MAJOR ARTICLE

Risk Factors and Predictors of Outcome in Patients with Cancer and Breakthrough Candidemia

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Hematogenous candidiasis adds substantially to the morbidity and mortality rates of patients with cancer. Little is known about the risk factors and outcome in patients with breakthrough (BT) candidemia while on systemic antifungal therapy. All 479 episodes of candidemia in 474 consecutive patients with candidemia that was diagnosed at M. D. Anderson Cancer Center from 1988 through 1992 were studied retrospectively. A total of 49 patients had BT candidemia, defined as candidemia that developed after at least 5 days of systemic antifungal therapy. Risk factors for BT candidemia and predictors of mortality were investigated. Multivariate analysis revealed that intensive care unit stay, neutropenia, use of corticosteroids, and duration of neutropenia as significant risk factors for BT candidemia. Seventy-six percent of patients with BT candidemia died, compared with 50% of patients with non-BT infection. In multivariate analysis, intensive care unit stay, being and remaining neutropenic, APACHE III score, and disseminated disease were independent prognostic factors. In conclusion, identification of risk factors and predictors of a poor outcome in patients with cancer with BT candidemia may have important implications in early diagnosis and appropriate therapy of these patients.

Candidemia is the fourth most common cause of nosocomial bloodstream infection in the United States [1]. This infection adds substantially to the morbidity and mortality rates of seriously ill patients and represents an independent factor for predicting risk of death and prolonged hospital stay [2]. Candidemia that develops during systemic antifungal therapy (breakthrough, or BT, candidemia) may differ from other forms of candidemia. Although several studies have described the demographic characteristics and risk factors in patients with BT candidemia [3–10], there are limited data for patients with cancer, particularly those with neutropenia. Superinfection with resistant *Candida* strains [6], inadequate serum levels of the antifungal agent [9], and catheter-related infection [11] have all been implicated as causes of BT candidemia. Much less is known about the factors that affect the outcome in this patient population.

To identify risk factors for BT candidemia and assess the related outcomes, we analyzed a consecutive series of patients with cancer hospitalized at M. D. Anderson Cancer Center (Houston) during a 5-year period.

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PATIENTS AND METHODS

Cases of candidemia diagnosed antemortem at the University of Texas M. D. Anderson Cancer Center from 1 January 1988 through 31 December 1992 were identified through microbiology reports. Data on age, sex, underlying condition (bone marrow transplantation, leukemia, lymphoma, myeloma, or solid tumor), status of the underlying disease (new diagnosis or relapse, or remission), patient location at the onset of infection (medical, surgical, or intensive care unit [ICU]), evidence for visceral dissemination of the *Candida* bloodstream infection, and timing and nature of antifungal therapy were abstracted from patient charts.

Severity of illness was estimated by the Simplified Acute Physiology Score (SAPS) [12], the APACHE III score [13] and the presence of shock at presentation. Microbiological data included the infecting *Candida* species, and the results of fungal cultures of catheter tips and other sites. Because of their potential relevance as causes of immunosuppression in general and risk for invasive fungal infection in particular [2], the following were assessed as risk factors: concomitant infection, broad-spectrum antibacterial therapy within the previous 2 weeks, treatment with the equivalent of >20 mg prednisone per day for >30 days or with a cumulative dose of 700 mg in the previous 30 days, abdominal surgery within the previous 60 days, or use of iv hyperalimentation or cytotoxic chemotherapy within the previous 30 days. Additional data included the presence of pneumonia, presence and management of catheters, and neutropenia (defined as <1000 neutrophils/mm^3).

Epidemiological and outcome data on this group have already been reported [14, 15]. We now describe the subset of patients with BT candidemia and the results of the univariate and multivariate comparisons between patients with BT and with non-BT candidemia.

Definitions. Candidemia was defined as the isolation of any *Candida* species from ⩾1 blood cultures from a patient who displayed signs and symptoms of infection. BT candidemia was diagnosed if the patient had received systemic antifungal therapy for any reason ⩾5 days before the first positive (index) blood culture. Hematogenous dissemination was diagnosed if multiple noncontiguous nonmucosal sites were infected. Pneumonia that developed within 1 week of a blood culture positive for *Candida* was judged as due to *Candida* if no other cause for the pneumonia was detected after suitable diagnostic tests had been performed.

Candidemia was considered to be definitely catheter related if quantitative roll-plate cultures of the catheter tip yielded at least 15 cfu of the same *Candida* species that was isolated from the bloodstream or if the colony count of the *Candida* organisms isolated from blood drawn through a catheter was ⩾10-fold greater than the count from culture of a simultaneously collected peripheral venous blood. An infection was considered possibly catheter related if it occurred in a patient with an intravascular line in place and no other origin for infection.

The infectious episode was considered to start the day of the first positive blood culture result and to end when infection at all proven or presumed sites had resolved and antifungal therapy had been discontinued. Unless otherwise noted, the term "infection" refers to the episode of candidemia under study.

Statistical analysis. Fisher's exact test and χ^2 test were used for categorical variables. Student's t test was used for continuous variables. Multivariate logistic regression analyses were performed to identify independent predictors of BT candidemia. Variables that were significant at the $P \leqslant .25$ level were selected by means of backward stepwise elimination. The possible explanatory variables of outcome in the subset of patients with BT candidemia were evaluated by the same method of multivariate analyses. Statistical analyses were performed with SPSS for Windows, version 7.0.1 (SPSS).

RESULTS

During the study period, a total of 491 episodes of candidemia occurred at M. D. Anderson Cancer Center. Adequate information was available on 479 episodes in 474 patients. Five patients had 2 separate episodes of candidemia. The characteristics of these patients are described twice, once for each episode. Forty-nine patients met the criteria for infection with BT candidemia.

Patient characteristics. The general characteristics of the patients with BT and non-BT candidemia are shown in table 1. Patients with leukemia and patients who had undergone bone marrow transplants experienced more BT candidemia episodes. More patients with BT candidemia were hospitalized on medical floors than surgery and in ICUs. The BT group was more acutely ill at the time of presentation with candidemia, as estimated by both the SAPS and APACHE III scores. Shock at presentation was observed in a similar frequency in both groups; however, disseminated disease and pneumonia were more common in patients with BT candidemia.

In the BT group, 30 patients received amphotericin B (AmB) deoxycholate at least 5 days before the first blood culture positive for *Candida.* The median daily dose of AmB given before candidemia was 0.6 mg/kg of body weight (range, 0.15–1.0 mg/kg), and the median duration of AmB therapy was 13.5 days (range, 6–98 days). Of 49 BT patients, 15 had received fluconazole before the index blood culture. The median daily dosage of fluconazole was 400 mg (range, 400–800 mg) and the median duration of fluconazole therapy was 12 days (range, 7–31 days). The demographic features of patients receiving AmB who developed candidemia were similar to those receiving fluconazole except that the fluconazole-treated group more often had lymphoma or multiple myeloma as the underlying disease (40%

Table 1. Demographic and clinical characteristics of patients with breakthrough and non-breakthrough candidemia.

Characteristic	Candidemia		*P*
	Breakthrough	Nonbreakthrough	
No. of patients	49	430	
Age, y	46 ± 17	51 ± 17	.55
Male	29 (59)	247 (57)	.81
Underlying disease			
Leukemia	34 (69)	125 (29)	<.0001
Lymphoma/myeloma	9 (18)	62 (14)	.46
Solid tumor	6 (12)	243 (57)	<.0001
Underlying disease status			
New/relapsed	45 (92)	380 (88)	.47
In remission	4 (8)	50 (12)	
BMT within previous year	12 (26)	41 (10)	.001
Intensive patient care			
ICU	17 (35)	85 (20)	.016
Non-ICU	32 (65)	345 (80)	
Location			
Medical unit	47 (96)	315 (73)	.0005
Surgical unit	2 (4)	115 (27)	
Disease severity score			
SAPS	12 ± 4	10 ± 5	.005
APACHE III	65 ± 25	51 ± 23	<.0001
Shock at presentation	3 (6)	29 (7)	.87
Disseminated disease at presentation	26 (53)	151 (35)	.0137
Pneumonia at presentation	26 (53)	114 (27)	.0001

NOTE. Results are shown as no. (%) or mean ± SE, along with the *P* value for the comparison of the patients with breakthrough and with nonbreakthrough candidemia in univariate tests. BMT, bone marrow transplantation; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score [16].

vs. 10%, $P = .015$). The remaining 3 patients had received AmB and fluconazole in combination, and 1 patient had received a lipid formulation of AmB.

Risk factors. By means of univariate analysis, we found that more patients had neutropenia, and the duration of neutropenia was significantly longer in BT candidemia episodes than in non-BT candidemia episodes (table 2). Previous exposure to broad-spectrum antibiotics, corticosteroids, or cytotoxic chemotherapy, or abdominal surgery was more common in patients with BT candidemia. Neither definite nor possible catheter-related candidemia were associated with BT candidemia ($P = .2$).

The risk factors of patients with BT candidemia who were receiving AmB were similar to those of patients receiving fluconazole except for a longer duration of neutropenia in the former group (median, 21 days vs. 10 days, respectively; $P = .034$).

Logistic regression was performed on the 479 episodes with complete data. Age, sex, and factors that had $P < .25$ in univariate analysis were evaluated. Presence of neutropenia at the time of first blood culture positive for *Candida* species (OR, 5.35; 95% CI, 2.01–14.23; $P < .001$), being in an ICU during the first positive blood culture (OR, 2.6; 95% CI, 1.28–5.29; $P = .008$), duration of neutropenia before index blood culture (OR, 1.02; 95% CI, 1.00–1.04; $P = .01$), and previous corticosteroid use (OR, 2.5; 95% CI, 1.23-5.15; $P = .01$) were found to be significant independent risk factors for BT infection.

Microbiology. More than one *Candida* species was isolated in 10% of BT episodes compared with 3.5% of non-BT episodes ($P = .026$) (table 3). *Candida glabrata* was the most common infecting *Candida* species in the BT group, whereas *Candida albicans* caused 45% of the non-BT candidemia episodes. *Candida krusei* was also more common in the BT group. Although it was not statistically significant, more candidemias were caused by *C. glabrata* (40% vs. 16%, $P = .075$) and *C. krusei* (27% vs. 7%, $P = .056$) in patients who developed BT infection on fluconazole when compared with those on AmB.

Outcome. The mortality rate at 3 months after the first

Table 2. Risk factors for candidemia in patients with breakthrough and nonbreakthrough candidemia.

Risk factor	Candidemia		*P*
	Breakthrough (*n* = 49)	Nonbreakthrough (*n* = 430)	
Broad-spectrum antibiotics in previous 2 weeks	48 (98)	356 (82)	.006
Corticosteroids in previous 30 days	33 (67)	150 (35)	<.0001
Chemotherapy in previous 30 days	44 (90)	298 (69)	.0026
Abdominal surgery in previous 60 days	2 (4)	80 (19)	.01
Intravenous hyperalimentation within previous 30 days	25 (51)	193 (45)	.41
Concomitant infection within previous week	36 (73)	260 (60)	.076
CVC in place at time of positive blood culture	44 (90)	378 (88)	.70
Neutropenia	43 (88)	175 (41)	<.0001
Duration of neutropenia, median d, mean d, (range)	18, 22 (0–95)	0, 6 (0–174)	<.0001
Colonization with the same *Candida* species	15 (31)	143 (33)	.71

NOTE. Data are no. (%) of patients, unless otherwise indicated. CVC, central venous catheter.

index positive blood culture was 75.5% (37 out of 49 patients) in the BT group compared with 49.5% (211 out of 426 patients) in the non-BT group. However, death due to *Candida* infection was not significantly different in 2 groups (63% vs. 70%).

In a univariate analysis of risk factors for death at 3 months after the index positive blood culture, being in an ICU ($P = .026$), severity of disease as evaluated by SAPS ($P = .002$) and APACHE III scores ($P = .025$), disseminated disease ($P = .025$), persistent neutropenia ($P = .002$), and the length of neutropenia ($P = .028$) were all found to be statistically significant. In analyses of the BT cases alone, APACHE III score was the only independent predictor of mortality ($P = .02$).

In a logistic regression analysis of risk factors for death, risk factors identified as predicting BT candidemia were also included. The diagnosis of BT candidemia was also included as a risk factor in this analysis to see if it actually affected the mortality rate when adjusted for other risk factors. This analysis showed that APACHE III (OR, 1.12; 95% CI, 1.02–1.05; $P < .001$), ICU stay (OR, 4.54; 95% CI, 1.88–7.23; $P < .001$), persistent neutropenia (OR, 10.53; 95% CI, 4.32–25.85; $P < .001$), and disseminated disease (OR, 2.63; 95% CI, 1.50–4.34; $P < .001$), but not BT candidemia ($P = .36$), were associated with increased mortality rates. Catheter removal or exchange over a guidewire within 2 days of the first positive blood culture was not significant in any analysis.

DISCUSSION

Candidemia that develops in patients while they are receiving systemic antifungal therapy has been described in several reports, but most of these studies either had a small sample size (range, 3–20 patients) [3, 5, 6, 8], or reported limited data on patients with BT candidemia in a whole group of candidemic or fungemic patients [4, 7, 10, 17, 18]. The presence of a hematological malignancy, longer duration of neutropenia, and central venous catheter have been implicated as potential risk factors descriptively or in univariate analyses. Predictors of outcome have not been studied.

In this report, we present a detailed analysis of risk factors and mortality rates in 49 patients with cancer who had BT candidemia. We compared the presence of risk factors and predictors of mortality in BT and non-BT candidemia cases. In logistic regression analysis, ICU stay, presence and longer duration of neutropenia, and corticosteroid treatment in the previous 2 weeks were associated with an increased risk for BT infection.

Our study has several limitations. First, we do not have data to evaluate the impact of in vitro susceptibility on BT candidemia. Although more-resistant isolates have been implicated as a cause of BT candidemia [4, 6, 17], this has not been described in other studies. We observed a trend toward more frequent BT among patients infected with such relatively azole-resistant species as *C. glabrata* and *C. krusei.* Our analysis of the entire group of patients with candidemia (not just the patients with BT candidemia) suggested a role for azoles in this shift [14], but the choice of antifungal agent did not emerge as a relevant factor in the smaller number of BT cases. Second, we tried to describe the risk factors for BT candidemia by comparing these patients to patients with non-BT candidemia. This approach may have led to underestimation of some risk factors. Ideally, risk factors should be assessed in a prospective or retrospective cohort study that includes all patients with cancer who receive systemic antifungal therapy or prophylaxis.

It has been suggested that the presence of a central venous catheter is a risk factor for BT candidemia [3, 5, 11]. It is well known that *Candida* species have surface receptors to adhere

Table 3. Infecting *Candida* species in breakthrough and nonbreakthrough candidemia.

Candida species	Candidemia	
	Breakthrough (n = 49)	Nonbreakthrough (n = 430)
C. albicans	10 (20)	192 (45)
C. tropicalis	3 (6.1)	82 (19)
C. glabrata	12 (24.5)	41 (9.5)
C. parapsilosis	10 (20.4)	74 (17.2)
C. krusei	7 (14.3)	13 (3)
C. lusitaniae	1 (2)	7 (1.6)
C. guilliermondii	0	3 (0.7)
Candida species (unspecified)	1 (2)	3 (0.7)
Mixed species	5 (10.2)	15 (3.5)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

to the thrombin biofilm. When a catheter becomes colonized during systemic antifungal therapy, *Candida* may survive in the relatively protected environment of the adherent biofilm [11]. In our series, we were unable to detect any difference in the frequencies of definite or possible catheter-related infection between patients with BT and those with non-BT candidemia.

Having BT candidemia alone did not affect the mortality rate in multivariate analysis; however, ICU stay, presence and longer duration of neutropenia, disseminated disease, and severity of illness (APACHE III score) were independent predictors of death. This finding again describes an acutely ill patient and suggests that host factors are the most important predictors of outcome.

The effect of catheter removal in the management of BT candidemia is unknown. In only 1 study was a favorable outcome reported in patients with BT candidemia after removal of the indwelling intravascular catheters and additional systemic antifungal therapy [4]. We failed to show that even an early full (or guidewire) removal within 2 days after the first positive blood culture had any effect on the survival of patients with cancer who had BT candidemia. Catheter removal or full exchange had only limited influence on the outcome in 479 episodes of candidemia [15]. Our findings should, however, be viewed with caution because of the retrospective nature of the study.

In conclusion, we found that 37 (75.5%) of 49 patients with cancer who had BT candidemia had died. Host factors such as the presence and longer duration of neutropenia and more severe illness were associated with an increased risk for both BT candidemia and for death. A prospective cohort study should be designed to address some issues, including the role of the central venous catheter and susceptibility of the infecting *Candida* organism to the particular antifungal used, and the impact of catheter removal on the outcome.

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