Breakthrough *C. parapsilosis* and *C. guilliermondii* blood stream infections in allogeneic hematopoietic stem cell transplant recipients receiving long-term caspofungin therapy

Since 2004, when caspofungin became available at our institution for empirical treatment of fever, we have been faced with the occurrence of candidemia due to unusual species, i.e. *C. parapsilosis* and *C. guilliermondii*, which have been reported to exhibit decreased susceptibility to echinocandins *in vitro*.[1-3] While only 5 episodes of candidemia (*C. glabrata* n=3, *C. albicans* n=1, and *C. krusei* n=1) were observed in 487 allogeneic hematopoietic stem cell transplant (HSCT) recipients between January 2000 and December 2004, 3 cases of candidemias (*C. parapsilosis* n=2, *C. guilliermondii* n=1) occurred out of 170 HSCT recipients from January 2005 to July 2006. The 3 patients were receiving long-term caspofungin therapy. Main characteristics of the patients and of the *Candida* infections are shown in Table 1.

Patient #1, an 18 year-old male, underwent a first unrelated HSCT in January 2004 with no sustained engraftment. Two months post-transplant he developed a definitive lung invasive aspergillosis successfully treated with voriconazole. He received a second transplant on May 2005. On day 7 post-transplant, secondary prophylaxis was switched from voriconazole to caspofungin due to liver toxicity. There was no granulocyte recovery. On day 48, he became febrile and a blood culture was positive for *C. parapsilosis*. Due to the patient's poor condition, the central venous catheter (CVC) was not removed. Skin and throat colonization with *C. parapsilosis* had been documented from day 39 onward.

Patient 2, a 46-year old male, underwent an allogeneic HSCT from an HLA matched sibling donor on May 2005. Antifungal prophylaxis consisted of fluconazole. Caspofungin was introduced on day 6 post-transplant as empirical treatment for a persistant fever. Granulocyte recovery occurred on day 28. He further experienced a severe acute graft-versus-host disease treated with multiple immunosuppressive regimens, and a cytomegalovirus infection. On days 58-60, three blood cultures were positive for *C. parapsilosis*. Skin, gastro-intestinal tract and upper respiratory airways were colonized with *C. parapsilosis* from day 33 onward.

Patient #3, a 32-year old male, underwent an unrelated HSCT on November 2005. Antifungal prophylaxis consisted of fluconazole. Granulocyte recovery occurred on day 21. He experienced recurrent episodes of acute graft-versus-host disease treated with multiple immunosuppression regimens. He developed several episodes of cytomegalovirus infections and bacteremia. Antifungal prophylaxis was switched to caspofungin on day 95 because of liver toxicity. On day 118, he became febrile and a blood culture was positive for *C. guilliermondii*. The gastro-intestinal and the respiratory tracts were colonized with *C. parapsilosis* from day 116 to day 123. We report here the emergence of *C. parapsilosis* and *C. guilliermondii* fungemia in 3 immunocompromised patients receiving long-term caspofungin therapy. From January 2005 to July 2006, 170 patients were recipients of HSCT in our unit of whom 103 (61%) received at least one day of caspofungin therapy. The overall incidence was 1/1,000 patient-days exposure to the drug. Caspofungin is an effective treatment of candidiasis and has been shown to be as effective as amphotericin B for the treatment of candidemia whatever the species involved.[4] Recent reports on another echinocandin, micafungin, in the treatment of candidemia and invasive candidiasis showed an identical response among patients with *C. parapsilosis* infections as compared with other species and no inferior result as compared with liposomal amphotericin B.[5,6] However, echinocandins are known to have less intrinsic *in vitro* activity against *C. parapsilosis* and *C. guilliermondii* than against the other *Candida* species. The MICs obtained with our isolates showed values comparable to those reported for other *C. parapsilosis* or *C. guilliermondii* isolates[1,2] (Table 2). The clinical studies together with the *in vitro* susceptibility results confirmed the unrealibility of these tests when considering echinocandin drugs.[7] However, Reboli *et al*. observed a markedly reduced response rate to anidulafungin (63.6%)

Table 1. Patients and candidemia characteristics and outcome.

Patient/ Candida species	*Underlying disease/ type of transplant*	*Risk factor for candidemia*	*From transplant to candidemia (days)*	*CAS exposure (days)*	*Reason for CAS treatment*	*Number of positive blood cultures/duration of candidemia (days)*	*CVC removal/ treatment/ response*	*Outcome/ cause of death*
Patient 1/ *C. parapsilosis*	AA 2nd UCB	CVC Neutropenia Steroids Colonization	48	41	Secondary prophylaxis	9/6	No/ Liposomal amphotericin B/ Cure	Death d 72/ MOF, no engraftment
Patient 2/ *C. parapsilosis*	ALL MR	CVC GVHD Steroids CMV	58	50	Empirical treatment	3/3	Yes/ Liposomal amphotericin B / Cure	Death d 86/ GVHD, ARDS
Patient 3/ *C. guilliermondii*	NHL MU	CVC GVHD Steroids Bacteremia	118	26	Primary prophylaxis	1/1	No/ Voriconazole/ Cure	Death d 197/ GVHD, ARDS

CAS: caspofungin; CVC: central venous catheter; AA: aplastic anemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin's lymphoma; UCB: unrelated cord blood; MR: matched related; MU: matched unrelated; GVHD: graft-versus-host disease; CMV cytomegalovirus infection; MOF: multi-organ failure; ARDS: acute respiratory distress syndrome.

Table 2. Minimal inhibitory concentrations (MICs) (mg/L) of the first blood isolate for the 3 patients.

	C. parapsilosis (Patient 1)	*C. parapsilosis (Patient 2)*	*C. guilliermondii (Patient 3)*
Amphotericin B	1	1	0.06
Caspofungin	1	1	0.5
Anidulafungin	2	2	1
Micafungin	8	8	2
Voriconazole	0.004	0.004	0.03
Serum Caspofungin (mg/L)	1.8	3.7	4.2

Serum caspofungin levels (mg/L) on day of the first positive blood culture (patients 1 and 3) or three days before the first positive blood culture (patient 2). (MICs were performed using the CLSI M27-A methodology)[10]

compared with fluconazole (83.3%) in 11 and 12 patients with invasive candidiasis due to *C. parapsilosis*.[8] Recently, Cheung *et al*. reported a case of *C. parapsilosis* candidemia in a patient on caspofungin therapy which was explained by the co-administration of phenytoin. A decrease in caspofungin serum levels cannot explain our 3 cases of candidemia since these levels were between 2 and 4 mg/L (Table 2).

In conclusion, we would like to warn physicians to the fact that, in deeply immunocompromised patients treated with caspofungin, breakthrough candidemia with organisms known to have a reduced susceptibility to this drug may occur. Persisting colonization with such *Candida spp.* may be an indication for switching to an alternative antifungal drug.

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Key words: Candida parapsilosis, Candida guilliermondii, caspofungin, echinocandin, candidemia.

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