Itraconazole was as effective as amphotericin B for fever and neutropenia in cancer and led to fewer adverse events


**Question**
In patients with cancer, is itraconazole as effective and safe as amphotericin B for eliminating fever and neutropenia?

**Design**
Randomized (allocation concealed*), unblinded,* controlled trial with median follow-up of 7 to 8.5 days.

**Setting**
60 oncology centers in 10 countries.

**Patients**
384 patients (median age 48 y, 60% men) who were ≥18 years of age and were hospitalized for hematologic cancer with intensive myelosuppressive cytotoxic therapy and who had an absolute neutrophil count of ≤0.5 × 10⁹ cells/L with an expected duration of ≥7 days and a body temperature ≥38 °C that was unrelated to blood product transfusions or medications and that persisted despite ≥3 days of treatment with antibiotics. Exclusion criteria included severe liver or renal dysfunction, HIV seropositivity, proven invasive fungal infection, chest radiographs or computed tomographic scans suggestive of invasive fungal infection during previous neutropenic episodes, and a fever caused by bacterial or viral infection. Follow-up ranged from 94% to 100%.

**Intervention**
192 patients were allocated to intravenous itraconazole, 200 mg as a solution in water, infused every 12 hours for the first 48 hours and then daily from days 3 to 14. Itraconazole, 400 mg/d, was given orally from day 15 or replaced the intravenous dose from day 7, if tolerated. 192 patients were allocated to intravenous amphotericin B deoxycholate, 0.7 to 1.0 mg/kg of body weight/d in 5% dextrose water, infused over 4 to 6 hours for up to 28 days. Treatment was stopped if patients recovered from fever and neutropenia.

**Main Outcome Measures**
Treatment response (defined as recovery from fever [daily oral peak temperature < 38 °C] and neutropenia [absolute neutrophil count > 0.5 × 10⁹ cells/L on ≥2 successive d]) and adverse events.

**Main Results**
Analysis was by intention to treat. Itraconazole was as effective as amphotericin B for eliminating fever and neutropenia and led to fewer adverse events (Table).

**Conclusion**
In patients with cancer, itraconazole was as effective as amphotericin B for eliminating fever and neutropenia and led to fewer adverse events.

*See Glossary.

**Itraconazole (Itracon) vs amphotericin B (Ampho B) for fever and neutropenia in cancer at end of treatment (median 7 to 8.5 d)†**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Itracon</th>
<th>Ampho B</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response</td>
<td>47%</td>
<td>38%</td>
<td>25% (−2.0 to 60)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related</td>
<td>4.7%</td>
<td>54%</td>
<td>91% (84 to 95)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td>Treatment withdrawal</td>
<td>19%</td>
<td>38%</td>
<td>51% (31 to 65)</td>
<td>6 (4 to 10)</td>
</tr>
<tr>
<td>Severe</td>
<td>19%</td>
<td>34%</td>
<td>43% (20 to 60)</td>
<td>7 (5 to 18)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in Glossary; RRR, RR, NNT, and CI calculated from data in article.

**Commentary**
Amphotericin B has been the standard drug used in practice and current treatment guidelines for antibiotic refractory febrile neutropenia (1, 2). The study by Boogaerts and colleagues, although limited by its open design and a slightly older amphotericin-B patient group, showed that empiric itraconazole was as effective as empiric amphotericin B for eliminating fever and neutropenia in patients with hematologic cancer.

Not surprisingly, this effect seems to be largely driven by the high rate of toxicity associated with amphotericin B. Over 3 times as many patients in the amphotericin-B group (21%) than in the itraconazole group (6.7%) had treatment failure because of toxicity-related discontinuation. Although a higher number of patients in the itraconazole group (11%) than in the amphotericin-B group (0.6%) changed antifungal regimens because of persistent fever (P = 0.001), groups did not differ for the number of breakthrough invasive fungal infections (2.8% in each group). However, no information is provided on differences between groups on types and outcomes of documented infections.

This study contributes to the literature on febrile neutropenia by suggesting that itraconazole is an effective and less toxic alternative to amphotericin B. Because newer and less toxic antifungal agents are substantially more expensive than amphotericin B deoxycholate, cost-effectiveness studies and local patterns of fungal epidemiology and resistance may be the most important factors driving treatment decisions for these patients (3).

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**References**