Successful treatment with voriconazole of cerebral aspergillosis in an hematologic patient

Aspergillosis is a fungal infection not rare in hematologic patients. The main localisation is usually in the lung; the embolic dissemination in the central nervous system carries a high mortality rate in the immunocompromised.

Voriconazole is a new triazole with in vitro and in vivo activity against a wide range of fungal pathogens including Aspergillus species. This report describes a case of pulmonary aspergillosis with concomitant cerebral localisation in a patient with advanced chronic lymphocytic leukaemia treated successfully with oral voriconazole.

A 53 year old woman affected by chronic lymphocytic leukaemia since September 1995, developed a disease progression with increasing lymphocytosis, multiple lymph nodes and diffuse marrow involvement in May 1996. She was treated with chlorambucil at a dose of 40 mg/m² every month for six months, obtaining improvement. In November 1998, because of disease progression, she was treated again with chlorambucil for three months without remission. Then she underwent multiple chemotherapy cycles without improvement: 1 cycle with fludarabine (30mg/m²) and cyclophosphamide (300 mg/m²) intravenously for 3 days, 2 cycles CHOP (cyclophosphamide vincristine, doxorubicin, prednisone) 1 cycle with 2-chlorodeoxyadenosine (4 mg/m² by continuous IV infusion daily for 7 days).

On 30 August 2000 she was admitted to our hospital with lymphocytosis, multiple lymph nodes, hepatomegaly, splenomegaly, and cytopenia caused by extensive bone marrow involvement. Furthermore she had intestinal bleeding from duodenal small arteries.

Blood tests on admission were: hemoglobin 4.7 g/dl, white blood cell count 20.9 x 10 ³/L (neutrophils 1%, lymphocytes 99%), platelet count 3 x 10 ⁹/L, lactate dehydrogenase 266 IU/L, beta-2-microglobulin 7.1 µg/ml, total serum protein 4.6 gr/L, gamma-globulin 0.35 gr/L, renal and hepatic function blood tests normal. After intestinal bleeding resolution she underwent salvage treatment with alemtuzumab, a humanized monoclonal antibody anti CD 52. The drug was given as intravenous infusion at a dose increasing from 3 mg to 30 mg three times every week. She had prophylactic oral treatment with itraconazole (400 mg daily), trimethoprim-sulfa, acyclovir. The monoclonal antibody was discontinued after a total dose of 163 mg because of the onset of fever and profound granulocytopenia (neutrophils <0.1x10⁹/L). Blood cultures yielded Corynebacterium propinquum and Staphylococcus coagulase negative. She was treated with amikacin, ceftazidime and vancomycin without remission of fever although blood cultures became negative.

A computerised tomographic (CT) chest scan revealed a pulmonary infiltrate in the median field, 3 x 4 cm in diameter with halo sign. Bronchial washing culture yielded Aspergillus Flavus. At the same time the patient developed left hemiparesis. A cranial CT scan without contrast in the first 24 hours was negative, but the magnetic resonance imaging (MRI) of the brain after 1 month of treatment revealed a right frontal-parietal lesion, 2 x 1.5 cm in diameter, with ring enhancement and perilesional oedema. Aspergillus antigen and antibodies were repeatedly negative. Severe thrombocytopenia (5 x 10⁹/L) prevented invasive procedures. On October 25th 2000, treatment with amphotericin B deoxycolate was begun (1 mg/kg/day). There was remission of fever and improvement of neurological symptoms after a few days, but neutropenia persisted for the whole duration of hospitalisation (60 days). After 20 days of amphotericin B therapy (total dose 775 mg) a CT scan of the chest showed increased size of the pulmonary lesion. The magnetic resonance imaging (MRI) of the brain, after 1 month of treatment, revealed a right frontal-parietal lesion, 2 x 1.5 cm in diameter, with ring enhancement and perilesional oedema. As the patient requested discharge from hospital, amphotericin B (total dose 1255 mg) was stopped and treatment with voriconazole was started at the dosage of 200 mg twice a day. Voriconazole was well tolerated, the only collateral effects were mild and transient visual disturbances and increase of serum aminotransferase concentrations below five-fold increase of baseline values.

After 50 days of treatment with voriconazole a lung CT scan showed a significant reduction of the lesion. A brain MRI revealed resolution of the right frontal-parietal lesion (figure 1) and appearance of a left frontal abscess, 1 cm in diameter. The patient was asymptomatic and continued with voriconazole. As an outpatient she underwent palliation chemotherapy with intermittent daunorubicin, methotrexate, vinblastine and etoposide alone or in combination. During these therapies the patient developed repeated neutropenia. However after 4 months of treatment a brain MRI showed only residual lesions (figure 2). Chest TC scans in April and June 2001 revealed significant improvement of pulmonary lesion.

In July 2001 the patient was admitted to our department and died because of progression of hematologic disease. During this hospitalisation, chest X-ray was negative. She continued voriconazole until the death.

Invasive aspergillosis is one of the more lethal opportunistic infections in immunocompromised patients and underlying hematological malignancies are one of the major risk factors for its onset.

The infection localises above all in lung, sinus, brain and mastoid process, but can spread to every organ. Usually cerebral aspergillosis is secondary to lung localisation due to embolic dissemination of fungus 1-6. Aspergillus species typically involves blood vessels producing thrombotic infarction. In the brain the more common histopathological features are areas of hemorrhagic or ischemic encephalomalacia and single or multiple abscesses; leptomeningeal localisation is rare 7.
Symptoms of cerebral aspergillosis are focal neurological defects, alteration of mental status, seizures.

Standard therapy of aspergillosis is amphotericin B deoxycholate; other effective drugs against Aspergillus species are lipid formulations of amphotericin B and itraconazole. The most recent reviews about outcome and therapeutic response in invasive aspergillosis show limited effectiveness of available drugs. Denning et al reviewed 1223 cases of invasive aspergillosis treated with amphotericin B deoxycholate or itraconazole from 1972 to 1995. The outcome was influenced by the underlying disease: patients with liver transplantation, bone marrow transplantation and AIDS had the worst prognosis with mortality range from 93% to 81%; in the contest of leukemia and neutropenia mortality was 77%. The mortality was also influenced by the site of infection: cerebral localization had a mortality of 99%

Lin et al reported a systematic review of 1941 patients with invasive aspergillosis treated from 1995 with principally amphotericin B or its lipid formulations and itraconazole. Also in their report the outcome was worst in patients with AIDS, bone marrow and some solid organ transplantations; the mortality in patients with leukemia and lymphoma was 50%. Prognosis was negatively influenced by neutropenia. In the patients with disseminated or cerebral aspergillosis the mortality was 88%

Patterson et al reported a retrospective survey of 595 cases of invasive aspergillosis treated between 1994 and 1995 with principally amphotericin B or its lipid formulations and itraconazole. In this report the mean of therapeutic failures was 36%; the outcome was worse in patients with bone marrow transplantation and other hematological diseases, it was related to the severity of immunodepression and to the site of infection with the lowest therapeutic response in cerebral aspergillosis (9%)

The outcome of invasive aspergillosis is also influenced by a high index of clinical suspicion and early appropriate treatment.

The high rate of mortality in cerebral aspergillosis is outlined by other authors who reported more limited series of patients.

In the series of 118 patients affected by acute leukaemia reported by Sparano et al 6% developed proven or probable cerebral aspergillosis and all died within 32 days from the onset of symptoms (the median was 7 days); no data were available on antifungal treatment.

Pagano et al reported 14 patients affected by acute leukaemia who developed cerebral aspergillosis; all the patients died within a median time of 5 days from the onset of neurological symptoms in spite of early treatment with amphotericin B deoxycholate.

In cerebral aspergillosis amphotericin B has been variably associated with local installation of the same drug, flucytosine, itraconazole and surgical treatment. Some cases responded well to liposomal amphotericin at high dosage.

High mortality of cerebral aspergillosis could be secondary to poor penetration across the brain-blood barrier, variable bio-availability, high toxicity and mediocre activity of antifungal drugs at present available. Major concentration in the brain of the lipid-associated preparations of amphotericin B has not been correlated to a major efficacy yet.

Voriconazole is a new orally active antifungal triazole with potent activity against species of Aspergillus in vitro and in animal models.

In literature some sporadic cases of cerebral aspergillosis in hematologic patients, treated with voriconazole because of resistance to standard therapy, have been reported.

In a case reported by Schwart et al a patient affected by refractory acute leukaemia with an aspergillar abscess and meningitis obtained recovery after 5 months of treatment with voriconazole.

Machetti et al reported a patient, who had undergone aploidentico allo-transplantation for acute lymphoblastic leukaemia, with probable cerebral aspergillosis treated with voriconazole obtaining an initial regression of neurological symptoms before patient’s death due to unrelated infection.

Recently in an immunocompromised patient population affected by invasive aspergillosis, treated with
voriconazole as salvage or primary treatment, there was 16% of good response in patients with cerebral aspergillosis 26.

Recently in a multicenter randomized trial voriconazole was proven more effective than amphotericin B as primary therapy in invasive aspergillosis (successful outcomes in 52.8% in the voriconazole group and 31.6% in the amphotericin B group) and retrospective stratification according to the site of infection did not change the results 19.

In our patient there were immunodepression with hypogammaglobulinemia inherent to the primary disease, several previous chemotherapy regimens, neutropenia caused by infiltration of bone marrow. The patient was treated with alemtuzumab, a humanized monoclonal antibody directed against CD52, an antigen expressed on T and B lymphocytes; this drug was responsible for a more severe neutropenia (neutrophils < 0.1 x 10^9/L) and responsible not only for further antibody reduction in a patient who had severe basal hypogammaglobulinemia, but also for further immunodepression also T-related.

The use of this novel and effective therapy in LLC has been related to a high incidence of opportunistic infections, including cases of aspergillosis, likely to be related to the profound lymphopenia; opportunistic infections were reduced after introduction of mandatory prophylactic antimicrobial therapy 20-22. Our patient underwent treatment with intravenous voriconazole as antifungal prophylaxis without success. In our patient a moderate response of systemic symptoms to amphotericin B was obtained; however after a month of therapy a large brain localisation was visible and lung infiltrates were increased. The utilisation of voriconazole as oral administration was the patient’s choice, which permitted her to be discharged. Oral voriconazole was also just as effective in a patient with a prolonged period of neutropenia and also lymphopenia secondary to administration of humanised monoclonal anti CD52. Despite this, the patient was able to periodically undergo palliative chemotherapy for her progressive hematologic disease, with constant improvement of radiologic picture and without any clinical symptoms of fungal infection. Voriconazole is usually given by intravenous infusion and then orally if possible. Voriconazole was given orally to our patient from the moment of radiologic picture and without any clinical symptoms of fungal infection. Voriconazole is usually given by intravenous infusion and then orally if possible.

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