Hepatic Candidiasis Responding to a Low-dose Infusion of Amphotericin B in a Patient with Acute Leukemia

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Introduction

Focal hepatosplenic candidiasis is a serious complication in leukemic patients. The conventional treatment with amphotericin B is 1 mg/kg per day given by intravenous (iv) infusion, but serious side effects such as renal dysfunction may develop. We report a patient in whom treatment with low-dose iv amphotericin B for hepatosplenic candidiasis was successful and avoided side effects.

Case Report

A 26-year-old man weighing 65 kg was diagnosed with acute myelogenous leukemia in March 1996, and underwent five courses of chemotherapy. During induction, multiple abscesses became apparent by computed tomography (CT). A biopsy was performed under ultrasonic guidances and histopathologic findings on examination of the specimen were consistent with fungal hepatic abscess. A serologic test detecting Candida antigen in blood (Cand-Tec, Ramco Laboratories, Houston, TX) was positive several times during the clinical course, and a diagnosis of hepatic candidiasis was made. Amphotericin B was given at a daily dose of 50 mg by iv infusion, but was discontinued after the second day, when the serum creatinine concentration increased to 3 mg/dL. Substitution of miconazole (iv) resulted in the disappearance of the abscesses, and this drug was given during the first four courses of chemotherapy. During the fourth course, the abscesses reappeared; whereby, 6 g/day of amphotericin B were given orally, and the abscesses resolved. The patient entered complete remission after the fourth course of chemotherapy.

Relapse of the myelogenous leukemia occurred in February 1997, and the patient underwent reinduction chemotherapy. He had a high fever and right quadrant pain, neither of which improved with antibacterial antibiotics. C-reactive protein concentrations increased. A diagnosis of relapse of candidiasis with multiple abscesses in the liver and spleen was made from CT findings and a positive Cand-Tec test. Oral amphotericin B (8 g/day) was reintroduced, but high fever persisted and C-reactive protein remained high (Fig. 1 days 50–77). Conventional treatment with amphotericin B (50 mg/day iv) was not given because of the earlier occurrence of renal toxicity. As Candida species are sensitive to concentrations of amphotericin B from 0.03 to 1.0 µg/mL\(^1\), we tried to attain a serum amphotericin B concentration of about 1.0 µg/mL using an iv infusion of 8 mg of amphotericin B.

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Fig. 1 Serum concentrations of amphotericin B and C-reactive protein.

On day 78, low-dose amphotericin B (AMPH) by iv infusion was started and oral AMPH was stopped. The serum concentration of AMPH increased and serum C-reactive protein (CRP) decreased. (iv, intravenous; po, per os)

daily (0.12 mg/kg per day). Eight milligrams of amphotericin B (Fungizone™) was dissolved in a 500 ml bottle of 5% dextrose and was given through a central venous catheter by iv infusion for 6 hours. The serum concentration was assayed weekly by high-performance liquid chromatography2). With this treatment, the patient recovered from the fungal infection with no adverse effects (Fig. 1 days 78–118).

Discussion

Amphotericin B is the strongest antifungal agent used clinically. Liposomal amphotericin B (encapsulation of amphotericin B molecules into liposomes), was developed to reduce nephrotoxicity and improve efficacy in target organs, and is currently available in the USA and some European countries, but has not yet been approved yet for clinical use in Japan and many Asian countries. Therefore, we administered conventional amphotericin B therapy by low-dose iv infusion.

Irreversible renal dysfunction can result from excessive levels of amphotericin B, so frequent monitoring of the serum amphotericin B concentration is important. Few studies have described either the relationship of serum concentration to administered dose of amphotericin B, or of effective concentrations in vivo to the MIC of isolated fungus. Table 1 summarizes data from a few relevant papers3)–6).

We are guided by two principles in treatment with amphotericin B: first, at minimum, the serum amphotericin B concentration needs to exceed the MIC of the isolated fungus; second, serum concentrations do not correlate with the daily iv dose of amphotericin B.

That patient 17 in the Table 1 died is quite understandable, since the serum amphotericin B concentration was not above the MIC of the isolated fungus, which was relatively high (0.78 µg/mL) compared to other isolates. Even so, some patients died although their serum amphotericin B concentrations were 51 to 132 times the MIC of their isolates (cases 8, 9, 18). Other patients recovered with serum concentrations only 1.55 to 1.75 times as high as the respective MIC (cases, 6, 7, 22). At minimum, given these findings, we should monitor the serum amphotericin B concentration frequently to keep it in excess of the MIC of the isolated fungus. Monitoring is essential since serum concentra-
tions do not always rise when doses are increased.

In our patient, low-dose iv amphotericin B therapy was able to raise the serum drug concentration to about 1.5 μg/mL. *Candida* species appear to be sensitive to amphotericin B at this concentration\(^1\), and accordingly, therapy was successful in this patient. However, the approach we tried in our patient may not be appropriate for all patients with hepatic candidiasis. This is because some *Candida* species isolated clinically show MIC levels higher than 2 μg/mL. On the other hand, if no other choice is available, as with our patient who had a past history of amphotericin B nephrotoxicity, low-dose amphotericin B therapy appears to be effective for treatment of hepatic candidiasis. In such a situation and if possible, MIC measurements of the isolated fungal pathogens should be obtained and assessed before starting this treatment.

References


急性白血病患者において併発したカンジダ性肝膿腫に対し低濃度アンホテリシン B 点滴静注療法が奏効した例

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要 旨
26歳の急性骨髄性白血病患者に併発したカンジダ性肝膿腫がアンホテリシン B の低濃度点滴静注療法によって治療することに成功した。この患者においては、通常のアンホテリシン B 点滴静注療法（50mg/day）も試みられたが、腎障害の為すぐに中止された。リポゾーム型アンホテリシン B は、海外では既に臨床使用が認可されているが、本邦に於いては未認可である。そこで、我々は従来型のアンホテリシン B を 1 日 8mg の低濃度で中心静脈カテーテルより点滴静注することを試みた（0.12mg/kg/日）。この患者は薬剤による副作用をみることなく、真菌感染症から回復することができた。文献的考察と共に、症例報告する。