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Fungal infections in neutropenia: current problems and chemotherapeutic control

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Invasive fungal infection is a significant problem in neutropenic individuals. The commonest causes of infection are *Aspergillus* and *Candida* spp., although a growing number of other organisms (including species of *Fusarium* and *Trichosporon*) have been implicated. The clinical manifestations of these infections are described here, and diagnostic problems are discussed. The role of lipid-based formulations of amphotericin B, and of the triazole compounds, itraconazole and fluconazole, in the treatment and prevention of fungal infection is discussed.

Introduction

Invasive fungal infection remains a major complication in neutropenic cancer patients and bone marrow transplant (BMT) recipients. The commonest causes of mycotic infection in these patients are *Aspergillus fumigatus* and *Candida albicans*, but a growing number of other organisms, hitherto regarded as harmless, are now being implicated in significant human infection. The death rate from fungal infection in neutropenic individuals is high, often in the order of ⩾80%. Too often this is because the infection is not diagnosed in sufficient time to be of help in patient management.

Predisposing factors

It is well recognized that some neutropenic patients are at much greater risk of developing an invasive fungal infection than others. The likelihood of an infection developing in a leukaemic individual depends on a number of factors, including the nature and status of the underlying illness, its treatment and the use of broad-spectrum antibacterial agents.[1–4] Among BMT recipients, the age and cytomegalovirus status of the patient, the nature of the conditioning regimen, the use of T-cell depletion and the development of graft-versus-host disease (GVHD) following the transplant are additional factors contributing to the risk of developing an invasive fungal infection.[3,5–8]

Prolonged neutropenia, due to delayed engraftment, is well recognized as a major risk factor for the development of invasive fungal infection among leukaemic patients and BMT recipients. Meyers & Atkinson[9] reported that mycotic infection occurred in 57% of BMT recipients who were neutropenic for 6 weeks or longer compared with 21% of those who remained neutropenic for less than 3 weeks. Guiot *et al.*[3] noted that few patients with malignant haematological disorders survived an invasive fungal infection unless their neutrophils regenerated. The use of peripheral blood stem cell transplants has shortened the duration of neutropenia in autologous transplantation[10] and should help to reduce the risk of invasive fungal infection in these individuals.

Environmental factors are also important in the development of invasive fungal infection. For instance, defective air-conditioning plants or construction work in, or near, units in which neutropenic patients are housed, may be important risk factors for the development of invasive aspergillosis.[11–13]

Spectrum of fungal infection

The fungal infections that occur in neutropenic patients are similar to those encountered in other groups of compromised individuals. The commonest infections are candidosis, aspergillosis and mucormycosis (zygomycosis), which together account for >80% of mycotic infections in these patients. However, a growing number of uncommon organisms, such as species of *Fusarium*, *Scedosporium* and *Trichosporon*, can cause invasive infection that is often unresponsive to current antifungal agents.

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Candidosis

Candidosis is the commonest invasive fungal infection in patients with malignant haematological disorders and BMT recipients. In most cases the infection is endogenous in origin,[14] but transmission of organisms from person to person can also occur in hospital. Neutropenia is still the most important factor predisposing cancer patients and BMT recipients to invasive candidosis. Guiot *et al*.[3] noted that patients with malignant haematological disorders did not recover from this infection unless their underlying illness was in remission. Other major risk factors include the use of broad-spectrum antibacterial agents, and disruption of anatomical barriers following antineoplastic treatment or the insertion of vascular catheters.[1,15]

The symptoms and clinical signs of invasive candidosis in the neutropenic patient are non-specific; the most frequent presentation is persistent or recurrent fever, resistant to treatment with broad-spectrum antibacterial agents. Macular or erythematous cutaneous lesions are sometimes evident. Other findings that suggest the diagnosis include muscular pain and tenderness and the development of renal impairment. Endophthalmitis is uncommon in neutropenic patients, but retinal lesions sometimes develop once the neutrophil count has recovered.

Chronic disseminated candidosis is a distinct clinical entity that only occurs in leukaemic patients and BMT recipients.[16,17] Infection is thought to occur during the neutropenic period, but the disease does not manifest itself until the neutrophil count returns to normal. The presenting signs and symptoms include persistent fever, abdominal pain, elevated levels of alkaline phosphatase and CT scan defects in the liver, spleen, lungs and other organs. Cultures of biopsied lesions and blood are often negative.

Candida albicans remains the predominant cause of both superficial and deep-seated forms of candidosis in compromised patients, although the proportion of serious infections attributed to other species is increasing. In the late 1970s, *Candidia tropicalis* emerged as an important pathogen in neutropenic cancer patients.[18–21] Its emergence was associated with the introduction of more intensive cytotoxic treatment regimens, which resulted in increased gastrointestinal mucosal damage and longer periods of neutropenia. Although *C. tropicalis* is less common in the mouth or gastrointestinal tract than *C. albicans*, its isolation from stool specimens is more often predictive of invasive infection in neutropenic patients.[22,23]

In recent years, the spectrum of organisms causing invasive candidosis in neutropenic cancer patients and BMT recipients has continued to change. One reason for this is the selection pressure resulting from changes in antifungal practice. Prophylactic treatment with fluconazole has reduced the number of *C. albicans* and *C. tropicalis* infections in BMT recipients,[24,25] but its use has led to increased rates of colonization and infection with *Candida krusei* in some hospitals.[24,26,27] Like *C. krusei*, *Candida glabrata* is much less susceptible to fluconazole than *C. albicans* or *C. tropicalis*[28] and there have been reports of higher colonization rates following prophylactic treatment.[24,29] *Candida lusitaniae* is less susceptible to amphotericin B than *C. albicans* and previous polyene usage might be a factor in the increased rates of infection with this organism that have been noted in several institutions.[30,31]

Aspergillosis

The incidence of invasive aspergillosis tends to vary greatly between institutions. In part this relates to patient selection and differences in conditioning regimens or other supportive measures. However, one critical factor influencing the infection rate is the level of environmental contamination. Elevated spore counts have been detected in haematological units with ongoing adjacent building work or defective air filtration and these have been associated with an increase in the rate of infection. Factors other than environmental contamination are also important in determining the risk of development of aspergillosis. As in candidosis, prolonged neutropenia is a major predisposing factor for this infection.[2,32] Chronic GVHD has also been shown to be a significant risk factor. Guiot *et al*.[3] noted that eight of ten BMT recipients with this complication developed fatal aspergillus infection compared with two of 36 without GVHD.

Moulds of the genus *Aspergillus* are among the most widespread of fungi in the human environment, being found in the soil, in the air, on plants and on decomposing organic matter.[33] In the home, these moulds are often found in dust and on food. Similar contamination occurs in the hospital environment and can result in outbreaks of aspergillus infection amongst neutropenic cancer patients and BMT recipients.[12,13,34] Air filtration can reduce the incidence of nosocomial aspergillosis,[35] but exposure to aspergillus spores cannot be avoided after patients have been discharged from hospital. Moreover, although inhaled spores have been suggested as the major source of invasive infection, there is evidence that reactivation of endogenous organisms can also produce significant infection.[36]

As in other groups of compromised patients, the commonest clinical presentation of aspergillosis is unremitting fever and the development of lung infiltrates despite treatment with broad-spectrum antibacterial agents. The diagnosis is difficult because the radiological signs are varied and non-specific, ranging from focal (often peripheral) nodules to diffuse consolidation or cavitation.[37] CT scanning is sometimes helpful in diagnosing aspergillus infection in a neutropenic patient with antibiotic-resistant fever: a distinctive halo of low attenuation tends to surround the lesions.[38]

The isolation of aspergillus from sputum is not a particularly sensitive method for confirming the diagnosis: no more than 25% of patients who are later shown to have invasive aspergillosis have positive sputum cultures *ante mortem*.[39] On the other hand, the isolation of an *Aspergillus* sp. (particularly *Aspergillus fumigatus* or *Aspergillus flavus*) from sputum of a high-risk patient, on even a single occasion, is often indicative of invasive infection and should never be dismissed.[40] The definitive diagnosis of invasive aspergillosis of the lungs depends on the demonstration of the fungus in histological sections, but patients are often too ill to undergo invasive investigations. In this situation, bronchoalveolar lavage (BAL) is the most helpful diagnostic procedure.[41,42] Isolation of aspergillus from BAL fluid in a BMT recipient is often indicative of invasive infection, but occurs in only 50–60% of patients. Nasal cultures were noted to be predictive of invasive *A. flavus* infection during one outbreak of nosocomial aspergillosis associated with building renovation.[43] However, their usefulness has not been confirmed in other studies of routine microbiological surveillance.[44,45]

The brain is involved in about 10% of cases of invasive aspergillosis, but cerebral infection is seldom diagnosed during life. This infection commonly follows haematogenous dissemination from the lungs and it is unusual for it to result from spread from the nasal sinuses.[46] Patients present with focal rather than meningeal signs. The prognosis is poor.

Mucormycosis

As in aspergillosis, long-term neutropenia is a major risk factor for mucormycosis. Many different organisms have been implicated, but the commonest cause of human infection is *Rhizopus arrhizus*. Other less frequent aetiological agents include *Absidia corymbifera* and *Rhizomucor pusillus.* These moulds are widespread, being found in the soil, in the air, in food and on decomposing organic matter. Infection usually follows inhalation. Nosocomial mucormycosis is not as common as hospital-related aspergillosis. Allan *et al.*[47] reported that three (11%) of 27 cases of lung infection following BMT at their institution were due to mucormycosis.

The two commonest presentations of mucormycosis in the neutropenic patient are rhinocerebral and lung infections. Rhinocerebral mucormycosis begins as a nasal or paranasal sinus infection and spreads, as a mass of ischaemic necrosis, through bone to the orbit or to the brain. The presenting symptoms and signs include painful unilateral facial swelling, proptosis and ophthalmoplegia, together with a serosanguinous nasal discharge. Characteristic black intra-nasal or palatal eschars are often found.[48] Since rhinocerebral mucormycosis is such an aggressive infection, a rapid diagnosis is essential for successful treatment. Sinus radiographs and CT scans are more useful in delineating the extent of infection than in establishing a diagnosis.[49] Smears of nasal scrapings or discharge are often helpful, but if these are unrevealing, biopsies or debridement of necrotic lesions should be performed.

Mucormycosis of the lungs is less common than aspergillosis, and is seldom diagnosed during life. Patients often present with cough and fever, but there are no characteristic clinical or radiological signs to distinguish mucormycosis from other bacterial and fungal infections.[50] The radiological signs are varied, but infiltrates or nodules are more common than cavitation or an effusion. Since the Mucorales are common culture contaminants, isolation of these organisms from BAL fluid must be interpreted with caution.[51] However, their isolation from a neutropenic patient must never be ignored.

Terminal widespread dissemination is common in neutropenic patients with mucormycosis of the lung. The commonest site of spread is the brain, but metastatic lesions have also been found in the spleen, heart and other organs. The condition is seldom diagnosed during life, but in occasional patients necrotic cutaneous lesions may permit an earlier diagnosis.[52] Amphotericin B is the most effective antifungal agent and, when combined with surgical resection of infected tissue, can improve survival. With progressive dissemination of the infection, surgical intervention becomes less beneficial.[50]

Other fungal pathogens

Numerous other fungi have been reported as occasional causes of serious infection in neutropenic patients. These include an increasing number of common environmental moulds, such as *Fusarium* spp. and *Scedosporium* spp., and yeasts such as *Trichosporon* spp. Infections with these fungi tend to be disseminated and are often fatal in neutropenic patients. Their treatment has not been standardized.

Invasive fusarium infections are becoming more important among neutropenic cancer patients and BMT recipients.[53–56] These infections usually follow inhalation, but some originate from cutaneous lesions associated with infected nails.[54,57] The characteristic signs include persistent fever and widespread nodular cutaneous lesions. The latter occur in 60–70% of patients with fusarium infection, compared with $<10\%$ of patients with aspergillosis.[54] The diagnosis depends on the isolation of the organism in culture because the septate, branching mycelium of a *Fusarium* sp. cannot be distinguished from that of other aetiological agents of hyalohyphomycosis or aspergillosis. The most frequent cause of human infection is *Fusarium solani*, but *Fusarium oxysporum*, *Fusarium moniliforme* and a number of other species have also been incriminated.[58] Infection with these organisms has been associated with a much higher rate of isolation from blood culture (about 50–60% of cases) than has been the case with aspergillus and other invasive mould infections.[54–56] Many neutropenic patients with invasive fusarium infection die before the condition is suspected. These moulds are often resistant to amphotericin B[56] and, even with high-dose treatment (1–2 mg/kg), the prognosis is poor unless the neutrophil count recovers. Limited experience suggests that shortening the duration of neutropenia with colony stimulating factors may be beneficial in treating invasive fusarium infection.

Two members of the genus *Scedosporium* have been associated with invasive infections in neutropenic cancer patients and BMT recipients. *Scedosporium apiospermum* (the current name for the imperfect form of the ascomycete *Pseudallescheria boydii*) and *Scedosporium prolificans* (which used to be named *Scedosporium inflatum*) can cause localized deep-seated infections, such as sinusitis, osteomyelitis and meningitis, in non-immunosuppressed individuals, but tend to become disseminated in neutropenic patients.[59–61] As in aspergillosis, the usual presentation is an unremitting fever and there are no specific symptoms or clinical or radiological signs. The diagnosis depends on the isolation of the organisms because microscopical examination will not distinguish them from other aetiological agents of hyalohyphomycosis or aspergillosis. This is important because *S. apiospermum* is often resistant to amphotericin B,[62] and infections are probably best treated with an azole such as parenteral miconazole or oral itraconazole, while *S. prolificans* appears resistant to all antifungal agents.[63]

The term trichosporonosis is used to describe infections due to *Trichosporon beigelii* (which used to be named *Trichosporon cutaneum*) and *Blastoschizomyces capitatus* (the current name for *Trichosporon capitatum*). In most cases these appear to be derived from an endogenous reservoir of organisms in the gastrointestinal tract. In neutropenic patients, trichosporonosis is a life-threatening infection and widespread dissemination often occurs.[64–66] Blood cultures are frequently positive and necrotic cutaneous lesions are common. All untreated patients with disseminated trichosporonosis have died as have 75% of those receiving treatment. Many strains of *T. beigelii* are resistant to amphotericin B[67] and, even with high-dose amphotericin B treatment, the prognosis is poor unless the neutrophil count recovers. Fluconazole is sometimes effective in the treatment of trichosporonosis.

Treatment of fungal infection

Empirical treatment with amphotericin B

Neutropenic patients, particularly BMT recipients and those receiving cytotoxic treatment for leukaemia, are at increased risk of developing an invasive fungal infection. For this reason, and because it has become clear that the earlier treatment is started the better the prognosis, it has become common practice to begin empirical antifungal treatment without waiting for formal proof that a patient with persistent unexplained fever, resistant to antibacterial agents, has a particular fungal infection. As with other groups of compromised individuals, amphotericin B remains the drug of choice for the empirical treatment of suspected fungal infection in neutropenic patients because no other agent has been shown to have as broad a spectrum of action.

Two randomized clinical trials[68,69] have demonstrated that empirical administration of amphotericin B results in a reduction in the number of patients developing invasive fungal infection. In the first trial, febrile patients received either amphotericin B or no antifungal treatment after 1 week of broad-spectrum antibacterial treatment.[68] Although the number of patients studied was small, a benefit was apparent in those who were treated with amphotericin B. In the second trial,[69] earlier and more frequent resolution of fever was found in the patients randomized to receive amphotericin B rather than no antifungal treatment after 4 days of antibacterial treatment. No difference in the overall survival rate was demonstrated, but four fatal fungal infections occurred among 64 patients who had not received amphotericin B compared with none among 68 patients given the drug.

These results are encouraging but, as Walsh *et al.*[70] have pointed out, empirical treatment with amphotericin B does not always prevent the development of invasive fungal infection. *Aspergillus* spp., *Fusarium* spp. and *T. beigelii* are among the organisms reported to have caused overt infection during such treatment.[54,67,71] Burch *et al*.[71] described the development of invasive aspergillus infection in patients receiving empirical amphotericin B and noted subsequent improvement when the dosage was increased to 1.0–1.5 mg/kg/day. Merz *et al*.[54] reported the development of *F. solani* infection in patients receiving empirical amphotericin B. These patients also improved after administration of higher dosages. In both of these reports, however, flucytosine was added to the higher-dose amphotericin B regimen in most cases and the relative contribution of the two compounds is unclear.

The unpleasant side effects of amphotericin B have prompted investigations into the role of other antifungal agents in the management of persistent fever in neutropenic patients. In one randomized trial, eight of 16 patients with antibiotic-resistant fever responded to parenteral fluconazole (4 mg/kg) while 21 of 25 responded to amphotericin B (0.5 mg/kg).[72] The death rate from fungal infection was four times higher in the fluconazole group and it was found that, although this drug was better tolerated, it was inferior to amphotericin B in terms of prevention of invasive aspergillus infection and death from aspergillosis.

Lipid-based formulations of amphotericin B

Amphotericin B remains the drug of choice for a substantial number of invasive fungal infections, including candidosis, aspergillosis and mucormycosis. Its advantages include its broad spectrum of action and its parenteral administration, often essential for the neutropenic patient with a serious infection. The major disadvantage of amphotericin B is that the dosage that can be administered is limited by unpleasant infusion-related reactions and harmful side effects, particularly renal damage. A further problem has been the poor results of treatment in patients with persistent neutropenia, an outcome seen with both aspergillosis and candidosis.

These problems have stimulated attempts to develop new formulations of the drug. Three promising lipid-based formulations have been licensed in the UK and they have been found to be less nephrotoxic than the conventional micellar suspension, because of their altered pharmacological distribution.[73–76] These are AmBisome, a liposome-encapsulated formulation of amphotericin B, Amphocil, a colloidal dispersion (ABCD), and Abelcet, a lipid-complexed formulation (ABLC).

Mills *et al.*[77] used liposomal amphotericin B (at dosages of up to 5 mg/kg) to treat suspected or confirmed fungal infection in 116 neutropenic patients not tolerating or not responding to conventional amphotericin B. Thirteen (62%) of 21 patients with confirmed aspergillosis showed a full or partial resolution of clinical and radiological signs of infection, as did 19 (53%) of 36 patients with suspected aspergillus infection. The patients who responded tended to have higher neutrophil counts which rose over the following 2 weeks when compared with the non-responding patients. However, three patients with proven infection responded to liposomal amphotericin B without the neutrophil count rising above 0.5×10^9/L, and in two others the drug was discontinued without recurrence of the infection while the count was $<0.5 \times 10^9$/L. These results indicate that liposomal amphotericin B is effective against aspergillus infection in neutropenic patients and can produce a response in cases where the conventional formulation has failed.

Oppenheim *et al.*[76] used ABCD to treat 168 patients with suspected or confirmed invasive fungal infection. All had earlier failed to respond to conventional amphotericin B, or had renal impairment, or other treatment-limiting toxic effects. Of the 97 patients who could be evaluated, 48 showed a full or partial clinical response, including 19 (58%) of 33 patients with candidosis and 11 (34%) of 32 patients with aspergillosis. The response rate was lower in patients who were neutropenic, but three of the four complete clinical responses among patients with aspergillosis occurred in individuals with neutrophil counts of $<0.5 \times 10^9$/L at the end of treatment.

To date, most reports of treatment of serious fungal infections with ABLC have been published in abstract form. In an open trial,[78] 52 cancer patients with confirmed or suspected mycotic infection were treated with this lipid-based preparation. Thirty-five had earlier failed to respond to conventional amphotericin B. Of the 43 patients who could be evaluated, 28 (65%) showed a full or partial resolution of clinical and radiological signs of infection. Anaissie *et al.*[79] reported the results of a randomized trial comparing ABLC (5 mg/kg) with conventional amphotericin B (0.6–1.0 mg/kg) in 231 patients with candidosis. The response rates were similar (63% and 68%), but ABLC proved less nephrotoxic.

There are also a number of individual case reports of successful treatment of neutropenic patients with different lipid-based amphotericin B preparations. These include several patients with fusarium infection[80–82] or mucormycosis.[83] Taken as a whole, the results of recent trials with the three new formulations of amphotericin B are encouraging. However, these agents are expensive and, until the results of larger randomized trials are available, their use should be restricted to those patients who fail to respond or who become intolerant to the conventional formulation.

Azoles

Fluconazole has proved an effective agent for mucosal forms of candidosis in neutropenic patients.[84] Two reports have indicated that it is effective in patients with chronic disseminated (hepatosplenic) candidosis who had failed to respond to amphotericin B.[85,86] Another report concluded that it is as effective as, but better tolerated than, amphotericin B in the treatment of candidaemia in non-neutropenic individuals.[87] However, it is ineffective as treatment for *C. krusei* infection in neutropenic patients[24,88] and it should not be used to treat infections with *Aspergillus* spp., *Fusarium* spp. or the Mucorales.[89,90]

Itraconazole is the only oral triazole drug available at present that is effective against both aspergillus infection and candidosis. In one small randomized trial, ten of 16 neutropenic patients with candidosis responded to itraconazole while nine of 16 responded to amphotericin B.[91] There have been several reports suggesting that invasive aspergillosis in neutropenic patients will sometimes respond to itraconazole treatment.[92–94] In the largest of these open trials, Denning *et al.*[93] treated 76 individuals and obtained a full or partial response in eight (61%) of 13 neutropenic patients and three (38%) of eight BMT recipients. These rates were similar to those reported elsewhere for amphotericin B treatment. Low blood levels of itraconazole were detected in some individuals who failed treatment, a problem that has often been encountered in neutropenic cancer patients and BMT recipients.[95,96] The new oral solution formulation of itraconazole, which is much better absorbed in these individuals, should reduce this problem.[97,98]

Prevention of fungal infection

The problems of detecting invasive fungal infections in neutropenic patients and the often disappointing results of attempts to treat established infections have stimulated interest in methods of preventing these lethal conditions. The main approaches have involved protective isolation of patients at risk or the use of prophylactic antifungal treatment. The most extreme attempts have involved creation of a total protected environment including laminar air flow rooms with HEPA filtration and the administration of combinations of topical and oral antifungal agents.

Aspergillus spp., *Fusarium* spp. and the Mucorales are among the numerous environmental moulds that can often be recovered from dust, food, plants or building materials. Therefore, the first steps in the prevention of infection in neutropenic patients should consist of measures to eliminate obvious sources of environmental contamination, such as removing plants from rooms where at-risk patients are being treated. Foodstuffs, such as nuts and spices, that are often contaminated with moulds should not be offered to neutropenic patients. These individuals should not be treated in units with ongoing, adjacent building work, but if this cannot be avoided, measures should be instituted to minimize the entry of dust and contaminated air.

Protected environment

Housing neutropenic patients in isolation rooms supplied with HEPA-filtered air has reduced the incidence of aspergillosis.[35] The benefits of this approach have, however, to be weighed against the disadvantages of isolation of the patient and the cost.[99] Infection can still develop if patients are colonized before their admission to hospital, or are moved from the protected environment to other parts of the hospital for irradiation,[100] or insertion of Hickman catheters.[101] Moreover, improper operation or poor maintenance of sophisticated ventilation systems can lead to outbreaks of fungal infection in units fitted with laminar air flow isolation rooms.[13]

Antifungal prophylaxis

Antifungal prophylaxis has involved the use of oral non-absorbable compounds, such as nystatin, and oral absorbed drugs, such as fluconazole, itraconazole and ketoconazole. The results with nystatin and ketoconazole have been unimpressive, but low-dose fluconazole (50–200 mg) has been found to reduce the incidence of mucosal colonization and superficial infection with *C. albicans* in neutropenic cancer patients and BMT recipients.[29,102] The benefits of higher dose fluconazole (400 mg) have been assessed in two randomized trials in BMT recipients.[25,103] In both trials, fluconazole reduced the incidence of fungal colonization, superficial and deep forms of candidosis, and the number of deaths associated with fungal infection. However, there was no reduction in the number of mould infections in either trial. In neutropenic cancer patients, a randomized trial showed that fluconazole (400 mg) prevented oral candidosis.[104] The incidence of invasive fungal infection was halved in the group of patients receiving fluconazole, but the difference did not achieve statistical significance. In another recent trial, prophylactic treatment with fluconazole (400 mg) proved as effective, but less toxic than parenteral amphotericin B (0.5 mg/kg three times per week) in preventing candidosis in leukaemic patients undergoing remission-induction treatment.[105] Neither treatment prevented mould infection.

The use of oral itraconazole represents another possible approach to the prevention of invasive fungal infection in neutropenic patients. To date, one randomized trial has been reported in which patients were treated with itraconazole (200 mg bd) plus oral amphotericin B or amphotericin alone.[106] No differences in the incidence of invasive fungal infection were detected. These discouraging results could be due to impaired absorption of itraconazole, leading to sub-optimal serum concentrations, which were not measured. The results of the larger randomized trials, now in progress, will be awaited with interest. An earlier open trial of itraconazole in neutropenic cancer patients showed a significant reduction in the number of deaths from invasive aspergillosis compared with historical controls who had received prophylactic treatment with ketoconazole.[107] Only one patient with adequate serum concentrations of itraconazole (>250 ng/mL measured by HPLC) developed invasive aspergillosis compared with five in the group with inadequate levels, an internal control that suggests that differences in patient exposure to aspergillus spores was a possible reason, though not the only one, for differences between the two trial periods. A second open trial of itraconazole prophylaxis for aspergillus infection during a period of hospital reconstruction also showed an encouraging response, except in those patients with long-term neutropenia.[108]

The development of a new oral solution formulation of itraconazole should help to overcome the problem of variable absorption in neutropenic patients, such as BMT recipients[97] and those undergoing remission-induction treatment.[98] Meanwhile, it has been recommended that the current formulation of itraconazole, at a dosage of 200–400 mg, should be used as antifungal prophylaxis in patients nursed without HEPA filters, where there is a high institutional incidence of invasive aspergillosis or where building works are being undertaken.[109] Itraconazole should also be substituted for other antifungal prophylaxis in such institutions in patients neutropenic for >3 weeks. Levels of itraconazole should be measured at 1 week intervals in BMT recipients with gastrointestinal damage.[109]

The use of low doses of parenteral amphotericin B (0.1–0.2 mg/kg) as prophylaxis has been reported to be successful in preventing aspergillus infection in allogeneic BMT recipients in one trial with historical controls,[110] but failed in a randomized trial in 182 neutropenic autologous BMT recipients.[111] The toxic side effects of the conventional formulation of amphotericin B preclude its prophylactic use at a higher dosage. However, a controlled trial of liposomal amphotericin B (AmBisome) for the prevention of fungal infection in BMT recipients suggests this approach is useful.[112] Thirty-six patients received the drug, at a dosage of 1 mg/kg, for between 1 and 11 weeks and 40 received no treatment. Presumed fungal infection occurred in five of the 36 patients given amphotericin B, and in none was it fatal. In the control group seven patients developed presumed fungal infection and two died.

Amphotericin B has also been administered to at-risk patients as a nasal instillation[113–115] or in a nebulized form.[116] Meunier[114] reported a randomized trial in which 46 neutropenic patients who received intranasal amphotericin B were compared with 44 controls who did not. Aspergillus infection developed in one patient receiving amphotericin and in five of the control group. Inhaled (nebulized) amphotericin B has also been reported to reduce the rate of aspergillus infection in neutropenic patients when compared with historical controls.[116]

Neutropenic patients who recover from aspergillosis or hepatosplenic candidosis can suffer from reactivation of these infections during subsequent periods of intensive cytotoxic treatment.[36] The use of high-dose amphotericin B (1.0 mg/kg) has been evaluated as a prophylactic treatment in patients who have had a previous invasive aspergillus infection and are again neutropenic.[37] Although this was an open trial, this approach did appear to bring about a significant reduction in reactivation of this infection and its use should be considered in at-risk solid organ and BMT recipients. The new liposomal and lipid-based formulations of amphotericin B have obvious potential for this indication. There is insufficient experience with itraconazole to recommend it as first-line treatment for this indication.

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