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Single-Drug Versus Combination Empirical Therapy for Gram-Negative Bacillary Infections in Febrile Cancer Patients With and Without Granulocytopenia

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Empirical therapy with cefoperazone was compared with cefoperazone plus amikacin in granulocytopenic and nongranulocytopenic febrile patients. In nonneutropenic patients the overall response rate to cefoperazone was 88%; 10 of 12 gram-negative bacteremic patients were cured. Cefoperazone plus amikacin resulted in an 88% overall response rate and cured 14 of 15 patients with bacteremia. In neutropenic patients the overall response rate was 77% with cefoperazone alone and 73% with cefoperazone plus amikacin; the cure rates for gram-negative bacteremias were 8 of 11 and 6 of 12 patients, respectively. Our findings support the concept of single-drug empirical therapy with cefoperazone in febrile cancer patients, whether granulocytopenic or not, especially when gram-negative bacteremias are predominantly caused by *Escherichia coli* or *Klebsiella* species. The issue of *Pseudomonas* spp. and other more resistant pathogens needs further assessment with a larger number of patients.

Infection in cancer patients can rapidly become a life-threatening situation, especially in the presence of gram-negative bacteremia and bone marrow failure (12). When sepsis is suspected, usually on the basis of fever, prompt antimicrobial therapy and adequate supportive care are needed before the nature and susceptibility of the pathogens are known. Empirical therapy should provide adequate coverage against all the likely pathogens. Gram-negative bacilli are the most common pathogens in severe infections of the immunocompromised host, especially neutropenic patients, and infection may be rapidly fatal under these conditions. Until now, a broad-spectrum activity could only be achieved with combinations of antimicrobial agents, namely, beta-lactam antibiotics and aminoglycosides; these combinations, which frequently have a synergistic action against members of the family *Enterobacteriacae* and *Pseudomonas aeruginosa*, have been shown to be associated with a better clinical outcome than single-drug therapy (6). However, antibiotic combination therapy is associated with an increased frequency of allergic and toxic reactions, a potentially difficult situation in cancer patients who are already exposed to the toxicity of their anti-cancer treatment.

This is why the possibility of using a single drug for empirical therapy in febrile cancer patients appears appealing, provided a broad antimicrobial spectrum and an adequate bactericidal activity can be obtained. The introduction of the so-called "third-generation cephalosporins" offers a possibility for single-drug therapy in immunocompromised patients.

The preliminary results of empirical therapy with the latest cephalosporins are encouraging (4); however, no final statement can be made at the present time as to whether this empirical monotherapy is more or less active than the aminoglycoside-containing combinations.

Cefoperazone is a cephalosporin of the third generation. It has low minimal inhibitory and bactericidal concentrations against most aerobic gram-negative bacilli and a satisfactory activity against anaerobes (with the exception of *Bacteroides fragilis*) and *Staphylococcus aureus*. Its pharmacological properties and therapeutic effectiveness have recently been reviewed (2).

We conducted a prospective randomized study to compare empirical therapy with cefoperazone alone with empirical therapy with cefoperazone plus amikacin in cancer patients, whether neutropenic or nonneutropenic. The purpose of the study was to compare the clinical and the bacteriological effectiveness of these two forms of empirical therapy and to analyze the results with regard to the emergence of cefoperazone-resistant strains and the level of bactericidal activity in the serum.

MATERIALS AND METHODS

Nongranulocytopenic cancer patients with presumed bacteremia and neutropenic febrile patients (less than 1,000 neutrophils per μl; temperature greater than 38.5°C) were eligible for the study.

Patients were randomly assigned to receive intravenously either 6 g of cefoperazone twice daily (BID) or 2 g of cefoperazone plus 500 mg of amikacin BID. The antibiotics were administered simultaneously. These regimens were chosen on the basis of our own studies that demonstrated identical bactericidal activities against common gram-negative bacilli of the serum of volunteers who had a high dose of cefoperazone (6 g BID) and the serum of volunteers who had a combination of a lower dose of cefoperazone (2 g BID) and amikacin (500 mg BID) (11). Antibiotics were dissolved in 150 ml of 5% dextrose in water and were infused over 15 min.

After informed consent and before the onset of antibiotic treatment, specimens for culture were collected from throat, urine, blood, sputum, and any other appropriate sites. A chest X-ray was obtained within the first 24 h. Appropriate follow-up cultures and X-ray examinations were obtained during the course of the treatment. Complete blood counts and an SMA chemistry panel were performed at least twice a week. The methods for determining the MIC, MBC, and

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bactericidal activities of serum samples have been described elsewhere (5, 11).

Death during therapy and clinical deterioration requiring a change in antimicrobial treatment were considered to represent failures of empirical therapy. An adjustment of therapy according to the microbiological characteristics of the isolated pathogen after a suboptimal response to empirical treatment was not considered as a failure but as the inability of the empirical regimen to definitely cure the infection. Since the primary goal of empirical therapy is to allow the survival of the patients, we dissociated "success of the empirical therapy" from "cure" of the patient. Patients were classified as "not evaluable" (i) when a change in antibiotic therapy was made within the first 48 or 72 h of treatment and was not justified by a clinical deterioration of the patient or (ii) when the febrile episode was subsequently classified as "doubtful infection."

If no significant pathogen was isolated, the assigned regimen was continued for 5 days after patient temperature had returned to normal. The definition of the febrile episodes was made as previously proposed (3). "Microbiologically documented" infections required the signs and symptoms of infection plus microbiological diagnosis from a suspected site, histological sections, or blood cultures. Infections were considered to be "clinically documented" if a site of infection was identified, but cultures from this site and from the blood were negative. "Possible infections" included episodes with signs and symptoms of infection but without a documented site of sepsis and no positive cultures despite repeated physical examination, history, X-ray, and cultures at least every 3 days. Finally, doubful infection was considered if infection was improbable on review of the clinical signs and course.

If a gram-positive infection was microbiologically documented, therapy was adjusted to the in vitro susceptibility of the pathogen, and the case was excluded from further evaluation.

"Superinfection" was defined as an infection caused by a different organism that occurred during or after treatment and required a change of therapy. In that case, the result of empirical therapy might have been considered as a success, but the actual outcome of the infectious episode was a failure.

RESULTS

A total of 49 neutropenic patients and 105 nonneutropenic patients were randomly assigned to one of the two treatment regimens.

TABLE 1. Patient characteristics

Patient group and treatment	Total no. of patients	Male/female	Median age (range)	Underlying diseases	
				Hematological malignancies[a]	Solid tumors
Neutropenic					
Cefoperazone	25	12/13	55 (17–67)	13	12
Cefoperazone + amikacin	24	16/8	50 (17–76)	14	10
Nonneutropenic					
Cefoperazone	55	31/24	66 (19–87)	5	50
Cefoperazone + amikacin	50	24/26	61 (25–90)	7	43

[a] Including lymphomas.

Distributions of sex, age, and underlying primary diseases are shown in Table 1. Among the neutropenic patients, the 49 infectious episodes could be classified as follows: 29 (59%) were microbiologically documented, including 23 gram-negative bacteremias; 4 (8%) were clinically documented; 13 (27%) were possible infections; and 3 (6%) were doubtful infections. Among the nonneutropenic patients (105 episodes), the corresponding distribution was 61 (58%) microbiologically documented infections with 27 gram-negative bacteremias, 9 (8.5%) clinically documented infections, 23 (22%) possible infections, and 12 (11.5%) doubtful infections.

Table 2 summarizes the clinical outcome in each treatment arm. Among the neutropenic patients, five were excluded: three patients with a doubtful infection in the cefoperazone arm and two patients with gram-positive bacteremia (*Streptococcus pneumoniae* and *Staphylococcus aureus*), in whom cefoperazone plus amikacin was discontinued on day 2, when the pathogens were identified, although no clinical deterioration had occurred. Among the nonneutropenic patients, for similar reasons, 13 patients receiving cefoperazone were considered as nonevaluable (6 doubtful infections and 7 gram-positive bacteremias), as well as 7 patients who received cefoperazone plus amikacin (six doubtful infections and 1 *Staphylococcus aureus* bacteremia).

No significant difference was found between the two regimens, whether response to empirical therapy or overall cure was considered (Table 2). In neutropenic patients, empirical cefoperazone was effective in 17 of 22 (77%)

TABLE 2. Evaluable infections and clinical outcome

Patient group and treatment (no. of evaluable patients)	No. of patients (%) who had:		No. of patients (successful empirical therapy/overall cure/evaluable) with:					
			Microbiologically documented infections				Clinically documented infections	Possible infections
			Bacteremia		No bacteremia			
	Successful empirical therapy	Overall cure	Gram negative	Gram positive	Gram negative	Gram positive		
Neutropenic								
Cefoperazone (22)	17 (77)	16 (73)	8/ 8/11	2/0/2	1/1/1	0/0/0	1/1/1	6/ 6/7
Cefoperazone + amikacin (22)	16 (73)	13 (59)	8/ 6/12	0/0/0	1/1/1	0/0/0	1/1/3	6/ 5/6
Nonneutropenic								
Cefoperazone (42)	37 (88)	35 (83)	10/10/12	0/0/0	9/7/10	2/2/2	5/5/5	11/11/13
Cefoperazone + amikacin (43)	38 (88)	32 (74)	14/14/15	3/0/3	10/7/11	0/0/0	2/1/4	9/ 9/10

TABLE 3. Pathogens responsible for gram-negative bacteremia and clinical outcome

Patient group and treatment	No. of patients (successful empirical treatment/overall cure/evaluable) infected with:				
	E. coli	*P. aeruginosa*	*K. pneumoniae*	Miscellaneous	Polymicrobial infection
Neutropenic					
Cefoperazone	4/4/4	2/2/3	1/1/1	1/1/1	0/0/2
Cefoperazone + amikacin	5/4/6	1/0/3	2/2/2	0/0/0	0/0/1
Nonneutropenic					
Cefoperazone	5/5/5	2/2/2	1/1/1	1/1/3	1/1/1
Cefoperazone + amikacin	6/6/6	0/0/0	3/3/3	4/4/5	1/1/1

patients, and cure was achieved in 16 patients (73%). Corresponding values for cefoperazone plus amikacin therapy were 16 of 22 (73%) and 13 of 22 (59%) patients, respectively. As will be shown later, three superinfections in the latter group accounted for this lower cure rate. Among the nonneutropenic patients, the empirical regimen was effective in 37 of 42 (88%) cases with cefoperazone and 38 of 43 (88%) cases with cefoperazone plus amikacin; rates of overall cure were 35 of 42 (83%) and 32 of 43 (74%) patients, respectively.

The results in gram-negative bacteremia deserve special consideration. Cefoperazone was effective in 18 of 23 (78%) of these episodes (8 of 11 neutropenic patients), and cefoperazone plus amikacin was successful in 22 of 27 (81%) of these episodes (8 of 12 neutropenic patients). The distribution of these bacteremias by organism is presented in Table 3.

Among nonneutropenic patients with gram-negative bacteremia, there were only three failures, whose characteristics are outlined in Table 4. The infecting organisms responsible for these infections were resistant in vitro to cefoperazone; the serum bactericidal activity (SBA) was relatively low in two patients and was difficult to interpret in the other patient, who was infected with a serum-susceptible strain.

Among the neutropenic patients, there was an equal distribution between the two treatment arms of prognostic factors such as underlying diseases, known or unknown site of infection, and initial granulocyte count (Table 5). The response rate was six of eight and five of seven for severely neutropenic patients (<100 granulocytes per μl) with gram-negative bacillary bacteremia who were treated with cefoperazone and cefoperazone plus amikacin, respectively. Overall, seven failures were encountered (Table 6): three in the cefoperazone arm and four in the cefoperazone plus amikacin arm. Of these seven patients with bacteremia who failed to respond to empirical therapy, three had polymicrobial bacteremia, four had severe granulocytopenia (<100 neutrophils per μl), and *P. aeruginosa* was isolated from the blood in five. Only two *P. aeruginosa* strains (one in each arm) were resistant in vitro to cefoperazone, but these two infections were not fatal; all the other gram-negative strains were susceptible in vitro to both cefoperazone and amikacin. The SBA, as determined 1 h after the administration of the antibiotics, was available for four granulocytopenic patients who failed to respond; it was at least 1:16 in the two cefoperazone-treated patients. Nevertheless, one of them died in septic shock. In the two patients who received cefoperazone plus amikacin and failed to respond, the serum bactericidal titer was 1:8; both patients survived after adjustment of antimicrobial therapy.

The median values of the serum bactericidal titers observed in our study in patients with gram-negative bacillary bacteremia are shown in Table 7. The figures were not different for patients who received cefoperazone and those who received cefoperazone plus amikacin but were high (1:128 to 1:512) with both regimens. As already mentioned, the SBA was lower in patients who failed to respond than in the others.

TABLE 5. Clinical response of gram-negative bacteremia to empirical treatment in neutropenic patients as related to prognostic features

Prognostic feature	No. of patients[a] treated with:			
	Cefoperazone		Cefoperazone + amikacin	
	No. treated	Failures	No. treated	Failure
Initial granulocyte count per μl				
501–1000	1	1	3	0
101–500	2	0	2	2
0–100	8	2	7	2
Site of infection				
Known	5	2	6	2
Unknown	6	1	6	2
Underlying diseases				
Hematological malignancy	7	2	7	2
Solid tumors	4	1	5	2

[a] A total of 11 and 12 patients were treated with cefoperazone and cefoperazone plus amikacin, respectively.

TABLE 4. Clinical and microbiological aspects of failures in gram-negative bacteremia in nongranulocytopenic patients[a]

Sex	Age	Underlying disease	Treatment group	Pathogen[b]	Susceptibility (Cef/Ami)	MBC (Cef/Ami)	SBA	Outcome
M	71	Intracerebral tumor	Cef	*Acinetobacter* sp.	R/S	100/0.4	1:4	Improved only after addition of Ami
F	69	Breast cancer	Cef	*K. pneumoniae*	R/S	50/25	1:64[c]	Died after three doses on day 2 in septic shock
F	45	Cervix cancer	Cef + Ami	*Acinetobacter* sp.	R/S	25/12.5	1:8	Blood cultures remained positive; improvement only after change to ceftazidime + Ami but death from disseminated candidiasis

[a] Cef, Cefoperazone; Ami, amikacin; R, resistant; S, susceptible.
[b] Primary sites of infection are unknown for these three patients.
[c] Serum-susceptible strain.

TABLE 6. Clinical and microbiological aspects of failures in gram-negative bacteremias treated with cefoperazone alone or cefoperazone plus amikacin in granulocytopenic patients[a]

Sex	Age	Underlying disease	Granulocytes per μl	Site of infection	Therapy	Isolates	Susceptibility (Cef/Ami)	MBC (Cef/Ami)	SBA	Outcome
M	64	AML	100[b]	Pulmonary	Cef	*P. aeruginosa* *Klebsiella* sp.	S/R S/S	6.25/12.5 0.1/0.8	1:16 1:1,024	Death on day 5 in shock in spite of addition of Ami + ceftazidime on day 3
F	31	Colon cancer	100[b]	Digestive tract (fistula)	Cef	*P. aeruginosa* *E. coli*	S/R S/S	1.6/25 0.1/0.8	1:32 1:512	Persistent septic shock; improvement after ceftazidime + tobramycin on day 3
M	59	Lymphoma	1,000	Unknown	Cef	*P. aeruginosa*	R/I	100/6.2	ND	No improvement after addition of Ami on day 3; response to ceftazidime + Ami
F	46	Breast cancer	500	Pulmonary	Cef + Ami	*E. coli*	S/S	ND	ND	Death in septic shock after 36 h of therapy; massive *E. coli* bronchopneumonia at autopsy
M	52	Small cell lung cancer	500	Unknown	Cef + Ami	*E. coli* *S. pneumoniae*	S/S —/—	ND ND	ND ND	Death in septic shock after two doses of antibiotics
M	20	Erythroleukemia	100[b]	Unknown	Cef + Ami	*P. aeruginosa*	S/R	6.2/25	1:8	No improvement after 46 h of therapy; response to ceftazidime + Ami (SBA = 1:32)
			100[b]	Pulmonary	Cef + Ami	*P. aeruginosa*	R/R	12.5/12.5	1:8	Blood cultures persistently positive; pathogen became highly resistant (MBC = 100/250); therapy was changed to ceftazidime + tobramycin, but improvement occurred only when the granulocyte count increased

[a] Cef, Cefoperazone; Cef + Ami, cefoperazone plus amikacin; S, susceptible; R, resistant; ND, not done.
[b] Severe granulocytopenia persisted.

Superinfection occurred more frequently in the patients who received cefoperazone plus amikacin (Table 8). Overall, cefoperazone was associated with superinfection in 4 of 80 (5%) patients, whereas the corresponding figure for cefoperazone plus amikacin was 9 of 74 (12%) patients. However, the difference is not statistically significant. Similarly, no significant difference between neutropenic and nonneutropenic patients could be detected; the overall rate of superinfection was 4 of 49 (8.2%) and 9 of 105 (8.5%) patients, respectively.

Both regimens were well tolerated; besides superinfection, no side effects that could be clearly related to the administration of the study regimens were noted. More specifically, diarrhea was not observed, although it might have been feared with 6 g of cefoperazone BID.

DISCUSSION

The present study indicates that cefoperazone is an effective and safe empirical therapy for cancer patients suspected of having gram-negative bacillary sepsis, whatever their granulocyte count is. In nonneutropenic patients, we observed an overall response rate to cefoperazone monotherapy of 88%; 10 of 12 (83%) bacteremic patients were cured. These results confirm previously reported studies from our hospital on the effectiveness of cefoperazone monother-

TABLE 7. SBA 1 H after antibiotic administration in patients with gram-negative bacteremia

Patient group and treatment	Total no. bacteremias	Total no. of determinations	Median SBA value	Range	SBA in failures
Neutropenic					
Cefoperazone	11	9	1:512	1:16–1:2048	1:16, 1:32, ND[a]
Cefoperazone + amikacin	12	10	1:128	1:8–1:2048	1:8, 1:8, ND, ND
Nonneutropenic					
Cefoperazone	12	8	1:256	1:4–1:2048	1:4, 1:64[b]
Cefoperazone + amikacin	15	9	1:512	1:8–1:2048	1:8

[a] ND,-Not done.
[b] Serum-susceptible strain.

TABLE 8. Pathogens responsible for superinfections

Pathogen	No. of patients[a] treated with:			
	Cefoperazone		Cefoperazone + amikacin	
	Neutropenic	Nonneutropenic	Neutropenic	Nonneutropenic
Klebsiella pneumoniae	1			
Morganella morganii			1	
Proteus mirabilis		1		
Pseudomonas cepacia		1		1
Staphylococcus aureus				2
Fungi (proven or suspected)[b]		1	2	3

[a] A total of 25 neutropenic and 55 nonneutropenic patients were treated with cefoperazone; the rates of superinfection were 4 and 5%, respectively. A total of 24 neutropenic and 50 nonneutropenic patients were treated with cefoperazone plus amikacin; the rate of superinfection for both groups was 12%.

[b] $P = 0.15$ (two-sided Fisher's exact test).

apy—even at a lower dosage—in cancer patients with gram-negative bacteremia and normal granulocyte counts (7).

However, these conclusions about therapeutic equivalence must be tempered because of the preponderance in our series of the more susceptible gram-negative pathogens. Certainly, when *Escherichia coli* and *Klebsiella* infections predominate, monotherapy might well be successful even in the granulocytopenic patients. However, there is still need for improvement in treating polymicrobial sepsis, particularly when it involves *Pseudomonas* spp. The combination of cefoperazone plus amikacin gave similar results in nonneutropenic patients, with an overall response rate of 88% and 14 cures in 15 (93%) patients with gram-negative bacteremia.

Likewise, among the 49 febrile neutropenic patients in this study, no difference in the clinical outcome could be detected between those treated with cefoperazone alone and those treated with cefoperazone plus amikacin; 77 and 73% of the patients, respectively, responded to empirical therapy with cefoperazone and cefoperazone plus amikacin; a definite cure was obtained in 8 of 11 and 6 of 12 patients, respectively, with gram-negative bacteremia.

Data on the use of the newest cephalosporins for empirical therapy in granulocytopenic patients are still fragmentary at the present time. Ceftazidime alone was investigated in several studies (4), with encouraging results, even in *P. aeruginosa* infection. With an overall response rate of 77% in this study, cefoperazone monotherapy also appears to be effective in neutropenic patients, but there were only three *P. aeruginosa* infections in our series, and one failed to respond. However, in a previous study, cefoperazone was found to be very active in cancer patients with gram-negative bacteremia (7).

Thus far, we have been unable to detect a difference in the responses of nonneutropenic and neutropenic patients to a high dose of cefoperazone or to the combination of lower-dosage cefoperazone plus amikacin given as empirical therapy for suspected sepsis; other studies failed to document a favorable effect of synergism on the outcome with nonneutropenic patients (1). However, in neutropenic patients, synergistic combinations capable of achieving high SBAs are regularly associated with improved clinical efficacy as compared with single-drug treatment or the use of nonsynergistic combinations (6).

In this study, as could be predicted from previous studies in our laboratory (10), cefoperazone alone resulted in a high SBA against pathogens which all were susceptible in vitro. It is possible that synergy is only one of several possible ways to produce a high bactericidal activity in the blood and that, in fact, the actual SBA level is the major factor responsible for the outcome in cases of gram-negative bacteremia (5, 9).

Only a few studies comparing, prospectively, a new cephalosporin to the same drug combined with an aminoglycoside are available, and preliminary data have been reported so far (4). Although these investigations do not suggest a superiority of the combinations over single-drug therapy, no definite statement can be made at the present time as to whether empirical monotherapy with cefoperazone or another new cephalosporin with adequate anti-*Pseudomonas* activity will be more or less successful than the conventional treatment with aminoglycoside-containing combinations.

High doses of antibiotics might be especially useful to treat deep-tissue infection, where aminoglycosides and beta-lactams, when given in relatively low doses, have suboptimal penetration.

Our recent studies of the SBAs of volunteers receiving new cephalosporins, such as cefoperazone or ceftazidime, with or without amikacin have shown satisfactory activity of these drugs against *P. aeruginosa* and most members of the family *Enterobacteriaceae* (11); cefoperazone and ceftazidime alone were as active as the combination of cefoperazone or ceftazidime with amikacin. However, the rate of killing was greater with the combinations as compared with cefoperazone or ceftazidime alone. Whether the rate of killing will prove to be clinically significant remains to be seen; at the present time, the actual value of the peak SBA appears to be a sufficiently accurate predictive test per se (5, 9).

Nevertheless, even if the SBA is useful to predict the clinical outcome, it does not necessarily provide an explanation for all the failures of antibiotic therapy; although we found that bacteremic patients who failed to respond had lower SBAs as compared with the median value for the entire group, in at least two cases, the SBA was theoretically adequate ($\geq$1:16). Besides the SBA, which reflects both the susceptibility of the pathogen and the levels of antimicrobial drugs achieved in the blood, the overwhelming importance of host factors, such as the effectiveness of phagocytic cells, the integrity of the anatomical barriers against the spread of infection, and probably many others, which all affect the outcome of any infectious process, should be reemphasized here: in our patients, the severity of the underlying disease, profound granulocytopenia, the presence of infectious sites not accessible to drainage, and *P. aeruginosa* and polymicrobial bacteremia were all poor prognostic factors, which may have accounted for the clinical failures in spite of adequate antimicrobial therapy as reflected by adequate SBAs.

The present favorable clinical situation with new cephalosporins, such as cefoperazone, might be related to the relatively rare occurrence of resistant strains. However, the emergence of cephalosporin-resistant strains has already been observed in several other clinical studies (8). We observed six cefoperazone-resistant initial pathogens in six patients, and five of the six patients were associated with a

failure to respond to cefoperazone or cefoperazone plus amikacin. One of these patients died, one improved after the addition of amikacin to cefoperazone, and three others improved only when an active cephalosporin (ceftazidime) was substituted for cefoperazone. There were three superinfections with resistant strains (one *Klebsiella pneumoniae* and two *Pseudomonas cepacia* strains).

In conclusion, our study supports to some extent the concept of single-drug empirical therapy with the newest cephalosporins for suspected gram-negative bacillary sepsis in cancer patients. In all patients with gram-positive-organism bacteremias, therapy could be safely adjusted when the nature and susceptibility of the offending pathogen were established. However, our conclusions might only apply for the time being, when resistance of gram-negative bacilli to these agents is relatively rare, and should be revised if the present favorable situation should change.

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