The use of amphotericin B deoxycholate as empirical antifungal therapy, nadir serum potassium levels and maximum daily need for intravenous potassium chloride. Acute renal failure was defined as an 8 h infusion, and each patient received daily intravenous potassium premedication, amphotericin B deoxycholate was delivered as a single daily dose. After antibiotic therapy, the median duration of amphotericin B deoxycholate treatment was 10 days (range 3–33), 10 (3–33) in the allogeneic subgroup and 9.5 (4–22) in the autologous subgroup. None of the patients in the no amphotericin B deoxycholate group experienced acute renal failure, although two allogeneic HSCT recipients had a doubling of baseline creatinine levels without reaching a value of ≥2 mg/dL. The median duration of amikacin treatment in the no amphotericin B deoxycholate group was 11 days (range 4–33), 15 (5–33) in the allogeneic subgroup and 11 (4–26) in the autologous subgroup. The nadir potassium value was 3 mEq/L (range 1.9–4.3) in the amphotericin B deoxycholate group and 3.5 mEq/L in the no amphotericin B deoxycholate group (range 2.6–4.2). Maximum daily intravenous KCl supplementation was 260 mEq (range 40–500) in the amphotericin B deoxycholate group and 80 mEq (range 0–200) in the no amphotericin B deoxycholate group.

The use of amphotericin B deoxycholate as empirical antifungal therapy was mandatory in our institution until 2005; during the previous 10 years, 123 haematopoietic stem cell transplantation (HSCT) recipients (79 males and 44 females; median age 43 years, range 17–66; 74 autologous, 49 allogeneic) had received 0.7 mg/kg starting 5 days after ineffective antibiotic therapy, including 15 mg/kg amikacin as a single daily dose. After antihistamine premedication, amphotericin B deoxycholate was delivered as an 8 h infusion, and each patient received daily intravenous hydration of more than 3 L, including at least 1 L of normal saline solution. Starting in 2005 and moving back, 123 consecutive HSCT recipients (63 males and 60 females; median age 54 years, range 19–69; 81 autologous, 42 allogeneic) were collected, who did not require empirical antifungal therapy and received the same amikacin–including antibiotic therapy (no amphotericin B deoxycholate group). A record was made of each patient’s blood creatinine and creatinine clearance (according to the Cockcroft-Gault formula) at the start and at the end of amphotericin B deoxycholate treatment, duration of amphotericin B deoxycholate therapy, nadir serum potassium levels and maximum daily need of intravenous potassium chloride. Acute renal failure was defined as the doubling of baseline creatinine levels with an absolute creatinine value ≥2 mg/dL. This retrospective study was approved by the local ethics board. The differences between pre- and post-treatment creatininemia and creatinine clearance were analysed by means of the matched pair two-tailed t-test and the between-group differences by means of the two-tailed t-test. The decreases in blood creatinine and creatinine clearance in the two groups were compared using the Mann–Whitney test.

Table 1 summarizes pre- and post-treatment renal tests in the two groups of HSCT recipients. Seven allogeneic HSCT recipients in the amphotericin B deoxycholate group experienced acute renal failure. Fourteen additional patients (12 allogeneic and 2 autologous HSCT recipients) had a doubling of baseline creatinine levels without reaching a value of ≥2 mg/dL. Blood creatinine began to increase at a median of 2 days after the start of amphotericin B deoxycholate and reached the highest value on the last day of treatment; the median duration of amphotericin B deoxycholate treatment was 10 days (range 3–33), 10 (3–33) in the allogeneic subgroup and 9.5 (4–22) in the autologous subgroup. None of the patients in the no amphotericin B deoxycholate group experienced acute renal failure, although two allogeneic HSCT recipients had a doubling of baseline creatinine levels without reaching a value of ≥2 mg/dL. The median duration of amikacin treatment in the no amphotericin B deoxycholate group was 11 days (range 4–33), 15 (5–33) in the allogeneic subgroup and 11 (4–26) in the autologous subgroup. The nadir potassium value was 3 mEq/L (range 1.9–4.3) in the amphotericin B deoxycholate group and 3.5 mEq/L in the no amphotericin B deoxycholate group (range 2.6–4.2). Maximum daily intravenous KCl supplementation was 260 mEq (range 40–500) in the amphotericin B deoxycholate group and 80 mEq (range 0–200) in the no amphotericin B deoxycholate group.

Interest in our data is apparently limited by the fact that new drugs have largely replaced amphotericin B deoxycholate in haematological patients, and Cagnoni et al. have shown that allogeneic HSCT cannot be considered a suitable indication for empirical amphotericin B deoxycholate antifungal chemotherapy. Nevertheless, even recent reports have indicated that amphotericin B deoxycholate toxicity can be substantially reduced if the drug is administered appropriately, with hydration and a sustained need for intravenous potassium chloride. Bates et al. found that the 79 HSCT recipients in their large and heterogeneous series experienced considerably unfavourable outcomes; although they do not give any information about the amphotericin B deoxycholate schedules, their data suggest that amphotericin B deoxycholate toxicity may be less severe in intensive care units or specialized medical wards whose staff are likely to be more trained in administering amphotericin B deoxycholate, thus justifying efforts aimed at minimizing its toxicity. It is worth mentioning that our findings were observed in patients receiving a low dose of amphotericin B deoxycholate over a short period of time, as is usual in the case of empirical therapy. Moreover, renal toxicity occurred, although the volume of intravenous fluid infusions was comparable to or even higher than that allowing amphotericin B deoxycholate to be delivered safely according to Girmenia et al. and Oto et al. We did not try to administer amphotericin B deoxycholate as a continuous intravenous infusion because of concerns about its activity. Possibly, renal damage has been somewhat overlooked by...
authors claiming that amphotericin B deoxycholate can be administered safely, as they have frequently reported losses in creatinine clearance exceeding 30% as negligible.3–6 Our results do not support making any more effort to administer amphotericin B deoxycholate as empirical antifungal therapy in HSCT recipients and raise some doubts as to its appropriateness in haematological patients. The outcomes of the patients receiving amikacin-including antibiotic therapy were more favourable even in allogeneic HSCT recipients, thus underlining the primary role of amphotericin B deoxycholate in inducing nephrotoxicity.

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Transparency declarations

C. A. has received a fee for speaking at a symposium organized by Pfizer and sponsorships for attending international congresses from Gilead, MSD and Pfizer. C. O. has nothing to declare. P. U. has received sponsorships for attending international congresses from Gilead and Schering. F. O. has received sponsorships for attending international congresses from Gilead, MSD, Pfizer and Schering. E. T. has received sponsorships for attending international congresses from Gilead, MSD, Pfizer and Schering. G. L. D. has received fees for speaking and acting as a Chairman at symposia organized by Gilead, MSD, Pfizer and Schering.

References


Table 1. Evolution of renal function in HSCT recipients treated or not treated with amphotericin B deoxycholate

<table>
<thead>
<tr>
<th>All patients</th>
<th>D-AMB</th>
<th>no D-AMB</th>
<th>P value</th>
<th>Allogeneic HSCT</th>
<th>D-AMB</th>
<th>no D-AMB</th>
<th>P value</th>
<th>Autologous HSCT</th>
<th>D-AMB</th>
<th>no D-AMB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLCR pre-treatment, median (range)</td>
<td>122.44 mL/min (53.4–336.1)</td>
<td>109.10 mL/min (43.8–262)</td>
<td>&lt;0.0001</td>
<td>131.16 mL/min (60.4–251)</td>
<td>120.37 mL/min (74.2–183)</td>
<td>&lt;0.0001</td>
<td>109.30 mL/min (53.4–336.1)</td>
<td>110.54 mL/min (43.8–262)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>CLCR post-treatment, median (range)</td>
<td>74.24 mL/min (28.4–224)</td>
<td>103.21 mL/min (41.4–262)</td>
<td>&lt;0.0001</td>
<td>61.76 mL/min (28.4–149)</td>
<td>93.49 mL/min (47.6–160)</td>
<td>&lt;0.0001</td>
<td>86.06 mL/min (30.9–224)</td>
<td>106.78 mL/min (41.4–262)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Decrease, median (range)</td>
<td>42.75 (0–138)</td>
<td>0 (0–113.6)</td>
<td>&lt;0.0001</td>
<td>46.60 (0–137)</td>
<td>25.53 (0–113.62)</td>
<td>&lt;0.0001</td>
<td>21.82 (0–57.14)</td>
<td>0 (0–113.62)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Creatinine pre-treatment, median (range)</td>
<td>0.7 mg/dL (0.3–1.7)</td>
<td>0.7 mg/dL (0.3–1.5)</td>
<td>&lt;0.0001</td>
<td>0.7 mg/dL (0.3–1.3)</td>
<td>0.7 mg/dL (0.4–1)</td>
<td>&lt;0.0001</td>
<td>0.75 mg/dL (0.3–1.7)</td>
<td>0.7 mg/dL (0.3–1.5)</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
<tr>
<td>Creatinine post-treatment, median (range)</td>
<td>1.1 mg/dL (0.4–3.2)</td>
<td>0.8 mg/dL (0.3–1.6)</td>
<td>&lt;0.0001</td>
<td>1.3 mg/dL (0.6–3.2)</td>
<td>0.95 mg/dL (0.5–2)</td>
<td>&lt;0.0001</td>
<td>1.0 mg/dL (0.4–1.7)</td>
<td>0.8 mg/dL (0.3–1.6)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>Decrease, median (range)</td>
<td>0.4 (0–1.6)</td>
<td>0 (0–1.3)</td>
<td>&lt;0.0001</td>
<td>0.6 (0–1.6)</td>
<td>0.2 (0–1.3)</td>
<td>&lt;0.0001</td>
<td>0.2 (0–0.7)</td>
<td>0 (0–0.7)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D-AMB, amphotericin B deoxycholate; CLCR, creatinine clearance.