Transpl Int (2004) 17: 545–548
DOI 10.1007/s00147-004-0753-0

CASE REPORT

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Refractory pulmonary aspergillosis treated with caspofungin after heart–lung transplantation

Received: 30 October 2003
Revised: 20 June 2004
Accepted: 5 July 2004
Published online: 8 September 2004

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Abstract Invasive pulmonary aspergillosis (IPA) is a serious complication of lung transplantation. Premortem diagnosis is difficult and is made according to defined criteria. Most patients with a post mortem diagnosis of IPA only reach the possible or probable levels of diagnostic certainty during life. Here, we report a case of probable IPA that was refractory to conventional treatment, including amphotericin, but which responded to therapy with caspofungin. A 23-year-old man underwent heart–lung transplantation for cystic fibrosis. Ten years after transplantation he developed IPA. His condition continued to deteriorate despite treatment with itraconazole, liposomal amphotericin and flucytosine together with treatment of a concomitant infection with *Pseudomonas aeruginosa*. Following treatment with caspofungin there was progressive and sustained clinical and radiological improvement. No adverse reaction occurred during treatment. Caspofungin should be considered as an alternative treatment for IPA in lung transplant recipients who fail to respond to other therapy.

Keywords Lung transplantation · Aspergillosis · Caspofungin

Introduction

Invasive pulmonary aspergillosis (IPA) is a serious complication of lung transplantation.[1]. Diagnosis is often difficult because of the need to differentiate colonisation from invasive disease and, frequently, the presence of co-infection with bacteria or viruses [2]. Standardised diagnostic (EORTC) criteria have been recently proposed for use in patients with malignant disease [3]. Recently, a study of the clinical applicability of this classification in 22 patients with haematological malignancies who had IPA at autopsy has been undertaken [4]. According to the criteria, only two patients were classified as having proven IPA, six as probable, 13 as possible and one was unclassifiable.

The prognosis of IPA remains poor, because of the limited range of effective anti-fungal agents that are available, their toxicity, and their interactions with the immunosuppressive drugs that are used after organ transplantation [5]. New anti-fungal agents are now becoming available that may offer improved efficacy with less toxicity, such as the echinocandin caspofungin [6]. Here, we report a case of IPA (EORTC "probable IPA") that was unresponsive to conventional treatment, including amphotericin, but that subsequently responded to treatment with caspofungin.

Case report

In 1992 a 23-year-old man under went heart–lung transplantation for end-stage lung disease due to cystic fibrosis (CF). As a further complication of CF he had insulin-requiring diabetes mellitus. He remained in good

health, taking maintenance immunosuppression consisting of cyclosporine, azathioprine and prednisolone. In January 1999, following a deterioration in his respiratory function, grade 2 bronchiolitis obliterans syndrome was diagnosed [7], and obliterative bronchiolitis was confirmed on transbronchial biopsy; his immunosuppression was changed from cyclosporine to tacrolimus, while azathioprine and oral prednisolone were continued. He then remained stable for a further 3 years but was then admitted for treatment of breathlessness associated with a productive cough and a fever.

The chest radiograph (CXR) showed patchy consolidation in the left lung. Since he was known to be colonised with *Pseudomonas aeruginosa* he was treated with intravenous ceftazidime and ciprofloxacin in accordance with the most recent laboratory antibiotic sensitivity tests. Sputum culture grew *Aspergillus fumigatus*, and CXR showed increasing patchy shadowing on the left side. A high-resolution computerised tomogram (HRCT) of the chest showed bilateral mild tubular bronchiectasis with areas of consolidation together with cavitation at the apex of the left lung and fissuring of the tracheal wall indicative of fungal disease (Fig. 1) [8]. Diagnostic bronchoscopy was precluded because the patient had developed type I respiratory failure. A diagnosis of invasive aspergillosis (EORTC "probable IPA") was made on the basis of the clinical picture, the HRCT, and the sputum culture [3, 9]. Treatment was started with oral itraconazole, intravenous liposomal amphotericin (Abelcet) and nebulised amphotericin. Following the patient's repeated pyrexial drug reactions to Abelcet, intravenous treatment was changed to the AmBisome preparation of amphotericin at a dose of 3 mg/kg. Anti-pseudomonal therapy was continued. Serial CXRs showed increasing consolidation in the left lung, with associated collapse.

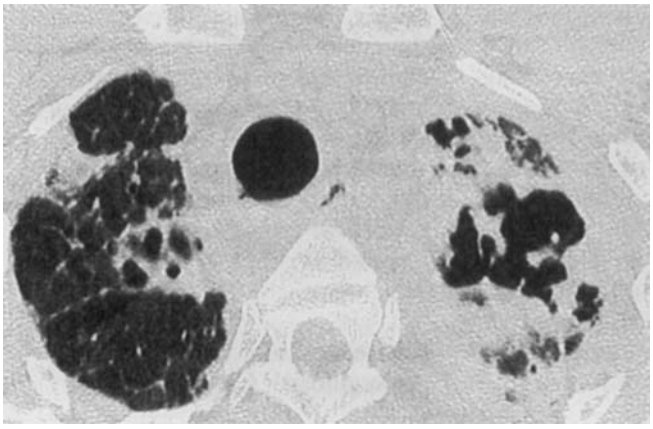

Fig. 1 HRCT of the chest showing a left apical cavity with consolidation and fissuring of the tracheal wall consistent with fungal disease

CT of the chest, repeated after 14 days, showed a marked increase in nodular shadowing in the left lung on a background of diffuse hazy shadowing consistent with progressive fungal disease. The patient remained bedbound and oxygen dependent. The dose of AmBisome was increased to 4 mg/kg, and flucytosine was added to the anti-fungal regimen.

Following 14 days' treatment with AmBisome and flucytosine as well as anti-pseudomonal therapy there was no clinical improvement. Treatment with intravenous caspofungin was substituted at this stage with a loading dose of 70 mg, followed by 50 mg/day thereafter. Other intravenous anti-fungal therapy was discontinued. No dose adjustment of tacrolimus was required to maintain stable blood concentrations. Following this, there was a progressive clinical improvement with decreasing oxygen requirements and after four weeks, a corresponding improvement in the radiological findings (Fig. 2). Thereafter, caspofungin was continued for 3 weeks with no further *Aspergillus* spp. isolated from the sputum. Renal function remained normal throughout. Following caspofungin treatment, long-term prophylaxis with oral itraconazole was administered. A

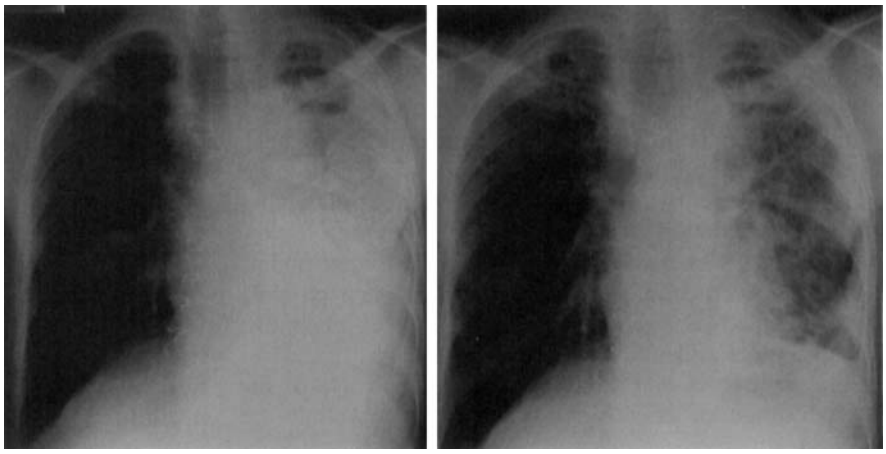

Fig. 2 Chest radiograph showing (*left*) left-sided consolidation and collapse prior to treatment with caspofungin and (*right*) improvement after treatment with caspofungin

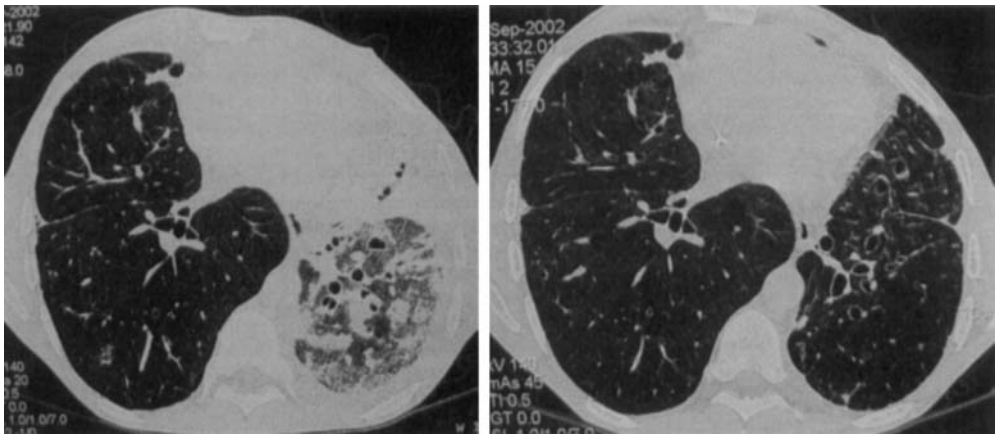

Fig. 3 (*Left*) HRCT of the chest after first-line anti-fungal treatment, (*right*) comparable HRCT cut following caspofungin treatment and hospital discharge

repeated HRCT scan after 8 weeks showed resolution of the gross interstitial and airways disease (Fig. 3). The patient remains well 2 years later, with no further hospital admission.

Discussion

To our knowledge, this is the first reported case of the use of caspofungin to treat IPA refractory to conventional anti-fungal therapy in a lung transplant recipient. Although our patient's clinical condition prevented us from obtaining a histological diagnosis of IPA, the clinical and radiological diagnostic criteria for IPA were present. There had been a progressive deterioration in his condition, despite treatment with anti-fungal agents and anti-pseudomonal antibiotics. A clinical response occurred only after treatment with caspofungin.

Caspofungin (MK-0991, L-743,872) is the first of a new class of anti-fungal agents. It acts by inhibiting synthesis of the glucan component of the fungal cell wall [10]. It has in vitro activity against *Aspergillus* and *Candida* species [11]. It has been found to be generally well tolerated, with no serious adverse effects [12]. The recommended dosage is a once-daily intravenous infusion of a 70 mg loading dose followed by a 50 mg/day maintenance dose. The primary route of excretion is via hepatic metabolism, and the dose does not need to be adjusted in patients with renal insufficiency, nor is the agent known to be nephrotoxic [11]. Caspofungin increases systemic exposure to tacrolimus and to cyclosporine [11].

Caspofungin has been found to be at least as effective as amphotericin for treatment of candidaemia and invasive candidiasis [12]. At present, there are few clinical data regarding the use of caspofungin to treat invasive aspergillosis. An ongoing safety and efficacy study has enrolled 90 patients whose underlying diseases include haematological malignancy, allogenic bone marrow transplant and solid organ transplant and who were suffering confirmed or probable invasive aspergillosis that had been refractory to other therapy. Caspofungin was effective in the treatment of many patients who had not responded to other treatment (Maertens et al., Abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy).

The case reported here supports the view that caspofungin treatment should be considered in lung transplant recipients who have not responded to other therapy for IPA. Its favourable toxicity profile may make it the drug of choice for patients with renal impairment. Potential pharmacokinetic interactions with drugs such as tacrolimus and cyclosporine will necessitate the careful monitoring of these drugs during treatment with caspofungin. If further studies demonstrate equal or superior efficacy to amphotericin, it may eventually become a first-line treatment for IPA.

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