Pharmacoeconomic analysis of caspofungin versus liposomal amphotericin B as empirical antifungal therapy for neutropenic fever

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Empirical antifungal therapy is frequently used in the management of patients receiving chemotherapy who experience neutropenia with persistent fever despite the use of broad-spectrum antibiotics. Antifungals are used because of the concern for occult invasive fungal infections that may be missed or discovered only late during the course of infection, resulting in morbidity and mortality.1-3

A variety of antifungal agents have been tested as empirical antifungal therapy.4-10 One commonly used agent is liposomal amphotericin B, which has been shown to be as effective as the conventional formulation of amphotericin B, amphotericin B deoxycholate, with a lower risk of impaired renal function (IRF).4 A subsequent pharmacoeconomic comparison of those two agents suggested that the lower rates of IRF among those treated with liposomal amphotericin B could generate some cost savings relative to amphotericin B deoxycholate.11 However, those savings would not be large enough to fully offset the higher acquisition cost of amphotericin B deoxycholate.12

Purpose. An analysis was conducted that evaluated and compared the cost differences between caspofungin and liposomal amphotericin B when the medications were used as empirical antifungal therapy for persistent fever during neutropenia.

Methods. Rates of drug use and impaired renal function (IRF) were based on data from published studies. IRF was defined as a doubling of the serum creatinine level or, if the creatinine level was elevated at enrollment, an increase of at least 1 mg/dL. The estimates of the costs for drug acquisition and treating IRF were derived using published data and applied to compare caspofungin with liposomal amphotericin B. Sensitivity analyses were performed by varying the IRF and relative acquisition costs to assess the effect of these factors on the cost differences.

Results. The acquisition costs per patient were $6942 for liposomal amphotericin B and $3996 for caspofungin. The estimated cost per patient from IRF was $2173 for liposomal amphotericin B and $793 for caspofungin. Combining drug acquisition costs and IRF costs, the overall treatment cost per patient for caspofungin was $5326 less than for liposomal amphotericin B. In sensitivity analyses of drug costs, the price of liposomal amphotericin B would have to be $23.95 per vial for the overall treatment costs to be equal.

Conclusion. Comparison of cost estimates derived from published data revealed that a combined estimate of acquisition costs and costs related to the treatment of IRF was lower for caspofungin than for liposomal amphotericin B for empirically treating patients with neutropenic fever.

Index terms: Amphotericin B; Antifungals; Caspofungin; Costs; Drug comparisons; Liposomes; Neutropenia; Pharmacoeconomics; Toxicity

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of liposomal amphotericin B relative to amphotericin B deoxycholate unless the acquisition cost of liposomal amphotericin B was less than 50% of its average wholesale price at the time of the analysis. A newer empirical therapy alternative is caspofungin, which was recently compared with liposomal amphotericin B in a head-to-head comparative clinical trial. The results of that trial suggested that caspofungin was equally effective as liposomal amphotericin B, but it was associated with a lower risk of IRF. That trial did not include an economic comparison of the two drugs.

In this analysis, we evaluate and compare the cost differences between caspofungin and liposomal amphotericin B when the drugs are used as empirical antifungal therapy for persistent fever during neutropenia. We do this in the context of an economic model that incorporates the rates of IRF and drug use from the recent comparative trial, estimates of the cost of treating IRF from the published literature, and estimates of U.S.-based drug acquisition costs based on sales data.

Methods

An economic model in which 100 patients receiving empirical antifungal therapy with either caspofungin or liposomal amphotericin B was developed and structured as if the difference in costs by using caspofungin instead of liposomal amphotericin B in a hospital was being considered. The time period is from one week to a few months, consistent with the mean duration of antifungal treatment observed in the trial (13 days; range, 1–90 days) and the time encompassing the occurrence and treatment of acute renal toxicity.

Synopsis of reference trial. The details of the comparative trial have already been described. Briefly, patients ages 16 years and older, who had received chemotherapy for cancer or underwent hematopoietic stem-cell transplants, had an absolute neutrophil count of <500/µL, and had persistent fever and antibiotic therapy for at least 96 hours without documented fungal infection or inadequately treated bacterial infection, were randomly assigned in a blinded manner to either caspofungin or liposomal amphotericin B. Caspofungin acetate was given at an initial dose of 70 mg on the first day and then 50 mg each subsequent day. Liposomal amphotericin B was given at a dose of 3 mg/kg/day. Doses could be increased if the clinician judged the response to be suboptimal: caspofungin to 70 mg/day and liposomal amphotericin B to 5 mg/kg/day. Therapy was continued until neutropenia resolved and, for individuals with subsequently documented fungal infections, was continued for a minimum of 14 days and at least 7 days beyond neutrophil recovery and resolution of symptoms.

An overall favorable response consisted of five components, including (1) no documented breakthrough fungal infection, (2) survival seven days after the end of treatment, (3) no discontinuation due to toxicity or lack of efficacy, (4) resolution of fever during neutropenia, and (5) successful treatment of documented baseline infections. The overall favorable response rates were 34% for both caspofungin and liposomal amphotericin B.

IRF was defined as a doubling of the serum creatinine level or, if the creatinine level was elevated at enrollment, an increase of at least 1 mg/dL (88 µmol/L). IRF occurred less frequently with caspofungin compared with liposomal amphotericin B (3% versus 12%, respectively; p < 0.001). Infusion-related events also occurred less frequently with caspofungin (35% versus 52%, respectively; p < 0.001). Overall, the occurrence of any drug-related clinical or laboratory adverse event was less frequent in the caspofungin group compared with the liposomal amphotericin B group (54% versus 69%, respectively; p < 0.001). Examples of the most common clinical drug-related adverse events include chills, fever, nausea, vomiting, and rash. Examples of the most common laboratory drug-related adverse events include a decrease in potassium and an increase in alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase.

Drug acquisition costs. The method used to estimate the difference in drug acquisition cost between caspofungin and liposomal amphotericin B is illustrated in Table 1. The daily doses were those used in the clinical trial. For caspofungin, this was generally 70 mg for the first day of therapy, followed by 50 mg/day thereafter. However, since higher doses were sometimes used if the clinician thought there was a suboptimal response, the number of 70-mg doses averaged 2.7. The consequent estimate of each average dose in milligrams was used to calculate the number of vials used for caspofungin and liposomal amphotericin B.

Mean acquisition costs for the antifungal drugs were estimated using sales transaction data for nonfederal hospitals from July 2003 through December 2003. There is anecdotal evidence that some hospitals received a large discount off of the list price of liposomal amphotericin B and thus may face a much lower acquisition cost than the average acquisition cost. Hence, a sensitivity analysis was conducted in which the costs for liposomal amphotericin B that were significantly below the average cost used in the base case were considered. This was achieved by allowing that cost to fall by 25% decrements.

The daily acquisition costs were combined with data on average days of therapy at given doses to calculate the total drug acquisition cost for the average patient in the study. The difference in drug acquisition cost was calculated.

Cost of treating IRF. To estimate the average cost of treating IRF, we
performed a literature search and identified four studies in which the cost attributable to amphotericin-induced IRF was estimated (Table 2).\textsuperscript{11,13-15} Three of those studies, involving the conventional formulation of amphotericin B, were summarized earlier.\textsuperscript{17}

Each of the IRF cost estimates represents a mean cost across a distribution of patients with IRF, including patients with a low-, moderate-, and high-attributable cost. These estimates were converted to December 2003 U.S. dollars using the medical care component of the U.S. Consumer Price Index for May 1995, May 1996, March 1998, and December 2003.\textsuperscript{18}

The fourth study,\textsuperscript{15} which involved lipid formulations of amphotericin B, resulted in an IRF cost estimate that was similar to the average of that found in the three other studies. Hence, the four studies were combined to derive a four-study average. This average cost ($26,440) was used to estimate the cost of IRF associated with the use of liposomal amphotericin B and caspofungin, as an IRF cost study for caspofungin has not been done. This average was then combined with the toxicity data from the clinical trial to estimate total treatment costs attributable to IRF.

Given the wide variation in published cost estimates, a wide range of

Table 1. Difference in Drug Acquisition Cost\textsuperscript{a}

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean Patient Weight (kg)</th>
<th>Total mg per Dose</th>
<th>Number of 50-mg Vials per Dose</th>
<th>Cost per Vial ($)\textsuperscript{a}</th>
<th>Cost per Dose ($)</th>
<th>Mean Number of Doses per Patient\textsuperscript{b}</th>
<th>Cost per Patient ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal amphotericin B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>73.6</td>
<td>221\textsuperscript{c}</td>
<td>5</td>
<td>102.85\textsuperscript{d}</td>
<td>514.25</td>
<td>11.1</td>
<td>5708</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>73.6</td>
<td>368\textsuperscript{c}</td>
<td>8</td>
<td>102.85\textsuperscript{d}</td>
<td>822.80</td>
<td>1.5</td>
<td>1234</td>
</tr>
<tr>
<td>Total acquisition cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6942</td>
</tr>
<tr>
<td>Caspofungin acetate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>75.2</td>
<td>50</td>
<td>1</td>
<td>291.29</td>
<td>291.29</td>
<td>10.3</td>
<td>3000</td>
</tr>
<tr>
<td>70 mg</td>
<td>75.2</td>
<td>70</td>
<td>NA</td>
<td>368.97</td>
<td>368.97</td>
<td>2.7</td>
<td>996</td>
</tr>
<tr>
<td>Total acquisition cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3996</td>
</tr>
</tbody>
</table>


\textsuperscript{b}Total number of specified doses that each patient received on average.

\textsuperscript{c}Based on mean patient weight.

\textsuperscript{d}Each vial contains 50 mg.

Table 2. Attributable Cost of Treating Impaired Renal Function (IRF) Associated with Amphotericin B

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients with IRF (No. Patients without IRF)</th>
<th>Definition of IRF</th>
<th>Increase in Treatment Cost Attributable to IRF ($)\textsuperscript{a}</th>
<th>Attributable Cost ($)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>114 (300)</td>
<td>Doubling of baseline creatinine level and &gt;1.2-mg/dL creatinine concentration in adults</td>
<td>25,206</td>
<td>33,486</td>
</tr>
<tr>
<td>13</td>
<td>212 (495)</td>
<td>50% increase in baseline creatinine level, with peak of ≥2.0 mg/dL</td>
<td>29,823</td>
<td>41,083</td>
</tr>
<tr>
<td>14</td>
<td>30 (292)\textsuperscript{c}</td>
<td>Doubling of serum creatinine level from baseline up to an absolute value of ≥2.0 mg/dL</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>22 (67)</td>
<td>100% increase in baseline creatinine level and creatinine concentration of at least 1.2 mg/dL in adults</td>
<td>24,758</td>
<td>31,190</td>
</tr>
</tbody>
</table>

Average attributable cost of IRF $26,440

\textsuperscript{a}Mean cost estimates, not charges, from a distribution of patients with IRF (i.e., low, moderate, or high attributable costs).

\textsuperscript{b}Converted using the medical care component of the U.S. Consumer Price Index for May 1995, May 1996, March 1998, and December 2003 converted to December 2003 U.S. dollars.\textsuperscript{18}

\textsuperscript{c}Mortality and length of stay were analyzed for 58 patients with IRF and 436 without. However, costs were available for only a subset of those patients.
IRF cost estimates was considered in the sensitivity analysis. Specifically, the base case estimate was varied by −25% ($19,830) and −50% ($13,220). A much wider variation in this cost was considered during the generation of the cost neutrality line (i.e., the combination of IRF and liposomal amphotericin B costs at which the overall treatment cost is the same for both drugs).

Results

Our base case assumptions suggest a drug acquisition cost of $6,942 per patient for liposomal amphotericin B and $3,996 per patient for caspofungin (Table 1). As for the cost associated with IRF, our calculations suggest that using caspofungin instead of liposomal amphotericin B in a group of 100 patients would result in 9 fewer patients with IRF. This would be associated with a treatment cost saving of $237,960 ($79,300 versus $173,300), or an average saving of $2,380 per patient averaged across the entire group at risk (Table 3). Combining drug acquisition and IRF costs, the overall treatment cost per patient would be $10,115 for liposomal amphotericin B and $4,789 for caspofungin. This suggests that the overall treatment cost difference between caspofungin and liposomal amphotericin B would be $5,326 per patient.

Table 4 and Figure 1 demonstrate the effects of varying the estimates of the cost of IRF and the acquisition cost of one drug relative to the other. (Variation in the latter was achieved by varying the cost of liposomal amphotericin B while holding the cost of caspofungin constant.) Although changes in the IRF cost estimate affect the saving achieved with caspofungin use to some degree, changes in the relative acquisition cost have a much larger effect. For example, a 25% reduction in the estimated cost of treating IRF reduces the cost saving by $595 per patient, but a 25% reduction in the acquisition cost of liposomal amphotericin B (to $77.14) reduces the cost saving by $1735 per patient. At $70, $60, and $50 per 50-mg vial for liposomal amphotericin B, the cost difference favors caspofungin by $3109, $2434, and $1759, respectively. Only when the vial cost of liposomal amphotericin B reaches $23.95 does the overall estimated treatment costs between the two drugs become neutral in the base case, and caspofungin becomes more costly in scenarios where IRF is less costly.

The cost neutrality line (Figure 1) indicates the estimates at which both drugs result in identical overall expenditures. Point estimates above the cost neutrality line indicate that the use of caspofungin is expected to be associated with lower overall treatment costs compared with liposomal amphotericin B. Point estimates below the cost neutrality line indicate that the use of liposomal amphotericin B would be expected to be associated with lower overall treatment costs.

Discussion

A variety of studies have demonstrated associations of invasive fungal infections with resource use, length of hospital stay, mortality, and health care costs.19-26 Cost assessments of antifungal therapy for many years focused on drug acquisition cost alone. The introduction of alternatives to amphotericin B, which were generally considerably more costly, yet offered safety advantages, gave rise to a number of studies that have examined amphotericin B treatment toxicities and their clinical and economic consequences.27-31 These studies suggested that the higher acquisition cost of the newer alternatives may be offset by treatment cost savings ensuing from less toxicity. This helped to spawn additional research into the costs associated with the use of novel antifungals, including lipid amphotericin B formulations,11,15 caspofungin,17 and voriconazole.32,33

In this analysis, we used an economic model to estimate the comparative costs of caspofungin and liposomal amphotericin B when used as empirical antifungal therapy in persistently febrile neutropenic patients, a common oncologic practice, especially for patients treated for hematologic malignancies. Relative to liposomal amphotericin B, the use of caspofungin demonstrated both lower drug acquisition costs and

### Table 3.

**Difference in Cost of Treating Impaired Renal Function (IRF)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate of IRF from Clinical Trial (%)</th>
<th>Projected Number of Patients Developing IRF</th>
<th>Cost of Treating IRF per Patient ($)</th>
<th>Projected Cost of Treating IRF per Patient at Risk ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin acetate</td>
<td>2.6</td>
<td>3</td>
<td>26,440</td>
<td>793</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>11.5</td>
<td>12</td>
<td>26,440</td>
<td>3,173</td>
</tr>
</tbody>
</table>

*IRF was defined as a nephrotoxic effect = at least a doubling of the serum creatinine level, or an increase of at least 1.0 mg/dL if the baseline level was elevated above the upper limit of the normal range.

*Based on rates taken from the comparative clinical trial17 multiplied by 100 patients.

*The average across four studies,11,13,17 each of which estimated the mean attributable cost from a sample of patients with IRF.

*Averaged across entire group at risk.
lower costs associated with the treatment of renal toxicity. We previously used a similar model to evaluate the comparative costs of caspofungin and amphotericin B deoxycholate for the treatment of candidemia.17 In that analysis, caspofungin was associated with lower overall treatment costs across a wide range of assumptions regarding the cost of treating IRF, even when one assumed that the cost of conventional amphotericin was zero.

Most estimates of the cost of IRF in prior studies were based on IRF caused by amphotericin B deoxycholate. It could be supposed that since the incidence of IRF with liposomal amphotericin B is less, the magnitude of IRF and its effect on resource use might also be less with a lipid amphotericin. The data in two studies suggest, however, that this is not the case. In one study in which liposomal amphotericin B was compared with amphotericin B deoxycholate, there was no difference in incremental hospital costs between the two agents.11 In another study in which the costs with amphotericin B lipid complex and liposomal amphotericin B were compared,15 the type of antifungal agent was not an independent factor associated with cost in a multivariate analysis and the cost associated with IRF was similar to the cost estimates in studies of amphotericin B IRF. Thus, we believe these data support our decision to include such studies in our analysis (Table 2).

In this analysis, we focused only on IRF to examine differences in drug toxicity. This choice was based on observations in previous studies emphasizing the clinical importance of IRF, associated with longer hospital stay, mortality, greater hospital resource use, and costs.11,13-15,17,26-33 Note, however, that infusion-related adverse events also occurred less frequently with caspofungin compared with liposomal amphotericin B.34 If the groups analyzed in the IRF cost studies were balanced in the sense

### Table 4.
Effect of Varying Cost Estimates of Liposomal Amphotericin B (LAMB) and Impaired Renal Function on the Difference in Cost Between Caspofungin and LAMB

<table>
<thead>
<tr>
<th>Acquisition Cost of LAMB (50-mg vial)</th>
<th>Cost of Impaired Renal Function ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13,220 (50% less)</td>
</tr>
<tr>
<td></td>
<td>19,830 (25% less)</td>
</tr>
<tr>
<td></td>
<td>26,440 (base case)</td>
</tr>
<tr>
<td>$102.85 (base case)</td>
<td>–4,136</td>
</tr>
<tr>
<td>$77.14 (25% less)</td>
<td>–2,401</td>
</tr>
<tr>
<td>$51.43 (50% less)</td>
<td>–1,260</td>
</tr>
<tr>
<td>$23.95 (77% less)</td>
<td>1,190</td>
</tr>
</tbody>
</table>

*Variations were achieved by varying the acquisition cost of LAMB while holding the cost of caspofungin constant.*

### Figure 1. Sensitivity analysis. Variation in results based on the acquisition cost of liposomal amphotericin B (LAMB) (vertical axis) and the average cost of treating impaired renal function LAMB (horizontal axis).
that they experienced similar rates of infusional toxicities, then the estimated differences in treatment costs between the two groups would not also account for the difference in cost attributable to drug-induced infusional toxicities. Hence, a separate analysis of the cost attributable to those toxicities might reveal additional differences in the costs associated with the two drugs. Unfortunately, there are no published estimates of costs attributable to infusional reactions, so such an analysis is not immediately possible. Finally, note that it is possible that there may be long-term cost implications of IRF not accounted for in this analysis of just short-term costs.

As with all models based on results taken from clinical trials, the reader should be aware that the generalizability of the model is greatly dependent on the generalizability of the clinical trial. If the pattern of care provided in the trial from which we drew our clinical information does not reflect that provided in real-world settings, then the conclusions of our model cannot reasonably be extrapolated to those settings. Given the seriousness of the condition studied in the trial and the intensiveness of care required to prevent mortality, we hope that real-world care does not deviate significantly from that seen in the trial. Nevertheless, this is still a possibility that the reader should take into account when interpreting the results of our model.

Another limitation of this study is that, because cost data were not collected during the comparative trial, we had to use estimates of costs, which may or may not reflect true costs. It would be desirable to determine such expenditures directly rather than by imputation. Moreover, it should be noted that the cost differences we derived might be greater or less if the drugs were used in different dosing schedules or in a different group of patients. Notwithstanding, this analysis provides a framework by which one can estimate the cost of empirical antifungal therapy with caspofungin and liposomal amphotericin B. Providers could use our modeling framework in conjunction with their own “local” data on costs and IRF incidence to tailor this analysis to their own specific situation.

There are a number of issues that could be addressed in future studies. Studies to assess true costs could help to validate, or invalidate, our findings. Further, certain subgroups of patients may be more or less susceptible to IRF, and cost estimates pertinent to these subgroups would be useful. Finally, longer-term cost assessments that go beyond the relatively short time frame used in this study may uncover additional economic considerations.

Conclusion

Comparison of cost estimates derived from published data revealed that a combined estimate of acquisition costs and costs related to the treatment of IRF was lower for caspofungin than for liposomal amphotericin B for empirically treating patients with neutropenic fever.

References

20. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hos-


