Successful treatment, and fewer had toxicity. However, most patients who received antifungal therapy did not have laboratory-confirmed infection.

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


**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/mm³ 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/mm³ 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).

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

*See Glossary.

**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**