Invasive Fungal Infections in Patients with Acute Leukemia

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Invasive fungal infections, a serious problem among cancer patients, are increasing in incidence, and can cause morbidity and mortality. Such infections may hinder additional treatment, especially for patients with leukemia. We report here our experiences in the management of invasive fungal infection in patients with acute leukemia. A total of 18 patients were enrolled in the study: 12 had microabscesses of the liver and/or spleen and/or kidneys; four had sinonasal infections; and two had pulmonary infections. Most of the patients (88.9%) received amphotericin B during treatment for fungal infection. Thirteen patients achieved complete response without evidence of fungal infection in follow-up. In the study, there were 11 mortalities, including five patients who died during therapy and six who later died as a result of relapse or refractoriness of the leukemia. We suggest that many patients may have a good response to antifungal therapy, and that fungal infection does not have to preclude additional chemotherapy after proper management. The state of the underlying disease has a strong impact on outcome.

Key Words: fungal infection, acute leukemia, hepatosplenic microabscess, *Aspergillus* infection (*Kaohsiung J Med Sci* 2006;22:217–22)

There has been considerable progress during the past decade in the treatment of patients with acute leukemia, with many of them achieving complete remission and long-term survival. Nonetheless, invasive fungal infections have become a serious problem that cause morbidity and mortality and may hinder further treatment [1–4]. Although the incidence of fungal infection varies among studies [5–7], the increasing trend merits attention in the management of such patients. Some improvements in therapy have been promoted; however, successful management of these infections is often quite problematic. Nonspecific clinical symptoms and/or signs, equivocal imaging results, and inadequate specimen sampling have hampered early diagnosis [8–10]. The toxicity and efficacy of antifungal agents also hinder appropriate treatment of the disease [11–14].

In this study, we retrospectively enrolled patients, in our hospital, with acute leukemia who suffered from invasive fungal infections. Clinical characteristics, treatment strategies, and outcomes of these patients were reviewed and analyzed in the hope of gaining more knowledge about fungal infections.

Materials and Methods

Patients

From January 2000 to August 2005, medical records of acute leukemia patients treated in the hematology ward of the Kaohsiung Medical University Hospital were reviewed.

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A total of 18 patients who met the criteria of invasive fungal infection were enrolled retrospectively. The diagnosis of invasive fungal infection was made according to the definition proposed by the Invasive Fungal Infection Cooperative Group (IFICG) of the European Organization for Research and Treatment of Cancer (EORTC) [15]. A proven case was defined as a patient with a comparable imaging in an immune-compromised state, and a diagnosis of fungal infection based on biopsy specimens or blood culture. A probable case was defined as a patient with a comparable imaging in an immune-compromised state. All patients received cytotoxic agents according to their state.

Antifungal therapy

Amphotericin B (0.5–1.0 mg/kg) or fluconazole (400 mg/day) was prescribed empirically for neutropenic patients who had persistent unexplained fever for 4–6 days after receiving empiric antibiotics [16]. If patients could not tolerate the toxicity or had poor response to previous agents, we switched to other agents for their treatment, such as voriconazole or caspofungin, which were used at standard doses. All regimens and doses were adjusted, based on clinical response, laboratory data, and radiologic findings.

Response

Response to treatment was assessed mainly by clinical evaluation and serial imaging studies. A complete response (CR) was defined as total resolution of all clinical symptoms and signs, the disappearance of fungal lesions in imaging studies, and negative culture findings.

Results

There was a total of 18 patients in the study, 10 males and eight females (Table 1). The median age was 38.5 years old (range, 15–68 years); 14 patients had acute myelogenous leukemia, whereas the other four patients had acute lymphoid leukemia. All patients suffered from neutropenic fever due to marrow suppression from cytotoxic agents and/or refractory leukemia. Twelve patients had microabscess of the liver and/or spleen and/or kidneys;

Table 1. Characteristics of patients with fungal infection (n = 18)

Characteristic	Number
Gender	
Male	10
Female	8
Median age in years (range)	38.5 (15–68)
Diagnosis	
AML	14
ALL	4
Site of infection	
Microabscess	12
Sinonasal	4
Pulmonary	2
Invasive procedure type	
Biopsy	4 sinonasal infections
Liver aspiration	6 microabscess infections
Bronchoscope washing	1 pulmonary infection
Confirmation	
Proven	3 (all *Aspergillus* infections from sinonasal lesions)
Possible	15
Response	
CR	13
PR	1
Poor	4
Mortality	11
5 (during therapy)	3 pneumonias, 1 brain hemorrhage, 1 pulmonary hemorrhage
6 (in the follow-up)	Relapse and/or refractory of the leukemia

ALL = acute lymphoid leukemia; AML = acute myelogenous leukemia; CR = complete response; PR = partial response.

four had sinonasal infections; and two had pulmonary infections. All blood cultures for fungal infection revealed negative findings. Invasive procedures were performed in 11 patients, including biopsies in all four sinonasal cases, computed tomography or echo-guided aspiration in six cases of microabscess, and bronchoscopy in one pulmonary infection. Only three patients, all who had sinonasal infections, showed positive results and were considered as proven cases from these procedures.

Although the treatment courses varied, most of the patients (16/18, 88.9%) had received amphotericin B in the course of therapy, especially those with sinonasal and pulmonary infections (Table 2). Only two patients with microabscess received fluconazole alone because of their poor general condition. Five of these received more than one agent. Thirteen patients had CR with no evidence of fungal infection in follow-up, whereas four patients showed poor response and one patient had partial response (no. 18, with improved symptoms and imaging, died from a pulmonary hemorrhage during therapy). All patients with CR later received additional chemotherapy without evidence of recurrent fungal infections, including two patients (nos 4 and 7) who received high-dose chemotherapy plus stem cell transplant.

There were 11 mortalities in the follow-up. Of these, five patients died from different causes during antifungal therapy, including three from pneumonia, one from brain hemorrhage, and one from pulmonary hemorrhage. Relapse and/or refractory leukemia caused the other six mortalities in the follow-up.

Table 2. Treatment courses and outcomes of patients

Patient no.	Age/ gender	Diagnosis	Treatment	Response	Outcome
Microabscess					
1	34/F	AML	Amp (2,625 mg)	Poor	Died, brain hemorrhage during antifungal therapy
2	40/F	ALL	Amp (2,006 mg) + Flu (400 mg/day)	Poor	Died, pneumonia during antifungal therapy
3	50/M	AML	Flu (400 mg/day) → Amp (586 mg)	CR	Died 4 months later, relapse of leukemia
4	32/M	ALL	Flu (800 mg/day)	CR	Died 8 months later, relapse of leukemia after stem cell transplantation
5	34/M	AML	Flu (400 mg/day)	CR	Died 2 months later, refractory of the leukemia
6	63/M	AML	Amp (1,005 mg)	CR	Alive (24 months)
7	44/F	AML	Amp (2,155 mg) → Flu (400 mg/day)	CR	Died 10 months later, relapse of the leukemia after stem cell transplantation
8	15/F	ALL	Amp (2,985 mg) + Flu (400 mg/day) + Vori + Cas	CR	Alive (6 months)
9	28/F	ALL	Amp (1,935 mg) + Flu (400 mg/day) + Vori	CR	Alive (16 months)
10	35/F	AML	Amp (1,455 mg)	CR	Alive (8 months)
11	63/M	AML	Amp (865 mg)	Poor	Died, pneumonia during antifungal therapy
12	34/M	AML	Amp (1,005 mg)	CR	Died 4 months later, relapse of the leukemia
Sinonasal infection					
13	68/F	AML	Amp (436 mg)	Poor	Died, pneumonia during antifungal therapy
14	36/M	AML	Amp (996 mg)	CR	Lost to follow-up 2 months later
15	40/F	AML	Amp (1,006 mg)	CR	Died 2 months later, refractory of the leukemia
16	37/M	AML	Amp (1,486 mg)	CR	Alive (4 months)
Pulmonary infection					
17	45/M	AML	Amp (1,006 mg)	CR	Alive (26 months)
18	48/M	AML	Amp (786 mg)	PR	Died, pulmonary hemorrhage during antifungal therapy

ALL = acute lymphoid leukemia; AML = acute myelogenous leukemia; Amp = amphotericin B; Cas = caspofungin; CR = complete response; Flu = fluconazole; PR = partial response; Vori = voriconazole.

Discussion

Invasive fungal infection is a serious problem among cancer patients, causing considerable morbidity and mortality [1–7]. This problem is not only confined to Western countries; Chen et al demonstrated a 7.4% frequency of hepatosplenic fungal infection in adult acute leukemia patients in Taiwan [17]. Although there has been some improvement in the management of fungal infection, successful therapy of invasive fungal infection still relies on early recognition of the infection, proper initiation of antifungal therapy, and improvement of the underlying neutropenic status [6, 8,11].

Early diagnosis of the fungal infection is often problematic because persistent fever may be the only clinical symptom [16–19]. In contrast to our patients with sinonasal and pulmonary infections, who had obvious symptoms, identification of intra-abdominal microabscess might depend on the skills of experienced physicians and diagnostic aids, such as imaging and microbiologic data. Although positive results from cytologic evaluation and/or positive results of culture from sterile body samples have been the gold standard to confirm fungal infections, our data showed a low incidence of positive results from these procedures. This was especially apparent in patients with microabscess, in whom no positive results were noted in all six patients who underwent invasive aspiration, even though multiple nodules were found in the imaging studies. This failure might be due to the difficulty in identifying the small lesions for aspiration or in demonstrating the pseudohyphae or yeast forms from the samples in the neutropenic phase [4,8,20]. Only three cases of sinonasal infection from *Aspergillus* were found from the biopsies, suggesting the importance of biopsy in this kind of fungal infection in patients at risk. Thus, novel diagnostic methods are needed to allow early identification of this type of infection [21,22].

The use of amphotericin B empirically is a standard practice in cancer patients with neutropenic fever that persists for 3–7 days and does not respond to broad-spectrum antibiotics [16,18–20,23]. Although amphotericin B causes many complications, including fever, chills, electrolyte imbalances, and renal failure [13,14], it remains the mainstay of therapy for systemic fungal infections. With respect to our study, most of our patients (88.9%) received amphotericin B therapy, especially patients with *Aspergillus* infection and pulmonary infection [22]. Although some patients had poor response and died during therapy, more than half of them had good response after a cumulative dosage of amphotericin B greater than 1,000 mg. However, optimal dosage depends on individual response to the drug, such as in case no. 8 who finally achieved CR with a cumulative dosage of greater than 2,900 mg of amphotericin B, after failing to respond to initial amphotericin B therapy (as high as 1,000 mg), fluconazole, voriconazole, and caspofungin. Even though many agents (including fluconazole, voriconazole, and caspofungin) had been prescribed for some of our cases, the efficacy of these agents against invasive fungal infection has not been well demonstrated [11,12]. The treatment course seemed effective in our cases; however, unknown pathogens in most of them hindered us from finding the optimal agent and dosage for these patients.

The response to the antifungal therapy seemed adequate, but the prognosis of patients relies mainly on the state of the underlying diseases [6]. Among our 11 mortalities, six patients died as a result of relapse and/or refractoriness of the leukemia. Four of the other five patients who died during antifungal therapy suffered from persistent neutropenia due to refractory leukemia. This result implies that the underlying state still strongly influences the outcome. Although the outcome seemed poor, a good response after adequate antifungal therapy made it possible for many of our patients to receive additional chemotherapy, without recurrence of fungal infection, even for stem cell transplantations. Our data concurred with other reports showing that fungal infection might not preclude further chemotherapy or be considered as an absolute contraindication for stem cell transplantation after appropriate treatment [17,24].

In summary, we report here our experience in the management of 18 acute leukemia patients with invasive fungal infections. Although there were some limitations to this retrospective work, our study showed that many of our patients had a good response to therapy, and that fungal infection might not preclude additional chemotherapy after proper management. The state of the underlying disease had a strong impact on the outcome.

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急性白血病病患之侵入性黴菌感染

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愈來愈多的侵入性黴菌感染對於癌症病患而言，是一個嚴重的問題。它不僅會引起癌症病患的死亡及損傷，也會影響後續的治療，尤其是急性白血病患更是如此。在此我們報告我們對於急性白血病患合併有侵入性黴菌感染的治療經驗。共有十八位病患於此分析中，其中有十二位是肝脾或腎膿瘍病人，四位鼻竇感染及兩位肺部感染。大部份的病患 (88.9%) 接受含 amphotericin B 在內的治療。其中十三位病患治療後達到完全反應，而於追蹤中均無發現再次黴菌感染，甚至於之後的化學治療中也無發現。在回顧中一共有十一位病患死亡，包括五位病人死於治療黴菌療程中，六位死於後續的白血病復發或頑固型白血病。因此我們認為大部份的病人對侵入性黴菌感染的治療療效不錯且在適當的治療後黴菌感染不會影響後續的化學治療。而病患本身疾病的狀態亦對其預後有相當重要的影響。

關鍵詞：黴菌感染，急性白血病，肝脾膿瘍，麴菌症

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