

Breakthrough filamentous fungal infections in pediatric hematopoietic stem cell transplant and oncology patients receiving caspofungin

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BACKGROUND: Caspofungin is an echinocandin class antifungal medication that is commonly used empirically in immunocompromised patients at high risk for invasive fungal disease.

OBJECTIVE: To describe the clinical characteristics of breakthrough fungal infections in pediatric hematopoietic stem cell transplant recipients, and oncology and hematology patients receiving caspofungin.

METHODS: A five-year retrospective review, from 2004 through 2008, of all cases of proven invasive filamentous fungal infection of children admitted to The Hospital for Sick Children (Toronto, Ontario) was conducted. A breakthrough infection was defined as new onset of symptoms that were later proven to be due to an invasive mold infection on day 3 or later after initiation of caspofungin therapy.

RESULTS: Six confirmed positive cultures (*Aspergillus fumigatus* [two cases], *Aspergillus niger*, *Fusarium oxysporum*, *Alternaria infectoria* and *Rhizomucor pusillus*) met the criteria for breakthrough filamentous mold infection while on caspofungin therapy. Underlying immunocompromising conditions included acute lymphoblastic leukemia (two cases), acute myeloid leukemia (two cases), Burkitt's lymphoma and aplastic anemia. Four of the patients underwent a hematopoietic stem cell transplant. All patients received a lipid amphotericin B product as part of their treatment for breakthrough infection. Five patients also received voriconazole and one received posaconazole. Four of the six patients died and two responded with a clinical and microbiological cure.

DISCUSSION: There are few descriptions of breakthrough fungal infections in pediatric patients receiving caspofungin. The six cases presented here, all microbiologically proven, are likely only a fraction of the total number of possible breakthrough invasive fungal infections that occurred over the study period.

CONCLUSION: Clinicians must remain aware that breakthrough fungal infections by species not covered by particular antifungals, including caspofungin, do occur and may have poor outcomes.

Key Words: Breakthrough; Caspofungin; Fungal infection; Mold; Pediatric

Caspofungin, the first licensed drug in the class of echinocandin antifungals, acts via noncompetitive inhibition of the synthesis of the fungal cell wall constituent 1,3-beta-glucan. Due to its wide spectrum of antifungal activity, including filamentous fungi, such as *Aspergillus* species and most yeasts, caspofungin is commonly used as empirical therapy in patients at high risk for invasive fungal infections; especially those with severe neutropenia, children at high risk for invasive fungal infections, including those receiving antineoplastic drugs, and recipients of hematopoietic stem cell transplants (HSCTs).

Des infections fongiques filamenteuses perthérapeutiques chez des patients d'âge pédiatrique ayant reçu une greffe de cellules souches hématopoïétiques ou atteints d'un cancer et qui prennent de la caspofongine

HISTORIQUE : La caspofongine est un antifongique de la classe des échinocandines souvent utilisée de manière empirique chez les patients immunodéficients très vulnérables à une maladie fongique envahissante.

OBJECTIF : Les auteurs visaient à décrire les caractéristiques cliniques des infections fongiques perthérapeutiques chez des receveurs de greffe de cellules souches hématopoïétiques (GCSH) ou des patients traités en oncologie ou en hématologie qui prennent de la caspofongine.

MÉTHODOLOGIE : Les auteurs ont procédé à l'analyse rétrospective de tous les dossiers après avoir repéré les cas d'infection fongique filamenteuse envahissante démontrés grâce aux dossiers de microbiologie d'enfants hospitalisés au *Hospital for Sick Children* sur une période de cinq ans, entre 2004 et 2008. Une infection perthérapeutique est définie comme l'apparition de nouveaux symptômes qui sont ultérieurement attribués à une infection à champignon envahissante, laquelle se manifeste à compter du troisième jour suivant le début du traitement à la caspofongine.

RÉSULTATS : Six cultures positives confirmées (*Aspergillus fumigatus* [deux cas], *Aspergillus niger*, *Fusarium oxysporum*, *Alternaria infectoria* et *Rhizomucor pusillus*) respectaient les critères d'infection fongique filamenteuse perthérapeutique pendant un traitement à la caspofongine. Les troubles d'immunodéficience sous-jacents incluaient la leucémie lymphoblastique aiguë (deux cas), la leucémie myéloïde aiguë (deux cas), le lymphome de Burkitt et l'anémie aplastique. Quatre patients ont reçu une GCSH. Tous les patients ont reçu un produit d'amphotéricine B en formulation lipidique dans le cadre du traitement de l'infection perthérapeutique. Cinq patients ont également reçu du voriconazole et un, du posaconazole. Quatre des six cas sont décédés et deux ont répondu à un traitement clinique et microbiologique.

EXPOSÉ : Il existe peu de descriptions d'infections fongiques perthérapeutiques chez les patients d'âge pédiatrique qui prennent de la caspofongine. Les six cas, tous confirmés par examen microbiologique, représentent probablement une fraction du total des infections fongiques envahissantes perthérapeutiques possibles tout au long de la période de l'étude.

CONCLUSION : Les cliniciens doivent savoir que des infections fongiques perthérapeutiques causées par des espèces qui ne sont pas éradiquées par un antifongique précis, y compris la caspofongine, se produisent bel et bien et peuvent s'associer à une issue sombre.

Caspofungin has excellent activity against the most commonly encountered invasive fungal pathogens; however, it has only limited activity against some filamentous fungi including the *Zygomycetes* class (including those most commonly described to cause human disease: *Rhizomucor pusillus*, *Rhizopus arrhizus* and *Absidia corymbifera*) and *Fusarium* species (1,2). Although only approved by the United States Food and Drug Administration in July 2008 for use in children three months to 17 years of age for the treatment of candidemia and other invasive *Candida* infections (intra-abdominal abscesses,

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peritonitis, pleural space infections, esophageal candidiasis, and invasive aspergillosis in patients refractory or intolerant to other therapies [3]), caspofungin has been used off-label in this population for a significantly longer period of time (4,5). A recent retrospective review conducted at The Hospital for Sick Children (Toronto, Ontario), designed to evaluate the response to and adverse effects of caspofungin, included 56 patients one to 17 years of age who had received cancer chemotherapy or who had undergone HSCT and were given caspofungin for the empirical management of febrile neutropenia (6). This study found that 79% of patients had a favourable response and that there were no confirmed breakthrough fungal infections. There are limited data examining breakthrough infections by filamentous molds in patients receiving empirical caspofungin. A large randomized placebo-controlled clinical trial involving adult patients with persistent fever and neutropenia found that there was no statistically significant difference in the number of breakthrough fungal infections between those receiving caspofungin versus those receiving liposomal amphotericin B (7). There were, however, three breakthrough infections with filamentous molds (*Zygomycetes* [two cases] and *Fusarium* [one case]) in the caspofungin group, whereas there were none in the amphotericin B group. A recent French study identified nine cases of breakthrough *Aspergillus* infections in a group of 156 HSCT patients who received caspofungin therapy (8). A study of 28 adult patients with a diagnosis of a hematological malignancy receiving caspofungin as secondary prophylaxis following treatment of an invasive fungal infection found that nearly one-third (29%) developed a proven or probable breakthrough invasive fungal infection (9). The one microbiologically proven breakthrough infection in this study was due to *Aspergillus fumigatus*. A recent study from France investigating febrile and neutropenic patients receiving empirical antifungal therapy found six cases of probable or possible invasive aspergillosis in 46 patients treated with caspofungin, while no cases were found in 16 patients treated with amphotericin B desoxycholate (10). Data regarding breakthrough fungal infections in children receiving caspofungin are even more limited. One study showed that two of 39 febrile and neutropenic children who received empirical caspofungin had breakthrough filamentous fungal infections (invasive pulmonary disease due to *Aspergillus flavus* in one and pulmonary zygomycosis in another [11]). Another small study examining nine febrile and neutropenic infants and toddlers (three to 24 months of age) who had received empirical caspofungin showed one possible breakthrough fungal infection of the lung and spleen based on radiological imaging (12).

At our institution, guidelines exist for the empirical use of antifungal agents in children, including oncology and HSCT populations (13). These guidelines apply to those who: experience fever and neutropenia as a result of a known or suspected malignancy or the use of antineoplastics; are HSCT patients who present with fever or evidence of infection within six months of their transplant, regardless of their actual neutrophil count; and HSCT patients with fever who continue to receive immunosuppressant agents after transplant, regardless of their actual neutrophil count. After five to seven days of persistent fever despite administration of empirical antibacterial therapy or in the event of a new fever after five to seven days of empirical antibiotic administration, consideration is given to the addition of either conventional amphotericin B (1 mg/kg/day intravenously) or caspofungin (50 mg/m²/day intravenously, maximum of 70 mg/day). In children <2 years of age, amphotericin B is considered to be the first-line empirical antifungal treatment, with liposomal amphotericin B being substituted in patients with underlying renal dysfunction. Caspofungin is the preferred empirical antifungal agent in children >2 years of age who are diagnosed with acute myeloid leukemia, relapsed acute lymphoblastic leukemia, or are undergoing autologous or allogeneic transplant, have pre-existing renal impairment (ie, a glomerular filtration rate ≤ 60 mL/min/1.73 m²) or develop renal impairment (ie, serum creatinine >150% of baseline or ≥ 1.5 times the upper limit of normal for age) while receiving conventional amphotericin B, have uncontrolled infusion-related reactions or uncontrolled hypokalemia while receiving conventional amphotericin B.

The objective of the present study was to describe the clinical and microbiological characteristics of breakthrough fungal infections in pediatric HSCT recipients, and oncology and hematology patients receiving caspofungin while admitted to our institution over a five-year period.

METHODS

The present study was conducted at The Hospital for Sick Children, a tertiary care pediatric hospital located in Toronto, Ontario, with large hematology, oncology and HSCT services. All cultures positive for filamentous molds from immunocompromised patients admitted to the oncology, HSCT and intensive care units between January 1, 2004 and December 31, 2008, were identified by reviewing microbiology records. A retrospective chart review of each of these patients was undertaken to identify the patient's underlying immune compromising condition, whether the positive culture represented a true infection, whether the patient was on caspofungin at the time of the diagnosis of infection, and the clinical characteristics of the case, treatment and outcome. Only oncology, hematology and HSCT patients were included in the present study. Breakthrough was defined as an infection with onset of symptoms of an invasive fungal disease on day 3 or later after initiation of therapy with caspofungin (7). Approval for the present study was obtained from The Hospital for Sick Children Research Ethics Board.

RESULTS

A total of 22 confirmed positive cultures for filamentous fungi were identified from oncology, hematology and HSCT patients over the study period. Six of these met the criteria for breakthrough filamentous mold infection while on caspofungin therapy. Of the 16 positive cultures that did not meet the definition of breakthrough infection, eight were noninvasive infections, seven were invasive infections in which the patients had not received caspofungin and one was an invasive infection in which symptoms began only two days after the onset of caspofungin therapy.

The microbiological and clinical characteristics of the six cases of breakthrough infection are listed in Table 1. Four of the patients were male, two were female, and their ages ranged from 20 months to older than 15 years of age. The organisms in these cases included *A fumigatus* (two cases), *Aspergillus niger*, *Fusarium oxysporum*, *Alternaria infectoria* and *R pusillus*. The anatomical location of infections included the lungs (two cases), the central nervous system (two cases), rhinitis (one case) and skin plus blood (one case). Underlying immune compromising conditions included acute lymphoblastic leukemia (two cases), acute myeloid leukemia (two cases), Burkitt's lymphoma and aplastic anemia. Four of the patients received an HSCT (two of which were after the onset of breakthrough infection) and all received significant immune-suppressing medications. The duration of treatment with caspofungin before onset of symptoms associated with the breakthrough infection ranged from seven days to 16 weeks (median nine days; mean 27 days). All patients received a lipid amphotericin B product as part of their treatment for the breakthrough infection. Five patients also received voriconazole and one received posaconazole. Four of the six patients died and two responded with a clinical and microbiological cure.

DISCUSSION

While breakthrough invasive fungal infections in adult patients receiving caspofungin are well described, there are few descriptions of such infections in pediatric patients. Patients at highest risk for invasive fungal disease are frequently critically ill or compromised to the extent that obtaining tissue or samples for microbiological or pathological analysis is difficult. Thus, the six cases presented here, all microbiologically proven, are likely only a fraction of the total number of possible breakthrough invasive fungal infections that occurred over the study period.

All of the patients presented were profoundly immunologically compromised due to their underlying conditions, medications and

TABLE 1
Characteristics of invasive filamentous fungal infections in oncology and hematopoietic stem cell transplant (HSCT) patients

Patient	Sex	Age, years	Organism identified	Site of infection	Underlying condition	HSCT before breakthrough infection	Time to symptoms post- HSCT	Therapy contributing to net state of immune suppression at time of breakthrough infection	Duration of caspofungin treatment	Neutrophil levels at breakthrough	Treatment	GVHD	Outcome
1*	F	1.7	<i>Fusarium oxysporum</i>	Skin and blood	Aplastic anemia	None	N/A	Methylprednisone, cyclosporin and Atgam (Pfizer, USA)	16 weeks	0x10 ⁹ /L	Liposomal amphotericin B, voriconazole	No	Death
2†	F	15.7	<i>Alternaria infectoria</i>	Nares	Relapsed acute myeloid leukemia	None	N/A	2 cycles of fludarabine and cytarabine	8 days	0x10 ⁹ /L	Liposomal amphotericin B, voriconazole	No	Cure
3	M	11.4	<i>Aspergillus fumigatus</i>	Lungs	Relapsed T-cell acute lymphoblastic leukemia	10/10 matched donor	1 year unrelated	Prednisone, budesonide and tacrolimus	20 days	2.28x10 ⁹ /L	Lipid complex amphotericin B	Extensive chronic GVHD of skin and gastrointestinal tract	Cure
4	M	4.3	<i>Aspergillus fumigatus</i>	Central nervous system	Acute myeloid leukemia	None	N/A	Danorubicin, cytarabine, etoposide and methylprednisone	5 days, then resolved for 5 days, then 7 days	11.85x10 ⁹ /L	Liposomal amphotericin B, voriconazole, posaconazole	No	Death
5‡	M	4.1	<i>Aspergillus niger</i>	Lungs	Stage 4 Burkitt's lymphoma	None	N/A	Cyclophosphamide, vincristine, prednisone and rituximab	7 days	0x10 ⁹ /L	Liposomal amphotericin B, voriconazole	No	Death
6	M	3.0	<i>Rhizomucor pusillus</i>	Perineum, central nervous system (presumed)	2nd relapse of infant acute lymphoblastic leukemia	Cord unrelated 5/6 match	15 days	Total body irradiation and cyclophosphamide as conditioning. Methylprednisone and cyclosporine as GVHD prophylaxis	10 days	0x10 ⁹ /L	Liposomal amphotericin B, voriconazole	No	Death

*Patient 1 underwent a cord-unrelated 5/6 match HSCT, with a transplant conditioning regimen consisting of alemtuzumab, cyclophosphamide and fludarabine;

†Patient 2 underwent a matched related donor HSCT after the onset of breakthrough fungal infection, with a transplant conditioning regimen consisting of busulfan and cyclophosphamide;

‡Patient 5 received rituximab one week before microbiological diagnosis of breakthrough infection but after computed tomography-diagnosed onset of pulmonary lesions. F Female; GVHD Graft-versus-host disease; M Male; N/A Not applicable

bone marrow transplants. Four of the six patients had no detectable neutrophils at the time of the diagnosis of breakthrough infection. The symptoms associated with the breakthrough infections manifested after a relatively short duration of caspofungin treatment; five of the six cases had received less than three weeks of caspofungin and four of the six cases had received less than two weeks. Several of the breakthrough infections occurred very early during chemotherapy, highlighting the significant state of immune compromise from the malignancy itself. The anatomical locations of the infections were diverse and, as previously reported, *Aspergillus* species were the most commonly isolated organisms (50%). All infections were treated aggressively with a liposomal amphotericin B-based regimen. Five of the six patients also received at least one azole antifungal; four patients received voriconazole and one received both voriconazole and posaconazole. Similar to reports from the adult literature, in spite of aggressive treatment of the breakthrough infections, four of six patients, including two of the three with *Aspergillus* species identified, died.

Two of the isolates from our patients, *Fusarium oxysporum* and *R pusillus* are considered to be inherently resistant to caspofungin. (14-16). Point mutations in the *FKS1* gene have been associated with decreased susceptibility to echinocandins (17). This gene is believed to code for a catalytic subunit of 1,3-beta-D-glucan synthase and is involved in cell

wall synthesis and maintenance. Mutations in *FKS1* are well described to cause clinical resistance to echinocandins in *Candida* species (17,18). Recent research suggests that the *FKS1* gene also has a potential role in resistance to caspofungin among *Aspergillus* species. Laboratory-generated mutant *Aspergillus* species with an amino acid substitution in the *FKS1* gene have created isolates with minimum inhibitory concentrations of 4 µg/mL (19) and >16 µg/mL (20). Additionally, sequencing of an isolate of *A fumigatus* from a patient who clinically failed caspofungin therapy found overexpression of the *FKS1* gene (21).

There is a growing body of literature, particularly involving immunocompromised adults, documenting breakthrough infections by specific fungal organisms in patients receiving antifungal therapies as either treatment or prophylaxis. In addition to breakthrough infections of filamentous fungi in patients receiving caspofungin, other groups have described breakthrough infections of *Candida parapsilosis* in patients on caspofungin (22,23) and zygomycosis in patients receiving voriconazole (24,25), micafungin (26) or posaconazole (27,28). The present study contributes further to this body of literature by highlighting the importance of ongoing postmarketing surveillance and monitoring in children for breakthrough infections following the introduction of new antifungal medications.

There are several limitations to our study, the most significant being its retrospective design and lack of controls. While including only microbiologically confirmed cases ensured that only breakthrough infections with filamentous molds were analyzed, there is no doubt that a significant number of possible and probable invasive fungal infections seen in the immunocompromised population at our institution over the study period were also caused by these organisms. Furthermore, due to the fact that electronic pharmaceutical records were not available for this time period, we could not determine a denominator value for the total number of immunocompromised patients who received empirical caspofungin therapy, we were unable to calculate an incidence rate for breakthrough invasive fungal infections. Finally, antifungal susceptibility testing was not available for the three *Aspergillus* species identified in the present study; thus, we are not able to comment specifically on whether they may have been resistant to caspofungin.

In many institutions, caspofungin is the drug of choice for the empirical treatment of presumed fungal infections in immunocompromised

populations. While rare, breakthrough fungal infections by species resistant to caspofungin do occur. Additionally, while caspofungin does have in vitro activity against *Aspergillus* species, only a minority of breakthrough infections occurring in patients with severe immunological compromise, have been shown to be due to caspofungin resistance. Clinically relevant breakpoints for caspofungin susceptibility and resistance for filamentous fungi do not exist, thus there is a need to develop interpretive criteria based on in vitro/in vivo studies.

CONCLUSION

While caspofungin remains an excellent choice as an empirical antifungal medication, clinicians must remain aware that breakthrough fungal infections by resistant (intrinsic, acquired or clinical species do occur and may have poor outcomes.

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