CASE REPORT

Control of invasive pulmonary aspergillosis with oral itraconazole in a bone marrow transplant patient

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Summary
Pulmonary aspergillosis following bone marrow transplantation carries a mortality of 94%, irrespective of current treatment. We treated a patient who had acquired aspergillosis some 80 days after allogeneic bone marrow transplantation, with oral itraconazole, 600 mg daily. After initial deterioration, clinical and radiographic resolution occurred during 3 months of therapy despite severe graft-vs.-host and cytomegalovirus disease. Itraconazole should be considered for therapy of pulmonary aspergillosis in this and other immunocompromised settings.

Introduction
Bone marrow transplantation (BMT) complicated by pulmonary aspergillosis carries a particularly poor prognosis. 1 Only four survivors are recorded in the literature. 2-4 It occurs both before, but more frequently after, resolution of neutropenia and after discharge from hospital. Three of the four survivors had lobectomies, 2,3 in addition to amphotericin B. Although many patients have died with little or no therapy so that the diagnosis was made at autopsy, at least 15 have received a minimum of 14 days treatment with amphotericin B, usually between 0.5 and 1.0 mg/kg/day, all with a fatal outcome. 5 Aspergillus sp. infection at sites other than the lung, such as the sinuses, although severe may not carry quite the same high mortality. 6

Itraconazole is an investigational triazole that has considerable activity against Aspergillus species in vitro, 5 in animal models 5 and in patients with invasive aspergillosis. 7 The synergistic renal toxicity of amphotericin B and cyclosporin in transplant hosts limits the amount of amphotericin B that can be given to these patients. 8 The encouraging results of high dose (1 mg/kg/day) amphotericin B therapy of neutropenic patients (with or without flucytosine) 9-11 are probably impossible to match in those treated with

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cyclosporin without significant loss of renal function. Extensive toxicity data indicate that itraconazole has no nephrotoxic properties. With this background we chose to administer itraconazole to an allogeneic BMT recipient with bilateral pulmonary aspergillosis and renal insufficiency. No previous reports of the success of itraconazole in this setting have been published.

**Case report**

A 43-year-old 48 kg woman with a myelodysplastic syndrome (refractory anaemia with excess blasts in transition) underwent allogeneic bone marrow transplantation on 5 January 1989 at Stanford University Medical Center. The donor was her HLA-identical ABO-mismatched sister. The preparatory regimen before transplantation consisted of high-dose busulfan followed by cyclophosphamide. Cyclosporin and methylprednisolone were given for graft-vs.-host disease (GVHD) prophylaxis. These drugs were maintained throughout her post-transplant course.

Transplantation itself was uneventful and she had no infectious complications during neutropenia, which lasted until day 12 after BMT. She received low-dose amphotericin B at 0.15 mg/kg/day intravenously for the first 20 days after transplantation for fungal-infection prophylaxis. Bone marrow biopsy and aspiration on day 30 documented trilineage engraftment. By day 20 after transplantation her creatinine had risen from 51 to 161 mmol/l. Her cyclosporin dose was adjusted and nephrotoxic drugs were avoided. On day 58 her creatinine rose to 305 mmol/l and she was hospitalized. Her renal function ultimately stabilized, with serum creatinine varying between 110 and 169 mmol/l. On day 66 she developed *Staphylococcus aureus* bacteraemia 2 days after injuring her finger with a sewing needle. She was treated with vancomycin and later cefazolin with removal of her Hickman catheter. She was discharged on 20 mg of prednisone and 500 mg of cyclosporin daily.

On day 84 she reported to the clinic complaining of mild right chest wall soreness, without respiratory symptoms or fever. A chest X-ray revealed two rounded nodular opacities in the mid-zone of the right lung, a patchy infiltrate in the left upper lobe and hazy opacities in the left base (Plate 1). A chest X-ray 8 days earlier had been unremarkable. Physical examination revealed a cushingoid woman with normal vital signs, no oral or nasal lesions, normal lung sounds, slight hepatomegaly and pretibial pitting oedema. Her WBC count was 1.7 x 10⁹/l with 71% neutrophils. The haemoglobin was 10.0 g/dl, and platelets were 24 x 10⁹/l with mildly abnormal liver function tests and a bilirubin of 102 µmol/l. A CT-guided transthoracic needle aspirate of a pulmonary nodule grew only *A. fumigatus*. A CT scan of the chest showed 13 spiculated nodules in the lung fields, varying in size between 5 and 35 mm, and two septate areas of segmental consolidation. There were no hepatic or splenic lesions seen in a CT scan of the abdomen. While awaiting the results of the lung aspirate culture she received two doses of 30 mg amphotericin B. There was concern that her kidneys would not tolerate a prolonged course of this drug and she was therefore given itraconazole 200 mg orally three times daily beginning on day 86. After 4 days the dose was reduced to 200 mg twice daily. Itraconazole was well tolerated without nausea or vomiting. During the first
Plate I. Chest X-ray on first day of itraconazole therapy showing nodules in the right middle and lower lobes and left upper lobe perihilar nodule.
Plate 2. Chest X-ray on day 7 of itraconazole therapy showing marked increase in diameter of most nodules (approximately unchanged from day 4).
Plate 3. Chest X-ray on day 82 of itraconazole therapy showing resolution of most lesions and reduced size of the pleural-based lesion on the right. The patient died 3 weeks later with an unchanged chest X-ray appearance.
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week of therapy the chest X-ray worsened, most of the nodules appearing to increase in size (Plate 2). She was more dyspnoeic on exertion but had no fever. Susceptibility studies7 showed the MIC and MFC against itraconazole to be 6.3 mcg/ml. The 4 h serum itraconazole concentration measured by bioassay7 was 3.8 mcg/ml after 1 week of therapy so the dose of itraconazole was increased to 300 mg twice daily on day 92. The 4 h serum itraconazole concentration on day 101 was 6.8 mcg/ml and rose during the next month to 9.0 mcg/ml. During the second week of itraconazole the radiographic findings stabilised and her symptoms improved. After 3 weeks of itraconazole she was ambulatory and her dyspnoea was markedly less. Her chest radiograph showed that the pulmonary nodules had become smaller.

On day 100 she developed a diffuse erythematous skin rash, and a biopsy revealed grade 2 skin GVHD. The prednisone dosage was increased. On day 118 she complained of abdominal pain, nausea, mild shortness of breath, non-productive cough and low-grade fevers. The chest radiograph showed continued regression of pulmonary nodules with no new abnormalities. She underwent bronchoscopy and bronchoalveolar lavage cultures grew an alpha-haemolytic Streptococcus sp. only. Fungal elements consistent with Aspergillus sp. were seen in the transbronchial biopsy specimen from the right lower lobe, but fungal culture of the BAL fluid was negative. Her bronchitis was treated with imipenem with rapid improvement. She underwent oesophagoduodenoscopy and sigmoidoscopy, and biopsies showed grade 1–2 GVHD. Prednisone and cyclosporin doses were temporarily increased. The duodenal biopsies showed evidence of CMV infection. She was given ganciclovir 5 mg/kg iv twice daily and high dose iv immunoglobulin for 6 weeks. Abdominal CT scan showed a homogeneously enlarged liver and pancreateomegaly. Because of persistent abdominal pain with right upper quadrant tenderness and progressive liver enzyme abnormalities, she underwent percutaneous liver biopsy. This showed no veno-occlusive disease, but moderate GVHD and active hepatitis B infection.

Her serial chest radiographs continued to show gradual shrinkage of all nodules (Plate 3) and she remained without pulmonary symptoms while on itraconazole. A follow-up CT scan of the chest on day 146 showed 12 lesions, all of which had diminished in size by between 15 and 70%. She continued to have nausea, anorexia and mild abdominal pain. No episodes of neutropenia attributable to ganciclovir occurred. Four-hour post-dose serum itraconazole concentrations reached a peak of 12.5 mcg/ml on day 140 but declined to 3.5 mcg/ml on day 151 on the same oral dose given in hospital (the decline presumably related to intestinal GVHD). She required total parenteral nutrition for caloric support. Her rash worsened on day 150 and she developed large tense bullae around the ankles and on the back consistent with clinical grade 4 skin GVHD. During the subsequent 3 weeks there was progressive clinical deterioration due to GVHD despite continued therapy. A sudden onset of presumed bacterial sepsis with acute renal failure supervened and she died 170 days after BMT.

Necropsy revealed six yellow nodules in emphysematous lungs, none greater in size than 12 mm. Microscopy revealed clusters of mostly degenerate aspergillus organisms associated with extensive necrosis and debris. Caseating
granulomas with multinucleated giant cells were also present in the pulmonary nodules. Hyphae had invaded and destroyed the surrounding lung tissue to a limited extent but there was no evidence of vascular invasion. Also present was acute cutaneous grade 3 GVHD, hepatitis B virus infection with intrahepatic cholestasis and steatosis, a B-cell lymphoproliferative process involving the adrenal glands and liver, evidence of marked cyclosporin nephrotoxicity, acute and chronic pancreatitis, and haemorrhagic erosions of the rectosigmoid colon. No other organs showed evidence of fungal disease. Fungal cultures were not taken.

Discussion

Many cases of invasive aspergillosis after BMT have been reported. We found a total of 127 patients in whom the outcome is described; all but seven died (94 % mortality).1-4, 6, 13-30 The lung was the organ most commonly affected although other sites included the trachea,29 sinuses,3, 6, 27 soft-tissue infections of the face and mouth,6 the orbit,3 central nervous system,3, 15, 24 pericardium,10, 15, 16, 26 myocardium,18, 23 gastro-intestinal tract,15, 22 spleen25 and a thigh abscess.1 Many patients had disseminated disease without the sites being specified; however in two patients, studied in detail at necropsy, the larynx, kidneys, bladder, oesophagus, stomach, vagina, breast and brain were found to contain hyphae histopathologically.15 At least two patients were fungaemic with aspergillus, but in both the culture became positive after death.1 Among 15 BMT patients with pulmonary aspergillosis who survived long enough to receive 14 or more days of antifungal chemotherapy, all died.1, 3, 13-16, 18, 20 All the reports of survivors with pulmonary disease give insufficient detail of therapy for complete evaluation. However, two were children who developed this disease just as neutropenia was resolving, and with aggressive antifungal therapy (not specified) and lobectomies they survived.2 In the same report 19 other patients died.2 Another survivor, in whom neutropenia was also resolving, developed a cavitary pneumonia on day 18 and received at least 150 mg amphotericin B. The fourth survivor received amphotericin B 1 mg/kg/day for an unstated period and had the infected tissue surgically excised.3

One study has examined the risk of acquiring aspergillosis and the subsequent outcome in autologous, allogeneic and syngeneic BMT.3 Although the overall risk was similar in the first two groups (3.5 % vs. 4.4 %), all five cases in the autologous transplants occurred before haematological reconstitution, compared with one out of 17 in the allogeneic group. No cases of aspergillosis occurred in the 20 syngeneic transplants. The perturbations to the immune system following autologous transplants are less profound after neutropenia has resolved, and this may account for some of the differences observed. Following allogeneic transplantation, major derangements of immune function persist after resolution of neutropenia. These defects include reduced circulating lymphocyte counts, lower circulating immunoglobulin concentrations, reduced antibody responses in vivo, reduced lymphocyte proliferation in vitro and poor skin test responses to recall antigens.31 More pertinent to pulmonary aspergillosis, alveolar macrophage function is also impaired after transplantation.32 Greater degrees of immune impairment are seen in patients
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with GVHD, especially if it is severe; in addition, impairment of splenic function may occur.\textsuperscript{33} Pertinent to the patient presented here, post-transplantation primary cytomegalovirus infection is itself immunosuppressive, especially with respect to early pulmonary infections.\textsuperscript{34} Our patient responded to medical therapy alone despite further immunosuppression and cytomegalovirus infection. This suggests that itraconazole may be therapeutically promising compared with amphotericin B in this setting.

Itraconazole is a new triazole that has considerable activity against \textit{Aspergillus} sp. \textit{in vitro}.\textsuperscript{5, 7, 35-38} Among 88 isolates of \textit{Aspergillus} sp. tested by broth dilution,\textsuperscript{7} itraconazole was inhibitory for 97\% isolates at clinically achievable concentrations (MIC $\leq$ 6.3 mcg/ml) and fungicidal for 42 of 60 (70\%) isolates at these concentrations. Itraconazole concentrates within macrophages where it may considerably exceed serum concentrations.\textsuperscript{39} The activity of itraconazole in animal models, including those with neutropenia, is impressive.\textsuperscript{36, 40-42} In some, itraconazole was equivalent, or superior, to amphotericin B.

To our knowledge only two other BMT patients have so far been treated with itraconazole. One responded to 200 mg daily given for bronchial aspergillosis following neutropenia.\textsuperscript{29} An HLA-matched allogeneic BMT was done 7 months later, but fever and aspergillus antigenaemia recurred 4 days after transplantation and \textit{A. fumigatus} was isolated from sputum. Very low serum itraconazole concentrations were detected, probably related to mucositis. Amphotericin B was substituted, but the patient died 5 weeks later with extensive bronchial aspergillosis. We have treated one other patient with disseminated aspergillosis (lung and skin) 2 months after allogeneic BMT.\textsuperscript{7} As she required mechanical ventilation, itraconazole was given by nasogastric tube and serum concentrations were less than 0.6 mcg/ml and she died after 5 days therapy. These unimpressive (but unevaluable with respect to itraconazole) outcomes contrast with generally favourable results in other immunocompromised patients.\textsuperscript{5, 7}

Adequate serum itraconazole concentrations appear to be important for a good outcome. Published and unpublished data indicate that adequate serum concentrations are probably important for efficacy; steady-state concentrations below 5 mcg/ml were associated with failure\textsuperscript{7} (and unpublished data) in 26 patients with invasive aspergillosis. In the patient discussed here, a relatively large dose was given (200 mg TID) because of concern about low serum concentrations (less than the MIC of the infecting organism) and the early deterioration radiologically. The later response was possibly related to higher serum concentrations.

Following solid organ transplantation, there is a marked interaction of itraconazole with cyclosporin, the blood concentrations of the latter rising two or three-fold within 48 h of commencing itraconazole.\textsuperscript{43} This interaction is not always found following bone marrow transplantation, and was not noted in our patient. This may however reflect the generally different attitudes to cyclosporin dosage and blood concentrations among physicians treating bone marrow transplant patients.

Further study of the role of itraconazole in this setting is warranted because of the extremely poor results with other therapy. Undoubtedly it will not
always be successful, but any improvement over a 94% mortality rate of pulmonary aspergillosis following bone marrow transplantation would be welcome.

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References


