Clinical activity of the new triazole drug voriconazole (UK 109, 496) against disseminated hepatosplenic aspergillosis in a patient with relapsed leukemia

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Abstract—There is presently a limited antifungal armamentarium comprising amphotericin and the azoles, fluconazole and itraconazole. In vitro studies have shown efficacy of the new drug, voriconazole, against a wide range of fungi, including most species of Candida and Aspergillus. We review here a case report of a young boy with acute myeloid leukemia who developed disseminated hepatosplenic aspergillosis. He failed therapy with itraconazole, amphotericin B and liposomal amphotericin. As he also had relapsed leukemia, there was a great urgency to control this infection in order to facilitate the administration of cancer chemotherapy. Voriconazole was given with good response resulting in virtual disappearance of all scan evidence of aspergillosis.

Key words: Voriconazole; disseminated aspergillosis; antifungal therapy; acute leukemia.

INTRODUCTION

In the battle against invasive aspergillosis, amphotericin B is effective but there are also many cases of treatment failure. In addition, adverse effects, principally nephrotoxicity, and the need to give the drug only by the intravenous route, also limit the utility of this drug. Lipid formulations may be safer, but their high price is still a drawback. Fluconazole has good oral absorption but offers no protection against invasive aspergillosis. Itraconazole, on the other hand, while effective against Aspergillus, has very unreliable absorption [1]. Voriconazole (formerly UK-109, 496) is a new monotriazole antifungal agent with high potency and a broad spectrum of
activity against fungi, including *Aspergillus*. Like many currently available antifungal drugs, it targets the ergosterol biosynthetic pathway used in fungal metabolism.

We review here a case report of a young boy with acute myeloid leukemia who developed disseminated hepatosplenic aspergillosis. He failed therapy with itraconazole, amphotericin B and lipid-complex amphotericin but subsequently had good response to voriconazole.

**CASE REPORT**

MF was a 13-year-old boy who was diagnosed to have acute myeloid leukemia in August 1996. He was given standard induction and consolidation chemotherapy followed by a course of high dose cytosine arabinoside but had disease relapse 6 months later. Salvage chemotherapy with the FLAG regime, comprising fludarabine, high dose cytosine arabinoside and granulocyte-colony stimulating factor (G-CSF) was given and he went into remission. This was quickly followed by peripheral blood stem cell harvesting and an autologous peripheral blood stem cell transplant.

In February 1998, he had a second relapse. Remission was reinduced successfully with salvage chemotherapy comprising idarubicin and high dose cytosine arabinoside. However, the pancytopenic phase was complicated by fever and subsequent abdominal pain associated with the finding of gross splenomegaly in late March 1998. Multiple hypodense lesions in the spleen and fewer but similar ones in the liver were shown on computerised tomographic (CT) scan (Fig. 1), suggesting the possibility of a fungal infection. Prior septic work-up did not review any pathogens on cultures of blood and other body fluids. Empirical anti-fungal treatment with intravenous amphotericin B at 1 mg/kg/day had been started 11 days prior to the onset of abdominal symptoms. In spite of ongoing treatment with amphotericin B, splenic lesions appeared after a cumulative dose of 440 mg. Treatment was therefore changed to amphotericin B lipid complex, given at 5 mg/kg/day. However, the lesions persisted despite recovery from neutropenia by 4 days after first evidence of invasive fungal infection, necessitating a splenectomy. This was done in mid-April after 3800 grams of liposomal amphotericin was given.

Gross pathology revealed a 290-gm, 15 × 10 × 4-cm spleen received in formalin, with its capsular and cut surfaces studded with multiple, soft, rounded, whitish nodules averaging several millimetres to a centimetre in diameter, many of which disclosed necrotic central umbilication, amidst a background of red pulp congestion. Areas of parenchymal infarction ranging 2 to 3 cm in diameter with irregular, yellowish-white borders were also noted towards one pole of the spleen. The histology of the rounded nodules was that of large, sometimes confluent granulomas, with supplicative centres (representing the grossly visible central umbilications) that often displayed serpiginous borders rimmed by palisaded epithelioid histiocytes (Fig. 2). The infarcts seen grossly were confirmed histologically to represent areas of coagulative necrosis. Special histochemical stains for fungi further revealed