Successful treatment of rhinocerebral zygomycosis with a combination of caspofungin and liposomal amphotericin b

Genera of the order Mucorales (*Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella, and Saksenaea*) cause an angioinvasive infection called zygomycosis. Mortality rates can approach 100% depending on the patient's underlying disease and form of zygomycosis. We report here on the unusual case of a patient with acute myelogenous leukemia and zygomycosis unresponsive to monotherapy with liposomal amphotericin B, who responded favorably following the addition of the echinocandin caspofungin acetate.

Haematologica 2005; 90:(11)e109-e110

In January 2003 a 63-year-old white male presented with acute myelogenous leukaemia (AML) FAB-M1 with normal karyotype. Complete remission (CR) was attained six months later after induction with cytarabine (200 mg/m^2/day over 7 days) and idarubicin (12 mg/m^2/day over 3 days) followed by two consolidation courses with cytarabine (1,000 mg/12 hours over 4 days) and mitoxantrone (12 mg/m^2/day over 3 days).

The patient developed febrile neutropenia on day +21 after two courses of consolidation chemotherapy. Despite empiric broad-spectrum antibiotics and G-CSF, the patient progressively presented with severe frontal headache, nasal congestion and serosanguinolent discharge, and intense pain upon percussion of the frontal sinusal area. CT imaging demonstrated diffuse inflammatory changes, suggestive of chronic frontal sinusitis. Over the next few days, there was a relentless progression of symptoms, particularly sinusal pain, with appearance of right-sided facial swelling and small cutaneous vesicles. On day +27 the patient developed diplopia and a new cranial CT revealed worsening of inflammatory changes and right maxillary and ethmoidal sinusitis with involvement of the contiguous orbit (Figure 1A-B). After the clinical and radiographic diagnosis of facial sinusitis, liposomal amphotericin B (L-AmphB) was started at 5 mg/kg/day. An ethmoidectomy was performed. Histological examination of biopsical materials demonstrated abundant necrotic material with the presence of mixed bacterial colonies and a dense growth of mucor as evidenced by a network of broad, non-septate, right-angled filamentous hyphae (Figyre 1C-D).

Since this deterioration had occurred despite L-AmphB therapy (total cumulative dose: 11,900 mg), caspofungin (70 mg load, thereafter 50 mg/day) was commenced in seeking synergism with amphotericin B against growing mucor. The patient's symptoms started to subside within a few days of initiating caspofungin, well before neutrophil recovery was substantiated (Figure 2). Additional surgical debridement of necrotic tissues was undertaken on day +48. Hospital discharge occurred after 24 days of combination therapy. The patient only developed hypopotasemia, which required potassium supplements and recovered fully after L-AmphB discontinuation. Caspofungin only was continued for 45 more days. Three months later, in consolidated CR of the AML, no evidence of fungal infection was detectable. The patient developed acute dacriocystitis, which resolved spontaneously resolved.

Genera of the order Mucorales (Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella, Saksenaea) and phylum Zygomycota are ubiquitous fungi that may cause an angioinvasive infection called mucormycosis or zygomycosis. Such infections are mainly diagnosed in patients with severe immunodeficiency, diabetes mellitus, trauma, cancer, and, most frequently, hematological malignancies, and are frequently prompted by the inhalation of conidia present in the air. Zygomycosis is typically associated with a significantly poorer prognosis than invasive aspergillosis, with quicker progression and very high mortality rates. Early diagnosis, surgery (often not possible in thrombocytopenic patients), and broad-spectrum antifungals are needed for successful outcome. In a recent review of 59 patients with proven or probable zygomycosis, amphotericin B –the mainstay of zygomycosis therapy- had a response rate of only 37%.[1]

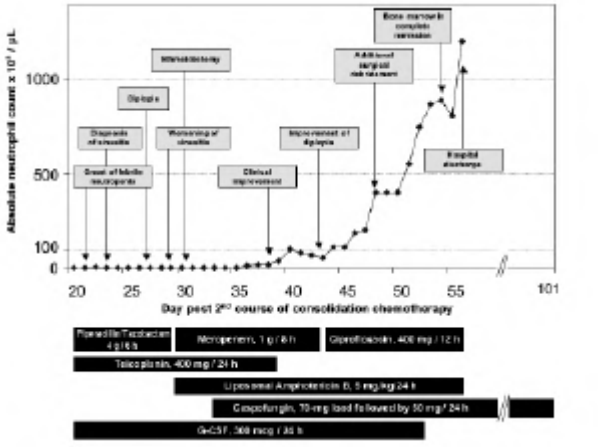

Figure 2. Absolute neutrophil count and drug therapy.

The echinocandins are a new antifungal drug class that inhibit 1,3-beta-D-glucan synthase (GS). The enzyme is a multisubunit complex, which includes an integral membrane protein and a regulatory subunit, encoded by members of the FKS and RHO1 gene families, respectively. GS inhibition results in disruption of the fungal cell wall leading to lysis of susceptible microorganisms, including Candida, Aspergillus, and multiple filamentous, dimorphic, and unclassified fungi.[2] In contrast, limited *in vitro* studies have reported that echinocandins have high MICs for zygomycetes.[3,4] As a consequence, the activities of caspofungin against the agents of zymomycosis have remained relatively unexplored.

Rhizopus oryze, the most frequently isolated organism

from patients with zygomycosis, has been shown to have both an FKS gene and membrane-associated GS, which was inhibited by relatively high concentrations of caspofungin in a dose-dependent manner.[5] Interestingly, caspofungin has also been shown to have significant but limited activity against R. oryzae in mice with diabetic ketoacidosis both alone[5] and in combination with amphotericin B lipid-complex.[6] Similarly, caspofungin was efficacious in a non-neutropenic murine model of invasive R. microsporus infection.[7]

We now report on anecdotal clinical experience of successful outcome in established zygomycosis likely to be attributable to the addition of caspofungin. Similarly, other investigators have reported favorable experiences with the use of caspofungin[8,9] or micafungin[10] in combination with other antifungals for the treatment of invasive zygomycosis. These isolated case reports and the activity found for caspofungin in animal models of disseminated Rhizopus infection, have raised the question about the usefulness of caspofungin for the treatment of zygomycosis. The potential for caspofungin to play a role in combination therapy against zygomycosis merits further investigation.

L. Vazquez,[1] J. J. Mateos,[1] C. Sanz-Rodriguez,[2] E. Perez,[1] D. Caballero,[1] J. F. San Miguel[1]

[1]Servicio de Hematología, Hospital Clínico Universitario, Salamanca, Spain; [2]Department of Clinical Research, Merck Sharp & Dohme of Spain, Madrid, Spain

Correspondence: Dra. Lourdes Vazquez Servicio de Hematologia, Hospital Universitario de Salamanca Paseo de San Vicente 58-182 37007 Salamanca
Tel: +34-923-291316 Fax: +34-923-294624
E-mail: lvazlo@usal.es
Key Words:Invasive fungal infection, Zygomycosis, Caspofungin acetate, Liposomal amphotericin B

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