

Successful combined antifungal salvage therapy with liposomal amphotericin B and caspofungin for invasive *Aspergillus flavus* infection in a child following allogeneic bone marrow transplantation

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Abstract. The emergence of new antifungal compounds with alternative mechanisms of action and improved tolerability has opened up new therapeutic possibilities for the use of combined antifungal treatment in life-threatening systemic fungal infections. A case report of an 8-year-old allogeneic stem cell transplant recipient who developed a central venous catheter tunnel infection caused by *Aspergillus flavus* is presented here. In spite of conventional and subsequent liposomal amphotericin B therapy the infection progressed rapidly and the necrosis extended further to the thoracic wall, pleura and the right lung. Combined treatment consisting of liposomal amphotericin B and caspofungin was instituted. After 30 days of dual therapy the deep fungal infection resolved and the extensive soft tissue defect showed scarring. One year post-transplant, the patient is well, with normal bone marrow function and full donor chimerism. Although there is limited clinical data on the effectiveness of echinocandins in pediatric patients with documented invasive fungal infections, this case report shows that combining liposomal amphotericin B with caspofungin could be advantageous. (www.actabiomedica.it)

Key words: *Aspergillus flavus*, antifungal compounds, tolerability

Introduction

Invasive aspergillosis has become a growing problem among allogeneic HSCT patients with an incidence that varies from 10-30% with an unacceptable mortality rate (1). Since the results with the former gold standard therapy with conventional amphotericin B were disappointing, new treatment options with the use of lipid formulations of amphotericin B, newer triazoles and echinocandins have been evaluated.

So far, there are only few case reports or case series with a limited number of patients reporting the use of combination therapy using caspofungin to-

gether with amphotericin B, voriconazole or other azole compounds. Available data are even more scarce regarding the effectiveness, safety and dosage regimens of caspofungin in children.

Case report

A previously healthy, 8-year-old girl presented with a short history of fatigue and jaundice to her family doctor in September 2003. Laboratory examinations revealed elevated hepatic transaminases. Tests for viral infections were negative but the hepatitis pro-

gressed rapidly. Coagulation parameters worsened, the jaundice became deeper and due to an imminent hepatic failure she was referred to the pediatric intensive care unit. As a part of a detailed examination, a liver biopsy was performed. Histology revealed viral hepatitis; extended viral tests were done but only transfusion transmitted virus (TTV) positivity was found by PCR. During the following few weeks her general condition significantly improved. Although synthetic liver function tests became normal, transaminase levels remained elevated (about 1500 U/l). By the end of October 2003 peripheral pancytopenia developed. A bone marrow biopsy revealed a marked hypocellularity. With further diagnostic workup other possible causes of pancytopenia were excluded and acquired severe aplastic anaemia was diagnosed. Considering her HLA identical sibling, an immediate allogeneic bone marrow transplantation was planned. The pre-transplant Hickman catheter insertion was complicated by a right-sided pneumothorax. After a few days of a thoracic drainage the pneumothorax resolved. The conditioning regimen consisted of anti-thymocyte globulin (80 mg/kg) and cyclophosphamide (200 mg/kg). By the end of the ATG course the hepatic enzymes became normal and despite the preceding hepatic failure the conditioning regimen was accomplished without any side effects. The patient received

$2,08 \times 10^6$ /kg body weight bone marrow stem cells from her HLA identical sibling donor on 19th December 2003. On day +2 mild erythema was detected around the entry site of the central venous catheter. One day later evident signs of infection appeared: rapidly spreading redness developed along the tunnel of the catheter, and the patient became febrile. The catheter was removed and combination antifungal treatment was instituted including a change from prophylactic fluconazole to a therapeutic dose of amphotericin B deoxycholate (1 mg/kg/day). In spite of the catheter removal a severe soft tissue necrosis developed along the tunnel. To reduce the burden of infection a necrectomy was performed. Histology showed an invasive mold infection and wound cultures grew *Aspergillus flavus*. While on conventional amphotericin B therapy the necrosis extended to the thoracic wall, pleura and the right lung (Figure 1).

As a consequence of her rapidly deteriorating condition, the conventional amphotericin B treatment which had lasted for 12 days was switched to liposomal amphotericin B (3 mg/kg/day). At the same time granulocyte transfusions from her HLA identical donor and family members were applied (altogether 7 times). Despite these interventions the patient developed a shortness of breath and pleural effusion, so the antifungal treatment was completed with caspofungin

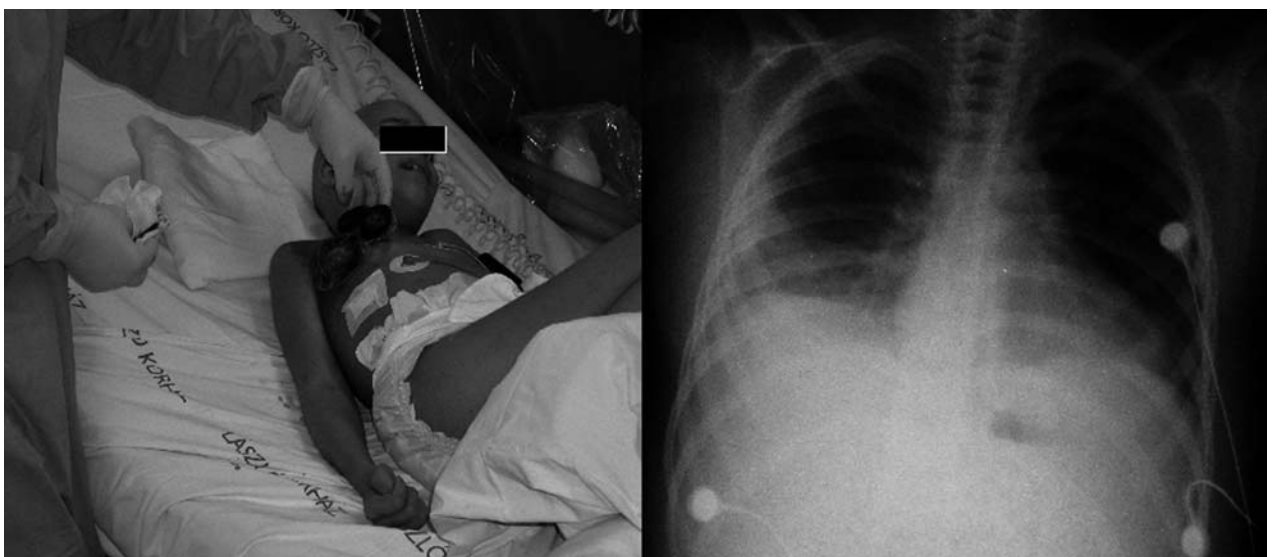


Figure 1. Depth of soft tissue *Aspergillus* infection. Necrotic mass could be easily removed. Chest X-ray indicates the involvement of the thoracic wall, pleura and the right lung



Figure 2. The healing process of chest wall aspergillosis and the scar formation 2 and 10 months post transplant

(50 mg/m²/day) after 3 days. After 48 hours the patient's cardiovascular status became stable, and 4 days later she became afebrile. As engraftment (absolute neutrophil count > 0.5 G/l) was observed on day +23, the infection started to show continuous regression (Figure 2). Follow up chest x-ray images showed that the pleural effusion and pulmonary infiltrate had disappeared. After the combined liposomal amphotericin B – caspofungin treatment for 30 days, she was switched to oral voriconazole for a further 6 months.

The post-transplant period was complicated by a biopsy proven grade I. acute skin graft versus host disease (GvHD) and cytomegalovirus (CMV) reactivation treated successfully with methylprednisolon and foscarnet, respectively. One year post transplant the patient is well with normal bone marrow and liver functions, as well as full donor chimerism. The former large open wound begins to cicatrize. Because of the obvious clinical regression of the infection, neither a follow-up biopsy nor invasive pulmonary diagnostics were performed at that stage.

Discussion

In our case, a histologically proven *Aspergillus flavus* infection progressed rapidly in spite of conventional and even subsequent liposomal amphotericin B treatment.

The emergence of new antifungal compounds with different mechanisms of action and improved tolerability has widened the therapeutic possibilities for the use of combined antifungal treatment for life-threatening systemic fungal infections (2). Systemic mould infections may represent the most important area for combination antifungal therapy due to their poor prognosis and the high cost of prolonged treatment. Potential advantages of a combination therapy (synergistic effect, enhanced spectrum of activity, decreased likelihood of resistance or tolerance) are in contrast with the possible disadvantages (antagonism, increased toxicity, drug interaction and costs) Few randomized clinical studies have examined the role of a combination antifungal therapy for invasive mycoses, and no prospective randomized trial investigating the use of antifungal combinations in invasive mould infections has been completed yet. Thus, in cases where invasive aspergillosis does not respond properly or tends to be progressive despite the use of a compound with proven in vitro activity against *Aspergillus*, it may be prudent to switch to or combine with agents that belong to another class of antifungals.

Caspofungin showed efficacy and safety in the treatment of invasive aspergillosis in patients refractory to intolerant of conventional or lipid formulations of amphotericin B or triazoles (3). The largest prospective multinational clinical trial conducted so far to compare the therapeutic effect and safety of caspofun-

gin and liposomal amphotericin B in febrile neutropenia not responding to first-line broad-spectrum antibiotics concluded that caspofungin was as effective as and generally better tolerated than liposomal amphotericin B (4). Cesaro et al. observed a favourable response in 9 of 10 adults with invasive mycosis who were treated with liposomal amphotericin B and caspofungin (5). In their retrospective study, Aliff et al. reported 30 leukemic patients with pulmonary aspergillosis and other invasive fungal infections who failed on conventional amphotericin (or liposomal amphotericin) treatment, therefore a combined therapy with liposomal amphotericin and caspofungin was instituted. Eighteen patients (60%) experienced a favorable antifungal response (6). In patients with invasive aspergillosis a somewhat less favorable response rate (3/6=50%) was seen, as presented recently by Maertens et al. at the 44th ICAAC (7). Kontoyiannis et al. reported an overall response rate of 42% with liposomal amphotericin/caspofungin combination used as primary or salvage treatment in 48 patients with invasive aspergillosis refractory to liposomal amphotericin B (8).

Some case reports or case series support the advantage of voriconazole and caspofungin combination in patients with invasive aspergillosis or disseminated candidiasis (9-12). Preclinical data suggest that the combination of an extended-spectrum triazole (e.g. voriconazole or posaconazole) and an echinocandin might be the most powerful regimen in animal models of invasive aspergillosis (13, 14).

Finally, it must be emphasized that caspofungin is not currently approved for pediatric use, and there are only a few published data that caspofungin and liposomal amphotericin B might be safe and efficacious in children with invasive fungal infections (15, 16). The use of echinocandins in children might be questionable but available evidence supports that the drug could be safely and effectively administered in this population of patients (17, 18). Franklin et al. reported 25 pediatric patients treated with caspofungin. Fourteen of the children had undergone allogeneic bone marrow transplantation, while 21 also received combination therapy with liposomal amphotericin B. An adverse event, mainly hypokalemia or elevated serum bilirubin concentration, was seen only in 12% of the pa-

tients. None of the drug-related events were considered to be serious (19).

It's important to stress, however, that antifungal therapy by itself cannot be curative. Clinical response usually requires resolution of neutropenia or remission of the underlying disease. Consequently, some authors consider the use of granulocyte transfusions in the treatment of invasive fungal infections during neutropenia after HSCT as an important adjunctive treatment option to antifungal therapy. As randomized trials are still ongoing in this field, this method should still be regarded as an experimental treatment modality. Another important aspect of this therapy is the immediate removal of infected foreign materials (catheters) and debridement of necrotic tissue.

In our case, granulocyte support and surgical intervention, in addition to combined antifungal treatment may have contributed to the favorable clinical response and cure.

In the future, large, multicentre, randomized trials are needed to reveal the role of different antifungal combinations and options for optimal supportive treatment of invasive aspergillosis in the HSCT setting.

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