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Fungal Infections and the Cancer Patient

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Fungi are becoming a serious public health hazard, especially for the growing numbers of immunocompromised patients in hospitals. These numbers will only increase and cancer patients will be at greater risk for developing fungal infections as the incidence of cancer continues to rise and as treatment strategies become more aggressive. Along with the increased incidence of fungal infections, established fungal pathogens are beginning to exhibit drug resistance, and new pathogens with reduced susceptibility to older antifungal drugs are emerging. The mortality rates using amphotericin B in *Candida* sepsis and aspergillosis in cancer patients are still high. Therefore, newer antifungal drugs, such as the triazoles fluconazole and itraconazole, as well as new modalities to administer amphotericin B (lipid formulations) have been developed in the hope of diminishing the toxicity and improving the response rates obtained with amphotericin B. A more thorough study of the epidemiology of fungal infection in cancer patients can help to determine which patients are most likely to develop infection. Thus, more intensive monitoring and diagnostic efforts will improve the rapidity and accuracy of diagnosis of fungal infection and can improve patient outcome by allowing intervention at an earlier point in the onset of invasive disease. Genetic typing of fungal species and strains can be used to identify drug resistant organisms. There is an urgent need for the development of new antifungal agents that attack fungal organisms at different sites than those targeted by currently available drugs. Finally, the value of large, well-controlled clinical studies of antifungal agents, as well as the use of growth factors in certain types of cancers, can greatly increase our understanding of the most effective means of treating disseminated fungal disease in the immunocompromised cancer patient. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

FUNGI ARE becoming a serious public health hazard, especially for the growing numbers of immunocompromised patients in hospitals [1]. Data compiled over the past decade confirm a dramatic increase in invasive fungal infections in cancer patients with an attendant increase in mortality. This increase will only continue, as the incidence of cancer continues to rise and as treatment strategies become more aggressive. Along with the increased incidence of fungal infections, established fungal pathogens are beginning to exhibit drug resistance, and new pathogens with reduced susceptibility to older antifungal drugs are emerging [2].

Amphotericin B, an antifungal drug that has been used for more than 40 years, is still the 'gold standard' for the treatment of invasive fungal infections, despite a lack of efficacy against certain fungi and its toxicity profile. Promising new antifungal drugs have become available over the past decade, but these new agents, especially the azoles, may be shifting the population of fungal pathogens towards species which are intrinsically drug resistant or may be selecting resistant strains of species which are usually sensitive. Therefore, there is a need to develop drugs that target different fungal structures and that will not only have a different mechanism of action than currently available agents, but also different toxicity profiles. Evaluation of cytokines and growth factors is another area of investigation for the management of invasive fungal disease in cancer patients [2].

Progress in the management of invasive mycoses in patients with cancer will arise from a better knowledge of the epidemiology of fungal infections, improved diagnostic tools, a greater awareness of the risk factors for fungal infections in certain populations of patients, and a more comprehensive approach to combination antifungal treatment.

EPIDEMIOLOGY OF FUNGAL INFECTIONS IN CANCER PATIENTS

Fungal infections are increasing in frequency in patients with acute leukaemia and cancer and are now responsible for most fatal infections [3]. Factors leading to an increased incidence of fungal infections in these patients include more aggressive cancer chemotherapy and irradiation leading to 'long-term' granulocytopenia (>14 days) and damage of mucosal barriers, complicated surgical procedures, invasive treatments and procedures, including the use of indwelling catheters, prolonged serious illness, use of potent broad-spectrum antibiotics, and pharmacological doses of corticosteroids [3, 4].

Causative organisms

The most common fungal pathogens responsible for disseminated infections in granulocytopenic patients are *Candida* and *Aspergillus* species [3]. The rate of nosocomial fungaemia has increased dramatically over the past decade. *Candida* species account for 10–15% of all hospital-acquired bloodstream pathogens found in large hospitals around the world and are increasing at dramatic rates [5, 6]. Autopsy studies have shown that the incidence of fungal infections in cancer patients is 15–25% for patients with leukaemia or those undergoing bone marrow transplant, 10% for those with lymphoma, and 5% for those with solid tumours; infections are primarily due to either *Candida* or *Aspergillus* species [7–9]. Infections with *Candida* in hospitalised patients (this includes all patients, not just those with cancer) can cause mortality rates of approximately 50% and can increase the length of stay by as much as 30 days [10, 11]. In a study of the epidemiology of *Candida* sepsis in two cancer institutions, the major species responsible for the infections were *Candida albicans*, followed by *Candida tropicalis* [12, 13]. Other candida species found in neutropenic cancer patients include *Candida parapsilosis*, *Candida guilliermondii*, *Candida lusitaniae*, and *Torulopsis glabrata* [12]. *Candida krusei* also has emerged as a significant pathogen in this patient population [14].

The Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer (EORTC) recently conducted a surveillance study of candidaemia in cancer patients in 30 centres, one of the largest series of its kind in Europe [15]. Over a 2-year period, a total of 249 episodes of candidaemia were identified. In patients with solid tumours, 30% of the cases were due to non-albicans *Candida*; in patients with haematological malignancies, the incidence was 64% ($P<0.001$). The overall 30-day survival rate was 57% in the solid tumour group and 64% in the haematological malignancy group (not significant), and was better for *C. parapsilosis*, than for *C. albicans*, *C. krusei*, and *C. tropicalis*. *Candida glabrata* was associated with the highest risk of death.

Aspergillus species, chiefly *Aspergillus fumigatus* and *Aspergillus flavus*, are a serious problem in immunocompromised cancer patients. Environmental exposure and prolonged granulocytopenia are major risk factors for invasive aspergillosis in these patients [3]. Mortality rates for aspergillosis have been reported to be in the range of 60–85% [16]. This was confirmed in a 1991 study of bone marrow transplant patients which revealed that more than one-third of the cases of hospital-acquired pneumonia were caused by *Aspergillus* species; 85% of the cases were fatal [1]. This study also showed that fewer patients would have died from transplantation or its complications if they had not developed *Aspergillus* infections. Further, the need for more control of *Aspergillus* contamination of hospital rooms with better ventilation techniques was demonstrated [1].

The EORTC Invasive Fungal Infections Cooperative Group recently conducted a prospective survey of all cases of invasive aspergillosis occurring in cancer patients in 20 European hospitals over a 12-month period (1994–1995) [17]. Overall, 73% of patients were neutropenic (<500) at the time of suspicion of invasive aspergillosis, and 87% were receiving steroids. The underlying condition most frequently associated with aspergillosis was acute myeloid leukaemia (50%). Invasive aspergillosis occurred despite itraconazole or intravenous (i.v.) amphotericin B prophylaxis (14% and 39%, respectively). Treatment was given to 91% of patients (amphotericin B, lipid amphotericin B, itraconazole, 5-flucytosine, growth factors, or lobectomy); at 3 months, 40% had died from invasive aspergillosis alone.

Neutropenic patients are also susceptible to newer pathogens such as *Fusarium* species and *Trichosporon beigelii*, which are generally resistant to most antifungal agents [5, 18].

DIAGNOSIS OF FUNGAL INFECTIONS IN CANCER PATIENTS

Fungal infections need to be diagnosed by identification of the responsible pathogen by culture, or by histology when there is invasive disease. However, it has been found that patients who die from disseminated candidiasis often do not have a positive blood culture, and cultures from other sites are often inaccurate [2]. Diagnosis of *Aspergillus* infection requires culture of the deep tissue; invasive procedures to obtain these cultures are often difficult and risky in neutropenic and thrombocytopenic patients [2, 16]. Diagnostic procedures such as X-rays, computer tomography (CT) scans, and magnetic resonance imaging (MRI) are often misleading in patients with low white blood cell counts that do not produce an appropriate inflammatory reaction, and are, therefore, not always reliable. In spite of this, a CT scan of the chest is of major importance in the diagnosis of pulmonary aspergillosis in these patients.

In order to improve the diagnosis of fungal infections, serodiagnostic tests have been developed over the past two decades, but like other diagnostic tests, reliability is questioned when they are used in immunocompromised patients [2]. Several new diagnostic methods for rapidly identifying specific fungi in tissue are being developed, including immunohistochemical and fluorescent antibody as exo-antigen techniques (although used infrequently); serological procedures, such as latex agglutin; detection of fungal antigen; detection of fungal metabolites present in a host with infection; DNA and RNA gene probes; and other molecular techniques, such as polymerase chain reaction [19]. An example of a newer diagnostic test is the *Candida* enolase antigen, a diagnostic immunoassay test used to detect invasive candidiasis in cancer patients. This test can aid in the earlier diagnosis of candidal disease [20]. The use of an *Aspergillus* antigen test for diagnosis of invasive aspergillosis has proved to be somewhat successful, but not reproducible [21]. Unfortunately, none of these tests are completely reliable, some are still experimental, and few are commercially available. Another detriment to their use will probably be their cost, which may not be justified by their lack of clinical utility.

TREATMENT OF FUNGAL INFECTIONS IN CANCER PATIENTS

Morbidity and mortality from fungal infections are considerable, and the impact of these conditions on patients' quality of life cannot be understated. The economic cost is also high, with prolonged hospital stays and expensive treatment costs. Despite often successful treatment of the cancer, a patient's ultimate survival can be imperiled by a subsequent bout of an invasive fungal infection. Because debilitated cancer patients may not be able to withstand the diagnostic procedures necessary to establish firmly the presence of disseminated disease, therapy for invasive fungal disease in cancer patients remains largely empirical, often initiated on the basis of clinical observation, without a histologically confirmed diagnosis.

Infections due to Candida

Infection with *Candida* species in the immunocompromised patient is managed either by prophylaxis with antifungals, empiric treatment based on clinical signs and symptoms, or treatment of an established fungal infection. Prophylaxis with i.v. amphotericin B in bone marrow transplant patients has been shown to decrease the number of fungal infections, reduce the need for higher doses of amphotericin B for treatment of established infection, decrease the number of days spent in the hospital, and to improve survival [22, 23]. For empiric treatment of fungal infections, amphotericin B's efficacy over placebo has been established in two major clinical trials of febrile neutropenic patients who had received 4–7 days of antibacterial therapy [24, 25]. For the treatment of documented candidal sepsis, amphotericin B has been the 'gold standard' for over 40 years; the total dose and duration of therapy for the management of fungal infections in neutropenic cancer patients have not been fully established in clinical trials [2]. One accepted criteria for discontinuation of amphotericin B therapy in documented fungal infection in cancer patients is the resolution of granulocytopenia that responds with defervescence of fever and healing of lesions [3]. Amphotericin B's toxicity profile includes rigors, fever, chills, renal dysfunction, anaemia and thrombocytopenia, which interfere with its usefulness. Although fairly uncommon, a number of *Candida* species, including *C. tropicalis*, *C. lusitaniae*, *Torulopsis glabrata*, and *C. krusei* have been reported resistant to amphotericin B [14, 26, 27]. This also limits its usefulness, especially in an immunocompromised patient population.

The mortality rates using amphotericin B in *Candida* sepsis in cancer patients are still high [3]. One way to improve outcome in these patients is to restore bone marrow function and resolve granulocytopenia. This has been accomplished more quickly with the use of colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage-colony-stimulating factor (GM-CSF). These agents can shorten the duration of neutropenia and decrease the length of hospital stay in patients with neutropenic fever [28, 29].

Infections due to Aspergillus

Treatment of invasive aspergillosis has not been very successful with amphotericin B, and restitution of bone marrow function is only one important determinant of a successful outcome [18]. Persistent steroid-induced immunosuppression (as seen in allogeneic bone marrow grafts) is associated with a poor outcome, even in the absence of granulocytopenia. Lipid formulations of amphotericin B, less nephrotoxic preparations of amphotericin B, have been utilised for the treatment of *Aspergillus* infections and are potentially useful [30].

Problems with the use of amphotericin B for the management of fungal infections in cancer patients still persist. Despite its efficacy, its use as an empirical agent remains controversial because of its toxicity profile, the fact that patterns of fungal pathogens are changing, and because resistant fungal strains are emerging. Therefore, new methods of administering amphotericin B, such as lipid formulations of amphotericin B, are being attempted and new classes of antifungal agents are being investigated [2].

NEWER ANTIFUNGAL AGENTS

Azoles

Newer antifungal drugs have been developed with the hope of diminishing the toxicity and improving the response rates obtained with amphotericin B. The imidazole-derivative antifungal agents, miconazole and ketoconazole, and the triazole derivatives, fluconazole and itraconazole, were developed as alternatives to amphotericin B. Earlier work in cancer patients demonstrated that ketoconazole was not effective for the empiric treatment of documented disseminated fungal infection in neutropenic cancer patients; the response rate with localized fungal infection was only 27% [31]. In addition, its oral only use was limiting in very ill patients.

Fluconazole has several advantages over the older ketoconazole, including its high bioavailability, extensive distribution to tissues, and availability in both intravenous and oral forms [32]. Fluconazole's absorption is unaffected by damaged mucosa and achlorhydria [18], conditions which occur often in cancer patients and limit the usefulness of the older agent, ketoconazole. Fluconazole has been studied for the prophylaxis and treatment of fungal infections in cancer patients. For prophylaxis, fluconazole was as effective as orally administered amphotericin B (and better tolerated) in preventing fungal infections in neutropenic patients with acute leukaemia [33]. In another study, patients undergoing allogeneic or autologous bone marrow transplantation who received fluconazole prophylaxis instead of placebo had a marked reduction in invasive fungal infections (2.8% versus 16%) [34]. Those patients who received fluconazole prophylaxis were less likely to receive empiric amphotericin B (56% versus 66%, $P = 0.0035$). However, resistant fungal strains, such as *C. krusei*, can appear in neutropenic patients being treated prophylactically with fluconazole [35], thus limiting widespread use as empirical antifungal therapy. For the treatment of candidemia in *non-neutropenic* patients, fluconazole at higher doses was shown to be as effective as intravenous amphotericin B [36]. Its efficacy in the treatment of fungal infections in immunocompromised patients remains to be defined.

Itraconazole and saperconazole are the two triazoles that are being investigated as alternatives to amphotericin B for the treatment of invasive *Aspergilllus* infections. Saperconazole appears to be useful in animal models [18]; clinical information will be forthcoming. Itraconazole has demonstrated positive response rates in invasive aspergillosis; however, these studies did not include a large number of immunocompromised patients [16]. Studies are planned to compare itraconazole to liposomal amphotericin B preparations for the treatment of aspergillosis [18].

Further clinical collaborative trials must be conducted with the newer antifungal agents, especially in combination with other antifungals, to establish more clearly their efficacy in the treatment of fungal infections in immunocompromised patients. Cost, quality-of-life issues, and morbidity associated with the drugs must also be taken into account when addressing their usefulness [2].

OTHER FUNGAL TARGETS

The antifungal agents of the polyene derivative class, to which amphotericin B belongs, exert their antifungal effect by binding to ergosterol in the fungal cell membrane. The triazoles, such as fluconazole, itraconazole and saperconazole, exert their effect by inhibition of cytochrome P-450 14-α-desmethylase in susceptible fungi, leading to accumulation of C-14 methylated sterols and decreased concentrations of ergosterol [32].

One area of new antifungal development is the study of new triazoles with greater activity against fungal pathogens than the ones currently available. Another area of antifungal development is the exploration of new targets for antifungal agents. This includes 1,3-βD-glucan in the fungal cell wall using 1,3-βD-glucan synthase inhibitors, such as cilofungin and the echinocandins and pneumocandins. These agents are being studied *in vitro*, in animal models, and in human clinical trials, and appear promising [18]. Also in development are antifungal vaccines, although not for the types of infections that usually affect cancer patients [2]. The use of cytokines and growth factors, which are immunomodulators, are another way to manage invasive fungal infections; not only can they help to control the fungal infection, but they may allow the use of higher doses of chemotherapeutic agents for more aggressive management of the underlying cancer [2].

CONCLUSION

Results with current antifungal therapies have prompted exploration of other methods of improving survival in cancer patients with fungal infections. Failure of antifungal therapy is not solely a function of the efficacy of a given drug; factors such as the underlying disease state, multiple organ or system failure, the site of fungal infection, drug pharmacokinetics, and patient compliance all influence the ultimate treatment outcome [2]. Because many of these factors are beyond the scope of medical intervention by the time invasive fungal infection becomes apparent, the focus has shifted to earlier interventional strategies.

A more thorough study of the epidemiology of fungal infection in cancer patients can help to determine which patients are most likely to develop infection. Thus, more intensive monitoring and diagnostic efforts can be directed where they will be most efficacious. Epidemiological data can also provide reinforcement for application of general preventive measures, including improving hospital staff hygiene, isolation of susceptible patients from construction areas that can stir up pathogen-laden debris, monitoring of catheters and other invasive mechanical devices for fungal colonization, and avoidance of foodstuffs known to be sources of fungal contamination.

Improvements in the rapidity and accuracy of diagnostic procedures should also improve patient outcome by allowing the medical team to intervene at an early point in the onset of invasive disease. Arresting fungal spread before the organism becomes established systemically or gains entry to tissues that are not easily accessible to drug therapy should increase the chances of treatment success. Genetic typing of fungal species and strains can be used to identify drug resistant organisms so that appropriate therapy can be instituted quickly. Continuous surveillance of high-risk patients could help detect fungal colonization in its earliest stages. Prophylactic administration of antifungal drugs in neutropenic patients undergoing bone marrow transplantation or with leukaemia has been shown to reduce the incidence of fungal disease, but remains somewhat controversial. Criteria to consider before instituting prophylaxis in all patients at risk for developing fungal infections are safety, efficacy, cost, consequence of doing so, prevalence of fungal infections in a given population, and potential for development of resistant strains of fungi [37].

There is an urgent need for the development of new antifungal agents which attack fungal organisms at different sites than those targeted by currently available drugs. Such new agents might be used synergistically with older drugs to increase the success rate of treatment, especially if the failure of therapy is caused by resistant fungal strains. Exploration of surgical solutions to invasive fungal disease in cancer patients should also be pursued [2]. Finally, the value of large, well-controlled clinical studies of antifungal agents cannot be overestimated [2]. Information gained from rigorously controlled, and statistically valid, studies could greatly increase our understanding of the most effective means of treating disseminated fungal disease in the immunocompromised cancer patient.

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