Early initiation of appropriate treatment is associated with increased survival in cancer patients with *Candida glabrata* fungaemia: a potential benefit from infectious disease consultation

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Abstract

In patients with malignancies, *Candida glabrata* is one of the most frequent non-*albicans Candida* clinical isolates. As antifungal resistance in *C. glabrata* is common, we investigated the relationship between early appropriate antifungal treatment, infectious disease (ID) consultation and mortality in a contemporary cohort of cancer patients with *C. glabrata* fungaemia. We included patients with at least one *C. glabrata*-positive blood culture and symptoms or signs of infection seen at the MD Anderson Cancer Center between March 2005 and September 2013. *In vitro* susceptibility to antifungals was defined according to the 2010 CLSI clinical breakpoints. One-hundred and forty-six episodes of candidaemia were studied. Thirty isolates (20.5%) had fluconazole MIC $\geq$ 64 mg/L and 15 (10.3%) were caspofungin-resistant. Early (within 48 h after blood culture collection) initiation of appropriate antifungal treatment (hazard ratio 0.374, p 0.003) and early ID consultation (hazard ratio 0.421, p 0.004) were associated with decreased mortality, after adjustment for significant confounders. Thirty-two of 58 patients (55.2%) followed by ID were on appropriate antifungals within 48 h, compared with 16/88 patients (18.2%) who were not followed by ID an ID specialist (p <0.001). The median time-to-reporting of blood culture positivity for yeast was 71 h. Delayed time-to-reporting was associated with increased 28-day all-cause mortality (log-rank p 0.023). The benefits from early initiation of appropriate antifungal treatment and ID consultation were more prominent in patients with non-catheter-related candidaemia. In conclusion, in cancer patients with *C. glabrata* fungaemia, early ID consultation may lead to timely initiation of appropriate treatment and improved clinical outcomes.

Keywords: Antifungal resistance, cancer, *Candida glabrata*, candidaemia, infectious disease consultation
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Introduction

In patients with cancer, the widespread use of antifungals in the setting of prophylaxis and pre-emptive or empiric treatment protocols has led to a notable shift from *albicans* to non-*albicans Candida* species [1–4]. *Candida glabrata* is among the most frequent species isolated from patients with malignancies, and the main species exhibiting multiazole, echinocandin and multidrug resistance (MDR; resistance to at least two classes of antifungals) [5,6].

Previous studies of candidaemia showed that early administration of fluconazole improved survival rates [7,8]. Adherence to national guidelines and infectious disease (ID) consultation led to a significant decrease in mortality rates [9,10]. Nevertheless, the relationship between early appropriate antifungal treatment and clinical success is not clear in the current era of high prevalence of resistance, especially in immunocompromised

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hosts: some recent studies showed improved outcomes with early initiation of appropriate treatment [11–14], whereas others did not [15–18].

As cancer patients with *C. glabrata* bloodstream infections often have multiple risk factors for treatment failure and adverse outcomes [2,4,5,19], it is important to identify interventions associated with increased survival, independent of host factors and source control. Therefore, we sought to investigate the correlation of clinical outcomes with early initiation of appropriate treatment and ID consultation, in a contemporary cohort of cancer patients with *C. glabrata* fungaemia.

Patients and methods

Data collection

We included patients with at least one blood culture(s) positive for *C. glabrata*, in addition to symptoms, signs (fever, hypothermia, tachycardia, hypotension or altered mental status) and/or laboratory findings (leucocytosis or leucopenia, thrombocytopenia or acidosis) consistent with infection, seen at MD Anderson Cancer Center between March 2005 and September 2013. We retrospectively reviewed electronic medical records for clinical and laboratory data on the day of blood culture collection, treatment, ID consultation, 28-day mortality and in-hospital all-cause mortality. Speciation of *C. glabrata* and antifungal susceptibility testing were performed as previously described (see Supporting information) [2–4,20,21]. The study was approved by the Institutional Review Board.

Definitions

Catheter-related candidaemia was defined as a patient with a colony count in a blood culture obtained via a central venous catheter (CVC) at least fivefold greater than the colony count in a peripheral blood culture, or a case with positive catheter tip culture [2,22].

Appropriate treatment was defined as amphotericin B for susceptible isolates, an echinocandin for isolates with caspofungin MIC <0.5 mg/L, or 800 mg of fluconazole daily for isolates with fluconazole MIC <64 mg/L (dose-dependent) [1,11,23]. Given the suboptimal responses of serious *C. glabrata* infections to azoles and the lack of clinical breakpoints for voriconazole, voriconazole was considered appropriate treatment only for fluconazole dose-dependent isolates with MIC <1 mg/L (one dilution above the epidemiological breakpoint) [21,23]. ID consultation within 48 h after blood culture collection referred to both the initial consultation and patients who were already followed by ID an ID specialist.

Statistical analysis

Normality of distribution was tested with the Kolmogorov–Smirnoff test. Continuous variables were compared with Student's *t*-test or the Mann–Whitney *U*-criterion for variables that were not normally distributed. Categorical variables were compared using the chi-square or Fisher exact test (expected frequency <5). We identified early interventions as those that occurred within 48 h after blood culture collection, and repeated all survival analyses after excluding patients who died within that time period.

Time-to-event survival analyses have been widely implemented in studies of candidaemia [11,24] as they allow more power to unmask potential physiological benefits [25], given the complex patient populations and frequent small sample sizes. However, in the critically ill, it has been argued that logistic regression using a dichotomous outcome is more appropriate, because for patients who die in the hospital, a prolonged stay does not reflect actual benefit [25]. Therefore, we addressed two outcome measures: a) 28-day survival analysed by the log-rank test and Cox regression, and b) all-cause in-hospital mortality rates, compared by binary logistic regression. The proportional hazards assumption was tested graphically and by building time-dependent variables. Numerical parameters were tested in different models both as scale and dichotomous variables (greater than versus less than the mean and/or widely used cut-off values of clinical significance). Clinically relevant parameters (univariate $p < 0.2$) were included at model entry. Appropriate treatment and ID consultation were forced separately in all multivariate analyses. Variables were retained in the final model if the p value was <0.05.

All analyses were performed with SPSS statistical software, version 21, IBM Corporation (Armonk, NY, USA). Two-tailed p values <0.05 were considered statistically significant. Values of $p > 0.05$ but <0.1 were noted as indicating trends.

Results

Patient population and *in vitro* susceptibilities

We identified 146 episodes of *C. glabrata* fungaemia. The demographic, clinical and laboratory characteristics of all patients are listed in Table 1. Thirty isolates (21%) had fluconazole MIC ≥64 mg/L. Twenty-four isolates (16%) were intermediate and 15 (10.3%) were resistant to caspofungin. Ten of 15 caspofungin-resistant isolates (67%) met the definition for MDR [6]: nine had fluconazole MIC ≥64 mg/L and one was resistant to amphotericin B. Antifungal MIC distributions are summarized in the Supporting information, Fig. S1.

Factors associated with all-cause mortality

The 28-day all-cause mortality rate was 40% (58/146), and the in-hospital mortality rate was 46.6% (68/146). Factors