Amikacin and Cephalothin: Empiric Regimen for Granulocytopenic Cancer Patients

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Amikacin (15 mg/kg per day) was used in combination with cephalothin (7 g/m² per day) as an empiric regimen for de novo febrile (°101°F [38.3°C]) episodes in 93 granulocytopenic (<1,000/mm³) cancer patients. Both drugs were given intravenously in four equal doses every 6 h. The response rate for all documented infections was 83%, including 11 of 17 (65%) bacteremias. Escherichia coli (14 cases) was the most common pathogen, whereas Pseudomonas aeruginosa (2 cases) caused fewer infections. Mean amikacin serum levels were 8.7 µg/ml at 1 h and 2.2 µg/ml at 5 h. Failure of bone marrow recovery in association with a bacteremia was a bad prognostic sign (only two of eight improving). Ototoxicity occurred in two (2%) patients, whereas presumed antibiotic-induced nephrotoxicity developed in six (7%) patients. Surveillance cultures (nose, gums, axilla, and rectum) of all hospitalized patients revealed no significant change in the incidence of amikacin resistance. The combination of amikacin and cephalothin in this dose and schedule was safe and efficacious in these granulocytopenic patients.

Empiric treatment with broad-spectrum antibiotics is accepted therapy for de novo febrile episodes in granulocytopenic (granulocyte count, <1,000/mm³) cancer patients (5, 6, 17, 29) because 60 to 70% of these episodes are caused by documented infections. Prior to the appreciation that therapy in these patients had to be prompt, empiric, and with broad-spectrum antibiotics, gram-negative bacteremias were associated with a >90% mortality rate (5, 17), and, overall, the mortality from infection was >50% (5, 6, 17, 29). With current empiric treatment, 40 to 70% of these bacteremias and 70 to 80% of all documented infections respond to empiric broad-spectrum therapy (5, 6). Such empiric therapy usually consists of an aminoglycoside in combination with cephalothin and/or carbenicillin. Amikacin is a new aminoglycoside which has a spectrum similar to gentamicin but a lower incidence of resistance among gram-negative bacilli. We felt that its use in granulocytopenic patients would frequently be necessary in instances wherein gentamicin resistance was encountered. We wished, therefore, to evaluate the combination of amikacin and cephalothin concerning efficacy and potential renal toxicity with a modified dose schedule designed to hopefully decrease nephrotoxicity.

MATERIALS AND METHODS

Requirements for protocol. Patients were eligible for the protocol if they had an absolute granulocyte count of <1,000/mm³ and a temperature of >101°F (38.3°C) in the absence of an obvious noninfectious cause of fever (e.g., the administration of blood products just before the fever). Patients with allergic histories to cephalothin or aminoglycosides were excluded.

Pretherapy evaluation. The following evaluation was made before antibiotic therapy: (i) complete history and physical examination with specific reference to subtle findings of inflammation (29); (ii) at least two separate blood cultures; (iii) cultures of any clinically suspicious lesions; (iv) urine culture and urinalysis; (v) chest X ray; (vi) surveillance cultures of nose, gums, axilla, and rectum; (vii) serum electrolytes, blood urea nitrogen, serum creatinine, glucose, and liver function tests; and (viii) a complete blood count including differential. If a pneumonia were present, a transtracheal aspirate was performed if bleeding parameters permitted. If this aspirate was negative, a transtracheal selective bronchial brush biopsy was often then performed (1).

Antibiotic administration and dosage. The amikacin (kindly supplied by Richard Trompeter, Bristol Laboratories, Syracuse, N.Y.) dose was 15 mg/kg per day, with the average dose being 1 g/day, and the cephalothin dose was 7 g/m² per day, with
the average dose being 12 g/day. This daily dose was divided into four equal infusions dissolved in 50 ml of 5% dextrose and water and infused separately, intravenously each, over approximately 15 min every 6 h. If renal dysfunction was present or developed during therapy, the amikacin dose was adjusted by dividing the normal every-6-h dose by the serum creatinine and giving this calculated dose every 6 h.

Follow-up studies. A chest X ray usually was repeated daily for 3 days if no initial site of infection was found. Chemistries and hematology laboratory tests were repeated three times a week, and surveillance cultures of nose, gums, gingiva, and rectum were repeated one or two times a week. Biopsies or aspirates of any new lesions were performed when applicable.

Classification of infection. Based on clinical course and microbiological data, the febrile episodes were classified (29) as one of the following: microbiologically documented with and without bacteremia (site and pathogen defined); clinically documented (site defined but no pathogen); possible (equivocal); and infection doubted (fever and signs probably caused by a noninfectious cause).

Length of therapy. The patient remained on protocol for at least 4 days unless a therapeutic change was indicated by worsening clinical status or by bacteriological results, which indicated a resistant pathogen. If after 4 days it was determined that the patient was not infected, antibiotics were discontinued. If a clinical response occurred, the protocol antibiotics were continued until at least 5 days after all signs and symptoms of infection had disappeared.

Response categorization. Antibiotic response categories were similar to the ones previously used by the Baltimore Cancer Research Center (BCRC; 29): improvement (a return of temperature to normal or to a preinfectious state with complete disappearance of all signs and symptoms of infection); temporary improvement (a return to normal of all signs and symptoms of infection but followed by a relapse during or up to 1 week after antibiotic discontinuation); failure (poor response to antibiotics or an organism resistant to both antibiotics); and nonassessable (infection doubted, nonbacterial infection, or a protocol violation).

In the past, leukocyte (WBC) transfusions were given only after there had been clear progression of infection. Under these circumstances, all drug trials in which WBC transfusions were given were classified as antibiotic failures. At present, because WBC transfusions have been proven to be efficacious (27) in the treatment of certain severe infections such as gram-negative bacteremias in granulocytopenic patients, WBC transfusions are given at the BCRC in many instances prior to there being clear progression of infection. Thus, the category of improvement has been divided into improvement without WBC transfusions and improvement with WBC transfusions.

Antibiotic susceptibility testing and serum levels. Antibiotic susceptibility testing of all isolated pathogens was performed by the Bauer-Kirby method (2), recommended by the Food and Drug Administration (9). Amikacin-resistant, gram-negative bacilli were further evaluated by the microtiter technique to determine their minimal inhibitory concentration (MIC) (19). Serum levels of amikacin were determined in selected patients at 1 and 5 h after completion of antibiotic infusion by the modified agar-well diffusion method described by Bennett et al. (3), using Bacillus subtilis as the assay organism and beta-lactamase as the assay organism and beta-lactamase as the assay organism.

RESULTS

Patient population. There were 93 patient drug trials (50 patients treated once, 9 patients treated two times, 4 patients treated three times, 2 patients treated four times, and 1 patient treated five times). Forty-four were male and 39 were female. The mean age was 43 years. Patients' diagnoses were: acute leukemia, 66; solid tumors, 18; and lymphoma, 9. The average number of days that patients were granulocytopenic before therapy was 18 days, and the median initial granulocyte count was <100/mm³. Thirty-seven patients were responding to antitumor therapy, whereas 56 were not ("late-stage"). Eleven of the 93 drug trials could not be evaluated for antibacterial antibiotic efficacy; four of these had documented viral infections and one had a documented fungal infection, and during six drug trials protocol violations occurred.

Susceptibility and serum levels. By disk susceptibility, 87% of the pathogens were susceptible to amikacin, whereas 85% were susceptible to cephalothin. Seventy-six percent were susceptible to both antibiotics, and only 4% (one Pseudomonas aeruginosa and one Escherichia coli) were resistant to both antibiotics. At 1 h, the mean amikacin serum level was 8.7 μg/ml (range, 6.1 to 10.8 μg/ml), and at 5 h it was 2.2 μg/ml (range, 1.2 to 5.3 μg/ml).

Classification of infection and response. Of the 82 assessable febrile episodes, there were 30 microbiologically documented infections of which 17 were bacteremias, 17 were clinically documented, 2 were possible infections, and 33 were doubtful infections (Table 1). Of the 17 bacteremias, 5 improved with antibiotics alone and 6 improved with antibiotics plus WBC transfusions. Six bacteremias resulted in drug trial failure. Four of these were due to progressive infection, which ultimately led to the patient's demise (one received WBC transfusions), and two failures were due to gram-negative organisms resistant to both amikacin and cephalothin. One of these latter two im-
proved with polymyxin B and WBC transfusions, whereas the other patient died before receiving a WBC transfusion.

Of the 13 nonbacteremic, microbiologically documented infections, 11 improved with antibiotics alone, 1 improved with antibiotics plus WBC transfusions, and 1 had temporary improvement but ultimately relapsed and died from this infection. Sixteen of the 17 clinically documented infections improved with antibiotics alone, and one (granulocytopenic) improved with antibiotics alone, and WBC transfusions.

Organism and response. All five of the single pathogen gram-positive infections (Table 2) improved with antibiotics alone (despite persistent granulocytopenia in three cases). However, only 8 of 14 single pathogen gram-negative infections improved. Four (three persistently granulocytopenic) of these 14 improved with antibiotics alone, whereas four (two persistently granulocytopenic) improved with antibiotics plus WBC transfusions. Five of the six that failed had persistent granulocytopenia and bacteremia; two of these received WBC transfusions. The 11 multiple pathogen infections responded well, with 7 improving with antibiotics alone, 3 with antibiotics plus WBC transfusions, and 1 temporarily improving. Seven of these patients were persistently granulocytopenic.

E. coli (Table 2) was the most common pathogen and the most common cause of bacteremia. Five of eight bacteremias and, overall, 10 of the 14 infections caused by E. coli, improved. All seven Staphylococcus aureus infections improved. Proteus spp. and Streptococcus faecalis each were pathogens in five infections. Only one of these infections failed to improve. All three of the Klebsiella infections improved, but both of the Pseudomonas infections failed to respond (one was resistant to amikacin). The five infections caused by miscellaneous organisms all responded.

Infectious site and response. Mouth-sinus, skin, and perirectal lesions (Table 3) were the most common sites of infection, accounting for nine, eight, and seven infections, respectively; all of these improved. Four of the six pulmonary infections and four of the six genitourinary infections improved. All three pharyngeal infections improved. Bacteremias of unknown etiology were the worst prognostic group, with only four of eight responding to therapy.

Prognostic factors relating to bacteremia response. In eight of the 17 evaluable bacteremias, the patients' WBC counts either re-

<table>
<thead>
<tr>
<th>TABLE 1. Infection classification and response</th>
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<tbody>
<tr>
<td>Classification</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Microbiologically documented</td>
</tr>
<tr>
<td>With bacteremia</td>
</tr>
<tr>
<td>Without bacteremia</td>
</tr>
<tr>
<td>Clinically documented</td>
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<tr>
<td>Possible</td>
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<tr>
<td>Doubted</td>
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a An additional 11 patients were excluded (see text).
b No WBC transfusion.
c Three of four died of infection.
d Died from infection.

<table>
<thead>
<tr>
<th>TABLE 2. Pathogens and response</th>
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<tbody>
<tr>
<td>Pathogens</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Gram positive</td>
</tr>
<tr>
<td>Gram negative</td>
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<tr>
<td>Multiple</td>
</tr>
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<td>Total</td>
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c Organisms and number: E. coli, 15(10); S. aureus, 7(1); Proteus spp., 5(1); S. faecalis, 5(3); Klebsiella spp., 3(3); P. aeruginosa, 2(2); other, 5(3); numbers in parentheses represent bacteremias.
d No WBC transfusion.
Mouth-sinus............. 9 8 1 0 0 0
Skin .................... 8 8 0 0 0 0
Perirectal ............... 7 7 0 0 0 0
Genitourinary ........... 6 3 1 0 0 2
Lung ..................... 6 3 1 1 1 0
Pharynx .................. 3 3 0 0 0 0
Bacteremia (site unknown) 8 0 4 0 4 0

Total .................. 47 32 7 1 5 2

Table 3. Infection site and response

<table>
<thead>
<tr>
<th>Infection site</th>
<th>Total</th>
<th>Improved without WBC transfusions</th>
<th>Improved with WBC transfusions</th>
<th>Temporarily improved</th>
<th>Failed without WBC transfusions</th>
<th>Failed with WBC transfusions</th>
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</thead>
<tbody>
<tr>
<td>Mouth-sinus</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Perirectal</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pharynx</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia (site unknown)</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
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</tr>
</tbody>
</table>

remained the same (initial, ±100/mm³) or decreased. Six of these eight drug trials resulted in failures. In five of these six drug trial failures, the patient survived for at least 4 days before death; WBC transfusions were given in two of these trials. In the other drug trial, the patient died within 12 h of developing infection. All nine of the patients with a bacteremia who had an increase in granulocyte count cleared their infection. There was no apparent difference, however, in whether the patients were responding to antitumor therapy. Two of the three who were responding improved, whereas eight of fourteen refractory to antitumor therapy also responded.

Gram-negative bacilli resistant to amikacin. Two infections were caused by amikacin-resistant (MIC, 20 μg/ml) organisms. One subsequent infection was caused by an amikacin-resistant P. aeruginosa. This organism is of interest because the MIC levels and disk zone sizes varied widely over time, making it unclear whether this was a single organism that developed resistance or represented a number of different strains of P. aeruginosa. Initially, the patient's serotype 7 P. aeruginosa was susceptible (disk zone, 14 mm; MIC, 10 μg/ml), but after amikacin administration, isolates of P. aeruginosa serotype 7 varied: 6 mm, 20 μg/ml; 14 mm, 2.5 μg/ml; and 8 mm, 10 μg/ml.

The percentage of amikacin-resistant, gram-negative bacilli found in surveillance cultures during the 8 study months was 2% (48 resistant organisms of 2,392 gram-negative bacilli cultured). This percentage remained constant: 2% (22 of 1,107) during the first 4 months and 2% (26 of 1,285) during the second 4 months. For those treated with amikacin, the percentage of amikacin-resistant organisms in surveillance cultures was 2.8% (22 of 776) for the 8 months.

Side effects. Decreased hearing was clinically observed in two patients receiving this combination of antibiotic therapy; one of these patients had received amikacin for 35 days before her ototoxicity was noted. Audiograms (preinitiation and about 1 week post-therapy) were performed in 20 patients. None of these 20 audiograms showed any significant change.

Elevated serum creatinines (>1.5 mg/100 ml) occurred in 10 of the 93 patient trials, with initial creatinines of <1.5 mg/100 ml. This could be explained by shock in three cases and administration of amphotericin B in one. Six patients (7%) had no obvious cause other than drugs for their nephrotoxicity. Three developed intermediate drug-induced nephrotoxicity (rise to >1.5 but <2.5 mg/100 ml) and three had severe (rise to >2.5 mg/100 ml) nephrotoxicity (range, >2.5 to 4.3 mg/100 ml). Five of these six patients had normalization of their creatinine post-therapy. The other patient died from an infection as his creatinine remained elevated. With respect to age, 4% (3 of 77) <60 years old and 19% (3 of 16) >61 years old had drug-induced nephrotoxicity. All of the severe nephrotoxicities occurred in the younger age group.

Drug-related fever occurred in three patients. The following subsequent infections occurred in seven patients: (i) Torulopsis glabrata bacteremia; (ii) Aspergillus sp. pneumonia; (iii) resistant P. aeruginosa; (iv) susceptible P. aeruginosa; (v) susceptible E. coli bacteremia; (vi) susceptible K. pneumoniae bacteremia and T. glabrata septicaemia; (vii) susceptible E. coli bacteremia and Candida albicans septicaemia.

All of these infections occurred in persistently granulocytopenic patients who were refractory to chemotherapy (0 of 37 chemotherapy responsive patients and 7 of 56 chemotherapy refractory patients developed subsequent infections). When one divides the refractory group into those who received <5 days of systemic antibiotics and >5 days, the number of days of granulocytopenia and degree of granulocytopenia are similar, but there were 0 of 23 patients in the group that received <5 days of antibiotics who developed a subsequent infec-
tion, whereas there were 7 of 33 in the group that received >5 days of antibiotics. Five of these infections were ultimately fatal. One of these infections was an amikacin-resistant *P. aeruginosa*.

**DISCUSSION**

The overall response rate of 84% for this empiric antibiotic regimen compares favorably to other previously reported empiric antibiotic regimens (4, 6, 12, 13, 21, 25, 26, 28-31; W. H. Greene, S. C. Schimpff, V. M. Young, and P. H. Wiernik, Ann. Intern. Med. 78:825-826 [abstr.], 1973). The response rate of 83% for documented infections, 77% for bacterially documented infections, and 65% for bacteremias was also of note, as was the four of four patients who improved with mixed flora bacteremias. Even if one does not include in analysis the seven patients who received WBC transfusions and improved, the overall response rate for documented infections is still 80%.

Several factors in addition to prompt empiric antibiotic therapy may have contributed to this response rate. Infection prevention techniques, including oral nonabsorbable antibiotics, intensive hygiene measures, a cooked food diet, and environmental manipulations, have all contributed toward a reduced frequency of gram-negative bacillary infections, especially *P. aeruginosa* and *K. pneumoniae*, in our granulocytopenic leukemic patients. Thus, in this study, there were proportionally more *S. aureus*, *S. faecalis*, and *E. coli* infections than previously. Furthermore, there were relatively few gram-negative pneumonias and proportionately more oral, sinus, and skin infections. Additionally, granulocyte transfusions were utilized earlier in this study than previously. When possible, WBC transfusions were given within the first 24 to 48 h, when a patient was suspected or proven to have gram-negative bacteremia or pneumonia, or both, in a setting of marked granulocytopenia expected by narrow examination to persist longer than 1 week. All these factors probably contributed, in some part, to our high response rate.

The dose schedule for amikacin of 15 mg/kg per day given intravenously in four equal doses (instead of the usually recommended two equal doses) achieved acceptable mean serum levels at 1 h, which were above the MIC level for >90% of previously reported hospital-isolated, gram-negative bacilli (11, 20) and for 70 to 80% of previously reported gentamicin-resistant, gram-negative bacilli (24, 30). In only 1 patient, of our 16 tested, was the 1-h level below 7 μg/ml. Additionally, it should be noted that with intravenous administration, the 1-h serum level is approximately one-half the peak level (18).

Toxicity with this regimen was not excessive. Although only 20 patients had base line and follow-up audiograms, none showed any change.

Nephrotoxicity in our present study was less frequent and less severe than has been recently reported for several other antibiotic trials (4, 6, 22, 23), using comparable dose of cephalothin and gentamicin, but was more frequent than the estimated incidence with a high dose (5 mg/kg per day) of gentamicin alone (7, 10, 15). However, it is difficult to make a meaningful comparison of the incidences of nephrotoxicities in these studies. Even with respect to the EORTC (6) study of which the BCRC was a member, a valid comparison with the present study cannot be made. Although the base line creatinines, underlying disease processes, mean patient age, percentage of bacteremias, and length of antibiotic administration were comparable in the past (6) and present study, other important factors were not. In the present study, there were less pneumonias, less serious infections in general, and, in particular, less *P. aeruginosa* and *K. pneumoniae* infections. Further, more frequent surveillance of renal function was performed during the present study; this is probably the most important reason that severe nephrotoxicity occurred less frequently, i.e., earlier alteration of amikacin dosage.

The incidence of subsequent infections with this present antibiotic regimen is comparable to that in our previous studies (6, 28, 29; Greene et al., Ann. Intern. Med. 78:825-826, 1973). All these subsequent infections occurred in patients who were refractory to chemotherapy and had been profoundly granulocytopenic for a long period of time. Additionally, none of these subsequent infections occurred in those patients who had received less than 5 days of antibiotic administration. Perhaps, not surprisingly, these patients with late-stage nonresponding tumors and persistent granulocytopenia tended to develop serious gram-negative bacillary (i.e., *Pseudomonas* and *Klebsiella*) or fungal (i.e., *Aspergillus* and T. *glabrata*) infections. The role of the cephalothin and amikacin in predisposing to these infections is suggested by the observation that the degree of granulocytopenia was similar in those receiving both short- (<5 days) and long-term antibiotics, but the incidence of subsequent infections was much higher in the long-term systemic antibiotic group.

The results of this noncontrolled evaluation show that the combination of amikacin and
cephalothin is another effective empiric regimen for treatment of presumed infection in granulocytopenic patients, and that its toxicities are similar to other cephalosporin-aminoglycoside combinations. Because there were many E. coli bacteremias and few Pseudomonas spp., Serratia spp., and Klebsiella spp. bacteremias in our series, it is difficult to compare these results with our previous series or to other empiric antibiotic series. More information concerning the percentage of emergence of amikacin-resistant organisms and more comparative studies of amikacin combination therapy versus other empiric regimens are needed before final recommendations can be made concerning the use of empiric therapies containing amikacin.

At present, there are many acceptable empiric regimens, and no one regimen has consistently been shown to be superior. The final choice of which regimen to be used on a specific medical ward should not be based solely upon the results of prior antibiotic trials. The particular underlying diseases of a population at risk, common sites of infection in this population, colonizing and infecting organisms and the patterns of susceptibility and resistance of these organisms should all be used in determining which empiric regimen would be the most suitable in any given situation. Although other regimens such as ticarcillin and gentamicin might be more appropriate in many patient situations, cephalexin and amikacin would be an acceptable regimen in a setting of a high incidence of gentamicin-resistant, gram-negative organisms and a low incidence of P. aeruginosa infections among granulocytopenic cancer patients.

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LITERATURE CITED