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High weekly doses of liposomal amphotericin B as secondary prophylaxis after cerebral aspergillosis in a paediatric patient ☆

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ABSTRACT

A paediatric patient treated for acute lymphoblastic leukaemia developed cerebral abscesses caused by *Aspergillus fumigatus*. After surgical draining voriconazole treatment was started. The patient developed a Steven–Johnson syndrome and treatment was switched to L-AmB. The patient developed no new fungal lesions and L-AmB treatment was continued until the end of the therapy. Complete remission was achieved without neurological consequences.

High dose L-AmB represents an alternative for secondary prophylaxis of invasive fungal infections in patients intolerant to azoles.

1. Introduction

Invasive fungal infections (IFI) are increasingly encountered in clinical settings, in particular in immunocompromised patients with haematological malignancies, and cause significant morbidity and mortality [1]. *Aspergillus* species, mainly belonging to the *Aspergillus fumigatus* complex, are the most frequent causal agents [2] and produce a wide range of IFI, from opportunistic respiratory to disseminated infections, with mortality rates that can be well above 70% [1].

Amphotericin B [3], posaconazole [4], voriconazole [5] and, to a lesser extent, echinocandins [6–8] have all been used in the treatment and prophylaxis of IFI. Current Infectious Disease Society of America (IDSA) clinical practice guidelines recommend voriconazole as the first line treatment of invasive aspergillosis and posaconazole for its prophylaxis [9]. Although the prescribing information does not recommend it explicitly, there is evidence for voriconazole use in IFI prophylaxis [10]. Liposomal amphotericin B (L-AmB) for IFI secondary prophylaxis has been advocated for some patients [11], even if Cahuayme-Zuniga and co-workers have reported a frequent relapse of IFI and kidney injury [3].

Here we report the case of a paediatric patient under treatment for acute lymphoblastic leukaemia, who developed multiple cerebral abscesses from which *A. fumigatus* was isolated. The patient was treated with voriconazole with good response and this treatment was continued as secondary prophylaxis. During prophylaxis, however, the patient developed a severe dermatological allergic reaction to voriconazole; thus, a regimen of a weekly high dose of L-Amb was initiated and continued until the end of the antileukemic maintenance therapy.

2. Case

In September 2010 a 6-years-old male child was diagnosed standard risk acute lymphoblastic leukaemia and treated according to the protocol BFM-ALL-2000 [12]. In April 2011, during the intensive re-induction phase, he developed an IFI with lung and cerebral localisation. The galactomannan test yielded a value of 0.95 and a CT scan revealed several, bilateral nodular solid lesions compatible with a mould infection. A cerebral MRI showed at least two intraparenchymal lesions with concomitant ventriculitis and a biventricular obstructive hydrocephalus (Fig. 1A).

The abscess was drained and *A. fumigatus* isolated from the purulent material. Voriconazole was given under therapeutic drug monitoring in the blood and cerebro-spinal fluid (CSF) through an external ventricular catheter, with constant dose adjustments (Fig. 2).

Caspofungin (70 mg/m^2 as a first dose and subsequently 50 mg/m^2/day) was also added to the treatment, as proposed by some authors [6,8], even if its CNS penetration is considered to be generally low [13], to provide an additional systemic protection. Caspofungin was stopped after 4 weeks and voriconazole treatment (8 mg/kg/q12 h) continued. A cerebral MRI carried out 3 months after start of antifungal treatment showed a marked reduction of the abscesses but at the same time the appearance of new possible intracranial lesions (Fig. 1B), which, however, regressed in the following MRI controls. With the IFI under control, the antileukemic therapy (Phase

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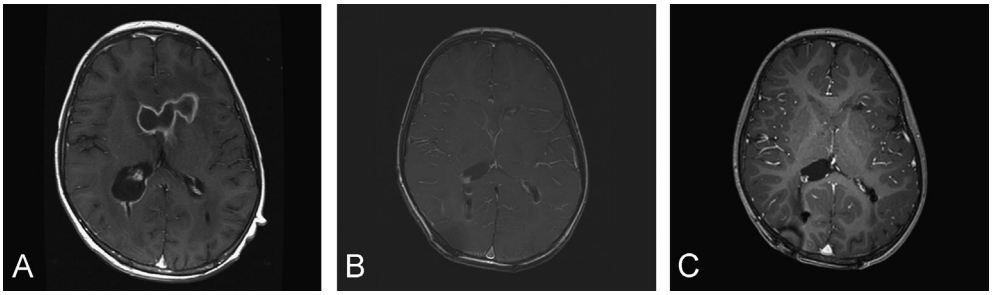

Fig. 1. A: MRI at diagnosis showing intraparenchymal lesions with concomitant ventriculitis and a biventricular obstructive hydrocephalus. B: MRI 3 months after start of antifungal treatment showing reduction of the abscesses and the appearance of new possible intracranial lesions. C: MRI at end of therapy after 12 months of treatment.

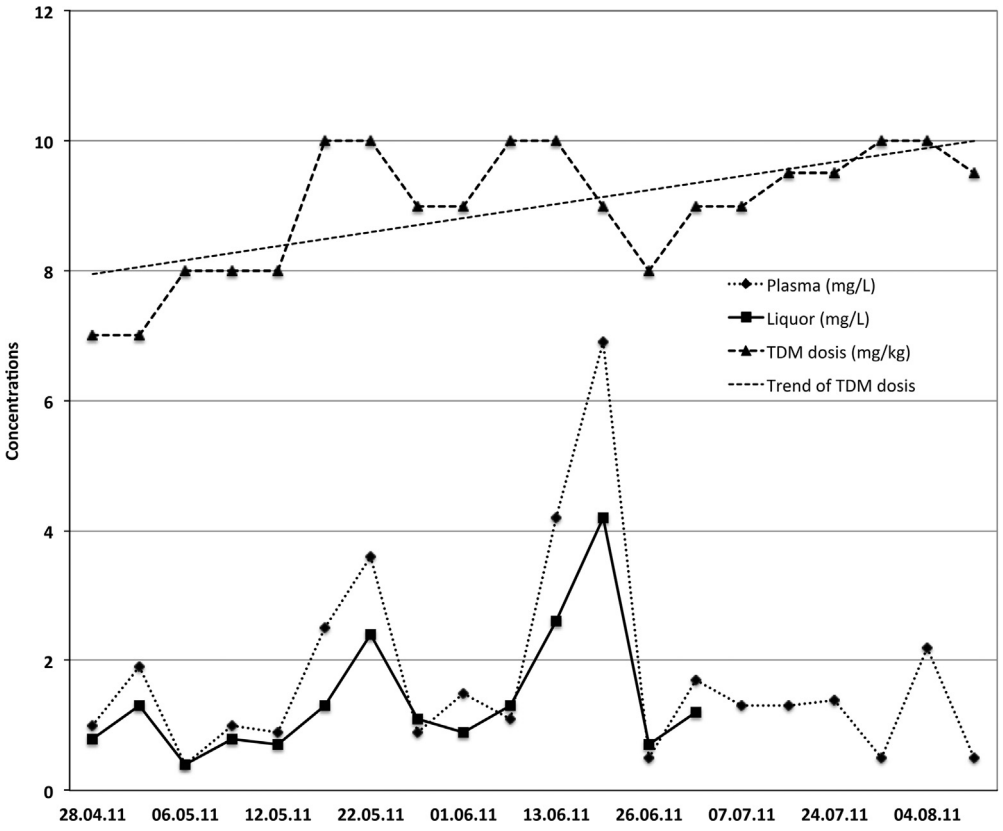

Fig. 2. Voriconazole blood and liquor levels during therapy.

IIB) could be resumed in August 2011 under secondary prophylaxis with voriconazole at drug blood levels higher than 1.2 mg/L. In February 2012 the patient developed a voriconazole-related Steven–Johnson syndrome. The drug was thus stopped and L-AmB* started at an initial dosage of 5 mg/kg/week, increased to 7.5 mg/kg/week after 7 days and further to 10 mg/kg/week for the rest of the maintenance therapy. During high dose L-AmB all intracranial lesions resolved without any evidence of side effects. The patient ended secondary prophylaxis in October 2012 after 8 months of treatment in total with high dose L-Amb and since then he is in good physical conditions, with no evident loss of cognitive functions or neurological impairment and negative repeated cerebral MRI and cerebral fluid investigations (Fig. 1C).

3. Discussion

Our observations have shown the importance of therapeutic drug monitoring to keep voriconazole trough levels in the therapeutic range. Continuous dose adjustments were needed, with a trend-wise need to increase dosage over time (Fig. 2). The use of caspofungin during the treatment phase was based on literature data showing that echinocandins may have a place in aspergillosis therapy [6–8].

After onset of the toxic allergic skin reaction to voriconazole, posaconazole could have been chosen to replace voriconazole during the secondary prophylaxis, considering that IDSA guidelines recommend its administration to neutropenic patients [9]. The lack of evidence for a correct paediatric dosage and the problems linked to therapeutic monitoring convinced us in this particular case to switch to L-AmB instead of using posaconazole. Additionally, we did not want to expose the patient to another azole derivate with the risk of another, possibly stronger toxic–allergic reaction. The choice of L-AmB as a replacement was based on the success reported by several authors in the treatment of pulmonary [11] or cerebral aspergillosis [14–16] with this drug. As it is generally assumed that amphotericin B penetration in the CNS is generally low [17,18], we decided to administer higher than commonly recommended doses of the drug [19]. The patient tolerated the treatment well, the efficacy was excellent and we

did not observe any signs of toxicity, contrary to a previously published review [3].

Overall, this case shows that weekly high doses of L-AmB represent a valuable alternative for secondary prophylaxis in patients with IFI who are intolerant to or not eligible for treatment with azoles.

Conflict of interest statement

The authors declare that they have no competing interests.

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