5 cases of candidemia caused by *C. tropicalis* in patients with hematological malignancies in our unit, and we note that 4 isolates were resistant to azole agents, including fluconazole, itraconazole, and voriconazole. In addition, 2 patients developed breakthrough candidemia caused by *C. tropicalis* while receiving prophylaxis with azole agents. Interestingly, 2 of the 4 patients with azole-resistant *C. tropicalis* isolates had never received any antifungal drugs. We also examined the susceptibilities of *C. tropicalis* to antifungal agents, using 39 non-blood isolates detected from 2003 to 2009. Around 40 % of the isolates were resistant to azole agents, and all of them were highly sensitive to amphotericin B and micafungin. The resistance to azoles was not associated with previous exposure to those agents. In our unit, 2 of the 4 cases of candidemia caused by azole-resistant *C. tropicalis* resulted in a poor prognosis. These findings suggested that empirical therapeutic strategies for candidemia should be modified based on the local antifungal resistance pattern.

Keywords *Candida tropicalis* · Azole · Resistance · Candidemia

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Introduction

Candidemia is a common cause of nosocomial bloodstream infections, and systemic *Candida* infections have a high mortality [1]. Therefore, it is important to maintain the susceptibilities of *Candida* species to antifungal agents, particularly azole antifungals. In worldwide surveillance studies, most *Candida* species tested, including *C. albicans* and *C. tropicalis*, retained favorable susceptibilities to azole agents [2]. However, surveys of blood isolates of *Candida* spp. have shown lower susceptibilities of *Candida* spp. to azoles than to echinocandins [3, 4]. Moreover, the emergence of *Candida* isolates resistant to fluconazole has been reported, and patients with hematological malignancies and/or previous antifungal exposure may be at risk of acquiring infections from fluconazole-resistant strains [5, 6].

Analyses of patients with hematological malignancies and of non-blood isolates of *Candida* spp., including *C. albicans* and *C. tropicalis*, have shown that most strains were sensitive to azole agents, but that previous treatment with azoles was a risk factor for azole-resistance [7–9]. In another study, favorable susceptibility to azoles was also-seen in *Candida* blood isolates from patients with hematological malignancies [10]. Some of the blood isolates from patients with previous antifungal treatment were found to be

Published online: 18 April 2012

resistant to azoles, and candidemia caused by azole-resistant *Candida* spp. was linked to a poor prognosis [10].

The detection rates of *C. tropicalis* from blood isolates have been reported to be significantly higher in patients with hematological malignancies compared to rates in those with other diseases [11–13]. Moreover, candidemia caused by *C. tropicalis* may be related to neutropenia, a complication which possibly leads to a poor outcome in patients with the infection [14, 15]. In this study, we discuss candidemia caused by *C. tropicalis* in patients with hematological malignancies. Interestingly, 4 of the 5 blood isolates of *C. tropicalis* detected were resistant to azole agents, and 2 of the 4 patients with azole-resistant *C. tropicalis* isolates had not taken any antifungal drugs. We also examined the susceptibilities of *C. tropicalis* to antifungal agents, using non-blood isolates detected from 2003 to 2009 at our unit.

Patients, materials, and methods

Patients

Between January 2003 and December 2009, a total of 2143 patients were admitted to the blood and marrow transplantation unit at Hara-Sanshin Hospital. In the present study, the results of blood and non-blood cultures obtained from these patients during the abovementioned period were analyzed; these results were available through a computer database set up in 2003. Most patients who were expected to have neutropenia for more than 7 days had received antifungal agents, including fluconazole and itraconazole, prophylactically,with the prophylaxis ultimately being decided upon by the patients' physicians. Until December 2005, antibiotic prophylaxis with levofloxacin was administered to all inpatients with neutropenia. The routine use of quinolone prophylaxis for neutropenic patients was discontinued from January 2006.

Febrile neutropenia was defined as a neutrophil count of $<$500 cells/μL and an axillary temperature of $>$38.0 °C. In our unit, blood culture tests are conducted for all patients with febrile neutropenia. When *Candida* spp. were isolated from a blood culture, antifungal therapy was adjusted according to the resistance pattern of the organism to antifungal agents. The prophylactic use of azoles was discontinued when definitive therapy was initiated. Blood cultures were also conducted when bacteremia and candidemia were suspected, even in patients with no neutropenia.

Detailed information on patients was collected from computer databases. The data included age, sex, malignant disease classifications, coexisting illnesses, presence of indwelling catheters, neutrophil counts, prior antibiotic and antifungal usage, prior steroid usage, and clinical outcomes. Information on isolated strains, including etiology and susceptibility to antifungal agents, was obtained from a microbiology laboratory computer database.

Microbiology

Candida spp. were isolated from blood using an automated blood culture system (BACTEC, BD, Sparks, MD, USA) and were identified by morphological (CHROMagar Candida, BD, Sparks, MD, USA) and biochemical (Vitek2 systems; bioMerieux Japan, Tokyo, Japan) examinations. Species identification of non-blood samples was also conducted using the same systems. Susceptibilities to the antifungal agents amphotericin B, flucytosine, fluconazole, itraconazole, and micafungin were determined from the breakpoints standardized by the Clinical and Laboratory Standards Institute (CLSI) [16, 17], using the microdilution method (Yeast-like fungi DP Eiken trays; Eiken Chemical., Tokyo, Japan). Growth reduction was judged after 24- and 48-h incubation. The susceptibilities of *C. tropicalis* to azole agents were determined from the minimum inhibitory concentration (MIC) reading after 24-h incubation to exclude false azole-resistance caused by trailing growth. From 2008, the isolates' susceptibilities to voriconazole were also determined. All culture, identification, and susceptibility tests were conducted in accordance with the manufacturers' instructions.

Statistical analysis

The abovementioned variables (i.e., prior antibiotic and antifungal usage) were compared between patients with fluconazole-resistant and those with fluconazole-sensitive *C. tropicalis* isolates in order to identify relevant factors. Odds ratios and 95 % confidence intervals were calculated; $P < 0.05$ was considered to be statistically significant. All statistical calculations were performed using SAS software (SAS Institute, Inc., Cary, NC, USA).

Results

Candidemia caused by azole-resistant *Candida tropicalis* strains

Between January 2003 and December 2009, a total of 8 *Candida* spp. were isolated from blood cultures in patients with hematological malignancies in our unit. *C. tropicalis* isolates accounted for 5 of the isolates, and the other isolates were *C. glabrata* and *C. parapsilosis*. The 3 isolates detected after 2008 were all *C. tropicalis.* The clinical features of the 5 patients with the candidemia caused by *C. tropicalis* are shown in Table 1. The underlying diseases