Randomized Controlled Trial of Once-Versus Thrice-Daily Tobramycin in Febrile Neutropenic Children Undergoing Stem Cell Transplantation

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**Background:** The benefits of aminoglycoside antibiotics, such as tobramycin, administered as a once-daily dose to manage febrile neutropenia, have been demonstrated in many patient populations. However, toxicity and safety data are lacking for pediatric stem cell transplant recipients, who are at especially high risk for aminoglycoside-related toxicity and infectious morbidity. In particular, the relative nephrotoxicity and efficacy of tobramycin administered as a single daily dose or as three daily doses among this patient population is not known. **Methods:** We conducted a randomized, double-blind controlled study of tobramycin dosing among children 18 years or younger who had fever and neutropenia while undergoing stem cell transplantation. From October 2000 through November 2002, 60 children were randomly assigned to receive intravenous tobramycin, as either a single daily dose (n = 29) or every 8 hours (n = 31), in combination with either piperacillin or ceftazidime (intravenous). Tobramycin doses were adjusted to achieve pharmacokinetic targets. The primary outcome was nephrotoxicity, as represented by the maximal percent increase in serum creatinine concentration throughout the episode of febrile neutropenia relative to the baseline serum creatinine concentration. Efficacy was a secondary outcome and was defined as survival of the episode without modification of the antibacterial regimen. All statistical tests were two-sided. **Results:** In a modified intent-to-treat analysis, the mean maximal percent increase in serum creatinine concentration was 32% (N = 26) in the once daily dose group and 51% (N = 28) in the every 8 hour dose group (difference = 19%, 95% confidence interval [CI] = 0% to 38%; P = .054). Among patients evaluable for efficacy, 12 (46%) of 26 patients in the once daily dose group and five (19%) of 27 patients in the every 8 hour dose group survived the episode of febrile neutropenia without requiring antibacterial treatment modification (difference = 27%, 95% CI = 4% to 52%; P = .03). There was one death in each group. **Conclusions:** In febrile neutropenic children undergoing stem cell transplantation, tobramycin may be less nephrotoxic and more efficacious when administered as a once daily dose than when administered every 8 hours. [J Natl Cancer Inst 2003;95:1869–77]
quently, we sought to individualize once-daily doses of tobramycin using predefined pharmacokinetic targets in children with fever and neutropenia who were undergoing stem cell transplantation. We expected that this patient population would have a higher degree of infectious morbidity related to myeloablative therapy (17) as well as more nephrotoxicity (18,19) and ototoxicity (20,21) than pediatric patients with febrile neutropenia who were receiving standard-dose chemotherapy regimens.

Our primary objective was to examine whether administration of tobramycin as a single daily dose was associated with less nephrotoxicity than tobramycin administered every 8 hours among febrile neutropenic children undergoing stem cell transplantation. Our secondary objectives were to examine whether once-daily dosing of tobramycin was more efficacious and less ototoxic than thrice-daily dosing.

**Patients and Methods**

**Patients**

All children 18 years or younger admitted to The Hospital for Sick Children (Toronto, Canada) for their first stem cell transplantation from October 2000 through November 2002 were evaluated for study eligibility. Children who developed a fever (defined as an oral temperature of 38.0 °C over a 12-hour period on two or more occasions or an oral temperature of 38.5 °C on a single occasion) while experiencing neutropenia (defined as an absolute neutrophil count of <0.5 × 10⁹ cells/mL) were included in our study. Neutropenia was expected to begin around the time of stem cell infusion and resolve approximately 1–4 weeks later. Children who were started on broad-spectrum antibiotic therapy for a clinical infection in the absence of fever and children with fever but without neutropenia but in whom neutropenia was expected were also included in our study.

Patients were excluded if they were allergic to piperacillin, ceftazidime, or tobramycin; if they had received aminoglycosides within 2 weeks of study enrollment; or if they presented with septic shock at the onset of fever. Patients participated in our study only once.

**Study Design**

Written informed consent and assent (when applicable) was obtained from the patient or his or her guardian upon the patient’s admission to the stem cell transplantation ward during the conditioning phase. Immediately prior to randomization (i.e., at the onset of febrile neutropenia), we performed a clinical evaluation and obtained cultures from each patient. The cultures consisted of a peripheral blood culture, blood cultures from each lumen of the central venous line, and a urine culture. Patients were then randomly assigned to receive tobramycin (Eli Lilly Canada, Toronto, Canada) intravenously as a single daily dose or every 8 hours. (Specific dosing information is given below.) Randomization was performed by computer allocation, and the randomization sequence was maintained in the pharmacy at The Hospital for Sick Children. The sequence remained concealed from all members of the research team and from those participating in clinical care until conclusion of the study. Randomization was performed in blocks of four or six assignments and stratified by stem cell donor type (allogeneic versus autologous) and patient age (<5 years, 5 to <12 years, and ≥12 years).

The study patients and the entire clinical treatment team were blinded to the randomized assignments; only investigators not involved with patient care (L. L. Dupuis and T. Taylor) were unblinded so that they could make adjustments to individual tobramycin doses in response to serum concentrations of tobramycin. To maintain blinding, each tobramycin dose was prepared by the pharmacy staff in a 50-mL syringe, and all patients received a 50-mL injection three times a day (i.e., every 8 hours). Patients assigned to receive tobramycin every 8 hours received tobramycin in each of the three daily syrings, whereas patients assigned to receive a single daily dose of tobramycin received tobramycin in the first syringe and normal saline in the next two syringes. Doses could also be administered in a volume of 25 mL to patients who were fluid restricted. Serum tobramycin levels were available only to the two investigators responsible for adjusting tobramycin dose (L. L. Dupuis and T. Taylor).

According to our institutional protocol, tobramycin for febrile neutropenia was always used in conjunction with a second antibiotic with activity against gram-negative bacteria. However, the specific second antibiotic changed during the course of the study. At the onset of the study, piperacillin (at 50 mg/kg/dose, maximum 2000 mg, injected intravenously every 6 hours) was used. However, in March 2002, piperacillin became unavailable from the supplier (Wyeth-Ayerst Canada, St-Laurent, Quebec) and consequently, ceftazidime (50 mg/kg/dose, maximum 2000 mg, injected intravenously every 8 hours; Eli Lilly Canada, Toronto, Ontario) was substituted.

Each study patient was assessed daily by a clinical evaluation and a complete blood count and chemistry, which included determination of serum creatinine levels, until antibiotic treatment was discontinued. Blood for cultures was drawn on a daily basis from patients with persistent fever. The clinical treatment team made decisions regarding the management of these patients including whether patients required ancillary investigations, modification of antibiotics they were taking, or treatment with antiviral or antifungal medications. A patient could be withdrawn from the study at the discretion of the treatment team if the patient displayed hemodynamic instability; in this event, the patient was placed on open-label tobramycin every 8 hours. Tobramycin was discontinued at the discretion of the treatment team.

Episodes of febrile neutropenia were categorized as microbiologically documented, clinically documented, or as fever of unknown origin, as previously described (22). Filgrastim was given universally except to those patients undergoing autologous stem cell transplantation for acute myeloid leukemia and to those with myelodysplastic syndrome. Three patients in the once daily dose group and two patients in the every 8 hours dose group did not receive filgrastim.

Patients undergoing stem cell transplantation for immune deficiency were treated with prednisone and cyclosporine to prevent graft-versus-host disease; all other patients undergoing allogeneic stem cell transplantation received methotrexate and cyclosporine. This study was approved by the Research Ethics Board of The Hospital for Sick Children.

**Tobramycin Dosing and Pharmacokinetic Considerations**

Patients randomly assigned to the once daily dose group received an age-dependent initial dose of tobramycin that was...
previously determined using the WinNonlin computer simulation program (version 3.1; Pharsight, Mountain View, CA) as previously described (23); the simulation used a pre-existing pharmacokinetic database containing data from more than 100 children with febrile neutropenia treated at The Hospital for Sick Children. Doses of tobramycin were designed to achieve a serum tobramycin concentration at the end of the infusion (C_{\text{max}}) of 20–22.5 mg/L and a drug-free interval (defined in this study as the time interval during which the tobramycin serum concentration was <1 mg/L) of at least 4 hours during the 24-hour dosing interval. Patients younger than 5 years received 9 mg/kg/dose, those aged at least 5 years but younger than 12 years received 8 mg/kg/dose, and those aged 12 years or older received 7 mg/kg/dose. Patients randomly assigned to the every 8 hours dose group received tobramycin at 2.5 mg/kg/dose (maximum of 120 mg tobramycin per dose prior to serum concentration determination). All tobramycin doses were infused over a 30-minute period that included the time required to flush the intravenous line.

Serum concentrations of tobramycin were analyzed by the Department of Pediatric Laboratory Medicine at The Hospital for Sick Children at 2 hours and 8 hours after the beginning of the first infusion with the use of an Immuno 1 microparticle immunnoassay (Bayer, Tarrytown, NY). On the basis of those results, the initial tobramycin dose was adjusted, if necessary, within 24 hours of the initiation of therapy to achieve the target parameters as outlined above for once-daily dosing. For those patients receiving tobramycin every 8 hours, the tobramycin dose was adjusted to achieve a steady-state C_{\text{max}} of 7–9 mg/L and a steady-state serum tobramycin concentration at the end of the dosing interval (C_{\text{min}}) of less than 2 mg/L.

After the pharmacokinetic targets were achieved, we monitored the serum tobramycin concentrations at 2 hours and at 6 or 8 hours after a dose at least once weekly and adjusted the tobramycin doses as necessary to ensure continued achievement of the pharmacokinetic targets. We determined serum tobramycin concentrations more frequently for patients with increasing serum creatinine levels or if coadministration of nephrotoxic agents (such as vancomycin or amphotericin B) was initiated.

Pharmacokinetic parameters were calculated using standard first-order, one-compartment equations. Steady-state equations were used to calculate pharmacokinetic parameters in the every 8 hours dose group only when a patient had received at least three equivalent tobramycin doses prior to the determination of serum tobramycin concentration. The area under the curve (AUC) for serum tobramycin concentration versus time was calculated to infinity via the trapezoidal rule using the extrapolated serum tobramycin concentration at the end of the infusion and the serum tobramycin concentration at 2 hours and 6 (or 8) hours after the start of the infusion (24).

Outcome Measures

All outcome measures, with the exception of the audiologic evaluations, were collected and scored by a single investigator (L. Sung) who was blinded to treatment allocation. Audiologic outcomes were evaluated by a second investigator (B. Bliss) who was also blinded to treatment allocation.

The primary outcome measure was nephrotoxicity, which was defined as the maximal percent increase in serum creatinine concentration from the baseline serum creatinine concentration that was measured just prior to the initiation of tobramycin treatment. We chose to use the relative increase in serum creatinine level rather than an absolute increase in serum creatinine level as the primary outcome, because the former accounts for the large differences in baseline creatinine level between smaller and larger children.

The secondary outcome measures were efficacy and ototoxicity. Treatment was considered to be successful if the patient survived the episode of febrile neutropenia without requiring any modification of the assigned antibacterial regimen (25). Treatment was classified as a failure if the patient died of infection, the bacteremia persisted, breakthrough bacteremia occurred, or any modification of the initial antibacterial regimen was made (25). The addition of antiviral or antifungal medications was not considered a failure but was recorded. Recurrences of fever during the episode (defined as an oral temperature of ≥38 °C occurring after 48 consecutive hours without a fever) or after discontinuation of tobramycin (within 48 hours and up to 7 days after tobramycin discontinuation) were also not classified as failures but were documented.

Audiologic evaluations were performed prior to stem cell transplantation (baseline) and at 2–4 weeks after the completion of tobramycin treatment (follow-up). Audiometry was performed at 2, 4, and 8 kHz in both ears, and otoacoustic emission (OAE), a sensitive measure of cochlear function, was evaluated if the child was cooperative. A single audiologist (B. Bliss) examined all audiograms and coded each evaluation as normal or abnormal, with abnormal hearing considered a threshold at any frequency of greater than or equal to 20 dB (26). The same audiologist then compared each pair of evaluations for a given child and classified the follow-up audiogram as worse if a decline of at least 15 dB occurred at any frequency compared with the baseline audiogram and not worse if a decline of less than 15 dB occurred (27). Paired OAEs were also scored as worse or not worse according to guidelines suggested by others (28). If only the follow-up audiogram or OAE was available, the evaluation was included only if it was classified as normal; in that case, the evaluation was considered to be not worse than baseline.

Statistical Methods

For the primary outcome measure, we assumed that if the mean maximal increase in serum creatinine concentration from baseline was 50% among those receiving tobramycin every 8 hours, we would need a sample size of 48 patients to show a 50% decrease in maximal change in serum creatinine concentration among those receiving a single daily dose of tobramycin given a standard deviation of 30%, an α of .05, and a β of .20. It was decided a priori that 60 patients would be enrolled to allow for 20% of cases to be nonevaluable.

The prespecified study population evaluated for the primary and secondary outcome measures included the patients from the modified intent-to-treat analyses. The study population evaluated for toxicity outcomes (nephrotoxicity and ototoxicity) included patients who had received tobramycin for at least 48 hours. Patients excluded from the modified intent-to-treat analysis of clinical efficacy were those who had experienced episodes of febrile neutropenia in which a nonbacterial cause of the initial fever was documented, had tobramycin discontinued for a reason unrelated to efficacy (e.g., nephrotoxicity), or were in-
fected with a tobramycin-resistant microorganism. We also performed a separate analysis that included patients who failed treatment because of hemodynamic instability.

Differences between the once daily and the every 8 hours dose groups with respect to continuous variables were analyzed using Student’s t test for independent groups or Wilcoxon’s rank sum test, depending on the distribution of the variable. For example, the difference in the primary outcome measure between patients receiving once-daily dosing and those receiving doses every 8 hours (i.e., the maximal percent increase in serum creatinine concentration during the episode) was analyzed using Student’s t test for independent groups. Categorical variables were compared using the chi-square test or Fisher’s exact test as appropriate. Multiple regression analyses were performed when potential confounders were identified. Statistical analyses were performed using SAS-PC software (version 8.0; SAS Institute, Cary, NC) or the Statistical Package for Social Sciences for Windows (version 10.1; SPSS, Chicago, IL). All tests of statistical significance were two-sided, and statistical significance was defined as P<.05.

RESULTS

From October 2000 through November 2002, we assessed 119 children for study eligibility and excluded 59 children (Fig. 1). The remaining 60 children were enrolled in our study; 29 children were randomly assigned to receive tobramycin as a single daily dose and 31 children were randomly assigned to receive tobramycin every 8 hours. The baseline characteristics of patients in the two treatment groups are shown in Table 1.

Description of Episodes of Febrile Neutropenia

Of the 60 episodes of febrile neutropenia that occurred during our study, 17 (28%) were microbiologically documented, 18 (30%) were clinically documented, and 25 (42%) were fevers of unknown origin (Table 2). The 16 positive blood cultures were positive upon initiation of antibiotic therapy, and all bacteremias resolved by the end of treatment. No cases of breakthrough bacteremia with either the same or a different organism occurred during the study. On average, tobramycin was initiated 4 days after stem cell infusion (range = 2 days before to 11 days after stem cell infusion). Although the two study groups had similar numbers of episodes with a positive blood culture overall, the every 8 hours dose group had more episodes characterized by infection with a gram-positive organism, whereas the once daily dose group had more episodes characterized by infection with a gram-negative organism; however, these differences were not statistically significant.

Table 3 shows the serum tobramycin concentrations after the first tobramycin dose was administered and the resulting pharmacokinetic parameters for 22 (76%) of the 29 children

![Fig. 1. Flow diagram of patients in the study. *In the modified intent-to-treat analysis for toxicity, 26 were included in the once daily dose group and 28 were included in the every 8 hours dose group. In the modified intent-to-treat analysis for efficacy, 26 were included in the once daily dose group and 27 were included in the every 8 hours dose group.](image-url)
Nephrotoxicity

Table 4 presents our results for the primary outcome measure, the maximal percent increase in serum creatinine concentration from the concentration at baseline. Patients in the once daily dose group had a smaller percent increase in peak serum creatinine concentration than patients in the every 8 hours dose group (32% versus 51%; difference = 19%, 95% CI = 0% to 38%; P = .054). There was no statistically significant difference between the once daily dose group and the every 8 hours dose group in the mean number of days from initiation of tobramycin administration to the peak in serum creatinine levels (10 days versus 9 days, respectively; difference = 1 day, 95% CI = −2 days to 5.6 days; P = .5). Fig. 2 illustrates the mean daily serum creatinine levels for each dose group.

Three children in each dose group could not be evaluated for toxicity because they received the study drug for less than 48 hours. The reasons for the early discontinuation of study tobramycin were identical for the two dose groups; one child in each group had tobramycin discontinued because of infection with a tobramycin-resistant organism, and two children in each group had tobramycin discontinued because of hemodynamic instability.

The mean serum creatinine concentration at baseline was similar in the two study groups (31.0 μmol/L in the once daily dose group and 32.3 μmol/L in the every 8 hours dose group; P = .5) (Table 1). Among patients evaluable for nephrotoxicity, vancomycin was used to treat episodes of febrile neutropenia statistically significantly more frequently in the every 8 hours dose group (17 [61%] of 28 episodes) than in the once daily dose group (seven [27%] of 26 episodes; P = .01). Among patients evaluable for nephrotoxicity, there was no difference between the dose groups in the use of amphotericin B to treat episodes (13 [50%] of 26 episodes in the once daily dose group versus 16 [57%] of 28 episodes in the every 8 hours dose group; P = .6). In multiple regression analyses, patients in the once daily dose group did not have a statistically significant decrease in the maximal percent increase in serum creatinine concentration compared with patients in the every 8 hours dose group, after adjustment for vancomycin use (P = .1) or body surface area (P = .08) (data not shown).

Only one child required hemodialysis for renal failure; that child had been assigned to the every 8 hours dose group. Two children in the every 8 hours dose group required an increase in the dosing interval to every 12 hours because of reduced tobramycin clearance. No children in the once daily dose group required an increase in the dose interval.

### Table 2. Characteristics of episodes of febrile neutropenia by treatment arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Once daily dose group (N = 29)</th>
<th>Every 8 hours dose group (N = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode classification, No. (%)</td>
<td>1.0†</td>
<td>1.0†</td>
<td></td>
</tr>
<tr>
<td>Microbiologically documented</td>
<td>8 (28)</td>
<td>9 (29)</td>
<td></td>
</tr>
<tr>
<td>Clinically documented</td>
<td>9 (31)</td>
<td>9 (29)</td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>12 (41)</td>
<td>13 (42)</td>
<td></td>
</tr>
<tr>
<td>Episodes with positive blood culture, No. (%)</td>
<td>7 (24)</td>
<td>9 (29)</td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>4/7 (57)</td>
<td>8/9 (89)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative</td>
<td>5/7 (71)</td>
<td>2/9 (22)</td>
<td></td>
</tr>
<tr>
<td>Mean No. of days on tobramycin (95% CI)</td>
<td>12 (9 to 15)</td>
<td>12 (10 to 15)</td>
<td></td>
</tr>
<tr>
<td>Mean drug-free interval (95% CI)</td>
<td>13.0 to 15.1 hours; 95% CI</td>
<td>13.0 to 15.1 hours; 95% CI</td>
<td></td>
</tr>
<tr>
<td>Drug-free interval, h</td>
<td>1.8 (1.4 to 2.2)</td>
<td>2.1 (1.8 to 2.3)</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>0.4 (0.3 to 0.5)</td>
<td>0.5 (0.4 to 0.6)</td>
<td></td>
</tr>
<tr>
<td>AUC/dose, mg·h/L</td>
<td>17.8 (14.8 to 20.8)</td>
<td>18.5 (15.7 to 21.3)</td>
<td></td>
</tr>
<tr>
<td>AUC/dose, mg·h/L</td>
<td>2.6 (2.1 to 3.1)</td>
<td>2.6 (2.1 to 3.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical documentation, No. (%) 1.0†
†Polymicrobial bacteremia occurred in seven children (four in the once daily dose group and three in the every 8 hours dose group); three children had mixed gram-positive and gram-negative infections (two in the once daily dose group and one in the every 8 hours dose group).
‡Gram-negative isolates in one episode were Klebsiella pneumoniae in one episode, Pseudomonas aeruginosa in one episode, Escherichia coli in two episodes, and one episode with both Enterobacter cloacae and K. pneumoniae isolated. Gram-negative isolates identified in the every 8 hours dose group were E. coli in one episode and Moraxella in another episode.

### Table 3. Pharmacokinetic parameters following the first tobramycin dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Once daily dose group (N = 22)</th>
<th>Every 8 hours dose group (N = 23)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half-life, h</td>
<td>1.8 (1.4 to 2.2)</td>
<td>2.1 (1.8 to 2.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Vd, L/kg</td>
<td>0.4 (0.3 to 0.5)</td>
<td>0.5 (0.4 to 0.6)</td>
<td>.5</td>
</tr>
<tr>
<td>Cmax, mg/L</td>
<td>17.8 (14.8 to 20.8)</td>
<td>18.5 (15.7 to 21.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AUC/dose, mg·h/L</td>
<td>55.8 (47.8 to 63.8)</td>
<td>28.3 (25.0 to 31.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Drug-free interval, h</td>
<td>16.6 (15.7 to 17.5)</td>
<td>2.6 (2.1 to 3.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Parameters are presented as mean values (95% confidence intervals). Vd = steady-state volume of distribution; Cmax = concentration at the end of the infusion; AUC = area under the concentration-versus-time curve.
†Two-sided; Student’s t test for independent groups.
Clinical Efficacy

Patients in the once daily dose group had a higher percentage of successful episodes of febrile neutropenia than patients in the every 8 hours dose group (46% versus 19%, difference = 27%, 95% CI = 4% to 52%; P = .03) (Table 4). Among patients evaluable for efficacy, fewer patients in the once daily dose group had vancomycin added to their regimen than patients in the every 8 hours dose group (31% versus 67%; P = .009) (Table 4). Seven episodes were considered unevaluable for the efficacy analysis (three in the once daily dose group and four in the every 8 hours dose group). In the once daily dose group, one episode was not evaluable because of nephrotoxicity, one because of bacteremia involving a tobramycin-resistant organism, and one because the initial fever was caused by a rotavirus infection. In the every 8 hours dose group, three episodes were not evaluable because of nephrotoxicity and one was not evaluable because of bacteremia involving a tobramycin-resistant organism. The median duration of fever for patients in the once daily dose group (3 days, interquartile range = 2–10 days) was similar to that for patients in the every 8 hours dose group (5 days, interquartile range = 2–9 days; P = .3). There were no differences between the two treatment groups in the number of episodes in which the fever recurred after discontinuation of antibiotics (data not shown). There were no statistically significant differences in the drug-free interval or the Cmax between successful episodes and episodes that failed in the once daily dose group (data not shown).

Six patients in the once daily dose group and three patients in the every 8 hours dose group developed cardiovascular instability (i.e., hypotension) while receiving tobramycin. The median time that hypotension developed was on treatment day 5 (range = day 1 to day 11) for patients in the once daily dose group and on treatment day 3 (range = day 2 to day 7) for patients in the every 8 hours dose group (P = .7). Among the six hypotensive patients in the once daily dose group, three patients had positive blood cultures (one child had viridans streptococcus, one child had viridans streptococcus and Klebsiella pneumoniae, and one child had Streptococcus pneumoniae and Escherichia coli). Only one of the three hypotensive patients in the every 8 hours dose group had a positive blood culture; the organism was viridans streptococcus. One patient in each dose group died during an episode of febrile neutropenia. The death in the once daily dose group was attributed to overwhelming sepsis with viridans streptococcus; the death in the every 8 hours dose group was attributed to culture-negative septic shock, with pneumatosis intestinalis found on autopsy.

The three patients who received tobramycin every 8 hours and who became hypotensive had a statistically significantly longer mean drug-free interval after the first tobramycin dose than the 20 patients in this group who were hemodynamically stable throughout treatment (4.3 versus 2.4 hours; difference = 1.9 hours, 95% CI = 0.5 to 3.3 hours; P = .01). Although two of the hypotensive patients never achieved a Cmax within or greater than the target range, the average Cmax for hemodynamically stable patients (6.0 mg/L) was not statistically significantly different from that for hypotensive patients (4.6 mg/L; difference = 1.4 mg/L; 95% CI = -0.9 to 3.7 mg/L; P = .2). There were no statistically significant differences in the drug-

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**Table 4. Outcome measures by treatment arm**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Once daily dose group (N = 26)</th>
<th>Every 8 hours dose group (N = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean maximal percent increase in serum creatinine concentration compared to baseline level (95% CI)</td>
<td>32 (22 to 42)</td>
<td>51 (34 to 67)</td>
<td>.054†</td>
</tr>
<tr>
<td>Mean No. of days from initiation of tobramycin to peak serum creatinine concentration (95% CI)</td>
<td>10 (7 to 13)</td>
<td>9 (6 to 11)</td>
<td>.5†</td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 26)</td>
<td>(N = 27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful episodes, No. (%) (95% CI)</td>
<td>12 (46) (27 to 65)</td>
<td>5 (19) (4 to 33)</td>
<td>.03‡</td>
</tr>
<tr>
<td>Addition of other antibiotics, No. (%) (95% CI)</td>
<td>8 (31) (13 to 49)</td>
<td>18 (67) (49 to 84)</td>
<td>.009‡</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10 (38) (20 to 57)</td>
<td>5 (19) (4 to 33)</td>
<td>.1‡</td>
</tr>
<tr>
<td>Meropenem</td>
<td>12 (46) (27 to 65)</td>
<td>14 (52) (33 to 71)</td>
<td>.7‡</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Otoacoustic emission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiogram worse than baseline, No. (%) (95% CI)</td>
<td>4/17 (24) (3 to 44)</td>
<td>7/22 (32) (12 to 51)</td>
<td>.7‡</td>
</tr>
<tr>
<td>OAE worse than baseline, No. (%) (95% CI)</td>
<td>3/9 (33) (3 to 64)</td>
<td>7/10 (70) (42 to 98)</td>
<td>.2‡</td>
</tr>
</tbody>
</table>

*Based on evaluable episodes included in the modified intent-to-treat analysis. Otoacoustic outcomes were also based on patients for whom follow-up data were available. CI = confidence interval; OAE = otoacoustic emission.
†Two-sided; Student’s t test for independent groups.
‡Two-sided; chi-square or Fisher’s exact test.

**Fig. 2.** Scatter plot of mean daily serum creatinine concentrations with respect to the day of tobramycin administration by treatment group. ODD = once daily dose; QSH = every 8 hours dose. Error bars represent 95% confidence intervals.
free interval or the $C_{\text{max}}$ between hypotensive and hemodynamically stable patients in the once daily dose group (data not shown).

**Ototoxicity**

Patients in the two treatment groups had similar proportions of normal audiograms and OAEs at baseline: 12 (67%) of 18 patients in the once daily dose group and 14 (58%) of 24 patients in the every 8 hours dose group had normal audiograms ($P = .6$), and 10 (83%) of 12 patients in the once daily dose group and 10 (83%) of 12 patients in the every 8 hours dose group had normal OAEs ($P = 1.0$). There was no statistically significant difference between the treatment groups in the proportion of children with an audiologic evaluation at follow-up that was worse than their evaluation at baseline (Table 4).

**DISCUSSION**

Our results suggest that, in children with febrile neutropenia who are undergoing stem cell transplantation, administration of tobramycin as a single daily dose is associated with less nephrotoxicity and greater efficacy than tobramycin administered every 8 hours. To our knowledge, this study is the first to rigorously evaluate the effects of a single daily dose of tobramycin in a high-risk pediatric population in which individualized dosing based on pharmacokinetic parameters was used.

Compared with tobramycin administered every 8 hours, tobramycin administered as a single daily dose was associated with a 37% reduction in the relative increase in serum creatinine levels. However, this reduction in the maximal increase in serum creatinine concentration relative to baseline may, in part, also be related to lower vancomycin use in the once daily dose group. The once daily dose group also had a higher rate of successful episodes of febrile neutropenia than the every 8 hours dose group (46% versus 19%). Our definition of success (i.e., the patient surviving the episode of febrile neutropenia without requiring modification of the assigned antibiotic regimen) was similar to that proposed by the International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer (25). Our success rates, albeit low, are similar to those observed in other studies (29–32) that included patients undergoing stem cell transplantation. For example, one study (29) reported a 27% success rate among 234 patients receiving ciprofloxacin and piperacillin and a 22% success rate among 237 patients receiving tobramycin and piperacillin. It is possible that one factor contributing to our low success rate is that we did not mandate that changes to the initial antibiotic regimen be performed according to a set protocol for patients with persistent fever. We believe that the lack of a protocol for changes to the antimicrobial regimen should not have biased the results because of the blinded nature of the study, and may have improved their generalizability.

We observed a mean drug-free interval of 16.6 hours among patients who received tobramycin as a single daily dose. This finding was not unexpected given the pharmacokinetics of tobramycin previously observed in adult (33–35) and pediatric (36–38) oncology patients. We cannot compare the drug-free intervals we observed with those seen in other studies because most other studies of once-daily aminoglycosides did not report the drug-free interval. However, the drug-free intervals we observed are likely to be shorter than the drug-free intervals in other studies of once-daily tobramycin because those studies used lower doses of tobramycin (i.e., 4–7 mg/kg/day) and, unlike in our study, the doses were not adjusted to achieve pharmacokinetic targets (13,39,40). In our study, the length of the drug-free interval was not associated with clinical outcomes among patients who received a single daily dose of tobramycin. However, this lack of an association must be interpreted cautiously, given the small number of patients used in this analysis.

Most of the aminoglycoside-dosing nomograms that have been validated for use in adults do not consider dosing intervals of less than 24 hours (41,42). However, the nomogram created by Urban and Craig (1) suggests that adult patients who have a drug-free interval longer than 16 hours after receiving a single daily dose of tobramycin (aminoglycosides) should receive subsequent doses every 12 hours. Although dosing every 12 hours may achieve theoretical pharmacokinetic targets, the higher success rate we observed for patients in the once daily dose arm of our study suggests that drug administration every 12 hours is not necessary in most patients with febrile neutropenia.

Our results also suggest that once-daily administration of tobramycin, compared with thrice-daily administration, is not associated with adverse effects on hearing. Conversely, a review of eight studies in which audiologic evaluations were performed for children receiving aminoglycosides noted that ototoxicity was observed in seven (4.1%) of 171 children receiving a single daily dose and in two (2.4%) of 83 children treated with traditional (i.e., multiple daily) dosing regimens (43). However, because several of those studies were single-arm trials, it is difficult to directly compare the results of children treated with the different dosing regimens. Therefore, our results are important because they provide an evaluation of ototoxicity among comparable groups of children who received tobramycin either as a single daily dose or every 8 hours, in which the assessor was blinded to the treatment allocation.

Results of at least two studies (15,44) have suggested that monotherapy with agents such as ceftazidime is sufficient for the treatment of febrile neutropenia and thus raise the question of whether aminoglycosides are important at all in this setting. However, two-drug combination therapy remains an acceptable option for patients with febrile neutropenia, and the most commonly used two-drug combinations contain an aminoglycoside (16). There are theoretical advantages to using two-drug combination therapy, such as potential synergism against some gram-negative bacilli (45) and decreased emergence of breakthrough bacteremia due to growth of antibiotic-resistant isolates (46). Our results are important for those clinical centers that continue to use aminoglycosides in the treatment of febrile neutropenia.

Our results must be interpreted in light of several study limitations. First, because efficacy was a secondary outcome measure in our study, results concerning efficacy must be considered to be hypothesis-generating when they are examined in isolation. Second, our analysis of the ototoxicity data was underpowered to detect differences between dose groups. A meta-analysis of all randomized trials at the individual patient level may be better able to determine the relationship between once-
daily dosing with aminoglycosides and ototoxicity. Third, our findings are generalizable only to a setting of once-daily dosing in which doses of tobramycin are adjusted to achieve pharmacokinetic targets. In addition, our monitoring and dosing guidelines are only applicable to children with febrile neutropenia; tobramycin single-daily-dose requirements and optimal monitoring schedules are likely to be different in other groups of patients.

In summary, our results suggest that tobramycin administered as a single daily dose is associated with less nephrotoxicity and improved efficacy compared with tobramycin administered every 8 hours. We propose that once-daily dosing with tobramycin should be adopted for children with febrile neutropenia, including children who are undergoing stem cell transplantation.

REFERENCES


NOTES

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