Successful treatment of Trichosporon fungemia in a patient with refractory acute myeloid leukemia using voriconazole combined with liposomal amphotericin B

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Case Report

Successful treatment of *Trichosporon* funginemia in a patient with refractory acute myeloid leukemia using voriconazole combined with liposomal amphotericin B.

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Abstract

Trichosporon funginemia is a rare and fatal fungal infection which occurs in patients with prolonged neutropenia associated with hematologic malignancies. A 21-year-old male developed *Trichosporon* funginemia during remission induction therapy for acute myeloid leukemia (AML). Although two courses of induction therapy failed to induce a remission of AML, combination therapy with voriconazole and liposomal amphotericin B (L-AmB) followed by monocyte colony-stimulating factor (M-CSF) ameliorated the *Trichosporon* funginemia and enabled the patient to receive reduced-intensity bone marrow transplantation (BMT) from his HLA-A one-locus mismatched mother. The patient achieved a durable remission after BMT without exacerbation of *Trichosporon* funginemia. The combination therapy with voriconazole and L-AmB may therefore be useful in controlling *Trichosporon* funginemia associated with prolonged neutropenia after remission induction therapy for AML.

Key words: *Trichosporon* funginemia, voriconazole, L-AmB, Combination therapy, M-CSF, acute myeloid leukemia

Trichosporon funginemia is a rare and fatal fungal infection which occurs in patients with prolonged neutropenia associated with hematologic malignancies. The funginemia presents with persistent fever and often involves the skin, kidneys, and other organs. *Trichosporon* funginemia is becoming an increasing problem because it occurs as a breakthrough infection in patients being treated with antifungal agents due to its resistance to most antifungal agents. The treatment outcome is usually poor, with a mortality rate of 80% (1). We recently experienced a patient with acute myelogenous leukemia (AML) complicated by *Trichosporon* funginemia who was successfully treated with combination therapy consisting of voriconazole, liposomal amphotericin B (L-AmB) and monocyte colony-stimulating factor (M-CSF).

Case Report

A 21-year-old male was diagnosed to have AML M0 expressing CD7 and CD33 with complicated chromosomal abnormalities on May 7, 2009. He received induction chemotherapy consisting of idarubicin and cytosine

arabinoside. Ciprofloxacin, 600 mg/day, was used for antibacterial prophylaxis. Cefepime and micafungin were administered to treat febrile neutropenia that occurred on day10, and the high fever eventually resolved. However, a high fever (over 40°C) recurred on day18, and cefepime was therefore changed to meropenem in combination with vancomycin. *Trichosporon* species were cultured from 5 consecutively drawn peripheral blood cultures on days 18-20 in the absence of a central venous line. *T. asahii* was identified by a culture-based method using API ID32C clinical yeast identification system (Biomerieux SA, Marcy-L'Etoile, France). The *in vitro* antifungal susceptibilities of the isolates from patients to antifungal drugs were determined using the Clinical and Laboratory Standards Institute (NCCLS) M-27 microdilution method. The minimum inhibitory concentrations of each antifungal agent against the *T. asahii* isolate at 24h and 48h were as follows; amphotericin B, 0.5 and >16; 5-fluorocytosine, 4 and 32; fluconazole, 16 and 16; miconazole, 0.5 and 1; itraconazole, 1 and 2; micafungin, >16 and >16; voriconazole, 0.25 and 0.25. Treatment was changed to voriconazole on day 19 and supplemented by L-AmB (AmBisome, Dainippon Sumitomo Pharma Co., Osaka, Japan, 2.5 mg/kg) on day

20 because the outcome of treatment for *Trichosporon* funginemia with voriconazole alone in the absence of hematologic recovery is reported to be extremely poor (2-4). Vancomycin was discontinued on day 20. The blood cultures became negative for *Trichosporon* 2 days after the start of voriconazole and L-AmB, but a high fever surpassing 40°C persisted over the next 7 days. In addition to high fever over 40°C for a week, the patient complained of pains in the right testis and gingivae in association with high fever. He was diagnosed to have pericoronitis and acute epididymitis. Liver function abnormalities such as AST 29 IU/L, ALT 76 IU/L, and total bilirubin 2.2 mg/dL as well as an increase in the C-reactive protein level (9.1 mg/dL) appeared a week after the onset of high fever. All these data gradually normalized after the voriconazole/L-AmB treatment. The leukocyte count on day 20 was 0.26 x 10^9/l with 100% leukemic cells. Bone marrow aspiration performed on day 20 revealed that more than 90% of the cells were leukemic cells.

Since there was a fear that granulocyte colony-stimulating factor (G-CSF) might stimulate leukemic cell proliferation, M-CSF (mirimostim, Kyowa Hakko Kirin Co., 8 x 10^6 U/day) was administered on day 24. On

day 27, the leukocyte count was 0.32 x 10^9/l with a neutrophil count of 0.20 x 10^9/l (63%) and a leukemic cell count of 0.03 x 10^9/l (8%) and the patient's high fever gradually resolved. However, bone marrow aspiration performed on day 32 again showed 80% of the cells to be leukemic cells. Re-induction chemotherapy consisting of daunorubicin and cytosine arabinoside failed to induce a remission. The blood cultures remained negative for *Trichosporon*, although voriconazole alone had been continued during re-induction therapy.

The patient's white blood cell count was 1.75 x 10^9/l, with 85% leukemia cells on day 24 after the start of re-induction therapy. Allogeneic stem cell transplantation was considered to be the only curative measure for this patient due to the primary induction failure at this time point. His mother was selected as a donor because she was HLA-A one locus mismatched with the patient. Gemtuzumab ozogamicin (GO 6 mg/m^2) was started on day 24 from the re-induction therapy (day-21 of BMT) and 3 mg/m^2 was added on day-14 for reducing the the leukemic burden. Following a conditioning regimen consisting of fludarabine (25 mg/m^2, day-7 to day-3), melphalan (40 mg/m^2, day-3 to day-2), rabbit anti-thymocyte globulin (Thymoglobuline, 0.5 mg/kg day-3, 1.25 mg/kg day-2 to day-1) and 4

Gy of TBI (day-2), 1.52 x 10^8 bone marrow cells/kg per patient weight from his mother were infused. Cyclosporine A and short term MTX were used for GVHD prophylaxis. Engraftment was documented on day 15, and complete donor type chimerism was confirmed on day 21. Grade Ia GVHD (skin 1, gut 0, liver 0) proven by a skin biopsy developed on day 56. Intravenous voriconazole was continued until day 28, and *Trichosporon* remained negative from the start of GO until his discharge on day 99 after BMT.

The patient died of AML 4 months after undergoing a third stem cell transplantation from an HLA-haplo-identical brother due to a relapse of leukemia on day 140. *Trichosporon* funginemia never recurred after the first BMT. No autopsy was performed.

Discussion

The incidence of invasive *Trichosporon* infection in patients with acute leukemia was reported to be 0.4% in a previous multicenter study performed in Italy (5). Disseminated *Trichosporon* infections in immunocompromised or neutropenic patients are usually fatal, despite intensive treatments with

various antifungal agents (6, 7). *Trichosporon* species are resistant to most antifungal agents, including fluconazle, itraconazole, and flucytosine (8-10). *Trichosporon* shows varying sensitivities to amphotericin B from one species to another. The minimum concentration of amphotericin B at 24h that inhibited the growth of *T. asahi* isolated from our patient was 0.5 μg/mL. The *in vitro* sensitivity of the isolated *Trichosporon* to amphotericin B may explain the treatment success observed in our patient. New triazoles such as voriconazole, posaconazole, and ravuconazole show excellent fungicidal activities *in vitro* and may be promising agents for the treatment of trichosporonosis (11).

Fournier et al. reported a case of disseminated trichosporonosis which was refractory to combination therapy with FLCZ and AmB despite the fact that hematologic recovery was achieved, but the infection was later resolved with voriconazole (12). Matsue et al. recently experienced 4 cases of disseminated trichosporonosis that developed under micafungin therapy (4). One of their patients who showed hematologic recovery was successfully treated with voriconazole, but the remaining 3 patients without hematologic recovery did not respond to fluconazole or voriconazole. Some pediatric

reports have suggested the clinical efficacy of voriconazole in the treatment of trichosporonosis as monotherapy (2) or as a combination therapy with amphotericin B (3), but none of the reported patients who failed to achieve a hematologic recovery were cured from infection. Therefore, although voriconazole shows a potent antifungal activity against *Trichosporon* species *in vitro*, it cannot effectively control the *Trichosporon* funginemia that develops in patients with persistent neutropenia, such as those with AML refractory to chemotherapy.

Our current patient developed *Trichosporon* funginemia on day 20 after remission induction therapy for AML at the time when the induction failure became evident. Since a very poor outcome of voriconazole treatment was predicted from the reappearance of leukemic cells and the absence of neutrophils, L-AmB was co-administered. Despite the fact that severe neutropenia of less than 0.1 x 10^9/l persisted over a week, the patient's *Trichosporon* funginemia was well-controlled by the combination therapy, and was eventually remitted in association with hematologic recovery that was accelerated by M-CSF. Even though several factors other than antifungal therapy may have contributed to the treatment success, this is to

our knowledge the first case of *Trichosporon* funginemia that was ameliorated by combination therapy in the absence of neutrophilic recovery.

M-CSF is a cytokine known to exert anti-fungal activity through the activation of monocytes (13). Although *Trichosporon* became undetectable in the patient's blood after the start of voriconazole and L-AmB, the high fever persisted in our patient. G-CSF was not used due to the persistence of leukemic cells in the peripheral blood. However, his high fever readily resolved in association with a gradual increase in the neutrophil count that occurred 3 days after the start of M-CSF. Therefore, the antifungal activity of M-CSF may have contributed to the improvement of the patient's funginemia.

Allogeneic stem cell transplantation is a curative treatment option for patients with refractory acute myeloid leukemia (AML), but it is generally difficult to achieve success with this option when the patients are complicated by severe infections such as *Trichosporon* funginemia. Our patient achieved a complete remission (CR) after preconditioning with GO and a reduced-intensity regimen followed by BMT. The patient's clinical

course indicates that even when a patient with chemotherapy-resistant AML is complicated by *Trichosporon* funginemia, reduced-intensity BMT can induce a durable remission of AML with the help of voriconazole and L-AmB treatment. The combination therapy for *Trichosporon* funginemia therefore warrants further clinical investigation.

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