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ORIGINAL ARTICLE

**H. A. Torres**
**D. P. Kontoyiannis**
**K. V. I. Rolston**

# High-dose fluconazole therapy for cancer patients with solid tumors and candidemia: an observational, noncomparative retrospective study

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H. A. Torres · D. P. Kontoyiannis · K. V. I. Rolston (✉)
Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 402, Houston, TX, 77030, USA
e-mail: krolston@mdanderson.org
Tel.: +1-713-7926830
Fax: +1-713-7456839

**Abstract** *Background:* Response rates for candidemia treated with standard-dose fluconazole (400 mg/day) are approximately 70%. Higher doses of fluconazole have been recommended for susceptible dose-dependent *Candida* isolates. Herein, we describe the outcome of 20 patients with solid tumors and candidemia treated with high-dose fluconazole (HDF) at The University of Texas M.D. Anderson Cancer Center (1998–2002). *Patients and methods:* Patients were identified either by searching the microbiology laboratory database or through direct referral from primary oncology services to the Infectious Diseases Consultative Services. A retrospective review of cases was performed. HDF was defined as $\geq$600 mg/day. *Results:* Five patients were treated with 600 mg/day, whereas 15 patients received 800 mg/day. Only one patient was neutropenic. The median APACHE II score at the onset of candidemia was 12 (range 6–24). The most common species identified were *Candida albicans* (eight patients, 40%) and *Candida parapsilosis* (seven patients, 35%). Of 19 patients whose quantitative data were available, eight (42%) had high-grade candidemia [$\geq$200 colony forming units (CFU)/ml]. Fifteen (83%) of 18 isolates were fluconazole susceptible, and two (both *Candida glabrata*) were fluconazole resistant (MIC 64 each) in vitro. Nineteen patients (95%) responded to HDF therapy. The only HDF failure occurred in a patient with *C. glabrata* (MIC 64.0) infection. The other patient with *C. glabrata* (MIC 64.0) infection responded to HDF. Central venous catheters were removed from all patients with $\geq$10 CFU/ml candidemias. All patients with high-grade candidemias responded to HDF. The median duration of HDF therapy was 16 (range 6–42) days. No significant toxicity occurred. *Conclusions:* Although our data are limited, HDF appears to be well tolerated and may be associated with higher response rates than standard-dose fluconazole in a selected group of patients with solid tumors and candidemia caused by species that are susceptible to this triazole.

**Keywords** Candidemia · Fluconazole · Cancer

## Introduction

*Candida* species have emerged as major bloodstream pathogens in patients with solid tumors [3]. This common fungal infection is often associated with the sepsis syndrome and considerable attributable mortality [20]. Not only has the incidence of these infections increased, but also the distribution of *Candida* spp-causing infection has also changed, especially among patients with cancer [3]. Several randomized and observational studies have

demonstrated that fluconazole and amphotericin B are equally effective in patients without severe immunosuppression [13, 14, 15]. In a large, randomized study comparing fluconazole at a dose of 400 mg/day to amphotericin B at a dose of 0.5–0.6 mg/kg per day for the treatment of candidemia in patients without neutropenia, the response rate to fluconazole (70%) was not significantly different from that to amphotericin B (79%; $p$=0.22) [15]. With the emergence of non-*albicans* *Candida* species as frequent pathogens and the recognition of dose-dependent susceptibility to fluconazole among these isolates, high-dose fluconazole (HDF) (12 mg/kg per day, 800 mg/day in a 70-kg patient) has been recommended by some experts [16]. Data from observational studies indicate that HDF is well tolerated and may provide better clinical efficacy in selected patient populations [7]. On the basis of these data, we hypothesized that HDF therapy may be associated with increased clinical efficacy in bloodstream infections caused by all *Candida* species and may also be more beneficial than standard-dose therapy in patients with high-grade candidemia ($\geq$200 CFU/ml). Consequently, we modified our standard practice of treating solid-tumor patients with candidemia with standard-dose fluconazole to treating them with HDF. Herein, we describe a retrospective review of our experience with 20 patients with cancer and candidemia treated with HDF at The University of Texas M.D. Anderson Cancer Center.

## Patients and methods

### Patients

We identified all patients with candidemia from July 1998 through July 2002 either by reviewing the microbiology laboratory database or through direct referral from primary medical or surgical oncology services to the Infectious Diseases Consultative Services. Patients who were eligible for and willing to participate in ongoing investigative trials for candidemia were enrolled in such trials. Patients who were not eligible for or who were unwilling to participate in ongoing trials were offered HDF as monotherapy.

### Microbiology and antifungal susceptibility

*Candida* species in blood cultures were isolated and identified using standard microbiological procedures [19]. Susceptibility testing was performed on all but two *Candida* isolates. Breakpoints for susceptibility testing (for fluconazole and itraconazole) were derived from National Committee for Clinical Laboratory Standards recommendations for *Candida* isolates [12]. Amphotericin-B-resistant *Candida* isolates were defined as those with an amphotericin B minimal inhibitory concentration (MIC) >1 mg/L [3].

### Outcome

All patients were treated and followed by the Infectious Diseases Consultative Services. Response to treatment was defined as the resolution of clinical manifestations of candidemia and sterilization of the blood culture. Failure of treatment was defined as persistence of the clinical signs and symptoms of the infection and positive blood culture for *Candida* species.

### Definitions

Candidemia was defined according to the guidelines of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [4]. Catheter-related candidemia was defined as candidemia with no apparent source of infection other than the catheter plus isolation of the same *Candida* species from both peripheral blood and catheter-tip culture ($\geq$15 CFUs using the semiquantitative method), or candidemia with a quantitative blood culture collected through the central venous catheter (CVC) that had at least fivefold higher CFU/μl than a concurrent peripheral blood culture did [5, 10]. HDF was defined as $\geq$600 mg of fluconazole per day. High-grade, intermediate-grade, and low-grade candidemia do not have standard definitions; we defined them as $\geq$200CFU, 10–200 CFU, and $\leq$10 CFU/ml of blood, respectively.

## Results

### General characteristics

Twenty patients with solid tumors and candidemia were treated with HDF during the study period. General characteristics are depicted in Table 1. The most common underlying solid tumors were sarcoma (six patients, 30%) and melanoma (four patients, 20%). Only one patient had neutropenia [absolute neutrophil count (ANC) <500/mm$^3$] at the onset of candidemia, and three patients had received low-dose systemic fluconazole prior to the development of candidemia. All 20 patients had a CVC in place. The median APACHE II score at the onset of candidemia was 12 (range 6–24). Six (67%) of nine patients who had either cultures simultaneously collected through the CVC and from peripheral blood or collected from the peripheral blood and catheter tip had CVC-related candidemia.

### Microbiology and antifungal susceptibility

Microbiological data are shown in Table 1. The most common *Candida* species identified were *C. albicans* (40%) and *C. parapsilosis* (35%). In vitro susceptibility testing results were available for 18 of the 20 isolates (Table 2). Fifteen isolates (83%) were susceptible to fluconazole (MIC range 0.12–4.0 μg/ml), one isolate had dose-dependent susceptibility (*Candida lusitaniae*, MIC 32.0 μg/ml), and two isolates, both *C. glabrata*, were resistant (MIC 64.0 μg/ml each). Itraconazole susceptibilities mirrored those of fluconazole, except that two fluconazole-susceptible isolates had a dose-dependent susceptibility to itraconazole. All isolates were susceptible to amphotericin B, including the *C. lusitaniae* strain.

**Table 1** Patient characteristics of 20 solid-tumor patients with candidemia treated with high-dose fluconazole (HDF)

| Characteristic | No. (%) |
|---|---|
| Men/women | 13/7 |
| Median age, range (years) | 55, 37–80 |
| Underlying solid tumor | |
| Sarcoma | 6 (30) |
| Melanoma | 4 (20) |
| Gynecologic malignancy | 3 (15) |
| Gastrointestinal malignancy | 2 (10) |
| Other [a] | 5 (25) |
| Neutropenia at onset of candidemia | 1(5) |
| Central venous catheter in place | 20 (100) |
| Comorbidities [b] | 3 (15) |
| Median APACHE II score at onset of candidemia, range | 12 (6–24) |
| *Candida* species distribution | |
| *C. albicans* | 8 (40) |
| *C. parapsilosis* | 7 (35) |
| *C. glabrata* | 2 (10) |
| *Other* [c] | 3 (15) |
| Quantitative data [d] | |
| Low-grade candidemia | 5 (26) |
| Intermediate-grade candidemia | 6 (32) |
| High-grade candidemia | 8 (42) |
| Response to high-dose fluconazole | 19 (95) |

[a] Included one patient each with lung, prostate, renal, and peritoneal carcinomas, and mesothelioma
[b] Renal failure in three patients
[c] *C. guillermondii, C. lusitaniae,* and *C. tropicalis* in one patient each
[d] Of 19 patients with information available

Quantitative culture results ranged from 1 to more than 1,000 CFU (Table 3).

## Clinical response

Of the 20 patients, 15 (75%) received 800 mg/day fluconazole, whereas five (25%) were treated with 600 mg daily. Nineteen patients (95%) responded to HDF therapy, including all patients who had high-grade candidemia (Table 3). The median duration of HDF therapy was 16 (range 6–42) days. The only HDF failure occurred in a patient with non-CVC–related *C. glabrata* infection caused by a fluconazole-resistant strain (MIC 64.0 $\mu$g/ml); this patient had persistent fever, an APACHE II score of 24, and candidemia while on 600 mg/day of fluconazole. When the organism and its susceptibility data became available, this patient's therapy was switched to liposomal amphotericin B, with a subsequent complete response. This patient had intermediate-grade candidemia. Of note, the other patient with candidemia caused by a fluconazole-resistant strain of *C. glabrata* (MIC 64.0 $\mu$g/ml) had clinical and microbiological response to 800 mg/day of fluconazole. This patient had low-grade candidemia. The CVCs were removed from all patients who had $\geq$10 CFU/ml candidemia. No significant toxicity was documented.

**Table 2** Antifungal susceptibility of *Candida* isolates stratified by species ($n$=18)

| Isolate no. | Organism | Minimal inhibitory concentration | | |
|---|---|---|---|---|
| | | Fluconazole[a] | Itraconazole[a] | Amphotericin B[b] |
| 1 | C. *albicans* | 0.5 | 0.06 | 0.5 |
| 2 | *C. albicans* | 1.0 | 0.12 | 1.0 |
| 3 | *C. albicans* | 2.0 | 0.25 | 1.0 |
| 4 | *C. albicans* | 1.0 | 0.12 | 1.0 |
| 5 | *C. albicans* | 0.5 | 0.03 | 1.0 |
| 6 | *C. albicans* | 1 | 0.06 | 0.25 |
| 7 | *C. albicans* | 0.5 | 0.12 | 1.0 |
| 8 | *C. parapsilosis* | 0.5 | 0.06 | 1.0 |
| 9 | *C. parapsilosis* | 0.5 | 0.06 | 1.0 |
| 10 | *C. parapsilosis* | 1.0 | 0.25 | 0.5 |
| 11 | *C. parapsilosis* | 1.0 | 0.12 | 1.0 |
| 12 | *C. parapsilosis* | 0.5 | 0.12 | 1.0 |
| 13 | *C. parapsilosis* | 0.12 | 0.06 | 0.03 |
| 14 | *C. guillermondii* | 4.0 | 0.05 | 1.0 |
| 15 | *C. lusitaniae* | 32.0 | 0.25 | 0.5 |
| 16 | *C. tropicalis* | 1.0 | 0.12 | 2.0 |
| 17 | *C. glabrata* | 64.0 | 8.0 | 1.0 |
| 18 | *C. glabrata* | 64.0 | 4.0 | 1.0 |

[a] Susceptibility breakpoints (micrograms per milliliter): fluconazole $\leq$8 (susceptible), 16–32 (susceptible dose dependent), $\geq$64 (resistant); itraconazole $\leq$0.125 (susceptible), 0.25–0.5 (susceptible dose dependent), $\geq$1 (resistant)
[b] Susceptibility breakpoints have not been formally proposed by the National Committee for Clinical Laboratory Standards (NCCLS). Provisional breakpoint >1 mg/l (resistant)

**Table 3** Overall response rates of 20 solid-tumor patients with candidemia treated with high-dose fluconazole (HDF)

| Organism | Colony count (CFU/ml) | Fluconazole MIC[a] ($\mu$g/ml) | Fluconazole dose (mg/day) | Outcome |
|---|---|---|---|---|
| *C. albicans* | 3 | 1.0 | 800 | Response |
| *C. albicans* | 31–50 | 0.5 | 800 | Response |
| *C. albicans* | 51–100 | NA | 800 | Response |
| *C. albicans* | 201–500 | 2.0 | 600 | Response |
| *C. albicans* | 201–500 | 1.0 | 800 | Response |
| *C. albicans* | 201–500 | 0.5 | 800 | Response |
| *C. albicans* | 16–20 | 1 | 800 | Response |
| *C. albicans* | >1000 | 0.5 | 800 | Response |
| *C. parapsilosis* | >1000 | NA | 800 | Response |
| *C. parapsilosis* | 501–1000 | 1.0 | 800 | Response |
| *C. parapsilosis* | 501–1000 | 0.12 | 800 | Response |
| *C. parapsilosis* | 51–100 | 1.0 | 600 | Response |
| *C. parapsilosis* | 11–20 | 0.5 | 800 | Response |
| *C. parapsilosis* | 1 | 0.5 | 600 | Response |
| *C. parapsilosis* | NA | 0.5 | 600 | Response |
| *C. guillermondii* | 501–1000 | 4.0 | 800 | Response |
| *C. lusitaniae* | 1 | 32.0 | 800 | Response |
| *C. tropicalis* | 1 | 1.0 | 800 | Response |
| *C. glabrata* | 1 | 64.0 | 800 | Response |
| *C. glabrata* | 51–100 | 64.0 | 600 | Failure |

Abbreviations: *CFU* colony-forming units, *MIC* minimal inhibitory concentration, *NA* not available
[a] Susceptibility breakpoints (micrograms per milliliter): fluconazole $\leq$8 (susceptible), 16–32 (susceptible dose dependent), $\geq$64 (resistant); itraconazole $\leq$0.125 (susceptible), 0.25–0.5 (susceptible dose dependent), $\geq$1 (resistant)

## Discussion

Recent data from our institution showed that clinicians still prefer amphotericin B over fluconazole in patients with cancer who have candidemia, especially those with risk factors for a poor outcome [3]. However, published reports have failed to detect any differences in outcome between cancer patients with candidemia who are treated with amphotericin B and those who are treated with fluconazole [1, 2]. A randomized study has shown that fluconazole at a dose of approximately 6 mg/kg per day (400 mg/day in a 70-kg patient) is as effective for the treatment of candidemia in nonneutropenic patients as amphotericin B at 0.5–0.6 mg/kg per day but is associated with much less toxicity [15].

The availability of the standardized methodology for the susceptibility testing of *Candida* [12] provides additional information that may be useful in determining empiric therapy in cancer patients with candidemia [3]. Nowadays, the majority of *Candida* isolates obtained from the bloodstream in patients with cancer are either susceptible (MIC $\leq$8.0 $\mu$g/ml) or susceptible dose-dependent (MIC 16–32 $\mu$g/ml) to fluconazole [3]. HDF (12 mg/kg per day or 800 mg/day in a 70-kg patient) is a safe and effective option for the treatment of patients with susceptible dose-dependent *Candida* species [9], especially in less critically ill patients with cancer [8, 16].

Although our experience with HDF therapy is limited to 20 patients, it does suggest that the response rate might be substantially greater (>90%) if this dose is used for all *Candida* bloodstream infections in our selected group of solid-tumor patients. In the current series, the response rate to HDF was higher than the 56% recently reported in a larger study evaluating patients on HDF [17], but comparisons are limited between both studies. Of note, the low response rate reported by Rex et al. using HDF [17] is even lower than the response rate of 70% previously described by the same group using standard-dose fluconazole [15]. The authors did not give an explanation for such dissimilarity. Also, the combination of HDF and amphotericin B appeared to be better than HDF alone in a recent study [17]. However, it is well known that multiple factors influence outcome of patients with candidemia, especially in the setting of immunosuppression [3]. For example, differences in patient population, comorbidities for infection, APACHE II score, and a predominance of *Candida* isolates susceptible to fluconazole preclude comparisons between such reports. Some of these factors could have accounted for dissimilar response rates.

In our series, HDF was well tolerated, consistent with previous reports [17]. Of concern is the emergence of resistance among *C. glabrata* isolates. Although occasional responses might be seen (as in one of our patients), infections caused by *C. glabrata,* like those caused by *C. krusei*, should probably not be treated by the older triazoles (fluconazole and itraconazole), especially since polyenes and/or echinocandins (e.g., caspofungin, micafungin) might offer better therapeutic options [6, 11]. The favorable activity of echinocandins against *Candida* spp, and its good clinical results. imply that these antifungal drugs will become the treatment of choice for candidemia

[6]. However, poor absorption after oral administration limits use to the intravenous route. Therefore, fluconazole may still have a role for the treatment of candidemia, especially if long-term antifungal therapy using oral administration is required.

Few institutions routinely perform quantitative blood cultures, and no clear guidelines defining high-, intermediate-, or low-grade candidemia have been established [18]. Although a clinical impression exists that high-grade infections might be associated with response rates that are lower than those seen with low-grade infections, no published studies address this issue. Using our own arbitrary definitions based on experience with bacterial infections, our limited data do suggest that HDF is as effective for the treatment of high-grade candidemia as it is for low-grade infection. Larger studies to confirm this observation are needed.

Because our study is limited by its observational, noncomparative nature and small sample size, our data should be considered preliminary. In addition, patients evaluated in our study were those not eligible for, or unwilling to participate in ongoing trials for candidemia. This may represent a potential selection bias. Moreover, our antifungal therapy response data should be viewed with caution, since we studied a selected group of solid-tumor patients who were not critically ill, as reflected by a median APACHE II score of 12. Further studies examining the relationship between in vitro susceptibility/resistance and outcome are warranted. In addition, the management of CVCs remains an important confounder for evaluation of outcome in patients with candidemia [3]. We were unable to identify all cases of CVC-related candidemia, because only a small subset of patients (45%) had either simultaneous blood cultures collected through the CVC and peripheral blood, or both peripheral blood and catheter-tip cultures. Previous reports suggest that CVC removal is associated with better outcome in patients with cancer and CVC-related candidemia [3].

## Conclusions

Our experience suggests that HDF therapy is well tolerated and might be associated with higher response rates for the treatment of *Candida* bloodstream infections than standard-dose fluconazole in a selected group of cancer patients with candidemia caused by species susceptible to this triazole. Infections caused by *C. glabrata* should probably be treated with other antifungal agents (polyenes or echinocandins), since they have more reliable activity against these organisms.

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