Risk Factors for Death Among Cancer Patients with Fungemia


In order to identify prognostic factors for death among cancer patients with fungemia, an 18-month survey of fungemia in patients with cancer was undertaken in three hospitals in Rio de Janeiro. For the assessment of risk factors for death, the following variables were analyzed: age; gender; underlying cancer; last treatment for the underlying disease; previous surgery; use of antibiotics, antifungal agents, steroids, or total parenteral nutrition; use of a central venous catheter; chemotherapy; radiotherapy; presence and duration of neutropenia; etiologic agent of the fungemia; treatment of the fungemia; clinical manifestations; and performance status (Karnofsky score) on the day of the positive blood culture. In multivariate analysis, the variables associated with an increased risk for death were older age, persistent neutropenia, and low performance status. Identifying risk factors for death may help to define a group of high-risk patients for whom new therapeutic options should be tried.

Fungal infections represent a major challenge for those who care for patients with cancer. The frequency of fungal infections has increased substantially in the past decade [1], and many risk factors have been identified, including the use of antibiotics, central venous catheterization, neutropenia, and the use of more aggressive chemotherapy [2]. The mortality associated with systemic fungal infections is high. The mortality attributable to candidemia in hospitalized patients, including those without cancer, was 38% in a case-control study [3]. Among cancer patients, the crude mortality exceeds 70% [4].

Despite the high mortality, few studies have evaluated possible factors predictive of death among cancer patients with fungal infections. In 1994 we started a survey on fungemia in cancer patients in three hospitals in Rio de Janeiro, Brazil. The main objective of this survey was to obtain epidemiological data on fungemia in cancer patients in a developing country, since little information was available. In this article we discuss the influence of several clinical variables on the outcome for cancer patients with fungemia and identify prognostic factors.

Patients and Methods

In 1994 we started a survey on fungemia in cancer patients in three hospitals in Rio de Janeiro: two university hospitals with ~500 beds each and a 220-bed referring hospital for cancer patients. Two of these hospitals have bone marrow transplant units, with a total of 12 beds. The cases of fungemia were identified on the basis of positive blood cultures from the mycology laboratories of the hospitals. The blood cultures were ordered at the discretion of the attending physician. HIV-positive patients were excluded. A positive blood culture was defined by the growth of a fungal pathogen in at least one blood culture specimen taken from a peripheral vein and/or a central venous catheter.

The blood samples were inoculated into trypticase soy broth or brain-heart infusion medium and examined daily for at least 4 weeks. Blind subcultures were performed after 6–24 hours of incubation at 37°C or whenever examination of the bottles suggested growth of microorganisms. For yeast identification [5], germ-tube-negative isolates were submitted to an analysis of morphological and biochemical characteristics, including the assimilation of carbohydrates and nitrate as well as sugar fermentation. Identification of Candida albicans by the germ-tube test was confirmed by the presence of chlamidiformidia in cornmeal–Tween 80 agar. Molds were identified according to the morphological features seen by light microscopy.

The patients’ clinical courses were followed until death or the resolution of fungemia. A database was organized with use of the software Epi-Info (Epi-Info version 6.0, May 1994; Centers for Disease Control and Prevention, Atlanta), and the following data were collected: age; gender; underlying cancer; primary site of cancer (for solid tumors); last treatment for the underlying disease; previous surgery; use of antibiotics, antifungal agents, steroids, or total parenteral nutrition; use of a central venous catheter; chemotherapy; radiation therapy; presence and duration of neutropenia; etiologic agent of the fungemia; number of positive blood cultures; treatment of the fungemia (including dose of the antifungal agent); clinical manifestations; performance status; and outcome 15 and 30 days...
after the first positive blood culture. Performance status was measured with the Karnofsky scale [6] and determined weekly by the attending physician. The score closest to the date of the first positive blood culture was considered for the analysis.

Patients were considered neutropenic if they had fewer than 500 neutrophils/mm$^3$. The neutropenia was considered persistent if the neutrophil counts remained lower than 500/mm$^3$ until death or until 15 days from the positive blood culture. Shock was defined as a decrease of 30 mm Hg and 20 mm Hg in baseline systolic and diastolic pressures, respectively, for at least 30 minutes.

In the assessment of risk factors for death, patients who died were compared with patients who survived the episode of fungemia. The comparison was made initially by univariate analysis, and all variables with a $P$ value of less than 5% were entered in a stepwise logistic regression analysis. In the univariate analysis, continuous variables were compared by the Wilcoxon method, and for noncontinuous variables the $\chi^2$ test or Fisher's exact test (two-tailed) was used as appropriate.

Results

Fifty-four episodes of fungemia were identified in 54 patients. There were 30 males and 24 females. The median age was 18 years (range, 1–83 years). The underlying diseases were as follows: acute myeloid leukemia in 18 (33%), acute lymphoid leukemia in 9 (17%), lymphoma in 9 (17%), and solid tumors in 18 (9 carcinomas and 9 sarcomas). Only one patient had received a bone marrow transplant (autologous). In 20 patients (37%) the fungemia occurred during early treatment for the underlying disease, and the disease of only nine patients (17%) was considered terminal at the time of the fungemia.

Forty-nine patients (91%) were receiving antibiotics at the time of onset of the fungemia. Forty-two patients (78%) had a central venous catheter in place (32 tunneled cuffed silicone catheters and 10 nontunneled). Neutropenia (<500 neutrophils/mm$^3$) was noted in 26 patients (48%). The neutropenia persisted throughout the episode of fungemia in 19 (76%) of the 26 neutropenic patients. Other risk factors noted were use of steroids (17 patients), surgery (12 patients), and use of total parenteral nutrition (4 patients). Antifungal prophylaxis had been administered to eight patients (15%). The antifungal agent was itraconazole for five patients and oral nistatin, iv amphotericin B (low dose), and fluconazole in one patient each.

Neutropenia was more frequent in patients with leukemia and lymphoma than in patients with solid tumors (67% vs. 11%; $P = .0001$). The use of steroids was also more common among patients with hematologic malignancies (39% vs. 17%; $P = .09$). On the other hand, 50% of patients with solid tumors had undergone surgery, compared with only 8% of patients with hematologic malignancies ($P = .001$). Use of antibiotics and central venous catheterization were factors equally distributed among the two categories of underlying diseases.

The performance status of the patients was <40 in 30% of cases, between 40 and 60 in 31%, and >60 in 39%. Fever was the most frequent clinical manifestation (36 patients). Seven patients (13%) presented with signs of shock, and 6 had evidence of deep-seated infection: skin lesions in 5 (2 infections due to Fusarium species, 2 due to Candida tropicalis, and 1 due to Candida species) and, in the other case, alveolar infiltrates and documentation of pulmonary and renal involvement at autopsy.

There were 43 candidemias (38 non-albicans) and 11 other fungemias: 4 due to Rhodotorula rubra, 3 due to Fusarium species, 2 due to Cryptococcus neoformans, 1 due to Wangiella dermatitidis, and 1 due to Aspergillus flavus. The non-albicans species were C. tropicalis in 16, Candida parapsilosis in 6, Candida guilliermondii in 4, and Candida lusitaniae and Candida stellatoidea in 1 each. In 10 cases of candidemia the isolate was not available for species identification.

The death rate was 48%, and the median duration of survival after the diagnosis of fungemia was 33 days. Among the different causative species, the associated mortality ranged between 44% and 75%, but the differences in mortality were not statistically significant.

Table 1 shows the results of the univariate analysis for the assessment of prognostic factors. Older age and low performance status were associated with an increased death rate. In addition, the outcome was poorer for patients whose underlying disease was considered terminal ($P = .01$). Among clinical manifestations, shock was associated with an increased death rate ($P = .004$). The death rate was higher for patients without a central venous catheter than for those with such catheters ($P = .01$). On the other hand, among patients with central venous access, continued catheterization after the documentation of fungemia was associated with higher mortality (69%, vs. 23% for patients whose catheters were removed; $P = .003$). The absolute number of neutrophils was not a predictive factor for death, but among the neutropenic patients, the persistence of neutropenia was associated with a higher death rate ($P = .001$). Antifungal treatment had no influence on the death rate ($P = .89$).

As shown in table 2, the prognostic factors for death in the multivariate analysis were low performance status ($P < .0001$), older age ($P = .0001$), and persistent neutropenia ($P = .003$).

Discussion

The frequency of fungemia among cancer patients has increased substantially in the past decade [7]. Indeed, Candida species are some of the most frequent pathogens in bloodstream infections, regardless of the underlying disease [8]. In the present study, Candida species were also the most frequent causes of fungemia, but contrary to the situation at many other centers [1, 9], non-albicans species accounted for the great majority
Table 1. Risk factors for death among cancer patients with fungemia: results of univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonsurvivors</th>
<th>Survivors</th>
<th>P value</th>
<th>OR/DM</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>49.5</td>
<td>7</td>
<td>&lt;.0001</td>
<td>29.21</td>
<td>17.1–41.3</td>
</tr>
<tr>
<td>Poor performance status (&lt;60)</td>
<td>23</td>
<td>7</td>
<td>&lt;.0001</td>
<td>23.00</td>
<td>43–84</td>
</tr>
<tr>
<td>Persistent neutropenia</td>
<td>15/17</td>
<td>4/15</td>
<td>.0004</td>
<td>20.63</td>
<td>34–89</td>
</tr>
<tr>
<td>Catheter retention</td>
<td>11/17</td>
<td>5/25</td>
<td>.003</td>
<td>7.33</td>
<td>17–72</td>
</tr>
<tr>
<td>Shock</td>
<td>7</td>
<td>0</td>
<td>.004</td>
<td>. .</td>
<td>10–44</td>
</tr>
<tr>
<td>Underlying disease considered terminal</td>
<td>8</td>
<td>1</td>
<td>.01</td>
<td>12.00</td>
<td>8–46</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>17</td>
<td>25</td>
<td>.01</td>
<td>0.15</td>
<td>2–45</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>6</td>
<td>2</td>
<td>.13</td>
<td>3.90</td>
<td></td>
</tr>
<tr>
<td>Etiologic agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>19</td>
<td>24</td>
<td>.25</td>
<td>0.45</td>
<td>–8–34</td>
</tr>
<tr>
<td>Other fungi</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
<td>19</td>
<td>17</td>
<td>.33</td>
<td>1.76</td>
<td>–12–37</td>
</tr>
<tr>
<td>Solid tumor(s)</td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-seated infection</td>
<td>4</td>
<td>2</td>
<td>.41</td>
<td>2.36</td>
<td>–8–25</td>
</tr>
<tr>
<td>Sex (M:F ratio)</td>
<td>13:13</td>
<td>17:11</td>
<td>.43</td>
<td>0.65</td>
<td>–37–15</td>
</tr>
<tr>
<td>Median no. of neutrophils/mm³ (range)</td>
<td>100 (0–16,000)</td>
<td>900 (0–6,150)</td>
<td>.47</td>
<td>756.84</td>
<td>959–2,472</td>
</tr>
<tr>
<td>Antifungal treatment</td>
<td>19</td>
<td>20</td>
<td>.89</td>
<td>0.92</td>
<td>–22–25</td>
</tr>
</tbody>
</table>

NOTE. Data shown are numbers of patients, except as otherwise indicated. OR/DM = odds ratio/difference between means.
* For differences between proportions or means.
² OR undefined.

of cases. Even considering that in 10 cases the strains were not available for further species identification, all those strains were germ-tube-negative, and that test is reliable for discriminating between C. albicans and non-albicans species [10].

The apparent increase in the frequency of non-albicans species reported in many centers in developed countries seems to be related to the increased use of azoles in those countries [11–13]. In our study, only six patients were receiving an azole before the development of the fungemia. In a large multicenter survey of candidemia in tertiary hospitals in Brazil, we also observed a high predominance of non-albicans species despite the rare use of azoles [14]. Therefore, it seems that in Brazil non-albicans species predominate, and this phenomenon is not related to azole use.

In the present study, a solid tumor was present in 33% of the patients with fungemia. In a survey of fungemia in cancer patients, conducted by the European Organization for Research and Treatment of Cancer (EORTC) [15], the proportion of patients with solid tumors was 34%. Patients with solid tumors have many of the known risk factors for candidemia, including previous surgery, catheters, and the use of antibiotics. Furthermore, the proportion of patients with solid tumors who have received aggressive chemotherapy has increased in the past decade, rendering these patients more prone to develop neutropenia. In our survey, however, neutropenia was much more common among patients with hematologic malignancies and occurred in only 11% of patients with solid tumors.

Therefore, it seems that risk factors other than neutropenia played a major role in the development of fungemia in our patients with solid tumors. One of these risk factors may be surgery, which was far more frequent for patients with solid tumors than for patients with hematologic malignancies. The reason why surgery predisposes to the development of fungemia is presumed to be multifactorial. Yeast colonization of the gastrointestinal tract due to the use of broad-spectrum antibiotics, followed by migration of these colonizing fungi to the bloodstream owing to disruption of the mucosal barrier, is one of these factors [16]. In addition, surgical patients have central venous catheters and receive parenteral nutrition, which are additional risk factors for fungemia [17].

Neutropenia is one of the most important risk factors for fungemia in patients with cancer [18]. In a retrospective study [19], the frequency of neutropenia was 52.7% among 55 episodes of candidemia in cancer patients. In the European survey [15], neutropenia occurred in 51.8% of cases, and in the present study it occurred in 48%.

In the present study only 17% of the patients with fungemia were considered to have terminal underlying cancer. Furthermore, in 37% of cases the patient was beginning cancer treat-
ment. In the EORTC survey [15], 21% of the patients were considered to have terminal disease, and 25% were in the initial stage of treatment. Therefore, it seems that in almost 50% of cases the patients are not neutropenic, and the fungemia is not limited to patients with uncontrolled underlying cancer. This might have important implications for the treatment of the underlying disease, and attempts to prevent the occurrence of fungemia are certainly warranted.

Among the non-albicans species, C. glabrata is considered an emerging pathogen [1]. In a review article it was the third most frequent species [20]. In our study there was no fungemia due to C. glabrata, although in 10 cases we could not identify the species. In our multicenter survey of candidemia in tertiary hospitals [14], candidemia was due to C. glabrata in four (3.4%) of 143 episodes. In only one patient was the underlying disease a cancer. Therefore, it seems that C. glabrata is not an emerging pathogen causing candidemia in Brazil.

The mortality among patients with fungemia is high. The crude mortality for nosocomial candidemia is 70%, and the estimated attributable mortality is 38% [3]. Among cancer patients the mortality may be even higher. In the present study the overall mortality was 48%. Fifteen patients did not receive antifungal treatment. Since this study was observational, we cannot ascertain the reasons why these patients were not treated. Possible reasons include early death (because of a high fungal burden) or a delay in the diagnosis due to the fastidious growth of some fungi. In the analysis of risk factors for death, antifungal treatment had no impact on survival. This observation is in agreement with other reports [18, 21].

The influence of a central venous catheter and its removal on the prognosis of fungemia has been discussed in many studies [22, 23]. In a prospective study, Nguyen et al. [24] found that catheter-related candidemias had a better outcome than did non-catheter-related candidemias. However, this difference was significant only in the univariate analysis. In the present study we observed the same result. A possible explanation is that in many patients with a central venous catheter, the device was the source of fungemia, and its removal was immediately beneficial to the patient. On the other hand, in patients without a catheter, the source of the fungemia was possibly the gastrointestinal tract and therefore much harder to obviate.

As in the study by Nguyen et al. [24], we found that retaining the catheter was associated with a poorer outcome, at least in the univariate analysis. Since in both studies removal of the catheter was decided upon at the discretion of the attending physicians, it could be that patients with an underlying disease for which the prognosis was poor were not considered good candidates for catheter removal. In this context, nonremoval of the catheter would simply reflect a higher probability of death. This could also explain the weakness of this variable in the multivariate analysis in our study.

In the present study, the death rate was not significantly higher among patients with neutropenia. However, for patients with neutropenia, the persistence of this risk factor was associated with a poorer outcome in both the univariate and multivariate analyses. These findings highlight the importance of the recovery of the host defenses in the outcome of systemic fungal infections, even more so than the antifungal treatment administered [25].

Another variable identified in the multivariate analysis was older age. The median age of survivors was 7 years, and that of the nonsurvivors, 50 years. This finding may be explained by the fact that children are presumed to respond better than adults to the stress of aggressive chemotherapy, mucositis, and surgery. Therefore, it is possible that prognostic factors in children with fungemia are different from those in adults. The influence of increasing age on the prognosis of fungemia was also reported in other studies [24].

The performance status was the other variable identified in the multivariate analysis. The Karnofsky scale is an easy and reproducible score index to assess a patient’s performance status. The highest score is given to patients with no symptoms, and the worst to patients confined to bed and moribund. The Karnofsky scale is widely used for cancer patients and is correlated with the chance of complete remission.

Other score indexes have been evaluated in stratifying prognostic groups in fungemia. Abi-Said et al. [26] tested the Acute Physiology and Chronic Health Evaluation (APACHE) III and Sensory Action Potential scores for cancer patients and found them to be useful predictors of both the outcome of candidemia and the in-hospital mortality for cancer patients with candidemia. Nguyen et al. [24] used a scale based on mental status, presence or absence of fever, hypotension, mechanical ventilation, and cardiac arrest and found it to have a good correlation with the outcome in multivariate analysis. Likewise, in another study of candidemia in a tertiary care hospital, higher mortality was associated with higher APACHE II scores [17]. Therefore, it seems that all these scores are good markers for a group of patients with a high risk for death.

In summary, persistent neutropenia, older age, and poor performance status were predictive of death for patients with fungemia. The application of the performance status scale to cancer patients with fungemia might help define a group of high-risk patients for whom new therapeutic options should be tried.

References