A trial of caspofungin salvage treatment in PCP pneumonia

Pneumocystis jirovecii pneumonia (PCP) remains a major cause of mortality in patients with HIV; we read with enormous interest the recent PCP mortality prediction rule stratifying 451 patients by mortality at the time of illness presentation.\(^1\) The first-line treatment for this infection, cotrimoxazole, is associated with a number of adverse effects, including rash, leucopenia, thrombocytopenia and interstitial nephritis.\(^2\) Therefore, treatment with cotrimoxazole significantly adds to the morbidity associated with this condition and we note in this study that this was the main treatment used.

One of the identifying characteristics of \(P.\) jirovecii is the presence of (1,3)-\(\beta\)-D-glucan in its cell wall.\(^3\) As the cell wall of this organism does not contain ergosterol (the target of azoles and polyenes), echinocandins, which target the synthesis of (1,3)-\(\beta\)-D-glucan, are likely to be the only effective antifungals for PCP.\(^4\)

Caspofungin was the first echinocandin licensed for empiric antifungal treatment in candidiasis and aspergillosis. In animal models of PCP echinocandins have demonstrated prophylactic and therapeutic efficacy.\(^5\)\(^,\)\(^6\) Furthermore, there are reports that caspofungin is effective salvage treatment for PCP.\(^7\)\(^,\)\(^8\) Echinocandins are associated with a low incidence of adverse events. Caspofungin does not inhibit the CYP system and does not induce CYP3A4 drug metabolism.\(^9\)

We present our experience of the use of caspofungin in the context of severe PCP in HIV-infected individuals.

We performed a retrospective analysis of all patients treated for proven or probable PCP pneumonia over a 4 year period from our unit, the largest HIV cohort in Europe; appropriate ethical approval was obtained. For all patients, baseline demographics, CD4 count, viral load, PCP prophylaxis, radiological features, arterial blood gas analysis, PCP immunobluorescence, PCP treatment, ventilatory support, adverse reactions and outcomes were recorded. Treatment failure was defined as worsening hypoxia or radiographic features after 4 days of first-line treatment.

Over the 4 year study period 80 patients were treated for PCP, of whom 56 of the 76 tested had microbiologically confirmed PCP by immunofluorescence. The mean CD4 count measured 109 (4–676) cells/ml; nine patients (8.8%) had microbiologically confirmed PCP with a CD4 count of >200, and a further nine had confirmed PCP with an undetectable viral load while receiving highly active antiretroviral therapy (HAART). A total of six patients had been receiving PCP prophylaxis at diagnosis. Overall mortality was 6.25\% (5/83) and 5.3\% (3/56) for microbiologically confirmed PCP. Five patients died overall (3 from respiratory failure, 1 from persistent pneumothorax and 1 refused all treatment).

Of these patients, 67 received cotrimoxazole as first-line treatment, six with clindamycin/primaquine, six with atovaquone, and one patient received intravenous pentamidine. Twelve individuals required a treatment switch due to cotrimoxazole-related toxicities (7 rash, 2 hepatitis, 1 hyponatraemia, 1 diarrhoea and 1 nausea). A total of 12 patients with PCP not responding to first-line treatment received caspofungin in combination with other treatments. Of these patients, 10 had microbiologically confirmed PCP. None of these patients had other relevant fungi such as Candida or Aspergillus.

As the cell wall of this fungus is the presence of (1,3)-\(\beta\)-D-glucan, caspofungin isolated by bronchoalveolar lavage was de-identified. Of these 12 patients, 10 individuals received treatment with caspofungin as a component of salvage therapy after first-line treatment failure, and two received caspofungin following first-line drug toxicity. Patients received caspofungin in combination with clindamycin/primaquine (6/12), cotrimoxazole (4/12) or intravenous pentamidine (2/12).

For the 10 patients who received caspofungin as a part of salvage therapy, two died, one from bilateral pneumothoraces which had been present since day 2 of diagnosis and one from Burkitt lymphoma. The patient with Burkitt lymphoma did not have microbiological confirmation of PCP. Therefore, for patients with microbiologically confirmed PCP treated with caspofungin, mortality was 1 in 10 or 10\%.

Despite the advent of HAART for the treatment of HIV infection, PCP remains a major cause of mortality even in resource-rich settings.\(^10\) Recent data suggest that in the HAART era, mortality from this infection when microbiologically confirmed is ~10\%.\(^2\) Over the last 4 years we have used caspofungin adjunctive treatment for the management of severe or refractory cases of PCP. Caspofungin targets the synthesis of \(\beta\)-glucan, a major component of the \(P.\) jirovecii cell wall.\(^11\) Furthermore this drug has minimal side effects and drug interactions, allowing its use as adjunctive treatment.\(^9\)

This single cohort study suggests that caspofungin may improve outcomes from PCP, with favourable comparative mortalities in our cohort (5.5\%) compared with a recent study (9.7\%) of confirmed cases of PCP from a similar cohort of UK patients in the HAART era.\(^12\) Randomised controlled studies of caspofungin for PCP are warranted and further suggest that the prediction rule may require modification in the setting of newer treatments.

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