Invasive pulmonary aspergillosis is an emerging complication in patients with acute leukemia. Its increasing incidence has been dramatically documented in the last decade, in both ante- and post-mortem studies. The overall response rates to conventional amphotericin B (cAMB) is unsatisfactory, ranging between 35% and 45%; long-term therapy is badly tolerated owing to nephro- and infusion-related toxicity. More effective and less toxic drugs for this infection are needed. We report the use of i.v. itraconazole for the treatment of invasive pulmonary aspergillosis in two patients who had undergone intensive chemotherapy for acute lymphoblastic leukemia (ALL) and were subsequently included in an international phase IV study (protocol ITR-INT-92; Sporanox IV, Janssen Pharmaceutica, Beerse, Belgium).

Case report #1
Ph-positive ALL-L2 was diagnosed in a 39-year-old woman in November 1999. She proved to be resistant to 2 induction courses, and no bone marrow donor was available. In June 2000, she received additional chemotherapy (cytarabine 11 gr daily for 4 days and idarubicin 22 mg daily for 3 days). Antimicrobial prophylaxis with ciperoxacin and fluconazole was given. After 10 days of severe neutropenia, she started having high fever followed by chest pain, cough, dyspnea and moderate hypoxia, and received meropenem 3 gr daily, amikacin 1 gr daily and teicoplanin 400 mg daily. A week later, the persistence of symptoms and the appearance of pulmonary infiltrates (Figure 1C) prompted antifungal treatment (i.v. itraconazole 400 mg daily for 2 days, followed by 200 mg daily for 12 days). After starting itraconazole the clinical course rapidly improved with symptom regression. No pathogens were found in the culture of bronchoalveolar lavage. Two weeks later recovery from neutropenia occurred and the patient was discharged. Itraconazole was continued orally (5 mg/kg twice a day) for persisting pulmonary infiltrates, likely due to Aspergillus species (Figure 1D). A few months later a CT-scan found no pulmonary infiltrates. She underwent consolidation and maintenance chemotherapy; neither signs nor symptoms of pulmonary infection occurred. The patient is in continuous complete hematological remission from ALL and off-therapy.

Case report #2
In July 2000 a 43-year-old woman with ALL-L1 was admitted for induction chemotherapy including L-asparaginase, vincristine, daunorubicin and prednisone (GIMEMA 0496 Protocol). Standard antimicrobial prophylaxis was given. After 10 days of moderate neutropenia, she started having high fever followed by chest pain, cough, dyspnea and moderate hypoxia, and received meropenem 3 gr daily, amikacin 1 gr daily and teicoplanin 400 mg daily. A week later, the persistence of symptoms and the appearance of pulmonary infiltrates (Figure 1C) prompted antifungal treatment (i.v. itraconazole 400 mg daily for 2 days, followed by 200 mg daily for 12 days). After starting itraconazole the clinical course rapidly improved with symptom regression. No pathogens were found in the culture of bronchoalveolar lavage. Two weeks later recovery from neutropenia occurred and the patient was discharged. Itraconazole was continued orally (5 mg/kg twice a day) for persisting pulmonary infiltrates, likely due to Aspergillus species (Figure 1D). A few months later a CT-scan found no pulmonary infiltrates. She underwent consolidation and maintenance chemotherapy; neither signs nor symptoms of pulmonary infection occurred. The patient is in continuous complete hematological remission from ALL and off-therapy.

In only a few days are effective for treating invasive pulmonary aspergillosis, including conventional and lipid-based AMB, itraconazole, and, more recently, voriconazole and caspofungin. Few data are available on the use of i.v. itraconazole for invasive pulmonary aspergillosis in immunocompromised hosts. Our patients had a proven (case #1) or possible (case #2) invasive pulmonary aspergillosis within the frame of a trial on the use of i.v. itraconazole in invasive fungal infec-

Figure 1. Changing characteristics of invasive pulmonary aspergillosis on computed tomography scans. (A) Subpleural large parenchymal masses with a surrounding halo of ground-glass attenuation (halo sign), in the right lung, a small nodular lesion in the left lung. (B) Two weeks later, a fungus ball inside the right lesion. (C) Large triangular infiltrate in the left lung, and bilateral pleural effusion. (D) Two weeks later, cavitation described as the air-crescent sign inside the parenchymal lesion.
tions, this drug was introduced after informed consent as first-line treatment in case 2 and after failure of cAMB in case #1. During the following 2 weeks, even in the absence of neutrophil recovery, infectious symptoms completely disappeared in both cases. Complete disappearance of the pulmonary infection was achieved after switching to high-dose oral itraconazole (Sporanox Oral Solution), combined with surgical curettage in one case. At the dose used, i.v. itraconazole did not show any side-effect or hematological toxicity. In conclusion, this drug proved to be effective and well tolerated for the management of life-threatening invasive pulmonary aspergillosis. These observations warrant further investigations of i.v. itraconazole use in neutropenic patients with acute leukemia and Aspergillus infection.

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