

CLINICAL EXPERIENCE OF COMBINATION ANTIFUNGAL THERAPY WITH ECHINOCANDINS

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Background: Caspofungin is the first of a new class of drugs, the echinocandins. It exhibits selective antifungal activity via inhibition of the synthesis of β (1,3) D-glucan in the mycotic cell wall. In a noncomparative multicenter study, a complete or partial response to Caspofungin monotherapy was seen in 40.7% of immunocompromised adults with invasive aspergillosis who did not respond to or did not tolerate other antifungal agents. In vitro data has shown that the combination of Caspofungin and Amphotericin B was either synergistic or additive in greater than half the isolates of *Aspergillus* and *Fusarium*. No antagonism has been demonstrated between these two drugs. Limited in vivo data shows higher survival rates with combination therapy in a murine model of pulmonary aspergillosis. To date there are no reports assessing the clinical outcomes of such therapy. We report our experience in a group of severely immunocompromised patients who received an echinocandin in combination with another antifungal agent as treatment for deep-seated mycotic infections.

Methods: This is a retrospective chart analysis of all patients who received combination therapy with an echinocandin, at the University of Illinois hospital. Patients were classified as: 1. Definite invasive mycosis- histopathologic evidence of invasion and positive cultures, 2. Probable- 2a. No histopathologic evidence but with positive cultures, or 2b. No cultures but with histopathologic evidence, or 2c. Clinical syndrome consistent with invasive mycosis in the absence of histopathology and cultures. Neutropenia was defined as absolute neutrophil counts < 500 cell/mm³. Response to treatment was defined as: 1. Complete- when there was resolution of all attributable clinical and radiological features, 2. Partial- when there was clinically meaningful improvement in attributable signs, symptoms and radiographic features, 3. Failure- progression of clinical and/ or radiological features while on treatment.

Results: There were a total of 8 patients who were started on combination therapy and only 7 received more than one dose of an echinocandin. 6 patients received Caspofungin and one received micafungin (FK 463). The most common underlying diagnosis was Acute Myeloid Leukemia (AML) (n = 4/7patients). 3 of the 4 AML patients were s/p chemotherapy and one patient received peripheral blood stem cell transplant (PBSCT). Of the remaining 3 patients, the underlying diagnoses were diffuse large cell lymphoma, end-stage acquired immune deficiency syndrome and end stage renal disease on hemodialysis. All the patients had fungal pneumonitis by clinical criteria. 3 of the 7 patients met the criteria for definite diagnosis. Of these, 2 had pulmonary aspergillosis and one, *Candida albicans* pneumonitis. 5 of the 7 patients were severely neutropenic (ANC < 500 cells/mm³), with duration prior to combination therapy ranging from 11 to 66 days (mean = 23 days, median= 11 days). Mean duration of combination therapy was 5.3 weeks (range= 2 weeks to 12 weeks). 2 of the 7 patients received itraconazole with caspofungin, the remaining 5 received different formulations of amphotericin B. 2/7 had complete response and 1 had partial response to therapy. The remaining 4 patients failed therapy and died. One of these worsened while on treatment but died of an unrelated cause. In this analysis, only one patient developed acute hypoxia 30 minutes into caspofungin infusion and could not receive it further. No other adverse effects attributable to caspofungin were observed.

Conclusions: In this select group of patients, we observed that caspofungin was well-tolerated and can be used in combination with amphotericin or itraconazole. 88% of our patients had no major adverse reactions. 43% of our patients showed complete or partial response to therapy. However, the mortality from invasive pulmonary mycoses remains very high. Further studies are warranted to determine efficacy of combination antifungal therapy.