

Experience with liposomal amphotericin B at the Hematology-Oncology Department Children's Hospital Salata Medical School, University of Zagreb

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Abstract. The incidence and severity of fungal infections in children with malignant diseases treated with intensive chemotherapy or allogeneic hematopoietic cell transplantation on the hematology-oncology department Children's Hospital Salata Medical School University of Zagreb is analyzed. The efficacy of antifungal therapy is presented. (www.actabiomedica.it)

Key words: Invasive fungal infection, children, malignant diseases

Introduction

Immunocompromised patients are at increased risk for a variety of infections based upon their degree of immunosuppression and exposures. Despite the progress in microbiology, clinical pharmacology and supportive care, invasive fungal infections (IFI) for several decades are still remaining a major cause of morbidity and mortality in immunocompromised patients undergoing anticancer treatment. In immunocompromised patients, fungi most often cause serious or lethal infections. Fungal infections are opportunistic infections, whose pathogenicity is determined by the affected host's immune and clinical status. The overall incidence in immune compromised patients ranges between 2% and 40% depending considerably on diagnostic criteria and definition of infection. Most systemic fungal infections occur during the neutropenic phase, early after intensive chemotherapy or the transplant. However, infections may also occur later depending on the patient's clinical and immune status. Prolonged neutropenia, disruption of mucosal barriers by intensive chemotherapy, use of indwelling catheters

and broad-spectrum antibiotics are factors associated with IFI. The majority of fungal infections in immunocompromised patients are caused by *Candida species*, followed by *Aspergillus species* and only occasionally by other fungi such as *Fusarium*, *Histoplasma*, or *Coccidioides*. The diagnosis of IFI is difficult, and frequently the presence of fungal infection has not been discovered until the autopsy. The current methods of diagnostic and treating fungal diseases are suboptimal. Moreover, the treatment of IFI with conventional therapy (amphotericin B) may not be effective, even if introduced early (1, 2).

Patient and methods

The outcome of fungal infections in immunocompromised patients at the Department of Hematology and Oncology was analyzed from January 1st 2002 to December 31st 2005. A total of 118 immunocompromised children were analyzed for fungal colonization. In this period, 82 patients receiving intensive chemotherapy or hematopoietic cell transplanta-

tion were included into the study. Fungal infections were classified as proven infection (clinical signs of infection and positive blood or tissue culture for yeast or mold), probable infection (clinical signs of infection, typical lung CT scan and positive fungal colonization) or possible infection (clinical signs for infection and positive fungal colonization). For fungal prophylaxis 10-12/mg/kg/day of fluconazole was given to 118 patients. Amphotericin B deoxycholate was started as empiric antifungal therapy. In our institution amphotericin B deoxycholate is given to patients with persistent fever 48 hour after 2nd line antibiotic therapy was started or earlier in patients with high risk for invasive fungal infections and in patients with clinical signs for probable fungal infection. Lipid formulations of amphotericin B are administered to patients classified as high risk and/or patients with proved or probable fungal infection.

Results

From 1st January 2002 to 31st December 2005, fungal colonization was analyzed in 118 immunocompromised patients. Positive yeast isolates were documented in 85 or 72% of all hospitalizations, while mold was positive in 22 (18%) isolates, mostly samples from sputum.

Lipid formulations for therapy of invasive fungal infections have been given to 42 (36%) patients (male/female 24/18, median age 7 years with a range 3 to 18 years), 3 receiving allogeneic transplantation, 5 autologous transplantation, 33 intensive chemotherapy because of acute leukemia, non-Hodgkin lymphoma, neuroblastoma and 1 immunosuppressive therapy with high dose dexamethasone. Proven, probable or possible fungal infections were documented in 6, 25 and 11 patients respectively. Clinical and microbiological data suggested invasive candidiasis and aspergillosis in 35 and 7 patients respectively. The median dose of lipid formulations given was 1.5 mg/kg/day during 15-25 days. A good treatment response was documented in 29 patients, whilst in 13 patients there was no improvement. Seventeen patients died; the main causes of death were underlying disease and invasive fungal infection.

Discussion

The invasive form of fungal infection represents a serious clinical problem with high related mortality. Moreover, the diagnosis of IFI often leads to discontinuation of intensive anticancer and immunosuppressive therapy. It is often hard to determine when to start antifungal treatment due to difficulty in diagnosis. There is no consensus on treatment duration; rather, this depends on the patient's immune status. The time to stop therapy is also often uncertain.

The drug of choice for treatment of invasive fungal infections have since long been amphotericin B. It has a broad spectrum of antifungal activity with low risk of resistance development. Despite the fact that amphotericin B is regarded as the "gold standard" in antifungal therapy, it has formidable toxicities, and in most of cases must be discontinued after a short time (especially in patient with cancer, undergoing chemotherapy or/and immunosuppressive therapy) due to multiple organ toxicities and primary nephrotoxicity which may be agonistic with other nephrotoxic drugs. Incorporation of amphotericin B into small unilamellar liposomes, (AmBisome[®]) reduces the toxic side effects while retaining the *in vivo* and *in vitro* antifungal effectiveness of amphotericin B. Liposomal amphotericin B is well tolerated. AmBisome[®] safety data reveals low frequency of adverse reactions and few acute side-effects. There is little evidence to suggest any substantial impairment in renal function compared to conventional amphotericin B (3).

Safer and less toxic lipid-based versions of amphotericin B are available now in the majority clinical centers. At our department, AmBisome[®] has been used since 1995, and AmBisome[®] has demonstrated an improved efficacy compared to conventional amphotericin B. The reduced toxicity has led to earlier institution of treatment, in many cases only on suspicion of an infection in patient at risk and also prophylaxis has been made possible. Our patients received AmBisome[®] at the conventional dose of 1.0 mg/kg/day for a suspected infection, but if instituted earlier it might well prevent the development of serious infection. Other treatment regimens, using fungistatic agents might allow an infection to become established which would then result in the use of hi-

gher doses of AmBisome®. Early therapy is also the modern way of thinking about antifungal treatment, since today three types of antifungal treatment are given: prophylaxis, pre-emptive therapy/prophylaxis guided by laboratory tests or clinical characteristics in high-risk patients, and treatment of an established or suspected fungal infection (4).

In our experience therapy with AmBisome®, in case of IFI in children with malignant diseases was effective.

Currently, it is important to stress optimal diagnostic and treatment approach for severely immunocompromised patients mostly treated with aggressive chemotherapy

Conclusion

AmBisome® have reduced toxicity and improved efficacy in the treatment of suspected and proven in-

vasive fungal infections in severely ill, immunocompromised patients

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