Eur J Med Res (2007) 12: 337-340

Triple Antifungal Therapy for Severe Systemic Candidiasis Allowed Performance of Allogeneic Stem Cell Transplantation

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Abstract
Systemic candidiasis is a rare but life threatening complication in immunosuppressed patients undergoing allogeneic SCT. Combination of new antifungal agents may improve outcome in this patient population.

Here, triple anti-mycotic therapy is described in an relapsed ALL patient in urgent need of allogeneic bone marrow transplantation. The patient with T-cell acute lymphoblastic leukemia of thymic differentiation achieved remission after treatment according to the German ALL protocol 07/03. Two months after the consolidation therapy relapse occured requiring high dose chemotherapy with allogeneic stem cell transplantation. One day after start of the conditioning regimen the patient showed skin manifestations typical for septic mycosis and blood cultures became positive for Candida krusei while on fluconazol prophylaxis. Because of the limited sensibility of fluconazole resistant candida species to liposomal amphotericin B and the high mortality rate in patients with systemic candidiasis, voriconazole was added immediately to liposomal amphotericin B. Since fever did not resolve and the conditioning therapy for allogeneic transplantation was not yet completed caspofungin was added.

Skin manifestation responded to this triple anti-mycotic combination and peripheral blood stem cells from an unrelated donor were transplanted. With the triple antifungal therapy the patient finally became afebrile, skin manifestations showed complete resolution and blood cultures became negative. Three months after the onset of systemic candidiasis the patient was fully active with no signs of fungal infection and in haematological and molecular remission.

Mycotic sepsis at the start of myeloablative conditioning therapy in heavily pretreated acute leukemia patients is usually considered as not allowing succsessful allogeneic transplantation. Thus this case demonstrates, that allogeneic stem cell transplantation is feasable in patients presenting with systemic candidiasis if combined antifungal therapy with liposomal amphotericin B, caspofungin and voriconazol is given.

Key words: candidiasis, voriconazole, caspofungin, bone marrow transplantation

Introduction

The frequency of infections by Candida species is increasing worldwide and the risk of infection is particularly high in immunocompromised, hospitalized patients (Sims et al., 2005). In cancer patients with Candida blood stream infections (Safdar et al., 2004) and moreover in patients undergoing allogeneic hematopoetic stem cell transplantation systemic candidiasis is a potentially life-threatening infectious complication (Kruger et al., 1997) with an excess mortality rate in patients with C. krusei colonization (Safdar et al., 2002A). Though the frequency of fungal infections involving yeasts, such as Candida species, has decreased with the use of azole antifungals as prophylaxis in these heavily pretreated and immunocompromised patients (Marr et al., 2004), the prophylaxis and treatment of Candida infection have led to the emergence of resistant species and the acquisition of resistance in previously susceptible species (Safdar et al., 2002B). In clinical practice, liposomal amphotericin B has been preferentially used for treatment of invasive candidiasis, but the high mortality rate of up to 83% in patients after autologous or allogeneic hematopoietic stem cell transplantation (Kruger et al.,1997) emphasizes the need for better therapeutic options.

Additional treatment opportunities for disseminated candidiasis are offered by the recent introduction of new antifungal agents such as voriconazole and caspofungin.

Voriconazole is a second-generation triazole antifungal agent, that is structurally derived from fluconazole and potently inhibits ergosterol synthesis (Schafer-Korting et al., 2003). In vitro voriconazole was more active than amphotericin B and fluconazole against all Candida spp. and was the only drug of these agents with good activity against C. krusei (Pfaller et al., 2002). Compared to prior azoles it has an extended spectrum of activity against a wide variety of yeasts and moulds and appears to be an effective therapy option for invasive aspergillosis, esophageal candidiasis, fluconazole-resistant candidiasis and refractory or less-common invasive fungal infections (Kofla et al., 2005). In non-neutropenic patients with a positive blood culture for candida species and clinical evidence of infection voriconazole cleared blood cultures as quickly as amphotericin B and fluconazole (Kullberg et al., 2005). Moreover in patients with invasive candidiasis refractory to other anti-mycotic therapy or in patients not tolerating other antifungal agents voriconazole showed an overall response rate of 56%, achieving a 70% response rate in infections due to Candida krusei (Ostrosky-Zeichner et al., 2003).

Caspofungin, a semisynthetic derivative of the pneumocandin B(0), is the first licensed compound of a new class of antifungal agents, the echinocandins, which acts by the suppression of the enzyme glucan synthase (Schafer-Korting et al., 2003). In vitro studies have indicated a potent fungicidal effect on Candida species, and in vivo studies demonstrated a favourable outcome in immunocompromised animals with invasive candidiasis. Even though azoles displayed fungistatic activity in different Candida species, only amphotericin B and caspofungin demonstrated fungicidal activity in vitro (Di Bonaventura et al., 2004). In an immunocompromised patient with candidal meningitis refractory to systemic antifungal therapy (amphotericin B and fluconazole) the cerebrospinal fluid became sterile with caspofungin (Liu et al., 2004). In randomized clinical trials in patients with invasive candidiasis, caspofungin was at least as effective as amphotericin B deoxycholate, yet showed a significantly superior safety profile (Maschmeyer et al., 2005).

Due to these promising in vitro and in vivo data, showing susceptibility of Candida isolates to both anti-mycotic drugs, voriconazole and caspofungin, even in those strains resistant to amphotericin B (Ostrosky-Zeichner et al., 2003), we chose to treat the fluconazole refractory fungal infection in the seriously ill patient presented here during high dose chemotherapy and allogeneic peripheral blood stem cell transplantation with a triple combination of all the three Candida-specific antifungal drugs liposomal amphotericin B, voriconazole and caspofungin.

Case

A 26-year-old male patient with thymic type of acute T-lymphoblastic leukaemia was treated according to the German ALL protocol 07/03 achieving a CR after an induction therapy consisting of dexamethason, vincristin, daunorubicin, PEG-asparaginase, cyclophosphamide, cytarabin and 6-mercaptopurin, followed by radiation of his mediastinum. In addition he received a prophylactic cranial irradiation. After the first cycle of consolidation therapy with cytarabin, methotrexate, etoposide and vindesine, he relapsed and was resistant to a salvage protocol containing of fludarabin, cytarabin (FLAG), etoposide and amsacrine. Even after cladribine, etoposide and cytarabin (CLAEG) combined with alemtuzumab the patient achieved only a partial remission, still having 35% blasts in the bone marrow. Since allogeneic transplantation can lead to long lasting remissions in patients with refractory ALL an allogeneic stem cell transplantation with a full dose conditioning regimen was planned.

Imediately before the anticipated start of the conditioning regimen the neutropenic patient developed fever with signs of sinusitis confirmed by CT scan. Broad spectrum antibiotics were given. Allthough the fever decreased two days later skin efflorescences resembling cutaneous fungal infiltrations were visible and extensive work up was initiated. Systemic candidiasis was diagnosed based on candida cruzei in blood cultures. However, computed tomography of the chest did not show any pulmonary lesions.

Due to the severe clinical situation, a combination with amphotericin B lipid complex (3mg/kg) and voriconazole (6 mg/kg/day i.v. for two doses followed by 4 mg /kg i.v. bid) was started and the patient soon became unfebrile.

However, the day before transplantation, when the GvHD prophylaxis consisting of cyclosporin A and methotrexate was started, he again deteriorated with high fever. Because of the patients worsening clinical condition, the unimproved skin manifestations and the intensive immunosuppression, caspofungin (70 mg loading dose and then 50mg daily) was added to the combination of liposomal amphotericin B and voriconazole, to target the systemic candidiasis by all known therapeutic mechanisms. The clinical features improved rapidly, blood cultures became negative and the skin manifestations vanished.

When repeated cultures became negative for Candida, immunosuppression with mycophenolate mofetil was restarted and liposomal amphotericin B as well as caspofungin were discontinued. Finally the patient switched to oral voriconazole as maintenance therapy at 200mg twice daily and could subsequently be discharged.

Discussion

Systemic candidiasis is a rare but severe complication in immunosuppressed patients and associated with high mortality. Major risk factors for systemic candidiasis include prolonged neutropenia and severe long-lasting T-cell immunosuppression. Our patient was both neutropenic and lymphopenic caused by previous intense treatment protocols including lympocyte depleting therapy with fludarabin, cladribine, alemtuzumab as well as ATG. This T-cell depletion and functional T-cell alteration was further enhanced by the use of CSA and methotrexate for GvHD prophylaxis preventing T-cell activation. In addition fluconazole given for prophylaxis of Candida infection may have led to the emergence of resistant species. In systemic candidiasis monotherapy with liposomal amphotericin B is a standard. Due to the immediate need of an allogeneic stem cell transplantation given the very limited clinical success of fungistatic monotherapies in severely immunosuppressed patients we intended to enhance the antifungal effect. Supported by both, in vitro and in vivo data, we decided therefore to try a combination of the recently introduced voriconazole together with liposomal amphotericin B further extended to caspofungin. Actually the candida krusei species was cleared rather rapidly from the blood and the skin manifestations resolved.

It is important to note that recently synergistic effects have been shown in in vitro and in animal models between newer and more traditional antifugal agents (Lewis et al., 2001). Given the different mechanisms of action of amphotericin B, caspofungin and voriconazole against the fungal wall and fungal cell membrane the successful clinical course might be related to this combination of the use of caspofungin with other antifungal agents (Groll et al., 1998).

The initial combination of amphotericin B with a triazole has been questioned because of the potential antagonism between them arising from the azole medi-

ated inhibition of ergosterol, that is the substrate for amphotericin B (Antonidou et al., 2003). Though in vitro data differ showing antagonism, antagonism dependant on the sequential order of the antifungal agents and even no antagonism, a recent, prospective, randomized clinical trial showed compelling data, that candidemia cleared more rapidly with a combination therapy consisting of amphotericin B and fluconazole compared to the monotherapy with azole (Rex JH et al., 2003).

Unlike amphotericin B which binds to membrane sterols, caspofungin attacks the fungal cell by selective inhibition of the synthesis of the fungal cell wall component beta-(1,3)-D-glucan, which is not present in mammalian cells (McCormack et al., 2005). The mechanisms of synergic or additive effects for amphotericin B and caspofungin are likely to be the inhibition of (1,3)-ß-D-glucan formation by caspofungin leading to cell wall damage, that would allow amphotericin B easier access to the fungal cell membrane, where it binds to membrane ergosterol, resulting in pore formation and cell lysis (Franzot et al., 1997).

In a study evaluating the activity of amphotericin B and caspofungin against an azole-resistant C. albicans isolate neither in vitro nor in mice antagonistic interactions were observed between the two agents, but a trend towards additivity (Hossain et al., 2003). Clinical data about the treatment of systemic candidiasis with this combination of amphotericin B and caspofungin are limited. In a 3-yr-old child with persistent candidemia caspofungin was added to an antifungal regimen that included amphotericin B and flucytosine resulting in rapid clearance of the candidemia. The child recovered without evidence of further fungal infection or overt toxicity (Wertz et al., 2004). In a clinical study in 4 out of 5 immunosuppressed patients systemic candidiasis was cleared by the addition of Caspofungin to the standard Amphotericin containing regimens (Nivoix et al., in press).

For the combination of echinocandins with triazoles in vitro data permit optimism, although clinical trial data are still sparse (Lewis et al., 2001). In an intensive care unit patient with severe systemic Candida infection improvement of his clinical course was achieved with combined antimycotic therapy (voriconazole, caspofungin and fluconazole) (Lewejohann et al., 2005). In another patient hepato-splenic and kidney candidiasis complicating the chemotherapy of a myeloblastic leukaemia was reported. Following the lack of effectiveness of a first line treatment, using liposomale amphotericin B and 5-fluorocytosine, implementation of an association of the new molecules voriconazole and caspofungin has allowed a successful result (Elouennass et al., 2005). Also in the treatment of fungal endophthalmitis the combination of voriconazole and caspofungin appears to be very effective (Breit et al., 2005).

Based on this observation we feel that in critical situations due to mycotic sepsis the triple combination of ambisome, voriconazole and caspofungin might be an option in patients who do not appear to be improving on standard therapy. To our knowledge this is the first report of combined use of voriconazol, liposomal amphotericin and caspofungin with successful outcome in a allogeneic transplant patient with systemic candidiasis at the begin of conditioning. Given the recently reportet resistence of Candida species not only to amphotericin B but also to voriconazole (Mohammedi et al., 2005) physicians treating transplanted patients may consider this therapeutic option of the triple combination of amphotericin B, voriconazole and caspofungin in the management of systemic candidiasis.

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Received: July 10, 2006 / Accepted: May 21, 2007

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