ANTIFUNGAL THERAPY CONTROL IN NEUTROPENIC CHILD WITH ACUTE LIMPHOBLASTIC LEUKEMIA (ALL)

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Abstract

In recent years there has been an increasing incidence and awareness of mucosal candidiasis and invasive fungal infections in neutropenic patients. Early diagnosis (before serious morbidity and mortality) is often difficult, emphasizing the continuing need for adequate prophylaxis. Here is proposed a review of studies on the chemoprophylaxis of fungal infections in neutropenic patients. There are a limited number of large, prospective, well-designed studies using proper criteria and end points. No antifungal drug or drug combination has been shown to prevent invasive fungal infection with the exception of fluconazole (mainly Candida Albicans infections) in certain high-risk patient groups. Prophylaxis strategies are dependent upon local conditions, patient populations, types of therapies, available resources, etc. Future improvement will be based upon: improved study quality, new strategies for established drugs, development of new and safer drugs, strategies to eliminate or reduce immuno-suppression and cost-benefit studies.

Key words: neutropenia, disseminated candidiasis, prophylaxis, invasive aspergillosis.

Introduction

Beside bacterial pathogens, also fungal infections represent a risk for neutropenic child patients. In fact, fungal infections have emerged as a major problem in heavily pretreated (with antineoplastic agents) children who experience long periods of neutropenia and require extended treatment with broad spectrum antibiotics. Early studies with empirical antifungal therapy, in parallel with antibacterial therapy, have been effectively used to treat patients with persistent or new fever. Pizzo et al. demonstrated the utility of administering empirical antifungal therapy on day 7 of fever whereas the European Organization for Research and Treatment of Cancer showed a similar benefit at day 4. [1, 2] Although no two studies are in full agreement as to the preferred time of initiating empirical antifungal therapy, it is important to recognize that during this time frame, 4 to 7 days on therapy, strong consideration should be given to initiation of empirical antifungal therapy in the persistently febrile child with prolonged neutropenia. [3] Unfortunately, the choice of antibiotics is limited to amphotericin B, which has a relatively high toxicity profile. Nonetheless, the risk of fungal infection is high enough in the persistently febrile patient to warrant its use until return of neutrophil counts. The efficacy of fluconazole has not been established as a prophylactic measure in children at increased risk, in other words, those with an expected long duration of neutropenia (more than 7 to 10 days). Similarly, fluconazole has not been shown to be equivalent or superior to amphotericin B for the indication of empirical antifungal therapy.

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. [4-7] Prolonged neutropenia, due to delayed engraftment, is well recognized as a major risk factor for the development of invasive fungal infection among leukaemic patients. 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. [8-10]

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.

Candidosis

Candidosis is the commonest invasive fungal infection in patients with malignant haematological disorders. In most cases the infection is endogenous in origin, [11] but transmission of organisms from person to person can also occur in hospital. Neutropenia is still the most important factor predisposing cancer patients to invasive candidosis. Guiot *et al*. [6] 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. [4, 12] 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. [13, 14] 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, *Candida tropicalis* emerged as an important pathogen in neutropenic cancer patients. [15 - 18] 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. [19, 20] In recent years, the spectrum of organisms causing invasive candidosis in neutropenic cancer patients 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, but its use has led to increased rates of colonization and infection with *Candida krusei* in some hospitals. [21, 22] Like *C. krusei*, *Candida glabrata* is much less susceptible to fluconazole than *C. albicans* or *C. tropicalis* [23] and there have been reports of higher colonization rates following prophylactic treatment. [24] *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. [25, 26]

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. [5, 27] 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. [28] 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. [9, 10] Air filtration can reduce the incidence of nosocomial aspergillosis, [29] 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. [30] 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. [31] 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. [32] 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*. [33] 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. 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. Nasal cultures were noted to be predictive of invasive *A. flavus* infection during one outbreak of nosocomial aspergillosis associated with building renovation. However, their usefulness has not been confirmed in other studies of routine microbiological surveillance. 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. [34] 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. 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. [35] 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. [36] 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. 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. 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. 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.

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. These infections usually follow inhalation, but some originate from cutaneous lesions associated with infected nails. The characteristic signs include persistent fever and widespread nodular cutaneous lesions. 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. [37] Many neutropenic patients with invasive fusarium infec tion die before the condition is suspected. These moulds are often resistant to amphotericin B56 and, even with high-dose treatment, 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.

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.

TREATMENT OF FUNGAL INFECTION

Empirical treatment with amphotericin B

Neutropenic patients and those receiving cytotoxic treatment for leukemia, 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 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. Although the number of patients studied was small, a benefit was apparent in those who were treated with amphotericin B. In the second trial, 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 patients who had not received amphotericin B compared with none among patients given the drug. These results are encouraging but, as Walsh *et al.* [38] 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.

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. These are AmBisome, a liposome-encapsulated formulation of amphotericin B, Amphocil, a colloidal dispersion (ABCD), and Abelcet, a lipid-complexed formulation (ABLC).

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 or mucormycosis. 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. Two reports have indicated that it is effective in patients with chronic disseminated (hepatosplenic) candidosis who had failed to respond to amphotericin B. Another report concluded that it is as effective as, but better tolerated than, amphotericin B in the treatment of candidaemia in non-neutropenic individuals. However, it is ineffective as treatment for *C. krusei* infection in neutropenic patients and it should not be used to treat infections with *Aspergillus* spp., *Fusarium* spp. or the Mucorales. Itraconazole is the only oral triazole drug available at present that is effective against both aspergillus infection and candidosis.

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. [29] The benefits of this approach have, however, to be weighed against the disadvantages of isolation of the patient and the cost. 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, or insertion of Hickman catheters. 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. [10]

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. Fluconazole reduced the incidence of fungal colonization, superficial and deep forms of candidosis, and the number of deaths associated with fungal infection. In neutropenic cancer patients, a randomized trial showed that fluconazole prevented oral candidosis. The incidence of invasive fungal infection was halved in the group of patients receiving fluconazole, but the difference did not achieve statistical significance. The use of oral itraconazole represents another possible approach to the prevention of invasive fungal infection in neutropenic patients. The development of a new oral solution formulation of itraconazole should help to overcome the problem of variable absorption in neutropenic patients and those undergoing remission-induction treatment. Neutropenic patients who recover from aspergillosis or hepatosplenic candidosis can suffer from reactivation of these infections during subsequent periods of intensive cytotoxic treatment. [30]

Conclusions

In recent years there has been increasing incidence and awareness of mucosal candidiasis and invasive fungal infections in neutropenic patients. Early diagnosis (before serious mortality and morbidity) is often difficult, indicating the continuing need for adequate prophylaxis. Empirical antifungal therapy should always be instituted when invasive fungal infection is suspected. A number of factors

must be taken into consideration with regard to the use of prophylactic antifungal agents in neutropenic patients. [39] The prophylactic drug must be safe and have a well-established efficacy based on properly designed clinical studies. It is imperative to include cost-benefit analysis in such studies. Clinicians must also consider the frequency of fungal infections in their own patients prior to using prophylaxis regimens. In addition, widespread use of azoles in immuno-compromised patients for prolonged periods can potentially select for drug-resistant yeast and mold infections. An illustrative example is the emergence of resistant Candida spp. such C. krusei as systemic pathogens. There is a limited number of large prospective well designed studies using proper criteria and end points. No antifungal drug or drug combination has been shown to prevent invasive fungal infection with the exception of fluconazole in certain high-risk patient groups. Future improvement is mainly dependent upon a) improved study quality, b) new strategies for established drugs, c) development of new and safer drugs, d) new strategies to eliminate or reduce immuno-suppression and e) cost-benefit studies.

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