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Randomized Comparison between Two Ceftazidime-Containing Regimens and Cephalothin-Gentamicin-Carbenicillin in Febrile Granulocytopenic Cancer Patients

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Because the results of our published trial [R. Ramphal, B. S. Kramer, K. H. Rand, R. S. Weiner, and J. W. Shands, Jr., J. Antimicrob. Chemother. 12(Suppl. A):81–88, 1983] of ceftazidime versus cephalothin, gentamicin, and carbenicillin (KGC) revealed a preponderance of gram-positive superinfections, including those caused by clostridia, in patients treated with ceftazidime, we added vancomycin to the ceftazidime regimen at study entry 49 and continued with a 2:1 randomized comparison of ceftazidime-vancomycin (CV) versus KGC. Criteria for study entry were fever (temperature, ≥38.5°C on one occasion or ≥38°C on two occasions 6 h apart) and granulocytopenia (<500/mm³ or a falling count anticipated to be <500/mm³). Ninety-five entries (79 patients) were evaluable. The numbers of initial clinical responses for ceftazidime-, KGC-, and CV-treated patients were 9 of 21 (43%), 21 of 37 (57%), and 21 of 37 (57%), respectively; differences were not significant. The death rate was lower with CV (2 of 37 patients) than with KGC (10 of 37 patients) ($P < 0.05$ by two-tailed analysis) or with ceftazidime alone (7 of 21 patients) ($P < 0.025$). Death from presumed infections occurred in 9 of 37 KGC-treated patients versus 1 of 37 CV-treated patients ($P < 0.025$). Superinfections occurred in five ceftazidime-treated patients (24%) versus 7 KGC-treated patients (19%) but not in CV-treated patients (CV versus KGC, $P < 0.05$; CV versus ceftazidime, $P < 0.01$). CV appears to be superior to KGC or ceftazidime alone in the management of febrile granulocytopenic cancer patients.

The immediate institution of an empiric broad-spectrum antimicrobial regimen in febrile cancer patients with cytotoxic therapy-induced granulocytopenia has become accepted practice over the last decade (10, 11). Nevertheless, the optimal antibiotic regimen has not been defined, and the use of a variety of complex two- and three-drug regimens is commonplace (1, 3–5, 7, 8, 13–15). Some of the three-drug regimes involve up to 13 drug administrations per day, compounding costs and the potential for medication errors and sometimes requiring delays to allow for the administration of other medications or blood products. The ideal empiric regimen would therefore be a single antibiotic with efficacy at least equal to that of more complex regimens and with a low incidence of superinfections and toxicity, mitigating the need for subsequent additions of drugs and readjustments.

With these considerations in mind, we initiated a randomized comparison of ceftazidime versus cephalothin, gentamicin, and carbenicillin (KGC) in the initial empiric management of febrile granulocytopenic cancer patients. Ceftazidime has excellent activity against gram-negative bacilli, the most frequent serious pathogens in granulocytopenic patients. It has modest activity against gram-positive organisms. There had been at that time no significant reports of in vitro development of resistance or of a problem with serious superinfections clinically. An analysis of our trial after the first 48 study entries revealed comparable initial response rates between the two treatment programs; however, as previously reported, there was an alarming superinfection rate with gram-positive organisms in the ceftazidime-treated patients (9).

Because of this problem, improved gram-positive coverage was felt necessary. Ideally, the additional drug should not have significant effects on gut flora. Vancomycin was therefore chosen because of its excellent gram-positive coverage, including its effectiveness against *Staphylococcus epidermidis*, which has been emerging in some centers as a major pathogen, and because it has little or no biliary excretion (2). A randomized comparison of ceftazidime plus vancomycin (CV) versus KGC with a 2:1 imbalance in favor of CV was then begun. We now report the results of the entire study (101 study entries).

MATERIALS AND METHODS

Patient entry and management. Study entry criteria were as follows: (i) underlying neoplastic disease; (ii) ≥18 years old; (iii) granulocytopenia, as defined by an absolute neutrophil-plus-band count of <500/mm³ or <1,000/mm³ and falling rapidly; (iv) fever, as defined by an oral temperature of ≥38°C on two occasions 6 h apart or ≥38.5°C on one occasion not associated with blood product transfusions. Patients were excluded if they had received antibiotics in the preceding 96 h or had a known allergy to penicillin or to any of the study drugs. All patients gave written informed consent. Since granulocytopenia could be anticipated in many patients, informed consent was obtained prior to the onset of fever whenever possible. Neither the patient nor the person obtaining informed consent was aware of the treatment assignment at the time consent was obtained.

The initial evaluation at study included the following: (i) two blood cultures; (ii) cultures of any site clinically sus-

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TABLE 1. Unevaluable patients

Antibiotic regimen	Underlying disease	No. of granulocytes/ mm³	Initial infection	Outcome	Superinfection	Reason for exclusion
Ceftazidime	Lymphoma	0	*E. coli*	Died	None	Moribund at study entry; KCG added 5 h later
Ceftazidime	Leukemia	0	*P. aeruginosa*	Lived	*C. tertium* and *S. epidermidis*	Tobramycin[a] added on day 2
Ceftazidime	Leukemia	1,188	None	Lived	None	Not granulocytopenic
KGC	Lymphoma	1,044	None	Lived	None	Not granulocytopenic
C/V	Leukemia	500	None	Died	Pulmonary aspergillosis	Switched to KCG on day 3 after responding on day 1 to CV—had wheals felt 2° to vancomycin
C/V	Leukemia	42	None	Lived	None	Switched to KGC after itching subsequent to first CV dose

[a] Added because of an inaccurate laboratory report of susceptibility. The patient was afebrile and had a sterile blood culture at this time.

pected of being infected; (iii) chest roentgenogram; (iv) urinalysis; and (v) serum electrolyte, blood urea nitrogen, creatinine, and liver function tests.

The first 48 study entries were randomly assigned to receive either ceftazidime alone (2 g intravenously every 8 h) or cephalothin (3 g intravenously every 6 h), gentamicin (1.5 mg/kg intravenously every 8 h), and carbenicillin (500 mg/kg per day) (maximum, 36 g/day) (KGC) in six daily divided doses. From study entry 49 through 101, there was a 2:1 randomization to receive either ceftazidime as described above plus vancomycin (500 mg intravenously every 6 h) or KGC.

The antibiotics in any individual patient were changed only if cultures revealed organisms resistant to the assigned regimen. The antibiotics were continued until the granulocyte count was >500/mm³ on two successive days and the temperature was <38°C for at least 24 h. Amphotericin B was added empirically (0.5 to 0.7 mg/kg per day) on day 8 if the patient was febrile and granulocytopenic without a documented source of fever. It was added after day 8 if afebrile, persistently granulocytopenic patients subsequently redeveloped fever. Since the empiric addition of amphotericin B came no earlier than day 8, it did not in any way affect the determination of the initial clinical response. Serum gentamicin levels were monitored, and doses were adjusted to achieve a peak serum level of 4 to 8 mg/liter and a trough serum level of <2 mg/liter.

Chest roentgenograms were obtained weekly after study entry or more frequently if pulmonary symptoms or signs evolved. Two sets of blood cultures were obtained once daily if patients continued to be febrile. Bacterial isolates were tested for susceptibility to ceftazidime by microtiter and tube broth dilutions.

Definitions of response categories. A favorable clinical response was defined as a patient becoming afebrile (temperature, <38°C) within 96 h of the initiation of antibiotics and remaining afebrile for at least 48 h. A favorable bacteriological response was defined as the termination of documented bacteremia on repeat cultures regardless of the febrile response. There were no instances of microbiologically documented soft tissue infections which were not accompanied by bacteremia. Since cultures of cellulitis are insensitive in our experience, we relied on blood culture results for the determination of a bacteriological response. A new fever was one which occurred after a favorable clinical response. A superinfection was considered to be a documented infection by a new organism while the patient was receiving therapy.

Deaths were categorized as being due to initial infections (whether clinically or microbiologically defined), superinfections, or other causes (e.g., cerebral hemorrhage, myocardial infarction).

Statistical analysis. All comparisons of outcome by treatment group were done by a two-tailed chi-square analysis. All comparisons of means were done by the student *t* tests (and by the Wilcoxon rank sum test for patient age comparisons). Statistical significance did not change whether all patients entered were analyzed or the six unevaluable patients were excluded. There was no statistical difference between the 23 entries assigned to KGC in the first phase of the study and the 14 entries assigned to KGC in the second phase of the study with regard to initial granulocyte count, duration of granulocytopenia, clinical response, or death.

For an analysis of the intensity of chemotherapy of the three treatments, one of us, a medical oncologist (B.S.K.), made the assignments retrospectively. In general, the designation of intensive therapy was reserved for patients undergoing induction or consolidation therapy for acute leukemia and occasional patients with solid tumors who underwent high-dose therapy, which usually results in granulocytopenia for more than 2 weeks.

RESULTS

There were a total of 101 study entries (85 patients) from January 1982 through September 1984. Ninety-five entries (79 patients) were considered evaluable. Three patients in the ceftazidime group were considered unevaluable: one was ineligible because granulocytopenia was not achieved; another was moribund at study entry, and the treating physician decided to add KGC 5 h after study entry; and tobramycin was added on day 2 of the study in the third, despite a good clinical and bacteriological response, because of an erroneous susceptibility report. One KGC entry was ineligi-

TABLE 2. Patient characteristics (evaluable patients)[a]

Parameter	Ceftazidime (n = 21)	KGC (n = 37)	CV (n = 37)
No. of males/females	10/11	15/22	19/18
Median age (range)	43 (21–88)	56 (20–77)	35 (18–66)
Mean age	46	47	36
Diagnosis[b] (no. of patients)			
Acute leukemia	16	25	33
Solid tumor	5	12	4
Intensive chemotherapy (no. of patients)	17	25	32
Median granulocytes/mm^3 at study entry (range)	34 (0–435)	6 (0–888)	20 (0–1,000)
Mean granulocytes/mm^3 at study entry ± SD	82 ± 125	132 ± 303	167 ± 324
No. of days granulocytopenic			
Median (range)	12 (2–38)	10 (1–38)	15 (2–39)
Mean	15	12.7	15.6

[a] No differences between groups are statistically significant, except where noted.
[b] CV versus KGC, $P < 0.05$; others, P not significant.

ble because granulocytopenia did not occur. Two CV entries were unevaluable: both were switched to KGC after the patients had cutaneous reactions to the vancomycin infusion early in the course of therapy. These six unevaluable patients and outcomes are listed in Table 1.

The characteristics of the remaining 95 entries are listed in Table 2. There were no statistically significant differences among the three treatments with regard to sex, age, intensity of chemotherapy, initial granulocyte count, or duration of granulocytopenia at <500/mm^3. It should be noted that the median duration of granulocytopenia in each group was relatively long, 12, 10, and 15 days. There was an imbalance in the distribution of the treatments by diagnosis, since the CV group had a significantly higher proportion of acute leukemia patients than did the KGC group: 33 of 37 versus 25 of 37 ($P < 0.05$).

There were no significant differences between the KGC patients in the first versus the second parts of the study with regard to sex, age, diagnosis, proportion undergoing intensive chemotherapy, mean and median granulocyte counts at study entry, duration of granulocytopenia, or outcome.

Therapeutic responses and outcomes are shown in Table 3 for the three groups. Although the initial clinical response rate in the ceftazidime group was 43%, compared with 57% in each of the other two groups, this difference was not statistically significant. Similarly, the bacteriological response rates among the three groups were nearly identical. The initial organisms responsible for documented bacteremias and their outcomes are listed in Table 4. The sole bacteriological failure in the ceftazidime group was in a patient with overwhelming *Escherichia coli* sepsis in the setting of massive gastrointestinal ulceration resulting from high-dose 5-fluorouracil. The sole bacteriological failure in the KGC group was an episode of *Pseudomonas aeruginosa* sepsis. There were no failures in the CV group. The duration

TABLE 3. Therapeutic responses

Parameter	Ceftazidime (n = 21)	KGC (n = 37)	CV (n = 37)
No. (%) of clinical responses[a]	9 (43)	21 (57)	21 (57)
No. (%) with bacteriological cure of bacteremias[a]	4/5 (80)	4/5 (80)	4/4 (100)
Duration of fever in responders (days)[a]			
Median (range)	1 (1–4)	2 (1–4)	2 (1–4)
Mean	1.6	2.2	2.2
No. (%) of patients with new fevers during therapy[a]	7 (78)	12 (57)	15 (71)
Superinfections			
No. (%) of patients[b]	5 (24)	7 (19)[c]	0
No. of different organisms	8	8	0
No. of deaths[d] caused by:			
Infections	2	6	1
Superinfections	4	3	0
Other	1	1	1
No. of patients receiving amphotericin B/no. of patients eligible[a]	8/9	11/14	20/23

[a] Differences not significant.
[b] CV versus ceftazidime, $P < 0.01$; CV versus KGC, $P < 0.05$; ceftazidime versus KGC, P not significant.
[c] One KGC patient developed a new pulmonary infiltrate with a recurrence of fever after an initial clinical response, but there was no microbiological documentation of the etiology.
[d] CV versus ceftazidime, $P < 0.025$; CV versus KGC, $P < 0.05$; ceftazidime versus KGC, P not significant.

TABLE 4. Outcome of microbiologically documented bacteremias

Drug and no. of patients	Organism	Outcome
Ceftazidime		
2	*E. coli*	Died
18	*P. aeruginosa*	Cured
23	*C. subterminale*	Cured
28	*E. coli*	Cured
33	*Klebsiella* sp.	Cured
KCG		
7	*P. aeruginosa*	Cured
11	*Enterococcus* sp.	Cured
14	*P. aeruginosa*	Cured
17	*P. aeruginosa*	Died
63	*P. aeruginosa*	Cured
CV		
53	*S. aureus*	Cured
71	*S. aureus*	Cured
85	*S. aureus*	Cured
99	*S. aureus*	Cured

TABLE 5. Outcome of microbiologically documented superinfections

Drug and no. of patients	Superinfecting organism(s)	Day of superinfection	Outcome
Ceftazidime			
1	*C. septicum*	10	Died
3	*Enterococcus* sp.	14	Died (noninfectious cause)
18	*C. perfringens* and *Enterococcus* sp.	5 and 7	Died
45	*C. tertium* and *Citrobacter* sp.	17 and 17	Died
47	*C. septicum* and *Enterococcus* sp.	11 and 11	Died
KCG			
7	*E. coli*	9	Lived
11	*P. aeruginosa*	20	Died
27	*Candida albicans*	19	Died
32	*C. albicans*	8	Lived
34	*P. cepacia* 1, *B. fragilis*, and *P. cepacia* 2	18, 27, and 32	Lived
36	*P. aeruginosa*	10	Died
CV None	None		

of fevers in responding patients was quite similar in each group. The recurrence rates of fever in the ceftazidime, KGC, and CV groups were 78, 57, and 71%, respectively (*P* not significant).

Statistically significant differences, however, emerged for the analysis of death rate by treatment assignment (Table 3). Of 21 patients treated with ceftazidime, 7 died, compared with 10 of 37 KGC-treated patients and only 2 of 37 CV-treated patients (CV versus ceftazidime, $P < 0.025$; CV versus KGC, $P < 0.05$; ceftazidime versus KGC, *P* not significant). One death in each of the three groups was considered to have a noninfectious cause. Death due to presumed infections occurred in a total of 6 of 21 ceftazidime-treated patients, 9 of 37 KGC-treated patients, and 1 of 37 CV-treated patients (KGC versus CV, $P < 0.025$; ceftazidime versus CV, $P < 0.05$; KGC versus ceftazidime, *P* not significant). Of these, there were 4 deaths due to documented superinfections in the ceftazidime group, 3 in the KGC group, and none in the CV group.

There were also significant differences among the groups with regard to documented superinfections. Of 21 patients who received ceftazidime, 5 (24%) developed superinfections (eight organisms), compared with 7 of 37 (19%) patients who received GKC (eight organisms) and none of 37 patients who received CV (CV versus ceftazidime, $P < 0.01$; CV versus KGC, $P < 0.05$; ceftazidime versus KGC, *P* not significant). As previously reported, there was a striking difference in the profiles of superinfecting organisms between the ceftazidime and KGC regimens (Table 5). Seven of eight superinfections occurring in patients receiving ceftazidime were caused by gram-positive organisms, compared with a preponderance of gram-negative organisms (five of eight superinfections) in those receiving KGC. There were two episodes of candidemia in the KGC group, one of them fatal. The outcomes of all microbiologically documented superinfections are shown in Table 5.

Autopsies were performed on 5 of the 19 evaluable patients who died. One of the five, who had been given ceftazidime, was determined to have a noninfectious cause of death from progressive Hodgkin's disease and cardiac tamponade. The remaining four had autopsy-proven infectious causes of death, as follows: *Clostridium* sepsis, *Clostridium* sepsis with organisms in multiple organs, pulmonary aspergillosis, and overwhelming *E. coli* sepsis in the setting of bloody diarrhea caused by chemotherapy-induced bowel mucositis.

Since a potential bias in analyzing deaths among the groups would be an imbalance in the frequency of initiation of amphotericin B therapy on day 8 in febrile neutropenic patients, as stipulated in the study protocol, we took this into account. Indeed, some of the primary physicians were reluctant to add amphotericin B in a febrile neutropenic patient who appeared to be stable. Of nine patients who qualified for the addition of amphotericin B while receiving ceftazidime, eight actually received it. This compares with 11 of 14 patients receiving KGC and 20 of 23 patients receiving CV. None of these differences approached statistical significance (Table 3).

No cases of renal failure occurred, and no deaths were attributed to any of the antibiotics used. Rashes or pruritis occurred in one ceftazidime-treated patient, two KGC-treated patients and four CV-treated patients. Two cases of fluid overload occurred, both in the KGC group.

DISCUSSION

A variety of empiric broad-spectrum antimicrobial regimens have been used and compared in the initial management of febrile neutropenic cancer patients, but none has demonstrated clear superiority (1, 3–5, 7, 8, 13–15). A possible reason is that minor changes in spectrum cannot be expected to yield major differences in response rates, as long as most of the commonly infecting organisms in the patient population are within the spectrum of the regimen chosen. Indeed, the initial clinical response rates in our own study were similar in the single, double, and triple antibiotic regimens. Admittedly, the β error (chance of missing relatively small initial response rate differences) was large. Based on a two-sided analysis with an α error (chance of declaring a difference between two regimens exists when, in fact, none exists) of 0.05, the chance of detecting an improvement in the response from 45% with ceftazidime to 65% with KGC was only about 40% (β error, 0.6). Likewise, the β error was also about 0.6 in the ability to detect an improvement in the response from 55% with KGC to 75% with CV. Large differences in efficacy and outcome between groups did not emerge until later in the treatment course of these patients, at which time there were differences in

superinfection and death rates. Hence, a regimen which has the same initial response rate may ultimately prove superior to another if there are fewer superinfections or deaths. One might argue that it would be advantageous to start with a single broad-spectrum antibiotic such as ceftazidime and make adjustments in coverage as becomes necessary later in the treatment course. Indeed, a recent preliminary report by Pizzo et al. showed that ceftazidime may be as effective as KGC in the initial management of febrile granulocytopenic cancer patients (P. Pizzo, M. Thaler, J. Hiemenz, D. Cotton, J. Hathorn, J. Commers, J. Gress, D. Marshall, D. Longo, and M. Browne, Program Abstr. 24th Intersci. Conf. Antimicrob. Chemother., abstr. no. 380, 1984). However, that report was for a younger population (median age, 25) than our own, with a shorter duration of granulocytopenia (median, 8.5 days). Adjustments in antibacterial coverage were often necessary after the first 72 h of therapy. Moreover, one cannot accurately predict in any given episode precisely when a superinfection will emerge. In fact, one of our patients receiving ceftazidime developed a superinfection with *Clostridium perfringens* on day 5 of therapy. Serial surveillance cultures are generally of no benefit in predicting infective organisms (6).

Our initial hope was to find a single-agent regimen which would match the effectiveness of the broad-spectrum coverage of a cephalosporin, an aminoglycoside, and an antipseudomonal penicillin. Because of a surprisingly high rate of superinfection with gram-positive organisms, including anaerobes, we felt that the combination of ceftazidime and vancomycin would cover the "holes." After the initiation of our study, there was a report of the emergence of resistant organisms in patients treated with ceftazidime (12). However, these were primarily *P. aeruginosa* in patients with cystic fibrosis. We were subsequently impressed by the complete absence of documented superinfections with the two-drug combination. This appears to translate into a lower mortality rate than for either standard KGC treatment or ceftazidime treatment.

Nevertheless, several conclusions are probably warranted. (i) Ceftazidime, KGC, and CV had comparable initial response rates when used as initial empiric antimicrobial therapy in adult febrile granulocytopenic cancer patients. (ii) Ceftazidime alone was associated with a high superinfection rate with gram-positive organisms, and KGC was associated with predominantly gram-negative superinfections. This stands in contrast to CV, with which no superinfections were documented. (iii) CV was associated with fewer deaths than was ceftazidime alone or KGC and appears to be the superior regimen in febrile granulocytopenic cancer patients. Of course, as newer individual antibiotics with even broader spectra become available, the situation must be reassessed.

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