

EDITORIAL

Increased dose of echinocandins for invasive fungal infections: bonanza for the patient or the pharmaceutical industry?

Bone Marrow Transplantation (2007) **39**, 129–131.
 doi:10.1038/sj.bmt.1705563

Invasive fungal infections continue to plague allogeneic stem cell recipients despite aggressive prophylactic and empiric anti-fungal strategies. Regardless of our best efforts, mortality exceeds 50% in patients infected with aspergillus and other filamentous molds.¹ As the number of older patients undergoing transplantation increases and the transplant techniques involve long delays in immune reconstitution, life-threatening fungal diseases and other opportunistic processes are likely to prevail. Polyenes (amphotericin B or its lipid form), azoles (fluconazole, itraconazole) and pyrimidines (5-fluorocytosine) have long been available as anti-fungals; nephrotoxicity of the polyene class and numerous drug interactions associated with azoles have hampered their liberal use. Echinocandins, a recently introduced class of anti-fungal, are remarkably well tolerated, and have an excellent safety profile with minimal drug interactions.

Some comparative data of the three echinocandins are shown in the Table 1. These drugs, at varied doses, show excellent efficacy in esophageal and systemic candidiasis. Doses recommended easily achieve plasma levels above 1 µg/ml, a target selected to exceed the minimal inhibitory concentration (MIC) at which 90% of clinically relevant candidal species are inhibited throughout therapy. A loading dose is not recommended for micafungin, whereas the plasma levels for caspofungin were noted to fall below the target levels for the first 2 days of therapy when given at 50 mg/day without a loading dose.² Preliminary data show that micafungin at 100 or 150 mg/day has efficacy comparable to caspofungin (70 mg followed by 50 mg/day) in

invasive candidiasis.³ Interestingly, clinical success with anidulafungin was superior to that seen with fluconazole against invasive candidiasis.⁴ Whether the echinocandin's rapid cidal activity contributed to its overall superiority over the azole remains speculative. Echinocandins, at the currently used doses, appear to perform optimally against candida. Against aspergillus, however, these drugs do not exhibit the same level of activity. They kill the growing hyphal tips, but are inactive against the mycelial mass. Available data on the activity of the echinocandins against invasive aspergillosis are limited. At 'standard' doses, success rate of caspofungin as salvage therapy is 40–45%, whereas micafungin, as primary therapy, is reported to have 50% efficacy (six of 12 patients) when given alone and 29% efficacy (five of 17 patients) in combination with other drugs.^{5,6} As these drugs are known to have concentration-dependent activity, would higher than 'standard' doses have improved efficacy? Also importantly, would higher doses be as safe as the 'standard' doses?

In Phase I studies, caspofungin (single dose up to 210 mg, and multiple doses up to 100 mg/day) has been well tolerated. Preliminary data in 96 patients suggest no dose-dependent toxicity across different doses ranging from 35 to 100 mg/day of caspofungin; no difference in efficacy was noted between 50 and 70 mg/day regimens in esophageal candidiasis and invasive aspergillosis.⁷ In animal models, when caspofungin was given every other day, trough levels were difficult to achieve and breakthrough infections were noted. Clinical trial is underway examining caspofungin at doses of 70 mg load followed by 50, 100 and 150 mg/day for invasive aspergillosis. Another trial examining 50 vs 150 mg/day of caspofungin for invasive candidiasis has enrolled over 50 patients; no serious adverse events were noted (Nicholas Kartsonis, MD, personal communication, Merck & Co., Inc.). Micafungin was administered at

Table 1 Echinocandins: some comparative data

	<i>Caspofungin</i>	<i>Micafungin</i>	<i>Anidulafungin</i>
(A) Indications	esophageal candidiasis (EC), systemic candidiasis, febrile neutropenia (empiric therapy), invasive aspergillosis (salvage therapy)	esophageal candidiasis (EC), prophylaxis of candidiasis (pre-engraftment in stem cell transplant)	esophageal candidiasis (EC), systemic candidiasis (SC)
(B) Dose			
Initial	70 mg	No loading dose	100 mg/day (EC) 200 mg/day (SC)
Maintenance	50 mg/day	150 mg/day (EC) 50 mg/day (for prophylaxis)	50 mg/day (EC) 100 mg/day (SC)
(C) Higher doses found safe (package insert)	100 mg/day × 21 days (15 subjects) 70 mg/day (limited data)	8 mg/kg/day (up to 900 mg/day)	260 mg followed by 130 mg/day

3–8 mg/kg/day for a median of 18 days in 36 stem cell recipients; no patient had a grade 3 or grade 4 adverse event considered secondary to the drug.⁸ Based on the properties of concentration-dependent killing activity and post anti-fungal effect, an alternating day regimen of micafungin at a high dose of 300 mg was compared with 150 mg/day and IV caspofungin at 50 mg/day for the treatment of esophageal candidiasis.⁹ Efficacy rates were similar and importantly, serious adverse events and discontinuation rates were equally low for all three groups, thus providing proof-of-principle that alternate day administration of echinocandin is a viable option.

Poor outcomes of invasive aspergillosis, particularly in stem cell recipients have led to investigations of combination of two or more drugs. *In vitro* and animal model data suggest additive or synergistic activity when an echinocandin is combined with a polyene or azole.^{10,11} Of note, antagonism was noted when polyene/azole combination was used in a neutropenic rabbit model of invasive aspergillosis.¹² Retrospective clinical studies show conflicting data with echinocandin/azole combination.^{13,14} In this issue, Safdar *et al.* retrospectively evaluated the safety/efficacy of caspofungin at a high dose (100 mg/day) vs standard dose (50 mg/day) in combination with other drugs for invasive fungal infections (mostly invasive aspergillosis).¹⁵ Keeping with previous observations, the investigators found no serious adverse reactions with the high dose. Liver and renal functions were similar in the high- and standard-dose groups. Although the efficacy data were difficult to interpret owing to many confounding factors in this relatively small study, the safety of high-dose caspofungin was demonstrated. Whether the combination therapy is superior to monotherapy for invasive aspergillosis needs a prospective evaluation and until then, routine use of a combination of two or more drugs against this infection must be discouraged.

It is worth emphasizing that echinocandins have a limited spectrum of activity. They are not active against clinically relevant pathogens including cryptococcus, trichosporon, rhodotorula and blastoschizomyces among the non-candidal yeasts, and fusarium, zygomycetes and scedosporium among the filamentous molds. For non-albicans candida, higher than usual concentrations of echinocandin are required to inhibit *Candida parapsilosis*, *C. rugosa* and *C. guilliermondii*. Although active *in vitro*, clinical efficacy of the echinocandins against endemic fungi (histoplasma, blastomyces, coccidioides) has not been demonstrated.

Echinocandins are a worthy addition to our anti-fungal arsenal. Given their excellent efficacy, higher than standard doses of echinocandins for treatment of most cases of invasive candidiasis are not warranted. For primary therapy of invasive aspergillosis, more prospective data are needed to demonstrate the use of echinocandins as monotherapy or in combination with other drugs. Clinical relevance of the *in vitro* observation of paradoxical negative effect of the echinocandins, as mentioned by Safdar *et al.*, is of some concern.¹⁶ Lastly, but importantly, the improved safety profile of the recently available anti-fungal drugs has greatly increased the 'abuse potential' for these drugs. In cancer/transplant wards, these drugs are increasingly used in empiric, prophylactic and pre-emptive settings without

much evidence-based data. At our institution (Karmanos Cancer Institute/Harper University Hospital), the anti-fungal (mostly echinocandins and voriconazole) acquisition expense has more than doubled during 2004–2005. Restrained and judicious use of the anti-fungals is critical to avoid 'econo toxicity'.

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