Clinical Significance of Nephrotoxicity in Patients Treated with Amphotericin B for Suspected or Proven Aspergillosis

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The records of 239 immunosuppressed patients receiving amphotericin B for suspected or proven aspergillosis were reviewed to determine rates of nephrotoxicity, dialysis, and fatality. The mean and median durations of treatment were 20.4 and 15.0 days, respectively. The creatinine level doubled in 53% of patients and exceeded 2.5 mg/dL in 29%; 14.5% underwent dialysis; and 60% died. A multivariate Cox proportional hazards analysis showed that patients whose creatinine level exceeded 2.5 mg/dL (hazard ratio [HR], 42.02; \( P < .001 \)), allogeneic bone marrow transplantation (BMT) patients (HR, 6.34; \( P < .001 \)), and autologous BMT patients (HR, 5.06; \( P = .024 \)) were at greatest risk for requiring hemodialysis. Use of hemodialysis (HR, 3.089; \( P < .001 \)), duration of amphotericin B use (HR, 1.03 per day; \( P < .001 \)), and use of nephrotoxic agents (HR, 1.96; \( P = .015 \)) were associated with greater risk of death, whereas patients undergoing solid organ transplantation were at lowest risk (HR, 0.46; \( P = .002 \)). These data indicate that elevated creatinine levels during amphotericin B treatment are associated with a substantial risk for hemodialysis and a higher mortality rate, but the risks vary in different patient groups.

The rate of invasive fungal infections doubled during the 1980s in hospitals in the United States [1]. Contributing factors include the increasing use of antibiotics, the growing population of patients at risk—including patients receiving chemotherapy for neoplastic diseases and the recipients of solid organ transplants—and strides in preventing deaths due to bacterial infections. Despite the introduction of azole antifungals, amphotericin B remains the cornerstone of antifungal therapy because of its broad spectrum of activity, although nephrotoxicity remains a major shortcoming.

See editorial response by Rex and Walsh on pages 1408–10.

There is little information about the significance or long-term outcome of nephrotoxicity. Today, formulations of amphotericin B with lower risk for nephrotoxicity are available [2–11], and these could be used to reduce nephrotoxicity in those most vulnerable. Unfortunately, these less toxic agents are costly, and thus clinicians are being called upon to use them with discretion. Current recommendations are that they be used for patients whose infections do not respond to amphotericin B or who become intolerant to amphotericin B. An alternative strategy that might improve outcomes and/or lower costs is to use these agents early, when the outcome following use of amphotericin B is expected to be poor or when costly interventions, such as hemodialysis or prolonged hospital stays, are likely.

In this study, we attempted to identify the factors associated with hemodialysis and death, with the hope that subsequent studies could determine whether early use of less nephrotoxic antifungal agents for such high-risk patients could reduce the use of hemodialysis or decrease the risk of death.

Methods

Patients. As part of a study to evaluate relative efficacy and safety of a lipid formulation of amphotericin B in patients treated for suspected or proven invasive aspergillosis, the medical records from 5 centers treating patients undergoing solid organ transplantation or bone marrow transplantation and patients with neoplastic disease or nontransplantation-related immunosuppressive illness were reviewed for the period 1 January 1990 through 31 December 1993. The purpose of the review was to identify immunosuppressed
The underlying conditions were categorized into 1 of 4 groups: (1) allogeneic bone marrow transplantation (BMT), (2) autologous BMT, (3) solid organ transplantation (SOT), and (4) other immunosuppressive conditions not related to transplantation. Most of the patients in the latter category were receiving chemotherapy for hematologic malignancies.

Demographic factors assessed included sex, age, and body mass index. Clinical factors included BMT status (yes or no) and transplant type (allogeneic, autologous, or none); SOT status (yes or no); whether or dialysis occurred after the start of therapy with amphotericin B (yes or no) and the time of first dialysis; use of cyclosporin A or tacrolimus (FK506) during the first week of amphotericin B treatment (yes or no); use of other nephrotoxic agents, including aminoglycosides, during the first week of amphotericin B treatment (yes or no); baseline total bilirubin, absolute neutrophil count, and serum creatinine values; the additive and percent changes in serum creatinine level from baseline to day 7 after the start of amphotericin B; the time of doubling of serum creatinine level relative to baseline, whether or not the time to doubling was shorter than ("rapid doubling") or longer than ("slow doubling") the median time to doubling; and the time to occurrence of a serum creatinine level >2.5 mg/dL, as well as whether the time to such occurrence was less than the median time to occurrence.

Baseline blood value was defined as the maximum value observed on the first day of amphotericin B treatment or as the maximum value occurring on the day closest to the start of such treatment (when data were available for the week before its initiation). For patients given only a 1-mg test dose of amphotericin B on their first day of treatment, data from the first day after the start of amphotericin B treatment were also searched for a possible baseline serum creatinine value. The serum creatinine level at day 7 after the start of therapy with amphotericin B was defined as the maximum value observed on that day or the day closest to it (day 8, 9, 10, or 6, in order of preference), when data were available.

Analysis. The number of patients with a doubling of creatinine level from baseline or a creatinine level exceeding 2.5 mg/dL, the number who underwent dialysis, and the number who died within 30 days of the end of therapy with amphotericin B were compared between subgroups defined by categorical predictors, with use of the chi² test or Fisher’s exact test. Continuous variable means and rank sums were compared between patients who required dialysis and those who did not (or between patients who died and patients who survived), by means of the independent-sample t-test or the Wilcoxon rank-sum test. For each predictor, the hazard ratio (HR) of requiring dialysis or of dying was estimated univariately, along with 95% confidence bounds, with use of Cox proportional hazards regression. Score tests were used to evaluate the significance of predictors in the model. All possible multivariate Cox models were also evaluated, along with pairwise interaction.

Attempts were made to construct larger models on the basis of significant test scores. Because of the pattern of missing data among the predictors in the dataset, this process was carried out on 3 groupings of predictors. The first group of predictors, having the smallest amount of missing data, included all predictors except those based on blood values. The second group included all the

### Table 2. Rates of nephrotoxicity, hemodialysis, and fatality in 4 patient groups.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Creatinine value</th>
<th>Dialysis required</th>
<th>Fatality*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doubled</td>
<td>≥2.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Allogeneic BMT</td>
<td>42/69 (61)</td>
<td>21/63 (33)</td>
<td>14/69 (20)</td>
</tr>
<tr>
<td>Autologous BMT</td>
<td>12/15 (80)</td>
<td>7/15 (47)</td>
<td>3/15 (19)</td>
</tr>
<tr>
<td>SOT</td>
<td>19/55 (35)</td>
<td>15/42 (36)</td>
<td>10/55 (18)</td>
</tr>
<tr>
<td>Nontransplantation</td>
<td>41/76 (54)</td>
<td>17/86 (20)</td>
<td>6/87 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>114/215 (53)</td>
<td>60/206 (29)</td>
<td>33/227 (15)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of patients positive examined (%). BMT, bone marrow transplantation; SOT, solid organ transplantation.

* Hazard ratios of association to time until death in time-dependent analysis, compared with organ transplantation, were 2.09 (P = .004) for nontransplantation patients, 2.16 (P = .003) for allogeneic BMT patients, and 2.55 (P = .007) for autologous BMT patients.
Results

Two hundred thirty-nine patients met the eligibility criteria. Data for assessment of doubling of the creatinine level were available for 215 patients, and those for assessment of creatinine levels exceeding 2.5 mg/dL were available for 206 patients. Dialysis was assessable for 227 patients, and mortality was assessable for 239 patients. The characteristics of the patients studied are listed in table 1. The baseline creatinine level differed in the 4 groups: the mean (± SD) was 1.29 mg/dL ± 1.05 in allogeneic BMT patients, 1.26 ± 1.55 in the autologous BMT patients, 1.10 ± 0.66 in the nontransplantation patients, and 2.21 ± 2.25 in the SOT patients (P = .0001 for SOT vs. all others by Tukey’s studentized test).

Predictors of nephrotoxicity. The rates of nephrotoxicity in the 4 different patient groups are indicated in table 2. Creatinine levels doubled in 53% of the total number of patients. As can be seen in figure 1, a Kaplan-Meier analysis showed that the risk of creatinine level elevation increased over time. The creatinine level doubled at a median of 7 days after initiation of amphotericin B therapy. A multivariate Cox proportional hazards analysis showed that only a low baseline creatinine level (HR, 0.26; P < .001), duration of amphotericin B use (HR, 1.07 per day; P = .009), and use of corticosteroids (HR, 1.54; P = .027) were associated with a doubling of the creatinine level at any time during or within 30 days after completion of treatment with amphotericin B (table 3).

The creatinine level exceeded 2.5 mg/dL in 29% of patients (table 2). A creatinine level exceeding 2.5 mg/dL at any time occurred less frequently in nontransplantation patients (20%) than in autologous or allogeneic BMT and SOT patients (collectively, 36%). A multivariate analysis showed that only duration of amphotericin B use (HR, 1.056 per day; P = .075) and the baseline creatinine level (HR, 1.706; P = .06) were marginally associated with an elevation of the creatinine level to >2.5 mg/dL within 30 days after completion of the course of treatment with amphotericin B (table 3).

Predictors of hemodialysis. Dialysis was administered to 33 (14.5%) of 227 patients. The rates of dialysis in each of the patient categories are given in table 2. For 12 (36%) of the 33 patients given hemodialysis, dialysis was begun within the first week of the start of treatment with amphotericin B. When patients who received cyclosporin A were compared with those who did not, it was shown that a significantly higher proportion of the recipients underwent hemodialysis (19% vs. 9%; P = .024). There was a similar trend toward dialysis among those receiving concomitant nephrotoxic agents other than cyclosporin A during the first week of administration of amphotericin B (16% vs. 7%; P = .13).

Table 4 shows the relationship between hemodialysis and the use of cyclosporin A, other nephrotoxic agents, or both cyclosporin A and nephrotoxic agents. Among patients receiving both cyclosporin A and other nephrotoxic drugs, the rate of dialysis was 21%; in contrast, it was 11%–13% among patients receiving either but not both, and 0% among patients receiving neither (P = .053, Fisher’s exact test).

A Cox proportional hazards analysis showed that the only group at greater risk for hemodialysis was the allogeneic BMT group, in comparison with nontransplantation patients (HR, 2.96; P = .027). Other intergroup-comparison values were not significantly different. The absolute magnitude and percentage of change in creatinine level during the first week of amphotericin B administration were not associated with the administration of hemodialysis. Likewise, the rapidity with which the creatinine level doubled was not associated with the use of hemodialysis. Of the 56 patients in which the creatinine level exceeded 2.5 mg/dL, 31 (37.5%) underwent hemodialysis. A multivariate Cox proportional hazards analysis showed that both allogeneic BMT patients (HR, 6.34; P = .001) and autologous BMT patients (HR, 5.06; P = .024), as well as patients whose creatinine level exceeded 2.5 mg/dL (HR, 42.02; P < .001) were at greater risk for hemodialysis (table 3).

Use of the equation developed from this multivariate Cox proportional hazards analysis showed that after 10 days of therapy with amphotericin B, a patient had a variable likelihood of requiring dialysis over the next 45 days. We used this equation to estimate the risk of dialysis for various scenarios.
As seen in figure 2, a patient in a non-BMT treatment category whose creatinine level exceeded 2.5 mg/dL had a 35% likelihood of requiring hemodialysis. In contrast, a patient who was a recipient of an autologous or allogeneic transplant and whose creatinine level exceeded 2.5 mg/dL after 10 days of amphotericin B therapy had a >90% likelihood of requiring dialysis (figure 2). An autologous BMT patient whose creatinine level exceeded 2.0 mg/dL during the first 10 days of therapy with amphotericin B had an ~65% chance of requiring hemodialysis, whereas an allogeneic BMT patient had an ~55% likelihood of requiring hemodialysis (data not shown).

**Predictors of mortality.** One hundred forty-three (60%) of the 239 treated patients died, 27 within the first week of treatment. Mortality rates were different in the 4 patient groups (table 2). The use of nephrotoxic agents other than cyclosporin A and tacrolimus was associated with higher mortality (65% vs. 37%; P = .001). It is surprising that the risk was not greater for patients receiving steroids or for those whose creatinine level doubled at any time. The mortality among patients who required dialysis, however, was greater than among those who did not (76% vs. 57%; P = .039).

A multivariate Cox proportional hazards analysis showed that factors significantly associated with mortality were the use of hemodialysis (HR, 3.089; P < .001), the duration of therapy with amphotericin B (HR, 1.03 per day; P = .015), and the use of nephrotoxic agents (HR, 1.96; P = .017), whereas the risk for SOT patients was lower (HR, 0.46; P = .002; table 3).

### Discussion

Nephrotoxicity is a major dose-limiting toxic effect of amphotericin B. Rates of nephrotoxicity have varied widely in different reports [2, 3, 13–24]. Factors associated with higher rates of nephrotoxicity in earlier reports include dosage, dosing schedule, and duration of use; underlying disease; concomitant use of cyclosporin A or other nephrotoxic drugs and duration of their use; and definition of nephrotoxicity. Even in autologous BMT patients to whom cyclosporin A is not administered, nephrotoxicity is problematic because of sequelae from the intensive conditioning regimen [25, 26].

In this study, the 2 factors in multivariate analyses that predicted nephrotoxicity were the baseline creatinine level prior to the start of treatment with amphotericin B and the duration of amphotericin B therapy. The baseline creatinine level was inversely related to a doubling of the creatinine level, whereas more severe nephrotoxicity (creatinine level exceeding a threshold of 2.5 mg/dL) was associated with a higher baseline creatinine level. In agreement with earlier studies, the duration of amphotericin B therapy was directly related to the risk of nephrotoxicity.

The rate at which hemodialysis was used for severe nephrotoxicity was only 15% overall. However, among patients receiving cyclosporin A or other nephrotoxic drugs in addition to amphotericin B, the rate of dialysis was 21%. Of those with a creatinine level >2.5 mg/dL, 38% received dialysis. The rates of dialysis may be underestimated in this retrospective review, since some patients in poor overall condition (who otherwise would have been appropriate dialysis candidates) may not have been offered dialysis.

The patient category was highly associated with the use of dialysis. BMT patients, with either an allograft or an autograft, were 5-fold to 6-fold more likely to undergo dialysis. Moreover, BMT patients with creatinine levels >2.5 mg/dL almost always underwent dialysis if they received amphotericin B for >10 days (figure 2).

Accordingly, BMT patients appear to be especially vulner-

### Table 4. Necessity of hemodialysis among patients given cyclosporin A, other nephrotoxic agent(s), or both.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Dialysis required</th>
</tr>
</thead>
<tbody>
<tr>
<td>No nephrotoxic agents</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>3/23 (13)</td>
</tr>
<tr>
<td>Other nephrotoxic agent(s)</td>
<td>9/84 (11)</td>
</tr>
<tr>
<td>Both</td>
<td>21/101 (21)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients/total no. (%).
Figure 2. A Cox proportional hazards ratio multivariate analysis for the 3 risk factors associated with dialysis (allogeneic bone marrow transplantation [BMT], autologous BMT, and a creatinine level >2.5 mg/dL: see table 3). The figure shows a typical scenario for the probability of dialysis for a patient having none, 1, or more of these risk factors after 10 days of therapy with amphotericin B. The label for each curve indicates patient category first, then whether or not creatinine level exceeded 2.5 mg/dL. Bal, allogeneic BMT; Bau, autologous BMT; Cr, creatinine level >2.5 mg/dL; X, non-BMT category or creatinine level not >2.5 mg/dL.

applicable for severe nephrotoxicity that requires dialysis. This subgroup of patients, therefore, is well-suited for strategies designed to reduce nephrotoxicity (and to curtail the need for another costly intervention, dialysis). These findings emphasize that the significance of nephrotoxicity differs in different patient populations. For example, a rise in creatinine level to >2.0 mg/dL in a BMT patient carries as much risk of the need for dialysis as the probability of dialysis for a patient having none, 1, or more of these risk factors after 10 days of therapy with amphotericin B. The label for each curve indicates patient category first, then whether or not creatinine level exceeded 2.5 mg/dL. Bal, allogeneic BMT; Bau, autologous BMT; Cr, creatinine level >2.5 mg/dL; X, non-BMT category or creatinine level not >2.5 mg/dL.

It should be emphasized that the results of these analyses are applicable only to individuals who are severely immunocompromised, are found to have (or strongly suspected to have) an established invasive aspergillus infection, and are receiving intensive amphotericin B therapy. The rates of dialysis (and mortality) are likely to be lower among patients whose level of host compromise is less severe, among patients whose dosing schedule of amphotericin B is less intensive, and patients receiving antifungal prophylaxis or empirical therapy.

Certainly, these are not necessarily cause-and-effect relationships; thus it is not clear whether strategies to reduce dialysis will produce a concomitant reduction in fatality rates. Prospective studies that use less nephrotoxic agents in an attempt to avoid dialysis are necessary to ascertain whether this strategy will improve outcomes. Alternatively, the use of dialysis may merely be a marker of severe illness. If that is the case, then no intervention will alter the outcome.

Several controlled clinical trials using lipid formulations of amphotericin B have shown lower nephrotoxicity rates than trials with amphotericin B, but no improvement in outcome or reduction in mortality [2, 5–7, 11]. In several of these trials, the endpoint for sample-size calculations was nephrotoxicity; they may have been inadequately powered to detect differences in mortality. Moreover, several of these trials involved administration of a formulation as prophylaxis or as treatment of persistent fever during neutropenia, a situation in which the mortality rate is lower and the impact on fungal disease less certain. Therefore, further studies may be necessary to evaluate the effects of the lipid formulations of amphotericin B on dialysis and mortality rates.

In conclusion, nephrotoxicity occurs frequently in patients receiving amphotericin B for aspergillosis. Both the duration of treatment and the baseline creatinine level predict the likelihood for nephrotoxicity. Severe nephrotoxicity resulting in hemodialysis is much more likely in BMT patients than in SOT patients and nontransplantation-immunocompromised patients with similar elevations of creatinine level.

In this study, nearly 90% of BMT patients underwent hemodialysis if their creatinine level exceeded 2.5 mg/dL, and nearly half received hemodialysis if their creatinine level exceeded 2.0 mg/dL. Thus it is clear that when treating BMT patients, clinicians may be justified in switching to alternative treatments at lower levels of increase in the serum creatinine level than they would when treating SOT patients or nontrans-
plantation-immunocompromised patients. Because of the highly significant association of hemodialysis and a fatal outcome, it is hoped that alternative treatments that avoid nephrotoxicity will result in lower mortality rates. Such alternatives should be the subject of future study.

References