Case Report
Eradication of Pulmonary Aspergillosis in an Adolescent Patient Undergoing Three Allogeneic Stem Cell Transplantations for Acute Lymphoblastic Leukemia

Michaela Döring,1 Angelika Zierl,2 Markus Mezger,1 Peter Lang,1 Rupert Handgretinger,1 and Ingo Müller1,3

1 Department of Pediatric Hematology/Oncology, University Children’s Hospital Tübingen, Hoppe-Seyler-Sträß 1, 72076 Tübingen, Germany
2 Department of Pediatric Diagnostic Radiology, Olga-Hospital Stuttgart, Bismarckstraße 8, 70176 Stuttgart, Germany
3 Clinic of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Martinistraß 52, 20246 Hamburg, Germany

Correspondence should be addressed to Michaela Döring, michaela.doering@med.uni-tuebingen.de

Received 16 May 2012; Accepted 7 August 2012

Academic Editors: F. Keller and S. Le Gouill

Copyright © 2012 Michaela Döring et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Systemic fungal infections are a major cause of infection-related mortality in patients with hematologic malignancies. This report addresses the case of an adolescent patient with acute lymphoblastic leukemia who underwent three allogeneic hematopoietic stem cell transplantations and developed pulmonary aspergillosis. Combination therapy with liposomal amphotericin B (L-AmB, 3 mg/kg bw/day) and caspofungin (CAS, 50 mg/day) during the first allogeneic hematopoietic stem cell transplantation (HSCT) improved the pulmonary situation. After shifting the antifungal combination therapy to oral voriconazole (2 × 200 mg/day) and CAS, a new pulmonal lesion occurred alongside the improvements in the existing pulmonary aspergillosis. An antifungal combination during a second HSCT with L-AmB (3 mg/kg bw/day) and CAS showed an improvement in the pulmonary aspergillosis. A combination therapy with CAS and L-AmB (1 mg/kg bw/day) during the third HSCT led once again to progress the pulmonary aspergillosis, after increasing the L-AmB to 3 mg/kg bw/day for recovery. The presented case provides an example of how, despite severe immunosuppression, a combination of antifungal drugs administered intravenously at therapeutic dosages may be more efficient than either intravenous monotherapy or combinations of intravenous and oral antifungals in selecting pediatric and adolescent patients with proven fungal infections.

1. Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening infection in patients with hematopoietic diseases and patients following allogeneic hematopoietic stem cell transplantation (HSCT). Patients with acute lymphoblastic leukemia or with long-term immunosuppression following HSCT are at high risk to develop IPA, which is the most common cause of infectious pneumonic mortality [1, 2]. Antifungal monotherapy obviously lacks efficacy in these patients and consequently an increasing number of combination therapies are employed. In a pilot trial, combination therapy including caspofungin showed improved efficacy compared to liposomal amphotericin B alone [3].

In addition, no increased toxicity of liposomal amphotericin B (L-AmB) in combination with caspofungin was found in these high-risk patients with IPA.

Here, we report the unusual case of IPA in an adolescent patient with relapsed common acute lymphoblastic leukemia undergoing his third allogeneic HSCT within nine months. The infection was successfully treated by a combination therapy of caspofungin with L-AmB and with oral voriconazole.

2. Case Report

An 18-year-old male adolescent was diagnosed with common acute lymphoblastic leukemia in March 2004. In February 2006, under treatment after ALL-BMF 2000 trial protocol,
a bone marrow relapse was diagnosed. During the first course of chemotherapy according to the ALL relapse BFM 2002 trial, he developed neutropenic fever. As antibiotic treatment failed, he was treated empirically with L-AmB. During this therapy, he developed dyspnea and cough. A computed tomography revealed nodular pulmonary infiltration in the apical right lung (Figure 1, CT scan A). The patient tested positive for aspergillus galactomannan antigen (index 1.6; normal patient tested positive for aspergillus galactomannan antigen) in October 2006, the patient developed a mild fever of 38.3°C with a CRP of 2.2 mg/dL and first pulmonary symptoms, that is, mild coughing. The aspergillus galactomannan antigen had increased to an index of 0.9. Due to the aggressive leukemia, the patient received the first HSCT from an HLA-identical unrelated donor in July 2006. From the start of the conditioning regimen until day 31 after transplantation, he was again treated with a combination therapy of caspofungin (50 mg/day) and L-AmB (3 mg/kg bw/day). During this therapy, the pulmonary aspergillosis showed signs of marked improvement and the aspergillus galactomannan antigen decreased and finally became negative, even though the patient had undergone HSCT. We reduced the antifungal therapy to L-AmB (3 mg/kg bw/day) and local prophylaxis with oral amphotericin B. By the end of August 2006, the patient still tested positive for aspergillus galactomannan antigen (index: 0.9). Due to the aggressive leukemia, the patient received the first HSCT from an HLA-identical unrelated donor in July 2006. From the start of the conditioning regimen until day 31 after transplantation, he was again treated with a combination therapy of caspofungin (50 mg/day) and L-AmB (3 mg/kg bw/day). During this therapy, the pulmonary aspergillosis showed signs of marked improvement and the aspergillus galactomannan antigen decreased and finally became negative, even though the patient had undergone HSCT. We reduced the antifungal therapy to L-AmB (3 mg/kg bw/day) alone. Due to increase of urea to 70 mg/dL on day 15 after the second allogeneic HSCT, the patient was switched to intravenous voriconazole for a total of seven days and ten days before anticipated discharge to oral voriconazole (2 × 200 mg/day). On the day of discharge in October 2006, the patient developed a mild fever of 38.3°C with a CRP of 2.2 mg/dL and first pulmonary symptoms, that is, mild coughing. The aspergillus galactomannan antigen had increased to an index of 0.9 and thoracic computed tomography showed a clear progression of the pulmonary aspergillosis (Figure 1, CT scan D). Therefore, we treated with a combination of caspofungin and oral voriconazole. In December 2006, almost four months after the second allogeneic HSCT and eight months after the start of the second period of combination therapy with caspofungin-based antifungal therapy, the pulmonary aspergillosis had almost completely disappeared without surgical intervention necessary (Figure 1, CT scan H). Therefore, we continued the antifungal therapy as monotherapy with oral voriconazole. Since the small aspergillosis lesion in the left lung segment 3 remained unchanged, it was removed eight months after the third HSCT thoracoscopically. Unfortunately, the patient experienced an incurable ALL relapse shortly thereafter and died in the 12th month after his third allogeneic HSCT.

3. Discussion

Systemic fungal infections, especially invasive pulmonary aspergillosis (IPA), are major complications in patients with prolonged neutropenia due to a hematologic malignancy [4]. As high risk patients undergo intensive chemotherapy and bone marrow or stem cell transplantation, invasive fungal infections will continue to endanger their successful treatment. Without adequate therapy, IPA is further complicated by dissemination to the CNS, cardiovascular system or by spreading to adjacent intrathoracic structures like the mediastinum. A positive outcome depends on early diagnosis and prompt initiation of adequate antifungal therapy. Until a few years ago, deoxycholate amphotericin B (D-AmB) had been considered the preferred therapy of IPA. However, the high incidence of renal toxicity and electrolyte disturbance led to the increased use of less toxic formulations of amphotericin B like amphotericin lipid complex (ABLC) or L-AmB [5]. Randomized, controlled trials for treatment of IPA compared monotherapies with voriconazole versus ABLC or L-AmB, respectively. Voriconazole, a broad-spectrum triazole, which targets the fungal cell membrane, has been approved as the initial treatment of invasive pulmonary aspergillosis and is better tolerated than amphotericin B [6]. Herbrecht at al. reported a prospective, randomized, multicenter trial on the superiority of voriconazole over D-AmB as initial therapy.
for invasive aspergillosis in terms of response rate, survival rate, and safety [7]. Echinocandins, such as caspofungin, inhibit the synthesis of (1,3)-β-D-glucan, which represents an important component of the cell wall of many pathogenic fungi such as *Candida* spp. and *Aspergillus* spp. Echinocandins possess favourable pharmacokinetic properties and are not metabolised by the cytochrome P450 (CYP) enzyme system. Maertens et al. reported on the safety and efficacy of caspofungin in the treatment of IPA in patients refractory or intolerant of L-AmB or triazoles [8]. Walsh et al. showed that caspofungin is as effective as L-AmB when given as empirical antifungal therapy in patients with persistent fever and neutropenia; in addition, caspofungin was generally better tolerated [9]. In allogeneic HSCT patients treated for microbiologically documented invasive aspergillosis, Herbrecht et al. described first line treatment with caspofungin to be similarly effective as treatment with voriconazole or L-AmB in this patient population.
voriconazole was not suitable to improvement and monotherapy caused progression of the combination of L-AmB and caspofungin is promising for IPA [13]. A randomized pilot study was able to show that was reported in one retrospective analysis of salvage therapy and caspofungin compared with voriconazole monotherapy was successful in improving patients.

in order to assist in the decision-making process for these carefully evaluate the relevant prognostic factors, and in combination of intravenous and oral antifungal combination may be more efficient than either monotherapy or the combination of intravenous and oral antifungal combination therapy in the early posttransplant period in select pediatric and adolescent patients. Further studies are warranted to carefully evaluate the relevant prognostic factors, and in order to assist in the decision-making process for these patients.

Conflict of Interests

The authors declare that they have no competing interests.

References


