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BRIEF COMMUNICATION

Successful caspofungin treatment of persistent candidemia in extreme prematurity at 23 and 24 weeks' gestation

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Systemic fungal infection continues to be a major cause of mortality in extremely low-birth-weight premature infants. Amphotericin B has been recommended as the primary treatment; however, its use is limited due to drug-induced nephrotoxicity and amphotericin B-resistant candidemia. Caspofungin therapy was initiated in seven extremely premature infants at 23 and 24 weeks' gestation with persistent systemic candidiasis despite liposomal amphotericin B treatment. The gestational age was 23^{+1}–24^{+6} weeks, and birth weight was 530–825 g. Of the seven patients, the peripheral blood cultures of six patients were positive for *Candida parapsilosis* and one had positive culture for *Candida albicans*. The dosage of caspofungin was 2 mg/kg/day, and the mean treatment duration was 14 days. All of the persistent candidemia resolved on caspofungin therapy. There was no recurrent candidemia after discontinuing caspofungin. There were no adverse effects, hepatotoxicity, nephrotoxicity, anemia, or thrombocytopenia. Caspofungin successfully treated persistent candidemia in extremely premature infants at 23 and 24 weeks' gestational age.

Introduction

Fungal infection continues to be a major cause of mortality among extremely low-birth-weight infants (ELBWIs) and is the third most common cause of late-onset sepsis in neonates after Gram-positive sepsis and Gram-negative sepsis.[1,2] The risk of systemic candidiasis and mortality is inversely proportional to gestational age and birth weight.[1] The ELBWIs have numerous risk factors of systemic candidiasis.[3] Amphotericin B has been recommended as the primary treatment of choice. However, it causes infusion-related toxicities and serious renal toxicity, especially in ELBWIs with immature renal function.[4] Liposomal amphotericin B did not cause nephrotoxicity in a 10-year cohort of preterm infants with birth weight <1500 g.[5] Therefore, liposomal amphotericin B is sometimes used as the first-line agent for systemic candidiasis of ELBWI in certain neonatal

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intensive care units (NICUs) in Korea. However, amphotericin B- or liposomal amphotericin B-resistant candidemia has been on the rise.[6]

Caspofungin (an echinocandin), a newer type of antifungal agent, inhibits fungal 1,3-beta-glucan synthesis, and is highly selective to fungal cells because 1,3-beta-glucan synthesis does not occur in mammalian cell membrane; thus, echinocandins are safe and well tolerated with fewer side effects.[7,8] To date, however, there is limited experience with the use of caspofungin in extreme preterm infants.

This study presents our experience of caspofungin therapy in seven extremely premature infants at 23 and 24 weeks' gestation with persistent systemic candidiasis despite liposomal amphotericin B treatment.

Patients and methods

The protocol of this study was reviewed and approved by the Institutional Review Board of the Busan Paik Hospital. Data were collected retrospectively from medical records. Informed parental consent was obtained before caspofungin administration. Systemic candidiasis was diagnosed based on clinical signs of systemic infection with a positive blood culture for *Candida* species. Blood culture was obtained from a peripheral vein. Central catheters were removed immediately after systemic candidiasis was diagnosed.

Liposomal amphotericin B (AmBisome; Gilead Sciences International Ltd., Cambridge, UK) was administered at a dose of 5 mg/kg/day. Caspofungin (CANCIDAS; Merck & Co., Inc. Sumneytown Pike, West Point, PA, USA) was administered at a dose of 2 mg/kg/day. Demographic factors were evaluated to determine the factors related to systemic candidiasis and treatment outcome.

The efficacy was evaluated by eradication of *Candida* species, which means negative cultures after the initiation of antifungal treatment from positive cultures. The eradication time represents the days taken to sterilize after initiation of antifungal treatment.

The safety was evaluated based on infusion-related adverse effects, serum biochemistry profiles, and complete blood count.

Results

Demographics and patient characteristics

A total of seven extremely premature infants born at 23 and 24 weeks' gestation with systemic candidiasis resistant to liposomal amphotericin B were treated with caspofungin. The gestational age was 23^{+6} weeks (23^{+1}—24^{+6} weeks) and birth weight was 640 g (530—825 g). The peripheral blood cultures were positive for *Candida parapsilosis* in six, and *Candida albicans* in one. There was no vegetation in the heart on echocardiography. Ventriculitis and fungal microabscess were not found on the brain ultrasound. Renal fungal ball and microabscess were not identified on the abdominal ultrasound. Renal stones were identified in three patients who had negative urine cultures. The demographic and patient characteristics, and efficacy are shown in Table 1.

All of them had respiratory distress syndrome and needed prolonged ventilator care. All of them had bronchopulmonary dysplasia and patent ductus arteriosus. An umbilical catheter had been inserted for 7 days and a peripherally inserted central catheter for 44 days. Total parenteral nutrition had been infused for 47 days. Five received systemic antibiotic treatment before caspofungin therapy. Two received postnatal steroids therapy.

Efficacy

The mean cumulative amount and the mean duration of liposomal amphotericin B administered before caspofungin were 90 mg/kg (30—180 mg/kg) and 18 days (6—36 days), respectively. All cases of persistent candidemia resolved on caspofungin therapy. The mean cumulative dose of caspofungin was 27.7 mg/kg (4—48 mg/kg) and the mean duration of caspofungin treatment was 14 days (2—24 days). After initiation of caspofungin, blood cultures were sterile after 4, 13, 4, 8, and 3 days in each patient. There was no recurrent candidemia after the discontinuation of the caspofungin therapy. Six patients survived. In Patient 7, the blood culture could not be followed up because he passed away within 2 days after the initiation of caspofungin.

Safety

No infusion-related adverse effects, such as bradycardia, tachycardia, pyrexia, hypotension, hypertension, tachypnea, and rash, were observed. Blood urea nitrogen (BUN), creatinine, serum potassium, and urine output remained stable. One patient (Patient 7) had hyperkalemia, elevated BUN and serum creatinine levels before caspofungin treatment due to sepsis. Caspofungin-induced hepatotoxicity was not found. In Patient 2, elevated liver enzyme and bilirubin were noted before caspofungin infusion due to parenteral nutrition-induced cholestasis combined with sepsis. Drug-induced anemia and thrombocytopenia were not found. Thrombocytopenia was improved in three patients because of the eradication of *Candida* spp. (Table 2).

Discussion

Systemic candidiasis in preterm infants has markedly increased due to the increased survival of extremely immature infants.[9,10] The ELBWIs are prone to systemic fungal infection due to invasive procedures and immature mucocutaneous barrier function and host defenses. *C. albicans* had been the most prevalent pathogen of neonatal fungal infections.[11] However, non-albicans *Candida* species have been on the rise. Odio et al reported that six of the 10 neonates with systemic candidiasis in their study had non-albicans *Candida* species,[6] and Natarajan et al reported that *C. parapsilosis* was the most common *Candida* species in neonates,[10] which was the predominant pathogen in this study too.

The resistance rates to amphotericin B and liposomal amphotericin B were 2—7% in 1999,[12] and recent studies report that resistance to these drugs is increasing. As a

Table 1 Demographic and patient characteristics, and efficacy.

Pt	GA[a]	BWt[b]	Isolate	Sites of infection	Liposomal amphotericin B[c]	Caspofungin[d]	Outcome	Start day[e]	Sterilization[f]
1	23^{+3}	530	*C. parapsilosis*	Blood	65 (13 d)	24 (12 d)	Cure	38/50	4
2	23^{+2}	615	*C. parapsilosis*	Blood	180 (36 d)	42 (21 d)	Cure	17/53	13
3	24^{+0}	550	*C. parapsilosis*, *C. albicans*	Blood, urine	110 (22 d)	32 (16 d)	Cure	14/36	4
4	24^{+1}	670	*C. parapsilosis*	Blood, urine, tracheal aspirate	105 (21 d)	14 (7 d)	Cure	29/50	0
5	24^{+3}	725	*C. parapsilosis*	Blood	75 (15 d)	30 (15 d)	Cure	20/35	8
6	24^{+6}	825	*C. albicans*	Blood, urine, tracheal aspirate	30 (6 d)	48 (24 d)	Cure	7/13	3
7	23^{+1}	570	*C. parapsilosis*	Blood	65 (13 d)	4 (2 d)	Died	10/23	

[a] Gestational age (week^{+day}).
[b] Birth weight (g).
[c] Cumulative amount and the duration of administered liposomal amphotericin B before caspofungin treatment (mg/kg, days).
[d] Cumulative amount and the duration of administered caspofungin (mg/kg, days).
[e] Postnatal days when the drugs were initiated (liposomal amphotericin B/caspofungin).
[f] Days required to sterile blood culture after initiation of caspofungin (days).

result, newer antifungal agents that are more effective and well tolerated than amphotericin B and the lipid formulation of amphotericin B are needed. Caspofungin was approved by the Food and Drug Administration for the treatment of fungal infection refractory to amphotericin B or lipid formulations of amphotericin B only in adults and not in children. Caspofungin was tried in children based on the successful results in adults. It was effective and safe in immunocompromised pediatric patients.[13] In a multicenter prospective study in Spain, *C. parapsilosis* isolates were susceptible to echinocandins.[14]

Although not yet licensed in neonates, some case reports of caspofungin treatment in ELBWI indicate excellent therapeutic efficacy without significant adverse effects.[13] An 810-g baby boy with 25 weeks of gestation,[15] a 980-g baby boy with 27 weeks of gestation,[16] and a 660-g baby girl with 23 weeks of gestation[17] had persistent *C. albicans*, *C. parapsilosis*, and *C. glabrata* infection refractory to amphotericin B, respectively. Their blood was sterilized in only 8 days, 7 days, and 72 hours following caspofungin treatment, respectively. In another study, persistently culture-positive blood was sterilized in only 4.3 days following caspofungin therapy.[6]

The adequate dosage of caspofungin treatment is not clearly defined in neonates, because it is not yet licensed for neonates and there is a lack of prospective randomized controlled studies. Odio et al used 1 mg/kg/day for 2 days, followed by 2 mg/kg/day[6]; Natarajan et al used 1.5 mg/kg/day for 1 day, followed by 1 mg/kg/day[10]; Yalaz et al used a loading dose of 5 mg/kg/day (50 mg/m^2/day) for 3 days, followed by 2.5 mg/kg/day (25 mg/m^2/day)[16]; and we used 2 mg/kg/day without loading dose. The optimal treatment duration of caspofungin in neonates remains uncertain, too. A sufficiently long treatment period is required to prevent relapse of candidemia especially in infection foci such as vegetations of fungal balls. Therefore, the

Table 2 Safety.

Pt	BUN[a]/creatinine/potassium			ALT[b]/AST[c]/bilirubin/conjugated bilirubin			Hemoglobin/platelet		
	Before[d]	During[e]	After[f]	Before[d]	During[e]	After[f]	Before[d]	During[e]	After[f]
1	3/0.3/4	3/0.3/3.6	4/0.47/3.6	13/35/1.8/1.3	20/35/1.5/1.2	20/44/1.6/1.0	7.9/71	7.8/72	7.2/99
2	7/0.18/3.6	3/0.29/4.0	4/0.48/3.1	34/113/6.1/5.1	18/76/7.3/6.3	25/121/7.8/6.6	9.5/89	9.9/80	9.3/160
3	4/0.41/3.6	4/0.27/4.6	5/0.31/4.3	8/28/1.4/1.1	10/28/0.7/0.5	10/27/0.6/0.4	9.3/59	8.7/138	10.8/193
4	13/0.32/4.1	3/0.22/4.6	9/0.06/4.7	13/29/0.7/0.3	9/22/1.1/0.9	9/35/0.8/0.6	5.9/340	10.5[g]/334	10.3/268
5	4/0.47/3.7	6/0.32/4.2	8/0.41/4.8	15/25/0.3/0.2	11/23/0.2/<0.1	10/20/0.1/0.1	10.8/343	9.2/385	8.2/725
6	52/1.79/5.0	3/0.84/5.1	10/0.49/5.2	<3/31/2.1/0.3	10/41/0.3/0.1	12/24/0.1/0.1	10.6/127	10.1/125	8.0/104
7	20/1.69/6.3	—	—	15/31/3.7/3.2	—	—	7.0/103	9.1/70	—

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.
[a] Blood urea nitrogen (mg/dL); creatinine (mg/dL); potassium (mEq/L).
[b] Alanine aminotransferase (U/L).
[c] Aspartate aminotransferase (U/L); bilirubin (mg/dL); conjugated bilirubin (mg/dL); hemoglobin (g/dL); platelet (10^9/L).
[d] Before infusion of caspofungin.
[e] During infusion of caspofungin.
[f] After discontinuation of caspofungin.
[g] After red blood cell transfusion.

recommended treatment duration of caspofungin for candidemia is about 3 weeks.[18,19]

Azole antifungal agents (i.e., fluconazole, voriconazole) are metabolized by the hepatic cytochrome P450 system. There can be numerous drug interactions. However, caspofungin is not metabolized by the hepatic cytochrome P450 system, and therefore drug interactions are minimal. This is an important advantage of caspofungin because preterm infants in the NICUs use many concomitant drugs.[7] Caspofungin is mainly metabolized by the liver, and therefore, there is no need of dose adjustment in renal insufficiency.[20]

In summary, caspofungin successfully treated persistent candidemia despite liposomal amphotericin B treatment in extremely premature infants born at 23 and 24 weeks' gestation. Caspofungin can be thought as an alternative for the treatment of systemic candidiasis in extreme prematurity when there is persistent, or liposomal amphotericin B-resistant candidemia. The limitations of this retrospective study are the small number of patients (only seven ELBWIs) and there is no comparison with a liposomal amphotericin B group, or a placebo group. To understand the pharmacokinetics and safety of caspofungin before widespread use, a prospective randomized controlled study with a larger number of ELBWIs is needed.

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