Caspofungin-non-susceptible Candida isolates in cancer patients

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Objectives: To identify the frequency of caspofungin-non-susceptible Candida isolates in cancer patients with candidiasis.

Methods: We reviewed the in vitro susceptibilities (M27-A3 CLSI method) of 650 Candida spp. associated with invasive candidiasis episodes in 582 hospitalized cancer patients (2005–08).

Results and conclusions: We identified seven caspofungin-non-susceptible Candida strains (three Candida tropicalis, two Candida glabrata and two Candida albicans) from 650 Candida isolates (1%). C. tropicalis (three out of seven) was the most common non-susceptible species isolated. All patients responded to a change of antifungal therapy. Further surveillance should focus on the potential broader emergence of echinocandin resistance, as the clinical use of this antifungal class continues to expand in cancer patients.

Keywords: echinocandin resistance, invasive candidiasis, haematological malignancy

Introduction

Over the past two decades, the burden of invasive fungal infections has increased with Candida spp. remaining the most common pathogen. Surveillance programmes in the United States have reported Candida spp. to be the third to fourth leading nosocomial bloodstream pathogen, accounting for 8%–10% of all bloodstream infections acquired in the hospital with a crude mortality rate of 40%. Caspofungin, an antifungal compound introduced in 2001 that targets the fungal cell wall by blocking (1,3)-β-D-glucan synthase, has emerged as one of the main choices for primary treatment of candidiasis. Despite extensive use, resistance to caspofungin and cross-resistance to other echinocandins is considered rare in the clinic and only occasional caspofungin failure in infections caused by strains of Candida for which the MIC of caspofungin was elevated have been reported. An echinocandin MIC of >2 mg/L is used to identify caspofungin-non-susceptible Candida spp. However, the relationship between an elevated MIC of caspofungin for strains of Candida and clinical or microbiological outcome for caspofungin-treated patients remains unclear. Furthermore, relatively little is known regarding the epidemiology of caspofungin non-susceptibility in Candida spp. among cancer patients. In the present study, we report seven caspofungin-non-susceptible Candida isolates recovered from an equal number of cancer patients.

Materials and methods

We reviewed the in vitro susceptibilities (M27-A3 CLSI method) of 650 Candida spp. associated with invasive candidiasis episodes in 582 hospitalized cancer patients at the University of Texas M.D. Anderson Cancer Center (2005–08). An echinocandin MIC of >2 mg/L is used to identify caspofungin-non-susceptible Candida spp. Candida spp. were isolated from blood, pelvic abscess and urine. We followed established definitions for candidaemia. De novo candidaemia was an infection occurring in patients who were not receiving systemic antifungal therapy, while breakthrough infection occurred in patients receiving systemic antifungal therapy for at least 7 days before the onset of candidiasis either as empirical or prophylactic therapy. Neutropenia was defined as an absolute neutrophil count of <500 cells/mm³ at the time of onset of infection. Response to antifungal treatment was defined as the resolution of clinical manifestations of fungaemia with blood cultures negative for Candida spp., and failure was defined as persistence of the clinical signs and symptoms of the fungal infection without an intercurrent infection, blood cultures positive for Candida spp. or both.

Results

We identified seven episodes of invasive candidiasis due to caspofungin-non-susceptible Candida spp. isolates (1%) obtained from seven patients (median age 56 years, range 17–87; 57% were males). All patients had haematological malignancy, while two of them had a second cancer and four had received...
caspofungin in the previous 3 months. Neutropenia and prior corticosteroid treatment were seen in four and five out of seven patients, respectively. Six out of seven caspofungin-non-susceptible candidiasis episodes developed as breakthrough infections during receipt of systemic antifungal therapy. Five out of seven caspofungin-non-susceptible Candida isolates were isolated from blood and one each from pelvic abscess and urine (in a patient with nephrolithiasis). Table 1 summarizes the clinical characteristics of the patients. Candida tropicalis in three patients was the most common Candida spp. isolated. One isolate (Candida glabrata) also had multiresistance to azoles, amphotericin B and echinocandins. Table 2 summarizes the spectrum of Candida spp. as well as susceptibilities to various antifungal agents. All seven patients responded to a change of antifungal therapy (catheter was removed in all five candidaemic patients). Two patients died. The cause of death was unrelated to Candida spp. infection and was attributed to haemorrhagic shock in one and Aspergillus spp. pneumonia in the other patient (Table 1).

### Discussion

In the present study we reported seven cases of invasive candidiasis due to caspofungin-non-susceptible Candida spp. infection among cancer patients at a single institution. All patients had haematological malignancy as underlying disease.

The reduced susceptibility to echinocandins of Candida spp. has been associated with mutations in the fks1p subunit of the target enzyme (1,3)-β-D-glucan synthase. Cross-resistance to other echinocandins such as micafungin and anidulafungin is common, suggesting a similar mechanism of resistance of Candida spp. to all echinocandin drugs. Little is known about the incidence of echinocandin-resistant Candida spp. among cancer patients. Pfaffer et al. reported an MIC of caspofungin of ≥4 mg/L only in 6 (0.1%) of 5346 isolates tested without any evidence of increasing caspofungin resistance over the last 6 years of their study. In our study an MIC of caspofungin of ≥4 mg/L was observed for 1% of the isolates tested. The caspofungin-non-susceptible isolates reported included Candida parapsilosis and Candida guilliermondii, Candida albicans, C. glabrata, C. tropicalis and Candida krusei. In the present study C. tropicalis was the most common Candida spp. isolated, in three out of seven cases, which might be explained by the fact that C. tropicalis is a rather common pathogen in patients with haematological malignancy.

A few clinical cases of Candida spp. isolates with reduced susceptibility to caspofungin have been reported in immunocompromised and in immunocompetent patients. In the present study the majority of patients had candidaemia (five out of seven) while neutropenia was observed in four patients. Exposure to antifungal agents is an important factor for drug resistance. Caspofungin-non-susceptible Candida spp. infection has also been described during prolonged treatment for oesophagitis and endocarditis. In the present study two patients had a Candida breakthrough infection while they were receiving caspofungin prophylaxis, and four patients had received caspofungin within 3 months prior to the development of infection with the non-susceptible isolate. Generally, Candida strains resistant to echinocandin drugs infrequently display cross-resistance to azole and polyene antifungal drugs, although cases with pan-resistant

### Table 1. Characteristics of seven patients with caspofungin-resistant Candida spp. infection

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, sex</th>
<th>Underlying condition</th>
<th>Neutropenia</th>
<th>CAS treatment</th>
<th>outcome</th>
<th>Antifungal and/or other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87, F</td>
<td>rectal cancer, MDS</td>
<td>no</td>
<td>no</td>
<td>survived</td>
<td>lipoAMB+VRC</td>
</tr>
<tr>
<td>2</td>
<td>60, M</td>
<td>large B cell lymphoma-BMT</td>
<td>yes</td>
<td>yes</td>
<td>died</td>
<td>lipoAMB+VRC</td>
</tr>
<tr>
<td>3</td>
<td>66, F</td>
<td>AML-BMT</td>
<td>no</td>
<td>no</td>
<td>survived</td>
<td>liposomal+VRC+MFG</td>
</tr>
<tr>
<td>4</td>
<td>17, M</td>
<td>Burkitt’s lymphoma</td>
<td>no</td>
<td>yes</td>
<td>died</td>
<td>MFG+VRC</td>
</tr>
<tr>
<td>5</td>
<td>57, M</td>
<td>cutaneous T cell</td>
<td>no</td>
<td>no</td>
<td>survived</td>
<td>MFG+VRC</td>
</tr>
<tr>
<td>6</td>
<td>23, F</td>
<td>CML—BMT</td>
<td>no</td>
<td>no</td>
<td>survived</td>
<td>AFG+VRC</td>
</tr>
<tr>
<td>7</td>
<td>84, M</td>
<td>ALL—prestate cancer</td>
<td>yes</td>
<td>yes</td>
<td>survived</td>
<td>AFG+VRC</td>
</tr>
</tbody>
</table>

AFG, anidulafungin; lipoAMB, liposomal AmB; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CAS, caspofungin; ONL, chronic myelogenous leukemia; CVC, central venous catheter; ICU, intensive care unit; MDS, myelodysplastic syndromes; MFG, micafungin; VRC, voriconazole; +, at onset.
strains have also been reported.\(^1\),\(^12\) Although not all of the strains were available for retesting with anidulafungin and micafungin, it is likely that these isolates also would show non-susceptible MICs of all echinocandins.\(^1\),\(^7\) We found only one \(C.\) \(g\)labrata isolate that was resistant to all antifungal drugs tested. The mechanism of resistance of some \(C.\) \(a\)lbidans isolates to antifungals belonging to different classes is not known.

The relationship between in vitro resistance and clinical outcome can be difficult to establish in medically complex patients who may be predisposed towards developing echinocandin-non-susceptible strains, as the patients frequently have medical reasons (i.e. undrained abscess, infected catheters or profound lymphopenia in AIDS patients) for recurrent infection.\(^1\),\(^7\),\(^9\) In the present study all patients responded to a change of antifungal therapy. Whether this favourable outcome reflects lack of virulence of these strains remains to be seen. However, early studies utilizing both laboratory-generated and clinically isolated strains of \(C.\) \(a\)lbidans with \(F\)KS-1-mediated resistance found that these isolates are frequently less virulent in animal models and have a reduced propensity for dissemination into deep tissue.\(^1\),\(^7\),\(^9\)

In conclusion, although limited by small numbers, this study provides additional information regarding the incidence, and clinical and microbiological features of cancer patients with caspofungin-non-susceptible candidiasis. Further surveillance should focus on the potential broader emergence of echinocandin resistance as the clinical use of this antifungal class continues to expand.

### References


### Table 2. Susceptibility\(^6\) test results of seven caspofungin-resistant \(C.\) \(a\)lbidans strains

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>AMB</th>
<th>FLU</th>
<th>VRC</th>
<th>ITC</th>
<th>POS</th>
<th>CAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C.) (g)labrata</td>
<td>16 R</td>
<td>256 R</td>
<td>16 R</td>
<td>16 R</td>
<td>8 R</td>
<td>8</td>
</tr>
<tr>
<td>(C.) (t)ropicalis</td>
<td>0.5 S</td>
<td>32 DD</td>
<td>2 R</td>
<td>1 R</td>
<td>8 S</td>
<td>1 S</td>
</tr>
<tr>
<td>(C.) (t)ropicalis</td>
<td>0.5 S</td>
<td>1 S</td>
<td>0.06 S</td>
<td>0.25 S</td>
<td>0.2 S</td>
<td>16</td>
</tr>
<tr>
<td>(C.) (a)lbidans</td>
<td>0.5 S</td>
<td>2 S</td>
<td>0.03 S</td>
<td>0.06 S</td>
<td>0.015 S</td>
<td>16</td>
</tr>
<tr>
<td>(C.) (g)labrata</td>
<td>0.5 S</td>
<td>128 R</td>
<td>2 R</td>
<td>1 R</td>
<td>8 S</td>
<td>16</td>
</tr>
<tr>
<td>(C.) (a)lbidans</td>
<td>1 S</td>
<td>1 S</td>
<td>0.03 S</td>
<td>0.06 S</td>
<td>0.03 S</td>
<td>8</td>
</tr>
<tr>
<td>(C.) (t)ropicalis</td>
<td>0.5 S</td>
<td>8 DD</td>
<td>0.25 S</td>
<td>0.5 DD</td>
<td>0.2 S</td>
<td>8</td>
</tr>
</tbody>
</table>

AMB, amphotericin B; FLU, fluconazole; VRC, voriconazole; ITC, itraconazole; POS, posaconazole; CAS, caspofungin; R, resistant; S, susceptible; DD, dose dependent.

\(^6\)CLSI broth microdilution method.

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