Azlocillin, Cephalothin, and Tobramycin Therapy in Febrile Solid Tumor Patients With Chemotherapy-Induced Leukopenia

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Although the semisynthetic broad-spectrum acylureido-penicillin, azlocillin has been demonstrated to have significant antibiotic activity in leukemic patients, its role in combination therapy of febrile granulocytopenic patients with chemotherapy-treated solid tumors has not been clearly delineated. Thirty-five solid tumor patients with chemotherapy-induced absolute granulocytopenia (<1000 granulocytes/ml) associated with fever (>38.3°C) were treated on a prospective study with a combination of azlocillin 4 g intravenously (IV) every 6 hours, cephalothin 2 g IV every 6 hours, and tobramycin 80 to 100 mg IV every 8 to 12 hours. Prior chemotherapy included doxorubricin combinations in 18 patients and other combinations in 17 patients. Granulocyte counts preantibiotic therapy were <100 granulocyte/ml in 14 patients, 100 to 499 in nine patients, and 500 to 1000 in 12 patients. Granulocyte nadirs were <100 in 20 patients, 100 to 499 in nine patients, and 500 to 1000 in six patients. Times for granulocytes to rise towards normal were 1 to 3 days in eight patients, 4 to 6 days in 18 patients, and 7 or more days in nine patients. Tobramycin levels were primarily in the peak range of 3 to 6 μg/ml and trough range of 0 to 1.9 μg/ml. The site and pathogen were identified in nine patients, the infection site clinically documented without isolated pathogen in three patients, and no site or pathogen identified in 23 patients. Of the 35 patients, 34 had good responses to the antibiotic combination (complete disappearance of fever and other evidence of infection). Serum creatinine rose 0.4 to 0.6 mg/dl in nine patients, 0.7 to 1.5 in four patients, and 1.5 in one patient (obstructive uropathy). The only other noted antibiotic-related side effect was hypokalemia. This antibiotic combination had little toxicity with marked efficacy.

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GRANULOCYTOPENIC febrile patients are customarily treated with broad-spectrum intensive intravenous antibiotics, frequently in two-drug or three-drug combinations.[1-3] These combinations have included an aminoglycoside, a cephalosporin, and a semisynthetic penicillin.[2,3] Azlocillin, an acylureido-penicillin with potent anti-Pseudomonas activity,[4-7] has been studied in combination with amikacin by the European Organization for Research on Treatment of Cancer (EORTC) Antimicrobial Therapy Project Group.[8] In the latter study, performed predominantly in leukemic patients, the combination of azlocillin plus amikacin compared favorably to combinations of cefotaxime plus amikacin and ticarcillin plus amikacin.

Currently, solid tumor patients as well as leukemics, often are treated with intensive chemotherapy resulting in expected profound granulocytopenia. Because azlocillin is synergistic with aminoglycosides *in vitro*,[9] and because of the encouraging clinical results in leukemics in the EORTC trials, it seemed important to further define the clinical efficacy of azlocillin combination therapy by utilizing an azlocillin combination in leukopenic solid tumor patients. In the current study a combination of azlocillin, tobramycin, and cephalothin was chosen for investigation. A first generation cephalosporin was included in order to best cover penicillinase-producing *Staphylococcus aureus* as well as to take advantage of the agent's synergistic properties particularly with tobramycin against *Klebsiella*.[10]

Methods

Patients at Jewish Hospital, Louisville, Kentucky were candidates for study if they had solid tumors, were postadministration of chemotherapy, and had absolute granulcytes <1000/ml associated with fever (>38.3°C). Only patients 12 years of age or older were included.

Patients were excluded if they were thought to be terminally ill (due to problems other than infection) or if they had underlying disease that would seriously

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hamper evaluation of the therapeutic response. Also excluded were patients with known allergy to penicillin and/or cephalosporins, pregnant or breast-feeding women, patients who received prior recent unsuccessful antibiotic therapy (within 72 hours), and patients with concomitant nonbacterial infections which could confuse interpretation of the results of therapy.

The initial clinical evaluation included complete history and physical examination. Bacteriologic data included at least two separate blood cultures with sensitivities, urine culture and sensitivities, and cultures of any clinically suspicious lesion. Laboratory data included a complete blood count with differential, liver and renal function tests, electrolytes, chest x-ray, and other appropriate x-rays. Informed consent was obtained before entry on study.

Antibiotic therapy included azlocillin 4 g intravenously (IV) every 6 hours, cephalothin 2 g IV every 6 hours, and tobramycin 80 to 100 mg IV every 8 to 12 hours. Peak and trough tobramycin levels were checked after the second dose, and three times per week. Peak levels were done 30 minutes after completion of a one hour tobramycin infusion and trough levels were done 30 minutes before the next scheduled dose.

Minimum inhibitory concentrations of antibiotics were determined for all pathogens and colonizing organisms. For tobramycin and cephalothin serial dilution microtiter technique[11] was used and for azlocillin disc sensitivities were performed.[12]

Response criteria were defined as follows: good response, disappearance of fever and other clinical evidence of infection; no response, continued fever or evidence of infection; and unevaluable, antibiotics discontinued during leukopenic period (*e.g.*, allergy) or early death (noninfectious) or serious protocol violations.

Febrile episodes were classified into four distinct categories as follows: (1) site and pathogen identified, (2) clinically documented site but no pathogen isolated, (3) no site or pathogen identified, or (4) fever accounted for by cause other than bacterial infection.

Antibiotic toxicity was carefully monitored. Nephrotoxicity was defined as an increase in creatinine of 0.4 mg/100 ml in absence of other obvious clinical causes. Hypokalemia was defined as a drop of 1 mEq/l or more in serum potassium. (Routine potassium supplementation at 40–60 mEq per 24 hours was given to all patients with initially low or normal serum potassium levels.) Hyperbilirubinemia was defined as a two-fold rise in serum bilirubin. Superinfection was defined as colonization with a newly isolated organism from an infected site.

Leukocyte transfusions were not utilized. Protective isolation was practiced in general.

Results

Patient Characteristics

Thirty-five antibiotic trials were initiated in 31 patients and were believed to be evaluable. No additional trials were initiated and deemed to be unevaluable. The median age of the population was 54 years (range, 26–82 years). There were 18 men and 17 women. Fifteen patients had lung carcinoma, seven had breast carcinoma, and 13 had a variety of other solid tumors. Prior chemotherapy consisted of Adriamycin (doxorubicin) combinations in 18 patients, cisplatin combinations in three patients, and other antineoplastic combinations in 14 patients.

Hematologic Data

Granulocyte counts preantibiotic therapy were <100 granulocytes/ml in 14 patients, between 101 and 499 in nine patients, and between 500 and 1000 in 12 patients. Granulocyte nadirs were <100 granulocyte/ml in 20 patients, between 101 and 499 in nine patients, and between 500 and 1000 in six patients. Times for granulocytes to rise towards normal (*i.e.*, in patients with nadirs to <500 the time to rise to >500 and in patients with nadirs between 500 and 1000 to rise to 1000) were 1 to 3 days in eight patients, 4 to 6 days in 18 patients, and 7 or more days in nine patients.

Microbiologic Data and Response

As mentioned above, febrile episodes were classified into four categories: (1) there were nine instances in which both a clinical site and a pathogen were identified; (2) in three instances infection was clinically documented at a specific site, but no pathogen was isolated; (3) in 23 instances no site or pathogen was identified; and (4) there was no instance in which fever could be attributed to malignancy or nonbacterial source of infection.

Clinically and microbiologically proven sites of infection included the following: lower respiratory in four patients, urinary tract in two patients, maxillary sinus in one patient and chest wall (infected Hickman Catheter) in one patient. There was one patient with two documented sites of infection (urinary tract and lower respiratory). There were three instances of bacteremia, one of these associated with an inguinal abscess and two without an associated site of infection.

The bacterial isolates and their susceptibility to the study antibiotics are shown in Table 1. Of the gram-positive organisms, all were sensitive to cephalothin. One of these organisms, a Staph epidermidis, was resistant to azlocillin. Of the gram-negative organisms, all were sus-

ceptible to tobramycin except a Pseudomonas aeruginosa. The latter was susceptible to azlocillin. One Klebsiella was resistant to azlocillin but sensitive to the two other antibiotics.

Of the 35 patients, 34 had a good response to the antibiotic combination. The only patient who did not respond was the one with a soft tissue infection of the chest wall associated with an infected Hickman Catheter (Staph epidermidis and Enterobacter cloacae).

Tobramycin Serum Levels

Table 2 shows the peak and trough tobramycin serum levels. In general, peak tobramycin levels were in low therapeutic ranges. Trough levels were over 1.9 mEq/ml in only three instances.

Antibiotic Toxicity

There was no instance of drug-related rash or fever. Serum creatinine rose 0.4 mEq to 0.6 mEq in nine patients, 0.6 to 1.5 mEq in four patients and to >1.5 mEq in one patient. The latter patient had concomitant obstructive uropathy. Only in the latter patient was the rise in creatinine prolonged (>2 weeks). In the others the rise was transient (<72 hours) in five instances, and temporary (72 hours to 2 weeks) in three instances. One patient had greater than a two-fold rise in bilirubin which was transient.

Hypokalemia was a common occurrence during therapy. Despite all patients being routinely maintained on 40 mEq to 60 mEq per day of IV potassium supplementation, there was a median decrease of 1.1 mEq/l in serum potassium (range, 0.1–2.3 mEq/l).

TABLE 1. Initial Antibiotic Susceptibility

Bacterial isolate	Susceptibility		
	Cephalothin	Tobramycin	Azlocillin
Staph aureus	S	NP	S
Staph epidermidis	S	NP	R
Staph epidermidis	S	NP	S
Strep pneumoniae	S	NP	S
Strep pneumoniae	S	NP	S
Strep pneumoniae	S	NP	S
Escherichia coli	S	S	S
Escherichia coli	S	S	S
Enterobacter sakazaki	S	S	S
Enterobacter cloacae	R	S	S
Klebsiella pneumonia	S	S	R
Proteus mirabilis	S	S	S
Proteus mirabilis	S	S	S
Pseudomonas aeruginosa	R	R	S

NP: not performed; S: sensitive; R: resistant.

Discussion

As reported by Parry,[13] azlocillin inhibits *in vitro* 90% of Pseudomonas isolates at 16 mEq/l and was four-fold more active than ticarcillin and eight-fold to 16-fold more active than carbenicillin. The drug is also highly effective against enterococci, inhibiting 80% at ≤1 mg/l[13] and interacts synergistically with aminoglycosides against certain Enterobacteriaceae[14] and Pseudomonas aeruginosa.[7,14] It is very active against enterococci[15] species often associated with Pseudomonas in wounds and skin structure infections.[16] The clinical efficacy of azlocillin against Pseudomonas has been well documented.[4–7,17] Overall very few serious adverse reactions have been attributed to azlocillin, and coagulopathy cannot be clearly ascribed to the drug.[18]

A multitude of two-drug and three-drug antibiotic combinations have been utilized in febrile leukopenic patients.[1–3] Overall response rates in the order of 50% to 70% are representative. In our currently reported study, a higher response rate of 94% was obtained. It has been generally recognized that the two most important prognostic variables for response of granulocytopenic patients to infections are, first, the return of myeloid marrow function and, second, the nature of infections particularly as reflected by the infecting pathogens' antibiotic susceptibility.[2,19] In our solid tumor patient population, granulocytes generally rose towards normal within the relatively short median time of 6 days (range, 1–18 days). Although it is possible that this favorable prognostic variable accounts in part for the high response rate achieved, 85% of patients became afebrile within 24 to 48 hours of antibiotic initiation mitigating the role of this variable in accounting for the results achieved. It, however, certainly appears likely to help account for the lack of superinfections in the study population.

The fact that among our 35 treated febrile patients there were only three instances of bacteremia, and nine clinically and microbiologically proven infections also may help to explain the high response rate achieved. In studies reporting lower response rates, 40% to 80% of patients have had documented bacteremias or microbiologically proven infections[1–3] compared to only 34% in our study population. This factor could certainly help to explain the high response rate achieved in our study. Because we routinely initiate antibiotic therapy in severely granulocytopenic patients as soon as possible after detecting fever (>38.3°C), there would be less tendency to have overwhelming infections, particularly bacteremias. Routinely, antibiotics are started within 12 hours of the first febrile episode, primarily because all high-risk patients for developing severe granulocytopenia are instructed to call our office immediately upon

TABLE 2. Tobramycin Levels

	Antibiotic trials (no.)
Peak level* (mg/ml)	
0–3	4
3–6	24
6–9	4
9–11	0
≥12	0
Not determined	3
Total	35
Trough level*	
0–1	13
1–1.9	15
2–3	3
>3	1
Not determined	3
Total	35

* For patients in whom there was more than one tobramycin level done, the highest trough and highest peak were recorded.

development of fever. If they are found to be granulocytopenic they are then rapidly hospitalized.

The foregoing factors notwithstanding, it remains that our response rate was exceptionally high. The data shown in Table 1 on initial antibiotic susceptibility confirms that the theoretical considerations used in devising the three-drug combination were clinically confirmed by susceptibility patterns likely to achieve therapeutic efficacy. No isolated organisms lacked susceptibility to at least one of the three antibiotics. Noteworthy was the one Pseudomonas sensitive only to azlocillin, one Staph epidermidis sensitive only to cephalothin, and one Klebsiella resistant to azlocillin, but sensitive to the two other antibiotics.

Although standard doses of tobramycin were utilized in our study (80–100 mg every 8–12 hours), tobramycin serum levels as shown in Table 2 were rather low. These levels were determined within 1 to 8 hours of serum sampling making it unlikely that inactivation of tobramycin by cephalothin significantly influenced the general levels as determined. The low tobramycin levels obtained strengthen arguments for using concomitant antibiotics with synergistic potential. Also, the low serum levels are likely to help account for the low incidence of renal toxicity observed in our patients.

In conclusion, utilizing three antibiotics is certainly expensive. However, both from the standpoint of theoretical considerations and especially from the results achieved, it appears worth the price. Confirmation of our study's results would be desirable especially in controlled, comparative clinical trials.

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