Caspofungin was noninferior to amphotericin B for invasive fungal infections in persistent fever and neutropenia and was better tolerated

Walsh TJ, Teppler H, Donowitz GR, et al. **Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia.** N Engl J Med. 2004;351:1391-402.

QUESTION

In patients with persistent fever and neutropenia, is caspofungin (CF) noninferior to liposomal amphotericin B (AB) for preventing or reducing invasive fungal infections (FIs)?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and safety and monitoring committee).*

Follow-up period: 7 and 14 days.

Setting: 116 sites in 26 countries.

Patients: 1123 patients (median age 50 y, 56% men) who received chemotherapy for cancer or had hematopoietic stem-cell transplantation, an absolute neutrophil count < 500/mm^3 for ≥ 96 hours, fever (temperature > 38 °C), and who received parenteral antibacterial therapy for ≥ 96 hours. Exclusion criteria included inadequately managed bacterial infection and documented invasive FI.

Intervention: Patients were stratified by risk and use of systemic antifungal prophylaxis and allocated to intravenous CF (70 mg on d 1 and 50 mg once-daily thereafter) plus placebo (n = 556) or once-daily liposomal AB (3 mg/kg of body weight) plus placebo (n = 539). Premedication was not allowed on day 1 and only subsequently if an infusion-related reaction occurred. If fever persisted ≥ 5 days and condition deteriorated, the CF dose could be increased (if well tolerated) to 70 mg once daily or the liposomal AB dose to 5.0 mg/kg per day. In patients with no evidence of baseline or breakthrough FI, therapy was given until the absolute neutrophil count was ≥ 500/mm^3 and for ≤ 72 hours thereafter.

Outcomes: Favorable overall response (successful treatment of any baseline FI, absence of any breakthrough FI during or ≤ 7 d after completion of therapy, survival for 7 d after completion of therapy, no premature discontinuation because of drug-related toxicity or lack of efficacy, and resolution of fever [temperature < 38 °C for ≥ 48 h] during neutropenia), individual components of favorable overall response, survival, and adverse events.

Patient follow-up: 97% (modified intention-to-treat analysis).

MAIN RESULTS

94.2% of patients had underlying hematologic cancer. CF was equivalent to liposomal AB in favorable overall response (Table). Baseline FI was diagnosed in 27 patients in each group. More patients who received CF survived for ≥ 7 days after therapy, had successful treatment of baseline FI, and did not discontinue the study prematurely (Table). Groups did not differ for breakthrough FIs or rate of fever resolution during neutropenia (Table). Fewer patients in the CF group group died (P = 0.04), had nephrotoxicity (P < 0.001), or had infusion or drug-related adverse events (P < 0.001).

CONCLUSIONS

In patients with persistent fever and neutropenia, caspofungin (CF) was equivalent to liposomal amphotericin B (AB) for favorable overall response. CF was better tolerated than liposomal AB.

Source of funding: Merck.

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*See Glossary.

Caspofungin vs liposomal amphotericin B (AB) at 7 and 14 days†

Outcomes	Caspofungin	Liposomal AB	Difference (95% CI)
Overall favorable response	33.9%	33.7%	0.2 (–5.6 to 6.9)‡
Successful treatment of baseline FI	51.9%	25.9%	25.9 (0.9 to 51.0)§
Absence of breakthrough FI	94.8%	95.5%	–0.8 (–3.3 to 1.8)
Survival for ≥ 7 d after completion of therapy	92.6%	89.2%	3.4 (0.0 to 6.8)§
Resolution of fever during neutropenia	41.2%	41.4%	–0.2 (–6.0 to 5.6)
No premature discontinuation because of toxicity or lack of efficacy	89.7%	85.5%	4.2 (0.3 to 8.1)§

†FI = fungal infection; CI defined in Glossary.
‡Difference between groups met the criteria for noninferiority (2-sided 95.2% CI –10 to 0 for showing equivalence); adjusted for risk (high or low) and use of systemic antifungal prophylaxis (yes or no).
§Differences are significant.

COMMENTARY

Febrile neutropenia remains one of the most serious complications of cancer chemotherapy. Determining which patients have noninfectious causes of fever compared with those who have bacterial, fungal, or viral causes remains an inexact science. As a result, most patients require empiric treatment by algorithm to cover the most likely pathogens.

Currently, 5 potential empiric antifungal options exist: AB (the former gold standard), fluconazole, liposomal AB compounds, voriconazole, and CF. AB and fluconazole are no longer preferred as initial choices because of efficacy, resistance, and toxicity concerns. Many infectious disease specialists prefer liposomal AB, voriconazole, or CF as empiric regimens.

Walsh and colleagues have improved our knowledge about which empiric choices are best. Their study showed that CF is noninferior to liposomal AB. More patients in the CF group survived and had successful treatment, and fewer had toxicity. However, most patients who received antifungal therapy did not have laboratory-confirmed infection. Even assuming a significant rate of FI occurring in the absence of laboratory proof, the vast majority of patients still received an expensive and potentially toxic agent with no clear benefit. However, at the present time we cannot identify a priori which patients will benefit from treatment.

It is unknown whether the results of this study can be used to manage pediatric cancer because patients who were < 16 years of age were excluded. It is clear that AB and liposomal AB are poised to be retired as the champions of empiric fungal treatment. We now need a head-to-head trial comparing caspofungin and voriconazole, which has also shown superiority to liposomal AB in a large trial for the treatment of *Aspergillus* species (1).

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Reference

1. **Walsh TJ, Pappas P, Winston DJ, et al.** N Engl J Med. 2002;346:225-34.