

### Caspofungin in combination with itraconazole and amphotericin B for the treatment of invasive aspergillosis in humans, with a method to test *ex vivo* synergism

Caspofungin (Cancidas; Merck Italia, Rome, Italy) belongs to a new class of antifungal agents; the echinocandins [1]. It has an *in vitro* fungicidal activity against numerous fungal pathogens, including *Aspergillus* species [2]. Although no published studies have evaluated the use of caspofungin for the primary treatment of invasive aspergillosis (IA) in humans, limited data have been reported that clinical improvement or complete response occurred in 41% of caspofungin-treated patients with IA who were intolerant of, or had infections refractory to, standard antifungal therapy [3].

Few clinical data exist on the use of caspofungin in combination with other antifungal agents, which is an intriguing possibility, given the unique mechanism of action of the caspofungin [4].

We describe a method to evaluate the synergism between the antifungal activity of patient's serum taken during antifungal combination therapy, with further antifungal drug added *in vitro*.

A 28-year-old man with acute myeloid leukaemia underwent induction chemotherapy. By day 28 of the chemotherapy he was not in remission, so he underwent reinduction and soon developed a neutropenic fever and cough. An administration of broad spectrum antibiotics was started and a thoracic CT scan revealed cavitory lesions; two in the right lung and one in the left lung, suggesting aspergillosis. A culture of material obtained by bronchoscopy with lavage grew *Aspergillus fumigatus*. The antibiotic susceptibility of the *Aspergillus* strain was tested by a broth micro method according to the NCCLS guidelines [5], and it was found to be susceptible to amphotericin B, itraconazole and caspofungin (CSP). The patient received liposomal amphotericin B 3 mg/kg per day for 2 weeks. For persistent neutropenic fever, oral itraconazole 200 mg t.i.d. was added. During this therapy, the peak serum fungistatic activity (SFA) and peak serum fungicidal activity (SFCA) were 1:8 and <1:2, respectively. Because of the persisting fever, we tested synergism between patient serum and caspofungin by the checkerboard method. The combination of the peak serum with caspofungin gave a  $\Sigma$ FICI of 0.5 indicating full synergism. Caspofungin (50 mg/day) was

**Table 1** Peak serum fungistatic and fungicidal activity of different antifungal regimes

	SFA, peak	SFCA, peak
Serum taken during amphotericin B+ itraconazole	1:8	<1:2
Serum taken during amphotericin B+ itraconazole + <i>in vitro</i> caspofungin	1:32	1:8

therefore added to the current patient treatment. After 5 days, peak SFA and SFCA were 1:32 and 1:8, respectively (Table 1). The fever disappeared and the patient was transferred to the haematology unit after 3 weeks, with the thoracic lesions having improved.

*Ex vivo* synergism between the patient's serum during the antifungal therapy and further antifungal drugs might be a useful method to optimize antifungal therapy in difficult-to-treat infections.

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### REFERENCES

- Keating GM, Jarvis B. Caspofungin. *Drugs* 2001; 61: 1121–9.
- Arathoon EG. Clinical efficacy of echinocandin antifungals. *Curr Opin Infect Dis* 2001; 14: 685–91.
- Maertens J, Raad I, Sable CA *et al.* Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin (CAS) in adults with invasive aspergillosis (IA) refractory or intolerant to amphotericin B (AMB), AMB lipid formulations (lipid AMB) or azoles [abstract 1103]. In: *Programs and Abstracts of the 40th Interscience Conference On Antimicrobial Agents and Chemotherapy (Toronto)*. Washington, DC: American Society for Microbiology, 2000: 371.
- Rubin MA, Carroll KC, Cahill BC. Caspofungin in combination with itraconazole for the treatment of

- invasive aspergillosis in humans. *Clin Infect Dis* 2002; 34: 1160–1.
5. National Committee for Clinical Laboratory Standards 1998. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Proposed standard M38-P. Wayne, Pa: National Committee for Clinical Laboratory Standards.