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Ciprofloxacin Plus Piperacillin Is an Equally Effective Regimen for Empiric Therapy in Febrile Neutropenic Patients Compared With Standard Therapy

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The purpose of this study was to test the comparative efficacy and toxicity of empiric gentamicin and ciprofloxacin, in combination with piperacillin, in febrile patients with treatment-induced neutropenia. Fifty patients were prospectively randomized to receive piperacillin plus gentamicin (PG), and 46 were randomized to receive piperacillin plus ciprofloxacin (PC). The groups were similar in age, sex, diagnosis, duration of neutropenia, and incidence of positive cultures. The two antibiotic regimens were associated with comparable rates of defervescence in the patients with Gram-positive bacteremia. In the patients with Gram-negative bacteremia and those with negative cultures, however, defervescence was more prompt in the PC group. In particular, 27% of the culture-negative patients on PC, compared to only 5% of those on PG, defervesced within 72 hr ($P = 0.015$). Because of the more prompt defervescence in the PC group, amphotericin B was used less frequently; 78% of the patients on PG compared with only 56% of those on PC were started on amphotericin B ($P = 0.025$). PC is an effective alternative to the more traditional PG for treatment of febrile neutropenic hosts who have not been given prophylactic quinolones. More important, PC appears to hasten defervescence compared with PG, especially in culture-negative patients and those with Gram-negative bacteremia, and may decrease the necessity of additional antimicrobial agents such as amphotericin B. Am. J. Hematol. 58:293–297, 1998. © 1998 Wiley-Liss, Inc.

Key words: antibiotics; ciprofloxacin; neutropenia

INTRODUCTION

Fever in the setting of neutropenia is a universal complication of myeloablative therapy and is a common complication of chemotherapy in the treatment of tumors such as lymphoma, breast cancer, and multiple myeloma. The risk of rapid clinical deterioration and even death from sepsis warrants prompt initiation of broad-spectrum empiric antimicrobial therapy. No specific antibiotic regimen has consistently proved superior for initial therapy; a variety of acceptable combinations of antibiotics, as well as single agents, exist for this patient population. General guidelines for the treatment of neutropenic patients with fever have been well-outlined in recent reviews [1–3] and include initiation of parenteral antibiotics in febrile patients with an absolute neutrophil count (ANC) less than 500/mm^3 (or 1,000/mm^3 with an anticipated ongoing decline). Empiric therapy is tailored for each patient based on prevalence of resistant organisms in the institution and the clinical status of the patient. Further treatment decisions are fine-tuned based on culture results.

Traditional empiric antibiotic treatment includes combination therapy with an aminoglycoside plus either an anti-pseudomonal penicillin (such as ticarcillin, piperacillin, or mezlocillin) or a third-generation anti-pseudomonal cephalosporin (such as ceftazidime). Other

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regimens have been developed to avoid the nephrotoxicity of aminoglycosides. Therapy with two beta-lactam drugs, such as ceftazidime and piperacillin [2], or monotherapy with ceftazidime or a carbapenem, such as imipenem, are effective alternatives [4–8]. Monotherapy is particularly useful in patients expected to have a short duration of neutropenia (less than 1 week).

The fluorinated quinolones, another renal-sparing alternative, are a relatively new class of antibiotics that have activity against enterobacteriaceae, *Pseudomonas* species, and some Gram-positive species. The quinolones have been used empirically both in combination regimens [9–16] and as monotherapy [17–19] in the treatment of febrile neutropenic patients. Advantages of the quinolones in this setting include ease of administration (twice-daily dosing), lack of necessity of monitoring drug levels, reduced risk of nephrotoxicity, and the possibility of effective treatment via the oral route. Emergence of resistance to the quinolones is uncommon. The major disadvantage of these drugs is the suboptimal activity against Gram-positive organisms when given as single-agent therapy. These drugs are also more costly.

In order to test the comparative efficacy and toxicity of gentamicin and ciprofloxacin, we conducted a randomized prospective trial of empiric piperacillin plus gentamicin (PG) vs. empiric piperacillin plus ciprofloxacin (PC) in febrile neutropenic patients. The most commonly used doses of ciprofloxacin are 200 or 400 mg iv every 12 hr. Because of the potential severity of infection in neutropenic patients, we used a higher dosing regimen of the drug (400 mg every 8 hr).

STUDY POPULATION AND METHODS

Study Population

Patients undergoing bone marrow transplantation or treatment for hematologic malignancies were eligible if they were expected to have neutropenia lasting at least 7 days. Neutropenia was defined as a neutrophil count less than 500/mm^3 (or 1,000/mm^3 with an anticipated ongoing decline). All patients gave informed consent. Patients known to be hypersensitive to any of the antibiotics and those known to be infected with a pathogen resistant to any of the antibiotics were excluded from the study. Fever was defined as an oral temperature of 38°C or higher. No antibiotic prophylaxis was used.

Antimicrobial Therapy

When a patient developed a fever of 38°C or higher, three sets of blood cultures, urine culture, and oropharyngeal culture were obtained in addition to cultures of any other clinically indicated site. Each patient was then started on piperacillin 4 g iv q. 6 hr and was randomized to receive either gentamicin (loading dose of 1.5 mg/kg iv followed by therapeutic maintenance dosing) or ciprofloxacin 400 mg iv q. 8 hr. Gentamicin levels were adjusted according to peak and trough levels. Additional blood cultures were obtained every 24 hr if fever persisted or if the patient's clinical condition deteriorated. Recovered organisms were tested for sensitivity to all the study antibiotics and for beta lactamase production. If blood or sterile body site culture yielded an organism resistant to the regimen, the antibiotic regimen was changed to target the cultured organism. If a significant side effect was attributed to the piperacillin, imipenem was substituted. In patients in whom the side effect was attributed to gentamicin, the dose of gentamicin was decreased or aztreonam was substituted.

Vancomycin 750 mg q. 8 hr, with dosage adjustment to maintain therapeutic levels, was added if blood cultures yielded Gram-positive organisms in a febrile patient or if blood cultures were persistently positive for Gram-positive organisms regardless of the patient's clinical status. Vancomycin was also started in any patient with ongoing fever and erythema around the exit site of a central catheter.

Amphotericin B was started in any patient who remained persistently febrile for more than 48 hr after antibiotics were started in those with no identifiable source of fever. The initial dose of amphotericin B was 0.5 mg/kg iv q. day; the dose was increased to 1 mg/kg if there was clinical or culture evidence of candidemia. Patients suspected of having aspergillus infection were treated with doses of amphotericin B as high as 1.5 mg/kg, if tolerated.

Evaluation of Therapy

The rate of defervescence, the addition of other antimicrobial agents to the treatment regimen, the development of resistant organisms, the frequency of side effects, and the death rate were all evaluated in the enrolled patients.

Statistical Methods

The chi-square test was used to determine level of significance of differences in frequency of events between the two treatment arms. The Student's *t*-test was used to determine level of significant difference between the two groups for duration of fever and neutropenia.

RESULTS

Patient Characteristics

Between January 1992 and July 1993, 128 patients gave informed consent to participate. Thirty-two were excluded from analysis because of known allergy to study drugs (5), lack of neutropenia (2), lack of fever (4), incomplete records (8), and initiation of antimicrobial therapy before randomization (13). Of the remaining 96 patients, 50 were randomized to receive PG, and 46 were

TABLE I. Patient Characteristics

	Piperacillin + Gentamicin		Piperacillin + Ciprofloxacin (PC)	
Number of patients	50		46	
Age in years (mean ± SD)	45.1 ± 11.6		44.1 ± 13.2	
Male/female	22/28		15/31	
Bone marrow transplant (BMT)[a]	35 (70%)		28 (61%)	
Non-bone marrow transplant	15 (30%)		18 (39%)	
Mean duration of neutropenia (days ± SD)*	13.6 ± 10.4		11.0 ± 5.9	
Diagnoses	BMT	Non-BMT	BMT	Non-BMT
Breast cancer	9	3	14	4
Non-Hodgkin's lymphoma	15	1	7	1
Hodgkin's disease	2		5	1
Chronic myelogenous leukemia	2		1	1
Acute myelogenous leukemia	2	6	2	6
Acute lymphocytic leukemia	1	2		3
Myelodysplastic syndrome		1		
Multiple myeloma	3	1		
Aplastic anemia				1
Melanoma		1		
Total	35	15	28	18

[a]Bone marrow transplant (all autologous transplants except for one patient acute myelogenous leukemia in the PC group).
*$P = 0.27$.

randomized to receive PC. Patient characteristics are described in Table I. The two groups were similar in age, duration of neutropenia, and cancer diagnosis.

Microbiologic and Sensitivity Results

Fourteen (28%) of the patients in the PG group and nine (20%) of those in the PC group had positive blood cultures. The organisms identified in each of the groups are listed in Table II. Two patients in the PG group and three patients in the PC group had blood cultures positive for more than one organism. Coagulase-negative staphylococcal species were the most common of the Gram-positive organisms isolated, occurring in eight of the PG patients and five of the PC patients. *Streptococcus mitis* was isolated from two patients in the PG group and one of the patients in the PC group. *Staphylococcus aureus* was isolated from one patient in the PC group. The Gram-positive bacilli in two of the patients in the PC group were considered contaminants. Four patients in each of the two groups had blood cultures positive for Gram-negative organisms. One patient in the PG group had culture-proven fungemia. None of the patients had persistently positive blood cultures after antibiotics were started.

There were no significant differences in the sensitivities of the organisms in the two groups. Emergence of resistance to any of the study drugs was not seen during the duration of the study.

TABLE II. Microbiologic Results*

	PG	PC
Culture-negative	36 (72%)	37 (80%)
More than one bacterial organism	2	3
Gram-positive organisms		
SSCN	8	5
S. mitis	2	1
S. aureus		1
Gram-positive bacilli	2	
Gram-negative organisms		
E. coli	1	3
P. aeuruginosa	3	1
Candida species	1	0

*PG = piperacillin + gentamicin; PC = piperacillin + ciprofloxacin; SSCN = staphylococcal species, coagulase-negative.

TABLE III. Time to Defervescence*

	PG	PC	*P* value
Number of patients	50	46	
Number of days febrile (mean ± SD)	11.1 ± 6.5	6.7 ± 6.2	0.1
Culture-positive			
Number (percent) of patients	14 (28)	9 (20)	>0.3
Days febrile (mean ± SD)	13.8 ± 6.8	10.4 ± 7.2	0.29
Gram-positive (days febrile, mean ± SD)	11.8 ± 7.0	10.8 ± 9.3	>0.3
Gram-negative (days febrile, mean ± SD)	17.2 ± 5.5	10.0 ± 2.9	0.07
Culture-negative			
Number (percent) of patients	36 (72%)	37 (80%)	>0.3
Days febrile (mean ± SD)	10.0 ± 6.1	8.6 ± 5.8	>0.3
Number (%) afebrile within 3 days	2 (5)	10 (27)	0.015

*PG = piperacillin + gentamicin; PC = piperacillin + ciprofloxacin.

Rates of Defervescence (Table III)

The mean number of days until defervescence in the PG group was 11.1 (SD 6.5) compared with 6.7 days (SD 6.2) in the PC group ($P = 0.1$). Resolution of neutropenia did not predict for defervescence; fever resolved 2 to 30 days before the ANC reached 500/mm^3 in half of the patients in each group. Conversely, fever persisted after resolution of neutropenia in the remaining patients.

When analyzed by culture results, the number of days febrile was also comparable in both groups of patients with Gram-positive bacteremia: 11.8 (SD 7.0) in the PG group and 10.8 (SD 9.3) in the PC group ($P > 0.3$). In the four patients in each group with Gram-negative bacteremia, however, the mean duration of fever was shorter in the PC group than the PG group, being 10.0 days (SD 2.9) in the former and 17.2 days (SD 5.5) in the latter ($P = 0.07$).

In the patients with negative cultures, defervescence was likewise more prompt in the PC group. In particular, 27% of the culture-negative patients on PC, compared to only 5% of those on PG, defervesced within 72 hr ($P = 0.015$).

TABLE IV. Vancomycin and Amphotericin B Use*

	PG	PC	*P* value
Amphotericin B			
All patients	39 (78)	26 (56)	0.025
Culture-negative	27 (75)	20 (54)	<0.1
Vancomycin			
All patients	18 (36)	11 (24)	0.2
Culture-negative	12 (33)	6 (16)	<0.1

*Values are number (%) receiving. PG = piperacillin + gentamicin; PC = piperacillin + ciprofloxacin.

Additional Antimicrobial Agents (Table IV)

Amphotericin B was added to the antibiotic regimen in 78% of all PG patients compared with 56% of all PC patients ($P = 0.025$). Vancomycin was added to the antibiotic regimen in all patients with Gram-positive bacteremia. In the PG group, 33% of the culture-negative patients vs. only 16% of the culture-negative patients in the PC group were started on vancomycin ($P < 0.1$).

Adverse Effects

No significant differences were seen in the incidence of rash, mean rise in serum creatinine, and infectious and non-infectious deaths (Table V).

Gentamicin Serum Levels in the PG Group

Gentamicin peak serum levels were therapeutic (5–8 mcg/ml) after five doses in 34% of the patients and after ten doses in an additional 36% of the patients. Thirty percent of the patients had subtherapeutic gentamicin peak serum levels.

DISCUSSION

A prospective randomized study was conducted comparing two antibiotic regimens for the empiric treatment of febrile neutropenia in patients treated with high-dose or myeloablative chemotherapy, including patients undergoing autologous bone marrow transplantation. Sensitivity patterns at our institution have not changed since completion of the study.

Although rates of defervescence were similar in patients with Gram-positive bacteremia, in the patients with Gram-negative bacteremia and those with negative cultures, defervescence was more prompt in the PC group. Most notable was the fact that 27% of the culture-negative patients on PC, compared to only 5% of those on PG, defervesced within 72 hr ($P = 0.015$). The fact that culture-negative patients defervesced more quickly in one treatment group strongly suggests that infection is most likely the cause of fever in these patients.

Because of persistence of fever in the PG group, compared with the PC group, more of these patients were started on amphotericin B ($P < 0.015$), and more patients received vancomycin in the PG group, although the difference in vancomycin use was not statistically significant among all patients and was of borderline statistical significance in the culture-negative patients.

TABLE V. Adverse Effects*

	PG	PC
Skin rash	9	3
Mean rise in serum creatinine (±SD)	0.4 (±0.3)	0.3 (±0.4)
Deaths	6	2
Infectious	2	0
Non-infectious	4	2

*PG = piperacillin + gentamicin; PC = piperacillin + ciprofloxacin.

The differences between the two treatment arms do not appear to be due to differences in sensitivity patterns in the culture-positive patients since the groups had near-identical sensitivity patterns.

The different rates of defervescence between the two groups may be due, at least in part, to the delay in reaching, or failure to reach, therapeutic gentamicin serum levels in many of the PG patients. The use of extended dosage intervals of aminoglycosides [20], for example, once-daily dosing, may become more common in the treatment of neutropenic patients with fever and may thereby eliminate the delay in reaching therapeutic levels of gentamicin.

One limitation of this study is the small number of patients with each of the diagnoses, making it difficult to draw conclusions for management of febrile neutropenia for the diseases encountered in this study.

In conclusion, the combination of piperacillin-ciprofloxacin is at least as effective as piperacillin-gentamicin and may, through prompt achievement of therapeutic drug levels (or another mechanism), hasten defervescence and thereby decrease the necessity of additional antimicrobial agents. Piperacillin/ciprofloxacin is an effective alternative to more traditional combination regiments for treatment of febrile neutropenic hosts who have not been on prophylactic quinolones and may be particularly useful in patients with renal insufficiency in whom aminoglycosides are relatively contraindicated.

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REFERENCES

1. Pizzo PA: Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 328:1323–1332, 1993.
2. Hughes WT, Bodey GP, Meyers JD, Schimpff SC, Shenep JL, Wade JC, Young LS, Yow MD: Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Inf Dis 161: 381–396, 1990.

3. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG: Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 72:101–111, 1982.
4. Freifeld AG, Walsh T, Marshall D, Gress J, Steinberg SM, Hathorn J, Rubin M, Jarosinski P, Gill V, Young RC, Pizzo PA: Monotherapy for fever and neutropenia in cancer patients: A randomized comparison of ceftazidime versus imipenem. J Clin Oncol 13:165–176, 1995.
5. De Pauw BE, Deriskinski SC, Feld R, Lane-Allman EF, Donnelly JP: Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. A multicenter randomized trial. The Intercontinental Antimicrobial Study Group. Ann Int Med 120:834–844, 1994.
6. Cornelissen JJ, de Graeff A, Verdonck LF, Branger T, Rozenberg-Arska, Verhoef J, Dekker AW: Imipenem versus gentamicin combined with either cefuroxime or cephalothin as initial therapy for febrile neutropenic patients. Antimicrob Agents Chemother 36:801–807, 1992.
7. Leyland MJ, Bayston KF, Cohen J, Warren R, Newland AC, Bint AJ, Cefai C, White DG, Murray SA, Bareford D, Deaney NB: A comparative study of imipenem versus piperacillin plus gentamicin in the initial management of febrile neutropenic patients with haematological malignancies. J Antimicrob Chemother 30:843–854, 1992.
8. Rolston KV, Berkey P, Bodey GP, Anaissie EJ, Khardori NM, Joshi JH, Keating MJ, Holmes FA, Cabanillas FF, Elting L: A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. Arch Int Med 152:283–291, 1992.
9. Bayston KF, Want S, Cohen J: A prospective, randomized comparison of ceftazidime and ciprofloxacin as initial empiric therapy in neutropenic patients with fever. Am J Med 87:269S–273S, 1989.
10. Chan CC, Oppenheim RA, Anderson H, Swindell R, Scarffe JH: Randomized trial comparing ciprofloxacin plus netilmicin versus piperacillin plus netilmicin for empiric treatment of fever in neutropenic patients. Antimicrob Agents Chemother 33:87–91, 1989.
11. Flaherty JP, Waitley D, Edlin B, George D, Arnow P, O'Keefe P, Weinstein RA: Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. Am J Med 5(Suppl 5A):278S–282S, 1989.
12. Philpott-Howard JN, Barker KF, Wade JJ, Kaczmarski RS, Smedley JC, Mufti GJ: Randomized multicentre study of ciprofloxacin and azlocillin versus gentamicin and azlocillin in the treatment of febrile neutropenic patients. J Antimicrob Chemother 26(Suppl F):89–99, 1990.
13. Kelsey SM, Weinhardt B, Collins PW, Newland AC: Teicoplanin plus ciprofloxacin versus gentamicin plus piperacillin in the treatment of febrile neutropenic patients. Eur J Clin Microbiol Infect Dis 11:509–514, 1992.
14. Samuelsson J, Nilsson PG, Wahlin A, Lerner R, Winqvist I, Palmblad J: A pilot study of piperacillin and ciprofloxacin as initial therapy for fever in severely neutropenic leukemia patients. Scand J Infect Dis 24:467–475, 1992.
15. Johnson PRE, Lui Yin JA, Tooth JA: A randomized trial of high-dose ciprofloxacin versus azlocillin and netilmicin in the empirical therapy of febrile neutropenic patients. J Antimicrob Chemother 30:203–214, 1992.
16. Kattan J, Droz JP, Ribrag V, Azab M, Boutan-Laroze A, Andremont A: Non-nephrotoxic empiric antimicrobial therapy in febrile neutropenic cancer patients. Eur J Cancer 28A:867–870, 1992.
17. Malik IA, Abbas Z, Karim M: Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. Lancet 339:1092–1096, 1992. See erratum in Lancet 11:340(11):128, 1992.
18. Kelsey SM, Wood ME, Shaw E, Newland AC: Intravenous ciprofloxacin as empirical treatment of febrile neutropenic patients. Am J Med 87(Suppl 5A):274S–277S, 1989.
19. Johnson PRE, Yin JA, Tooth JA: High dose intravenous ciprofloxacin in febrile neutropenic patients. J Antimicrob Chemother 26(Suppl F): 101–107, 1990.
20. Rodman DP, Maxwell AJ, McKnight JT: Extended dosage intervals for aminoglycosides. Am J Hosp Pharm 51:2016–2021, 1994.