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Invited Article

Recent Developments in Diagnosis and Treatment of Invasive Fungal Infections in Patients with Neoplastic Diseases

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=Abstract=

Patients with neoplastic diseases are predisposed to develop invasive fungal infections as the result of impairment of host defense, due principally to pharmacological immunosu-ppression as the resulting from intensive cytotoxic chemotherapy, ablative radiation therapy, and corticosteroids[1]. *Candida spp., Aspergillus spp.,* and emerging opportunistic fungal pathogens comprise the principal etiological agents of opportunistic mycoses in cancer patients[2-9]. This paper will briefly review the recent progress in management of invasive fungal infections and the current problems of invasive mycosis, which currently confront patients with neoplastic diseases.

Key Words: Invasive fungal infection, Diagnosis, Treatment.

Deficits in Host Defense Predisposing to Infections in Patients with Cancer

The principal host defense mechanisms against invasive fungal infections include (1) phagocytes (neutrophils, monocytes and macrophages), (2) T lymphocyte cell mediated immunity, (3) mechanical barriers provided by the integrity of the mucocutaneous epithelial systems along the skin and mucosa. Intensive cytotoxic chemotherapy results in neutropenia, the duration of which is directly related to the frequency of invasive fungal infections. Total body irradiation may also cause profound and persistent neutropenia. Both cytotoxic chemotherapy and radiation therapy also may cause disruption of the integrity of mucosal barriers. Insertion of venous catheters may also compromise the host resulting in catheter-related fungemia. Adjunctive corticosteroid therapy as part of the antineoplastic regimen has a broad effect impairing the function of circulating neutrophils, monocytes, and macrophages, as well as profoundly compromislng T lymphocyte cell mediated immunity.

Principal Causes of Invasive Fungal Infection

Candida species constitute the most frequent causes of invasive fungal infections in patients with neoplastic diseases[1-3]. *Aspergillus species* constitute the next most common cause of opportunistic mycoses in patients with cancer[1-4]. Infections due to these organisms are particularly related to durations of granulocytopenia. Other variables, such as mucosal disruption due to a particular cytotoxic chemotherapeutic regimen, may increase the risk for invasive candidiasis and trichosporonosis. Environmental contamination in a particular institution may increase the frequency of these organisms as cau-

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sative agents[4]. Clearly major geographic differences exist for many of the emerging opportunistic fungi such as those due to *Fusarium species, Trichosporon species, Zygomycetes* and *Dematiaceous* fungi[5,9]. While *Cryptococcus neoformans* has been recognized as a major cause of central nervous system infection in HIV-infected patients, this organism is an unusual cause of infection related solely to granulocytopenia. Instead, cryptococcosis is seen particularly in patients who have other deficits such as impairment of cell mediated immunity due to corticosteroid therapy. As total body irradiation may also cause impairment of cell mediated immunity, cryptococcosis may emerge in this setting also. Region endemic in the United States for coccidioidomycosis in the Southwest Region or histoplasmosis in the Ohio-Mississippi River basins may be associated with reactivation of these endemic mycoses in intensively immunosuppressed cancer patients.

Candidiasis

Classification

Candidiasis is a spectrum of infections that may be classified as cutaneous, mucosal, and deeply invasive. Deeply invasive infection may be further classified as fungemia, tissue proven disseminated candidiasis, and single organ candidiasis. Disseminated candidiasis may be further classified as acute and chronic disseminated candidiasis, which constitute two ends of a clinical and pathological spectrum. Amongst the conditions of mucosal candidiasis commonly encountered in cancer patients are oropharyngeal and esophageal candidiasis.

Oropharyngeal candidiasis

Oropharyngeal candidiasis is common amongst patients undergoing cytotoxic chemotherapy, particularly in regimens causing mucosal disruption or containing corticosteroids. Although the diagnosis of oropharyngeal candidiasis is often made presumptively by visual inspection of the mucosal surfaces, this practice may not be reliable. Herpes simplex virus infections, bacterial infections, and nonbacterial mucosal disruption may easily simulate *Candida*-like lesions. Classic beige plaques and ulcers may or may not be due to *Candida species.* The most assured and practical way of establishing a diagnosis is the examina-tion of a wet mount or Gram stain for pseudohyphae and blastoconidia and culture for identification of the *Candida species.* A culture for herpes simplex virus is also important in excluding concomitant infection.

Therapeutic approach to oropharyngeal candidiasis traditionally includes administration of nystatin, clotrimazole, or, more recently, fluconazole. These agents may be given therapeutically for proven infection or prophylactically for prevention of infection. The use of fluconazole for treatment of oropharyngeal candidiasis in immunocompromised patients was recently described by in a double-blind randomized trial of fluconazole 100 mg/qd vs. ketoconazole 400 mg/qd[10,11]. Both regimens were effective in establishing clinical cure as well as eradication of pathogenic yeasts. Prevention of oropharyngeal candidiasis was studied another multicenter comparative trial of fluconazole versus oral polyenes with results currently demonstrating significant reduction of oropharyngeal candidiasis in the fluconazole group. A similar study also has recently been described by Rozenberg-Arska and colleagues[13] in a randomized study of oral fluconazole versus oral amphotericin B in the prevention of localized oropharyngeal candidiasis. Fluconazole in this regimen was studied at 50 mg each day and amphotericin B at 200 mg 4/qd. Both regimens effectively prevented oropharyngeal candidiasis but fluconazole was better tolerated.

Prophylaxis of oropharyngeal candidiasis is another approach in which clotrimazole, nystatin, or, more recently, fluconazole is utilized[14, 15].

A recent study of fluconazole versus placebo as antifungal prophylaxis during hospitalization using fluconazole by Samonis et al. found a significant decrease in oropharyngeal candidiasis[15]. As most studies of fluconazole, thus far, have been conducted in adults. Studies in children with granulocytopenia, who demonstrate distinct pharmacokinetics, are currently in progress.

Esophageal Candidiasis

Patients with defects in mucosal immunity and mechanical integrity have a high risk of developing esophageal candidiasis. For example, patients receiving corticosteroid therapy for lymphoid neoplasms as well as cytotoxic chemotherapy have a combined effect of impaired cell mediated immunity and disruption of mucosal integrity, as well as the increased risk of herpes simplex virus esophagitis, all of which will increase the risk for esophageal candidiasis. Mixed infections, which tend to be relatively common in infectious esophagitis in granulocytopenic patients, include combinations due to *Candida*, herpes simplex virus, cytomegalovirus or bacteria[16].

Fungemia

Fungemia in cancer patients is usually due to a *Candida species*. Horn et al[2] at the Memorial Sloan-Kettering Cancer Center identified increasing frequency, earlier onset and high mortality associated with fungemia in cancer patients. More recently, Richet et al.[17] found an increased incidence of candidiasis from 0.1% to 0.32% between 1983 and 1987, particularly in patients with acute lymphocytic leukemia whose burden of *Candida* in the gastrointestinal tract increased during antimicrobial therapy.

The detection of candidemia has been greatly improved by blood culture detection techniques, most notably the lysis centrifugation system (Isolator). This system has been able to detect candidemia earlier and more frequently than conventional broth and biphasic systems[18-20]. The non-radiometric resin broth system (Bactec 660) may be similar to lysis centrifugation in the detection of fungemia. Non-culture techniques such as antigen and antibody detection are investigational[21]. Detection of circulating mannan, and D-arabinitol in the setting of invasive candidiasis have been reported. The methods for widely utilizing d-arabinitol have been too cumbersome for efficient laboratory usage. More recently, a third biochemical marker of *Candida* enolase has been described in the circulation of patients with candidemia and invasive candidiasis[22]. This marker complemented but did not replace the utility of blood cultures, was more sensitive in detecting deeply invasive candidiasis than in detection of candidemia, and was more readily detected in neutropenic patients. More recent studies have demonstrated that among patients with disseminated candidiasis, some neutropenic and most non neutropenic patients have high titers of antibody which neutralize the antigen but which also may be useful in detection of the presence of invasive candidiasis. The data indicate that both antigen and antibody should be used in combination in order to optimize the detection of the marker. The appropriate configuration for detection of the enolase antigen and antibody remains to be further studied, especially as repeated samples are necessary for optimal sensitivity. Other diagnostic strategies include detection of circulating 1,3-beta-glucans and the use of polymerase chain reaction for detection of circulating *Candida*.

Treatment of fungemia in neutropenic patients remains amphotericin B at a minimum of 0.5 mg/kg/d and often at 1 mg/kg/d, particularly for infections due to *Candida tropicalis* which may be more resistant than those due to *Candida albicans*. There is no evidence that a "stepwise" escalation of the dose to the targeted daily dose decreases toxic effects. Indeed, fungemia may persist through such overdoses resulting in more deep-seeded infection. Although the issue of removal of catheters is

controversial, current data suggests that removal of the catheter, where possible, and concomitant administration of amphotericin B is an effective approach, as recently described by Dato et al[23]. Removal of the catheter alone for patients with fungemia is not tenable, as fungemia in cancer patients is generally a marker of deeply invasive candidiasis[2]. Patients who have infection due to *Candida tropicalis* or persistent fungemia may benefit from the combination of amphotericin B, 1 mg/kg/d plus 5-fluorocytosine. Following an episode of fungemia during granulocytopenia, deep tissue infection may become clinically overt as disseminated candidiasis as a later complication[24].

Disseminated Candidiasis

Disseminated candidiasis in cancer patients constitutes a spectrum of infections ranging from acute disseminated candidiasis to chronic disseminated candidiasis. Acute disseminated candidiasis at one extreme is characterized by persistent fungemia, hypotension, multi-organ failure, skeletal muscle involvement, and cutaneous lesions. By comparison, chronic disseminated candidiasis, is most commonly manifest as hepatosplenic candidiasis, as an indolent process in which the disease is established while the patient is neutropenic but becomes more clinically over as chronic refractory progressive lesions and tissues[25]. Unlike acute disseminated candidiasis, chronic disseminated candidiasis is seldom associated with hypotension, fungemia, or multi-organ failure. Earlier studies and more recent reports emphasize the chronicity and refractory nature of this infection[25, 26]. Conventional therapy consists of amphotericin with or without 5-fluorocytosine.

The administration of lipid formulations of amphotericin B offers an alternative strategy for treatment of this infection. Studies conducted by Lopez-Berestein and colleagues[27, 28] demonstrate that a multilamellar liposomal formulation of amphotericin B was effective in achieving a complete response of clearing *Candida* lesions in approximately 70% of patients with hepatosplenic candidiasis. Given the high concentrations of amphotericin B achieved in the reticuloendothelial system by use of these lipid formulations of amphotericin B, these agents have a pharmacodynamically rational basis for use in hepatosplenic candidiasis. The improved therapeutic index of several of the lipid formulations of amphotericin B permit the administration of higher dosages of amphotericin B with less nephrotoxicity. A recent comparative study of amphotericin B lipid complex (ABLC) versus amphotericin B desoxycholate in 16 healthy male volunteers found that ABLC was well tolerated at dosages of 0.1 to 0.5 mg/kg. Mild asymptomatic elevation of serum transaminase, which spontaneously resolved, was detected in three of eight ABLC recipients. Due to the increased estimated volume of distribution and a greater estimated clearance, ABLC had smaller peak serum concentrations and areas under the serum concentration time curve in comparison to those of desoxycholate amphotericin B. Clinical trials of ABLC in treatment of hepatosplenic candidiasis are currently in progress.

Fluconazole also has been used for treatment of hepatic candidiasis. Two studies with well-characterized patients demonstrated resolution or improvement of lesions by CT scan in patients who were intolerant of or not responding to amphotericin B with or without 5-fluorocytosine[30, 31]. However, as with other antifungal strategies for treatment of hepatosplenic candidiasis have also occurred[32].

Recent experimental studies demonstrate that the optimal activity of fluconazole against disseminated candidiasis may be best obtained in early treatment or prevention of infection[33]. Randomized clinical trials in granulocytopenic patients are currently being pursued to determine the value of fluconazole for prevention and early treatment of disseminated candidiasis and fungemia.

Aspergillosis

Pathogenesis

Invasive pulmonary aspergillosis continues to be the major opportunistic fungal respiratory pathogen in immunocompromised cancer patients[4]. *Aspergillus fumigatus* and *Aspergillus flavus* constitute the most frequently isolated pathogenic *Aspergillus species*. Persistent and profound granulocytopenia as well as corticosteroids constitute the major risk factors for development of invasive aspergillosis, Pulmonary involvement by *Aspergillus spp.* may develop as an invasive disease, as a saprophytic process, or as allergic bronchopulmonary aspergillosis. Patient with cancer are most frequently the victims of invasive pulmonary aspergillosis. Aspergillosis is established in immunocompromised hosts by inhalation of *Aspergillus* conidia into the respiratory tract. These 2-3μ-diameter particles may be inhaled directly into the alveolar spaces, where germination of hyphal forms occurs. Pulmonary alveolar macrophages form the first line of defense against *Aspergillus* conidia. Once germination occurs, polymorphonuclear leukocytes form the next line of host defense against *Aspergillus* hyphae[34].

Epidemiology

While most episodes of invasive aspergillosis occur as sporadic events, a review of the literature clearly demonstrates that outbreaks or clusters of invasive pulmonary aspergillosis continue to emerge in hospitals, where the most common environmental sources of *Aspergillus* conidia are contaminated ventilation systems and construction sites[35]. A recent report by Arnow et al. demonstrated the emergence of *A. flavus* and *fumigatus* in a new hospital, as evidenced by increasing concentrations of these organisms in air sampling studies[36]. These increasing concentrations of conidia occurred in parallel with an increasing incidence of aspergillosis in immunocompromised patients. Further inspection demonstrated heavy growth of pathogenic *Aspergillus species* on air filters. An investigation of the hospital wards revealed small foci of *A. flavus* in the environment. Following removal of the contaminated air filters and the environmental foci, a more than one-hundred fold reduction in *Aspergillus* air-sampling counts and a four-fold decrease in invasive aspergillosis was achieved during the subsequent two years.

Further underscoring the morbidity and mortality associated with pulmonary aspergillosis, Pannuti and colleagues[37] found *Aspergillus species* to be the cause of 36% (20 of 55) of cases of proven nosocomial pneumonia. The crude mortality for patients with *Aspergillus* pneumonia was 95%. Further analysis indicated that elimination 90% of cases invasive aspergillosis would reduce the overall associated crude mortality to 43%.

Diagnosis

The critical elements of successful management of invasive pulmonary aspergillosis are: 1) early diagnosis, 2) initiation of aggressive doses of amphotericin B at 1.0 to 1.5 mg/kg/d, and 3) reversal of immunosuppression (recovery from granulocytopenia and discontinuation of corticosteroid therapy).

Early diagnosis is based upon recognition of hosts at greatest risk with prolonged neutropenia and/or receiving corticosteroids. Isolation of *A. fumigatus* or *A. flavus* from respiratory secretions from febrile granulocytopenic patients with pulmonary infiltrates is strongly associated with invasive pulmonary aspergillosis[38, 39]. *A. fumigatus* or *A. flavus* are seldom contaminants when recovered from respiratory secretions. Computerized tomographic scan may reveal radiologic evidence of invasive pulmonary aspergillosis, characterized by subpleural nodules, some of which may be cavitating[40]. Ultrafast CT scanning may be an effective approach to rapid screening of high-risk patients with equivocal radiological infiltrates[41]. Radiological evidence of sinus opacifications

in a persistently neutropenic should prompt further otolaryngological evaluation for possible invasive aspergillosis of the paranasal sinuses. Bronchoalveolar lavage (BAL) is an important adjunct in detection of microbiological evidence of *Aspergillus spp*[42]. However, BAL may vary in sensitivity of detection of invasive aspergillosis[43]. Serum markers of invasive aspergillosis, such as galactomannan, may prove to useful but currently remain investigational[44, 45]. Open lung biopsy may yield a diagnosis of invasive aspergillosis when BAL is non-diagnostic[46]. Open lung biopsy performed after all other diagnostic studies have been exhausted has important therapeutic implications for invasive aspergillosis by providing a definitive basis for use of increased dosages of amphotericin B, the implementation of lipid formulations of amphotericin B, or the use of itraconazole.

Treatment

Amphotericin B with or without flucytosine remains is the mainstay of treatment of invasive aspergillosis[47, 48]. Invasive aspergillosis may develop during the course of empirical amphotericin B. Such cases warrant increasing the dosage of amphotericin B to 1.0 to 1.5 mg/kg/d. A single lesion may benefit surgical resection[49]. The addition of flucytosine or rifampin to amphotericin B for invasive aspergillosis is controversial and has not been studied rigorously in controlled clinical trials. As amphotericin B is the most active agent against *Aspergillus spp.* among these three agents, a guiding principle is for management of pulmonary aspergillosis is to first optimize the dosage of amphotericin B to maximally tolerated dosages targeted at 1.0 to 1.5 mg/kg/d. Rifarnpin or 5-fluorocytosine may be added to maximally tolerated doses of amphotericin B if there is no apparent clinical response.

Patients who recover from an episode of invasive aspergillosis have a risk of approximately 50% of relapsing aspergillosis if the patient receives another course of cytotoxic chemotherapy[50]. Such patients may be managed with early empirical administration of high dose of amphotericin B during the next cycle of chemotherapy[48].

Investigational Antifungal Agents for Aspergillosis

The development of lipid formulations of amphotericin B offer further hope that these agents may be effective in treatment of invasive aspergillosis of the respiratory tract. The lipid formulations of amphotericin B are also undergoing clinical trials and appear to have important activity against this mycosis. One such formulation, a small uni-lamellar vesicle formulation has been approved in some Western European countries[51-52]. Phase I studies and controlled clinical trails, which are clearly needed for these agents, are underway or soon to be initiated.

Itraconazole, a new antifungal triazole, also demonstrates activity against *Aspergillus spp.* Previous work and currently ongoing studies suggest that this agent may be active in the treatment of immunocompromised patients with invasive pulmonary aspergillosis[53]. Bioavailability remains a problem with this compound, particularly in the setting of gastric achlorhydria. The lack of availability for parental formulation of itraconazole further complicates the management of critically ill patients with pulmonary aspergillosis. Itraconazole ultimately may be more appropriately used for prevention of infection.

There are currently no randomized trials demonstrating the successful prevention of invasive aspergillosis in high-risk patients. While itraconazole appears to have the potential for this activity, only open label or historically controlled studies substantiate its potential clinical utility for prevention of aspergillosis. Episodes of aspergillosis may inexplicably wax and wane in a given center such that the use of these episodes as historical controls as a

guide to frequency of infection may not be reliable. Consequently, non-randomized trials using historical controls to study preventive or therapeutic strategies against invasive aspergillosis may be difficult to interpret. For example, recently reported historically controlled studies of low-does amphotericin B and intra-nasal amphotericin B prophylaxis will require further practice[54, 55]. Development of newer antifungal triazoles, such as itraconazole and, the newer antifungal triazole, saperconazole offer hope for a broad spectrum antifungal prophylaxis in patients with cancer.

Finally reversal of immunosuppression, the third arm of management of invasive aspergillosis, may be achieved by earlier recovery from neutropenia and discontinuation of corticosteroids, where applicable. Early recovery from granulocytopenia may be possible with the use of recombinant human cytokines, such as granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)[56-57]. The principles of early diagnosis, aggressive antifungal therapy, and reversal of immunosuppression also apply to other fungal organisms observed in patients with cancer.

Emerging Opportunistic Fungi in Immunocompromised Cancer Patients

There has been increasing recognition of the less common but potentially devastating opportunistic mycoses in children and adults with cancer[5-9, 58-62]. Amongst the organisms recognized more recently for these infection are *Fusarium species, Trichosporon species*, and dematiaceous fungi. *Cryptococcus neoformans, Zygomycetes*, and resistant species of *Candida* are well-recognized pathogens being observed in new hosts and settings.

Fusarium infections

Fusarium infections, which typically occur in patients with profound persistent granulocytopenia, produce a pattern similar to that of invasive aspergillosis[7, 61]. *Fusarium* infections in cancer patients are characterized by pulmonary infiltrates, cutaneous lesions, positive blood cultures, and sinusitis. Biopsy of the cutaneous lesions often reveals fine, dichotomously branching, acutely angular, septate hyphae. Unlike *Aspergillus spp.*, *Fusarium species* are frequently detected by advanced blood culture detection systems, such as lysis centrifugation. This emerging fungal pathogen often does not respond to conventional doses of amphotericin B and may require substantially higher doses for successful outcome[61]. Some cases of invasive *Fusarium* infection may be completely refractory to amphotericin B, therefore requiring investigational antifungal triazoles[7].

Trichosporon infections

Thichosporon beigelii is the most common of the *Trichosporon species* causing invasive infection[6]. Although invasive *Trichosporon* infections are uncommon in cancer patients, they often produce a fatal disseminated mycosis in patients with profound granulocytopenia or those receiving corticosteroids. Clinical manifestations are characterized by refractory fungemia, funguria, renal dysfunction, cutaneous lesions, pulmonary infiltrates, and chorioretinitis. Despite the administration of amphotericin B, fungemia may persist. Recent in vitro and in vivo studies indicate that the organism inhibited but not killed by safely achievable serum concentrations of amphotericin B[62]. Newer antifungal triazoles, however, such as fluconazole, have been found to be active *in vivo* against this organism.

Zygomycosis

Zygomycosis, most commonly due to *Rhizopus spp.*, is increasingly recognized as being caused by other species including Cunninghamella, and other members of the class of *Zygomycetes*[5]. These fungi characteristically invade blood vessels resulting in extensive tissue infarction in granulocytopenic or corticosteroid treated hosts. Amphotericin B is the

treatment of choice for the sino-pulmonary infections caused by these organisms. Surgical resection of lesions, where possible, may be the most critical therapeutic intervention. Recent studies suggest that patients receiving deferoxamine constitute a newly recognized group of patients at risk for severe pulmonary and disseminated zygomycotic infections[63].

Cryptococcosis

Cryptococcal infections in cancer patients typically occur in patients with impaired cell mediated immunity. Characteristically patients with human immunodeficiency virus type 1 are at high risk for cryptococcal infection. *Granulocytopenia per se* is not commonly associated with infections due to *Cryptococcus neoformans*. Instead, patients with HIV infe-ction, corticosteroid therapy, or other impairments of cell mediated immunity are more likely to develop pulmonary, disseminated, or meningeal cryptococcosis.

There has been a paucity of information of cryptococcosis in immunocompromised infants and children. A recent review conducted by Leggiadro and colleagues at St. Jude Children's Research Hospital and LeBonheur Children's Medical Center found that extra pulmonary cryptococcosis may be more common than previously recognized[60]. Eight of the nine patients identified in this study had acute lymphoblastic leukemia. Meningitis and cutaneous lesions were the most common manifestations of extra pulmonary cryptococcosis in these children. Impairment of cell mediated immunity, particularly that due to corticosteroids, has been the most common predisposing condition reported in patients in the previous literature. However, the patients reported in this most recent series were receiving cytotoxic chemotherapy, which was not being administered with corticosteroids in most instances at the time of diagnosis. Whether previous administration of prednisone may have contributed to the development of cryptococcosis is unclear. However, five of the eight reported patients were cured of their cryptococcosis, whereas the other patients had relapses.

The effective management of cryptococcosis depends upon the pattern of disease and the level of immunosuppression. Amphotericin plus fluorocytosine remains the treatment of choice for treatment of meningeal and disseminated cryptococcosis in immunocompromised cancer patients. Those patients who will continue to receive ongoing immunosuppression after clearing their cryptococcal disease should be considered candidates for fluconazole suppression during the course of their immunosuppression.

Infections due to *Pseudallescheria boydii*

Pseudallescheria boydii is an uncommon but highly aggressive organism in granulocytopenic patients which produces a pattern of infection similar to that of *Aspergillus species* with invasion of blood vessels and infection of the respiratory tract. This organism may be completely resistant to amphotericin B. Treatment with miconazole may be successful; however, in neutropenic patients this agent also may not be effective.

Infections due to *Candida krusei*

As fluconazole is used increasingly in the oncology setting, emergence of fungi resistant to this triazole becomes probable. *Candida krusei* was recently reported to emerge as a resistant pathogen in bone marrow transplant recipients[64]. Amphotericin B is active against *C. krusei* and is the appropriate treatment infections due to *C. krusei*.

Phaeohyphomycosis

Phaeohyphomycosis (infections due to dematiaceous or pigmented fungi), are caused by such organisms as *Bipolaris spicifera*, *Cladosporium (Xylohypha) bantianum (bantiana)*, *Wangiella dermatitidis*, and *Dactylaria constricta* var. *gallopava*, These dematiaceous fungi are uncommon but frequently fatal causes of invasive mycoses, particularly involving the central nervous system in immunocompromised

host[8]. These organisms may be initially treated with amphotericin B but are also amenable to therapy by itraconazole.

Fungemia due to *Malassezia furfur*

Malassezia furfur may occur in the setting of parenteral administration of lipids[65]. Fungemia due to *M. furfur* may be manifest as persistent fever, pulmonary infiltrates, and thrombocytopenia. Laboratory diagnosis is facilitated by addition of olive oil or other long-chain carbon nutritional supplement. Management of this infection includes discontinuation of the lipid, removal of the vascular catheter where possible, and administration of an antifungal azole.

Endemic Mycoses

Patients with cancer who live in endemic areas of the Southwestern United States and the Ohio-Mississippi river valley basin areas, are at risk, respectively for infection due to *Coccidioides immitis*[66] and *Histoplasma capsulatum*[67]. Disseminated histoplasmosis and coccidioidomycosis often develops in high risk patients. Amphotericin B should be considered the first line therapy for patients with these disseminated mycoses.

Recombinant Human Cytokines in the Management of Cancer Patients

Extraordinary developments in the investigation of recombinant human cytokines have lead to shortening of the duration of neutropenia and permitting more intensive cytotoxic chemotherapy[68-70]. The impact of these cytokines on invasive fungal infection has not been clear. Clearly, decreasing the duration of granulocytopenia should decrease the frequency of invasive fungal infections, However, some patients with profound persistent granulocytopenia such as those for acute non lymphocytic leukemia or those undergoing allogeneic bone marrow transplantation may have only a modest shortening of their duration of granulocytopenia, thereby still carrying a high risk for invasive fungal infections. Patients also undergoing repeated cycles of intensive cytotoxic therapy may become colonized with *Candida species* during the course of repeated cycles, resulting in the potential for invasive candidiasis despite an abbreviated course of granulocytopenia. Nevertheless, cytokines such as G-CSF and GM-CSF appear to have ameliorated one of the important risk factor for development of invasive fungal infections.

Whether cytokines are effective in treatment of proven fungal infections in cancer patients is not known. A phase I clinical trial of recombinant human macrophage colony stimulating factor (M-CSF) in patients with invasive fungal infections demonstrated that M-CSF was well tolerated but did produce a transient dose related thrombocytopenia[71]. The study design did not permit evaluation of the potential antifungal properties of M-CSF versus optimal antifungal therapy, alone. A randomized placebo-controlled clinical trial has been initiated to delineate the potential role of M-CSF in patients receiving conventional antifungal therapy.

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