Monotherapy with Intravenous Followed by Oral High-Dose Ciprofloxacin versus Combination Therapy with Ceftazidime plus Amikacin as Initial Empiric Therapy for Granulocytopenic Patients with Fever

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The aim of the present study was to obtain clinical experience with the use of high-dose ciprofloxacin as monotherapy for the treatment of febrile neutropenia episodes (granulocyte count, <500/mm3) compared to a standard regimen and to clarify whether ciprofloxacin administration may be switched to the oral route. In a prospective randomized study ciprofloxacin was given at 400 mg three times a day (t.i.d.) for at least 72 h followed by oral administration at 750 mg twice a day (b.i.d.). That regimen was compared with ceftazidime given intravenously at 2 g t.i.d. plus amikacin given intravenously at 500 mg b.i.d. The frequency of successful clinical response without modification at the end of therapy was almost identical for ciprofloxacin (50% [62 of 124 patients]) compared with that for ceftazidime plus amikacin (50.8% [62 of 122 patients]) in an intent-to-treat analysis; the frequencies were 48.3% (57 of 118 patients) versus 49.6% (56 of 113 patients), respectively, in a per-protocol analysis (P values for one-sided equivalence, 0.0485 and 0.0516, respectively; δ = 10%), with no significant differences among patients with bacteremia and other microbiologically or clinically documented infections and fever of unknown origin. For 82 (66.1%) patients, it was possible to switch from parenteral ciprofloxacin to the oral ciprofloxacin, and the response was successful for 61 (74.4%) patients. The efficacies of the regimens against streptococcal bacteremias were 16.6% (one of six patients) for the ciprofloxacin group and 33.3% (one of three patients) for the combination group (it was not statistically significant), with one breakthrough streptococcal bacteremia observed among the ciprofloxacin-treated patients. Adverse events were mostly self-limited and were observed in 27 (20.6%) ciprofloxacin-treated patients and 26 (19.7%) patients who were receiving the combination. This study demonstrates that high-dose ciprofloxacin given intravenously for at least 3 days and then by the oral route is therapeutically equivalent to the routine regimen of intravenous ceftazidime plus amikacin even in febrile patients with severe neutropenia (polymorphonuclear leukocyte count, <100 mm3). However, it is very important that before an empirical therapy is chosen each hospital determine bacteriologic predominance and perform resistance surveillance.

Cancer patients who become deeply neutropenic as a result of intensive myelosuppressive chemotherapy are at high risk of developing life-threatening infections, and unless they are treated at the first sign of infection, the rate of mortality is high (2, 16). Combinations of antibiotics, for example, an antipseudomonal beta-lactam plus an aminoglycoside, have been preferred as they may provide broad coverage, have high levels of bactericidal activity, and have potential synergistic effects, and there is the possibility that they protect against the development of resistance (7, 18, 19, 28). Predominantly, the combination of ceftazidime plus amikacin has been established as a standard regimen (10, 17, 23). However, aminoglycosides’ nephro- and ototoxic potentials are well documented. To avoid the latter effect, the efficacy of antibiotic monotherapy such as therapy with ceftazidime, cefepime, and the carbapenems has been studied and demonstrated in several studies (4, 24–27). As ciprofloxacin is a potent agent against gram-negative bacteria including Pseudomonas aeruginosa, it was expected that it would become a potential candidate for single-agent therapy in febrile neutropenic patients. While the efficacy of ciprofloxacin in combination with various antibiotics of different classes was demonstrated in early clinical trials (3, 13, 14), only a few studies with ciprofloxacin as monotherapy have been reported (1, 11, 20). However the poor in vitro activity of ciprofloxacin against gram-positive cocci (12, 29) has also been indicated in vivo by Meunier et al. (20), who reported a poor response against infections caused by gram-positive bacteria, especially streptococci, in febrile neutropenic patients. That event caused premature discontinuation of the trial in which intravenous (i.v.) ciprofloxacin at a low dose of 200 to 300 mg twice a day (b.i.d.) was less effective than piperacillin plus amikacin (20). The latter observation becomes more important when one considers the changing pattern of the prevalence of pathogens in favor of gram-positive microorganisms over the past 10 years (10, 22, 30). With the release of an i.v. dose of 400 mg given three times a day (t.i.d.), which is equivalent regarding bioavailability and serum concentrations in serum to 750 mg given orally (p.o.) b.i.d., renewed interest in ciprofloxacin monotherapy in febrile neutropenic patients has arisen.
This study was designed to compare administration of ciprofloxacin, given initially at the higher i.v. dose (400 mg i.v. t.i.d.), followed by administration by the p.o. route (a 750-mg tablet given b.i.d.), with the standard combination regimen of ceftazi
dime plus amikacin as empiric treatment in patients with febrile neutropenia.

**MATERIALS AND METHODS**

**Criteria for eligibility.** The protocol design was based on the guidelines pub-
lished by the Immunocompromised Host Society Consensus Panel (8) Neutro-
zidime plus amikacin as empiric treatment in patients with fol-
lowed by administration by the p.o. route (a 750-mg tablet
rofloxacin, given initially at the higher i.v. dose (400 mg t.i.d.),
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cessfully and patients were able to tolerate oral medication, parenteral cipro-
8 h) plus amikacin (15 mg/kg of body weight/day i.v. over 30 min divided into two
therapy or within the week after the discontinuation of antimicrobials; persis-
tance of the same pathogen (as indicated by species and susceptibility testing) at
fections) without any change to the assigned antibiotic regimen or the addition
without relapse for at least 7 days after the discontinuation of therapy and the
teremia), clinically documented infections, and fever of unknown origin.
ologically documented infections (subclassified into those with or without bac-
mended by the National Committee for Clinical Laboratory Standards (21).
The susceptibilities of all isolated infecting microorganisms were tested by the
sive routine laboratory tests including a urine culture and two sets of blood
history was obtained and physical examination, routine chest X rays, and exten-
Patients were subsequently assigned to one of the two treatment groups in accordance
were still febrile after day 5.

**Toxicity.** Nephrotoxicity was determined as an increase in the serum creatinine
criterion of ≥25% above the baseline concentration, provided that an increase

**Evaluation of response to therapy.** Therapeutic response was evaluated at 72
to 120 h after the onset of empiric therapy (early evaluation) and at the end of
r of therapy. Treatment was considered successful if fever (temperature, ≤37.5°C) and clinical signs (whenever present) of infection were resolved without relapse for at least 7 days after the discontinuation of therapy and the
fecting microorganism was eradicated (for microbiologically documented in-
fected infections) without any change to the assigned antibiotic regimen or the addition
of antibiotics to the assigned regimen. Treatment was classified as a failure if the
(i) the patient died from either the presenting infection or another one; (ii) the
(3) a clinical or microbiological relapse occurred within 7 days after the
discontinuation of therapy; or (iv) a superinfection was observed. Patients in-
ected with microorganisms resistant to the study drug were not excluded from
clinical evaluation. This was decided because the indication “empirical ther-
” was considered nonevaluable if the patient had a proven viral or
fungi infection or if a major protocol violation occurred. Bacteriological re-
sponses were defined as follows: eradication, causative organism absent at end of
therapy; relapse, causative organism absent at end of therapy but reappearance of
the same pathogen (as indicated by species and susceptibility testing) at a
follow-up 7 days posttherapy; superinfection, appearance of a new infection at
any site that was caused by another organism and that occurred either during
therapy or within the week after the discontinuation of antimicrobials; persis-
tence, causative organism present at the end of therapy.

**Antimicrobial drug regimens.** Patients initially received either ciprofloxacin at
400 mg i.v. t.i.d. over a period of 1 h or ceftazidime at (2 g i.v. over 10 min every 8 h)
and amikacin at 15 mg/kg of body weight/day (over 30 min divided doses). If after 72 h two patients who were receiving ciprofloxacin responded suc-
cessfully and patients were able to tolerate oral medication, parenteral cipro-
fluoxacin therapy was switched to the p.o. route at a dosage of 750 mg b.i.d. Patients in the comparator group continued the i.v. regimen.

**Blood ciprofloxacin levels.** In a limited group of five patients ciprofloxacin levels in serum were measured after administration of the third dose of
therapy at 0.5, 1, 2, 3, 4, 8, and 12 h postdosing. Excluded from the kinetic study
were patients with renal insufficiency, vomiting, diarrhea, mucositis, and gastro-
inestinal bleeding. Ciprofloxacin levels were measured by the high-pressure liquid chromatography method.

**Duration of therapy.** The duration of therapy ranged from 7 to 14 days. Study
patients with a successful response to therapy received the protocol medication
for a minimum of 7 days, the last 5 days of which had to be without fever, unless
a clinical deterioration, adverse reaction, or death occurred. For patients with an
early recovery from neutropenia, however (granulocyte count, >1,000/mm³), and
a complete resolution of signs and symptoms of infection, even after 3 days of
defervescence and a minimum duration of 5 days of therapy, antibiotic treatment
could be stopped. If the patient showed neither improvement of clinical signs or
symptoms nor a decrease in fever, therapy was discontinued after 72 h and other
antimicrobials were instituted. Usually, imipenem was empirically prescribed,
with addition of vancomycin in case of signs of infection, the history of

tival i.v. catheters or septic shock. These patients did not become asymptomatic
after 72 h but who had clinical improvement and whose fevers responded con-
tinued therapy for 2 more days. However, medications were withdrawn if they
were febrile after day 5.

**Sample size estimation and statistical plan.** The primary objective of this
study was to compare the clinical success rates of both study regimens. On the
basis of previously published data (8), a success rate of 75% for treatment with
ceftazidime plus amikacin and a success rate of 80% for treatment with ciprofloxacin
were assumed. By using 10% as a clinically relevant difference in success rates (α = 0.05, β = 80%), the sample size estimation resulted in the need for
108 valid patients in each treatment group to prove the hypothesis that high-dose
ciprofloxacin therapy is not less effective than therapy with cefazidime plus amikacin. The expected success rates assumed here were based on previous
studies not performed according to the guidelines applied in this study.

The primary efficacy variable was clinical outcome (success and initial response
without modification versus failure), and it was analyzed by a one-sided modifi-
cation of the Mantel-Haenszel statistic method. A supportive analysis of the
clinical outcome that consisted of a one-sided 95% confidence interval as well as
a two-sided 90% confidence interval was performed. A secondary efficacy vari-
ble, bacteriological response (eradication versus persistence and superin-
fecction) was analyzed exploratively in the same way that the primary efficacy
variable was.

**RESULTS**

The study was started in May 1992 and was completed in May 1995. A total of 263 febrile neutropenic patients were
randomized: 131 in the ciprofloxacin group and 132 in the ceftazi
dime plus amikacin group. In 79.1% of the patients acute leukemia was the underlying disease, another 17.9% of the
patients suffered from high-grade malignant non-
Hodgkin’s lymphoma, and the remaining 3% of the patients suffered from aplastic anemia and other malignances (Table 1).

Demographic data for patients in both treatment groups were generally comparable. No difference in the rate of acute
myelogenous leukemia or non-Hodgkin’s lymphoma was found (P = 0.177 and P = 0.382, respectively). Infection was hospital
acquired in 59% of the patients in the ciprofloxacin group and 60% of the patients in the ceftazidime plus amikacin group.
Two hundred forty-six patients were valid for intent-to-treat (ITT) analysis (124 in the ciprofloxacin group and 122 in the ceftazi
dime plus amikacin group), while 231 of them were valid
for per-protocol (PPR) analysis (118 in the ciprofloxacin group

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and 113 in the ceftazidime plus amikacin group). Among the patients not eligible for ITT analysis, 7 were randomized into the ciprofloxacin regimen and 10 were randomized into the ceftazidime plus amikacin regimen. The reasons for noneligibility for the patients in the two groups were temperature of 38°C (two and two patients, respectively), wrong diagnosis (one and four patients, respectively), and missing clinical evaluation (four and four patients, respectively). The reasons for the exclusion of 15 patients (valid for ITT analysis) from the PPR analysis for the patients in the two groups were as follows: antibacterial prophylaxis was not withdrawn (four and two patients, respectively), a granulocyte count of <500 cells/mm³ was never fulfilled (one and five patients, respectively), concomitant i.v. antibiotics like vancomycin or teicoplanin were used (one and one patients, respectively), and ciprofloxacin treatment was underdosed (one patient). Four patients given ciprofloxacin and seven patients given ceftazidime plus amikacin had granulocyte counts between 500 and 1,000 cells/mm³ at enrollment. A rapid fall below 500 cells/mm³ (in 48 h) was seen in three patients in the ciprofloxacin group and two patients in the ceftazidime plus amikacin group, with the decrease remaining in all patients in the subsequent days.

Response to therapy. The response to therapy was first determined at 72 h after the onset of empiric therapy. Of the evaluable febrile patients at this time, 66 of 124 (53.2%) in the ciprofloxacin group and 70 of 122 (57.4%) in the ceftazidime plus amikacin group had successful clinical responses. Patients with bacteremia had a better initial response (16 of 31 [51.6%]) when they were treated with ciprofloxacin than when they were treated with the comparator drugs (11/29 [37.9%]). However, this difference was not statistically significant. An additional 17 patients (13.7%) in the ciprofloxacin group and 13 patients (10.7%) in the ceftazidime plus amikacin group who did not become afebrile after 72 h but who had either clinical improvement or who were at least clinically stable and for whom no change in empiric therapy was required became afebrile after another 48 h. Therefore, in total, at day 5 of therapy 66.9 and 68.1% of the patients in the two groups, respectively, were considered to have been successfully treated (Table 2).

### Table 1. Demographic characteristics of study population with febrile neutropenia treated with ciprofloxacin or ceftazidime plus amikacin

| Characteristic                                | Ciprofloxacin | Ceftazidime plus amikacin |
|-----------------------------------------------|---------------|---------------------------|
| No. of patients                              | 131           | 132                       |
| Mean ± SD age (yr)                           | 54.0 ± 17.1   | 54.8 ± 16.9               |
| Mean ± SD wt (kg)                            | 71.2 ± 12.1   | 71.6 ± 11.9               |
| Sex (no. of males/no. of females)             | 89/42         | 90/42                     |
| No. (%) of patients with the following underlying disease: |               |                           |
| Acute myelocytic leukemia                     | 73 (55.7)     | 88 (66.7)                 |
| Acute lymphocytic leukemia                    | 26 (19.8)     | 21 (15.9)                 |
| Non-Hodgkin’s lymphoma                       | 29 (22.1)     | 18 (13.6)                 |
| Other                                         | 3 (2.4)       | 5 (3.8)                   |
| No. (%) of patients with:                    |               |                           |
| Oral antibacterial prophylaxis               | 6             | 5                         |
| Hospital-acquired infection                   | 79 (59)       | 89 (60)                   |
| Mean ± SD (range) treatment duration (days)   | 7.6 ± 3.4 (4–20) | 7.5 ± 3.5 (2–19) |
| No. (%) of patients with:                    |               |                           |
| Myelosuppressive chemotherapy during empiric treatment | 31            | 22                        |
| Central venous catheter                      | 121           | 119                       |
| Median granulocyte count at study entry (no. of cells/mm³ [10³]) | 0.040         | 0.050                     |
| Range of neutrophil counts (no. of cells/mm³ [10³]) | 0.000–0.972   | 0.000–0.950               |
| No. of patients with <100 cells/mm³ at study entry | 69            | 69                        |
| % Patients with granulocyte count at defervescence that was: |               |                           |
| Increasing                                    | 57            | 54                        |
| Stable or declining                          | 28            | 28                        |

* Co-trimoxazole with or without colistin.

b Fever appeared at least at 48 h postadmission.

### Table 2. Early response rates as defervescence at 72 and 120 h after the start of treatment (ITT analysis)

| Infection* | Ciprofloxacin | Ceftazidime plus amikacin |
|------------|---------------|---------------------------|
| 72 h       | 66 (53.2)     | 17 (13.7)                 |
| 120 h      | 60 (48.4)     | 20 (16.4)                 |
| 72 h       | 70 (57.4)     | 13 (10.7)                 |
| 120 h      | 66 (53.2)     | 17 (13.7)                 |

* MDI, microbiologically documented infection; CDI, clinically documented infection; FUO, fever of unknown origin.
should be pointed out that because therapy was initiated on an empirical basis, patients infected or colonized with organisms resistant to the study drug were not excluded from the clinical evaluation. Therefore, among the patients in the ciprofloxacin group, 13 patients with bacteremia caused by ciprofloxacin-resistant microorganisms were clinical failures; however, 2 patients with urinary tract infections caused by organisms resistant to ciprofloxacin were clinical successes. Twelve microorganisms resistant to ceftazidime were isolated from patients in the group treated with ceftazidime plus amikacin, and 11 of the patients were clinical failures; 1 patient with bacteremia caused by *Escherichia coli* resistant to ceftazidime but susceptible to amikacin was a clinical success.

In the ITT analysis a successful clinical outcome was documented for 50.0% of the patients receiving the ciprofloxacin treatment, whereas a successful clinical outcome was documented for 50.8% of the patients receiving the ceftazidime plus amikacin treatment. The clinical response rate in the PPR analysis was 48.3% (57 of 118) for patients receiving ciprofloxacin and 49.6% (56 of 119) for patients receiving ceftazidime plus amikacin. Success rates for both treatment groups were further analyzed by documented type of infection (Table 3). Of the 75 patients (33.7%) with microbiologically documented infections, 60 (26.5%) presented with bacteremia which was caused in 55 patients by a single organism and in 5 patients by multiple organisms (Table 3). Among the patients with bacteremia caused by a single organism, 27 (49.1%) patients were infected with gram-positive organisms and 28 (50.9%) were infected with gram-negative organisms. Coagu-

### Table 3. Clinical success rates by class of infection and infecting microorganisms at end of therapy (ITT analysis)

| Infection | Ciprofloxacin | Ceftazidime plus amikacin |
|-----------|---------------|----------------------------|
| Microbiologically documented infection | 18/40 (45.0) | 16/35 (45.7) |
| Bacteremia | 14/31 (45.1) | 12/29 (44.8) |
| Bacteremia caused by single gram-positive organism | 5/14 (35.7) | 3/13 (23.1) |
| Coagulase-negative staphylococci | 4/7 (57.1) | 1/8 (12.5) |
| *Staphylococcus aureus* | 0/1 | 1/2 |
| Viridans group streptococcus | 1/4 | 0/1 |
| *Streptococcus agalactiae* | 0/1 | 1/1 |
| *Streptococcus pneumoniae* | 1/1 | 0/1 |
| *Streptococcus sanguis* | 9/16 (56.2) | 8/12 (66.7) |
| *Enterococcus faecalis* | 3/5 (60.0) | 5/7 (71.4) |
| *Klebsiella* sp. or *Enterobacter* sp. | 0/3 | |
| *Pseudomonas aeruginosa* | 5/7 (71.4) | 2/3 (66.7) |
| Other gram-negative bacteria | 1/1 | 2/2 |
| Polymicrobial | 0/1 | 1/4 |
| Gram-positive organism | 0/2 | 0/2 |
| Gram-negative organism | 0/1 | 0/1 |
| Mixed gram-positive organism and gram-negative organism | 4/9 (44.4) | 3/6 (50.0) |
| Nonbacteremic | 12/28 (42.9) | 12/30 (40.0) |
| Clinically documented infection | 32/56 (57.1) | 12/30 (40.0) |
| Fever of unknown origin | 62/124 (50.0) | 60/122 (50.8) |
| Overall | 62/124 (50.0) | 60/122 (50.8) |

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positive bacteria and 40 (53.3%) were gram-negative bacteria (Table 5). The most frequently identified microorganisms were *E. coli* (24%), *Staphylococcus epidermidis* (17.4%), *P. aeruginosa* (13.4%), and viridans group streptococci (9.4%). Bacterial superinfections as breakthrough bacteremias were documented in eight patients; six receiving ciprofloxacin and two receiving ceftazidime plus amikacin. The organisms isolated from blood during monotherapy were *P. aeruginosa* (*n* = 1), *Enterococcus faecalis* (*n* = 1), *Staphylococcus aureus* (*n* = 1), *S. epidermidis* (*n* = 1), *Streptococcus agalactiae* (*n* = 1), and *Acinetobacter baumannii* (*n* = 1), while the organisms isolated during combination therapy were *Klebsiella pneumoniae* (*n* = 1) and *S. aureus* (*n* = 1). Among the patients in the ciprofloxacin group three superinfections occurred while the patients were receiving i.v. therapy and three superinfections occurred while the patients were receiving oral therapy. All strains except *E. faecalis* were resistant to ciprofloxacin. In the two superinfected patients in the comparator drug treatment group the microorganisms isolated in blood cultures, with the exception of a *Klebsiella* strain susceptible to amikacin and resistant to ceftazidime, were resistant to both ceftazidime and amikacin.

**Switch from i.v. to p.o. ciprofloxacin.** Treatment with i.v. ciprofloxacin was switched to treatment with p.o. ciprofloxacin in 82 patients after at least 72 h of i.v. therapy (61 after 3 days, 11 after 4 days, and 10 after 6 days of i.v. treatment). This was done if the patient had responded clinically to the i.v. regimen and was able to tolerate p.o. medication. Among patients switched from i.v. to p.o. therapy, 61 (74.4%) responded successfully and 21 (25.6%) were considered failures at the end of the evaluation of therapy.

**Adverse events.** All 263 patients included in the study were evaluable for safety, including 131 in the ciprofloxacin group and 132 in the ceftazidime plus amikacin group. The proportions of patients who experienced adverse events were similar in both treatment groups: 27 (20.6%) receiving ciprofloxacin and 26 (19.7%) receiving ceftazidime plus amikacin. Regarding single adverse events 8 were reported as probable and 13 were reported as possible for the ciprofloxacin group, whereas 6 were reported as probable and 20 were reported as possible for the comparator treatment group. The types of adverse reactions are described in detail in Table 6. Because of adverse events, p.o. ciprofloxacin was discontinued prematurely in one patient with pseudomembranous colitis and ceftazidime plus amikacin was discontinued in five patients.

**Blood ciprofloxacin levels.** Mean ± standard deviation serum ciprofloxacin levels at 0.5, 1, 2, 4, 6, 8, and 12 h after the administration of ciprofloxacin at 750 mg p.o. were found to be...
and to fill the gaps in the antimicrobial activity of patients over the past 10 years in favor of gram-positive cocci activity against MRSA and streptococci is minimal (9, 12, 29). Pseudomembranous colitis, incomplete ileus, diarrhea, crystalluria, and nephrotoxicity were seen in patients who were treated with ciprofloxacin at 200 mg i.v. daily, while the other antibiotic regimens were more effective against bacteremias resistant to ciprofloxacin and ceftazidime among the major gram-positive organisms isolated from this study. In the latter settings the following rates of resistance were reported: 71.4% for patients given piperacillin plus gentamicin and 35.7 versus 29% for patients given piperacillin plus netilmicin and reported total response rates of 66 and 65%, respectively, while a favorable response rate of 78% for patients receiving ciprofloxacin plus teicoplanin versus a favorable response rate of 49% for patients given piperacillin plus gentamicin was observed by the same investigators (13). Testing ciprofloxacin as monotherapy at a dose of 400 mg b.i.d., Johnson et al. (11) reported similar success rates for patients treated with ciprofloxacin (44%) and azlocillin plus netilmicin (48%). Among patients receiving ciprofloxacin at 200 mg i.v. daily, Bayston et al. (1) described successful outcomes for 71% of patients with treatment modification and successful outcomes for only 14% of patients without treatment modification; these rates were 64 and 28%, respectively, among patients receiving ceftazidime at 2 g t.i.d.

From the reported overall results it is evident that within the limited power of this study, monotherapy with high-dose ciprofloxacin i.v. and then ciprofloxacin p.o is as effective as the standard combination of ceftazidime plus amikacin (50 versus 50.8%). The findings of lower efficacies than those predicted in the initial power calculation (about 75%) probably be attributed to the fact that success rates were taken from previous studies not based on Immunocompromised Host Society guidelines applied in this study. According to the Immunocompromised Host Society, success was defined as a lasting return of body temperature from a fever to a normal level (<37.5°C) and a resolution of all signs and symptoms of infection without the addition of any other antimicrobial agent; any modification was considered a failure. It was not anticipated during the planning for the study that compliance with Immunocompromised Host Society guidelines would lead to lower success rates. It may be confusing because the wide ranges of results reported from various trials that indicate treatment success are different. This can be explained by the variety of definitions used to evaluate the therapeutic efficacy of empirical therapy, therefore demonstrating the necessity of clear and similar terms to render results from different studies comparable (5, 17).

In the evaluation of the causative organisms, it was apparent that both regimens are more effective against bacteremias caused by gram-negative organisms than those caused by gram-positive organisms (Tables 3 and 4), at least among patients from the two Greek tertiary-care hospitals which participated in this study. In the latter settings the following rates of resistance to ciprofloxacin and ceftazidime among the major gram-negative organisms isolated from 1992 to 1995 were observed: E. coli, 6 versus 3%; P. aeruginosa, 20 versus 29%; and methicillin-susceptible S. aureus and MRSA strains resistant to ciprofloxacin, 5 versus 95%. The numerical superiority of the combination therapy against bacteremia caused by gram-negative organisms (66.7 versus 56.2%) may be explained by a synergistic effect of the combination, but it should be pointed out that ciprofloxacin was at least as effective as ceftazidime plus amikacin against P. aeruginosa infections (71.4 versus 66.7%) (Table 3). On the other hand, the fact that in this study treatment with ciprofloxacin resulted in a higher success rate against bacteremia caused by gram-positive cocci (35.7 versus 23.1%) may be attributed to its better efficacy against coagulase-negative staphylococci (57.1 versus 12.5%). However, the differences were not statistically significant.

In a clinical study conducted by the European Organization for the Research and Treatment of Cancer (EORTC), an over-

### TABLE 6. Adverse events in 263 neutropenic patients treated with ciprofloxacin or ceftazidime plus amikacin

| Type of adverse event                        | Ciprofloxacin | Ceftazidime + amikacin |
|---------------------------------------------|---------------|------------------------|
| Abnormal elevation of levels of:            | 6             | 7                      |
| SGOT<sup>a</sup>                            | 8             | 9                      |
| SGPT<sup>a</sup>                            | 3             | 5                      |
| Bilirubin                                   | 5             | 3                      |
| Alkaline phosphatase                        | 2             | 1                      |
| Crystalluria                                | 1             | 1                      |
| Diarrhea<sup>a</sup>                        | 1             | 1                      |
| Incomplete ileus<sup>a</sup>                | 1             | 1                      |
| Pseudomembranous colitis<sup>a</sup>        | 1             | 1                      |
| Otoxicity                                   | 1             | 1                      |
| Nephrotoxicity                              | 1             | 1                      |
| Total                                       | 27            | 26                     |

<sup>a</sup> SGOT, serum glutamic oxaloacetic transaminase.
<sup>b</sup> SGPT, serum glutamic pyruvic transaminase.
<sup>c</sup> Reported in patients while on oral ciprofloxacin they were receiving.

2.34 ± 2.05, 3.30 ± 2.13, 3.74 ± 2.10, 4.0 ± 0.55, 4.17 ± 1.80, 2.80 ± 2.40, and 0.46 ± 0.40 µg/ml, respectively.

**Mortality.** A total of 12 deaths (5%) were reported during the study: 7 in the ciprofloxacin group and 5 in the ceftazidime plus amikacin group. All patients who died had persisting profound neutropenia. Two of them responded to ciprofloxacin and became afebrile but died of cerebral hemorrhage. One patient with pneumonia that was not microbiologically documented died on day 3 with septic shock. Another two patients with pneumonia that did not respond to ciprofloxacin died 2 and 3 days, respectively, after their treatments were shifted to other antibiotic regimens. The first patient developed septic shock due to bacteremia caused by P. aeruginosa resistant to all protocol agents, and in the second patient pneumonia was complicated by adult respiratory distress syndrome. Finally, antibiotic treatments for two more patients who did not respond to ciprofloxacin were changed, but the patients died on days 13 and 19 after the beginning of treatment, respectively, with the patients never becoming afebrile. The documented causes of death were pulmonary infection in the one patient and renal and hepatic failure in the other one. Among the patients who were given ceftazidime plus amikacin, one died on day 2 because of cerebral hemorrhage. Four other nonresponders to therapy were given alternative empiric antibiotic regimens. The causes of death were severe pneumonia (not microbiologically documented) with respiratory failure (n = 2), septic shock without microbiologically documented infection (n = 1), and septic shock due to bacteremia caused by methicillin-resistant S. aureus (MRSA) (n = 1) resistant to all protocol agents. In patients who died because of sepsis, alternative therapeutic regimens included imipenem (n = 2) or vancomycin plus ceftazidime (n = 1) or the combination of imipenem plus vancomycin (n = 5).

**DISCUSSION**

Ciprofloxacin is very active against members of the family Enterobacteriaceae and P. aeruginosa, which are frequently implicated in infections in neutropenic hosts. However, its in vitro activity against MRSA and streptococci is minimal (9, 12, 29). Because of the changing pattern of infection in neutropenic patients over the past 10 years in favor of gram-positive cocci (10, 22, 30) and to fill the gaps in the antimicrobial activity of ciprofloxacin, in preliminary studies ciprofloxacin was given to febrile neutropenic patients at the conventional dose of 200 mg b.i.d., mostly combined with antibiotics active against gram-positive cocci and rarely as monotherapy. Kelsey et al. (14) compared ciprofloxacin combined with benzylpenicillin to piperacillin plus netilmicin and reported total response rates of 66 and 65%, respectively, while a favorable response rate of 78% for patients receiving ciprofloxacin plus teicoplanin versus a favorable response rate of 49% for patients given piperacillin plus gentamicin was observed by the same investigators (13).
all success rate of 65% was achieved for patients treated with 200 or 300 mg of ciprofloxacin i.v. b.i.d., whereas an overall success rate of 91% was achieved for patients given piperacillin plus amikacin (20). Patients with gram-positive coccal bacte-
riaemia caused by gram-positive cocci, however, had particularly poorer outcomes. In six of eight patients (75%), therapy with ciprofloxacin failed, whereas no failure was seen in the four corresponding patients in the comparator treatment group. In
the present study the dose of i.v. ciprofloxacin was increased to 400 mg t.i.d. (1,200 mg/day), which is two- to three-fold greater than that used previously with the hope of increasing the effi-
cacy of treatment against gram-positive organisms compared to the dose used in previous studies, in which the dose was much lower. However, similar to the EORTC study (20) only
5 of 14 patients (35.7%) with bacteremia caused by gram-
positive cocci responded to high-dose ciprofloxacin, while the response rate to cefazidime plus amikacin was even worse (3 of 13 patients [23.1%]) (Table 3).

The test for the null hypothesis that treatment with cipro-
floxacin has a success rate more than 10% lower than that of treatment with cefazidime plus amikacin could be rejected at the 5% level (P = 0.485), but the lower limit of the 95% one-sided confidence interval was from −12.12 to infinity (due to different underlying test procedures). The 95% two-sided confidence interval goes from −14.13 to 12.49. Current U.S. Food and Drug Administration regulations require an equi-
valence delta of 20% for demonstration of noninferiority for success rates in the better of the two arms of less than 80%. Therefore, according to U.S. Food and Drug Administration criteria noninferiority was demonstrated in this study.

Recently, an effort has been made to replace parenteral antibiotics with p.o. therapy, at least for low-risk patients with febrile cancer and neutropenia (6). To our knowledge, this is the second study with febrile neutropenic patients reported in the literature in which ciprofloxacin was switched from the i.v.
to the p.o. route with a successful outcome. In two studies (6, 15), it was shown that in febrile low-risk hospitalized patients with cancer who had neutropenia that was expected to resolve within 10 days, oral empirical therapy with ciprofloxacin at 750 mg b.i.d. plus amoxicillin-clavulanate at 625 mg t.i.d. was as effective as i.v. therapy. In the present study, in contrast to the results of previously reported trials, more than 75% of the patients included in the study were suffering from acute leuk-
emia, were mostly deeply neutropenic (granulocyte counts, <100 mm³), and were expected to have protracted neutrope-
nia. The fact that 82 of the 124 patients in the ciprofloxacin group could be switched from i.v. to p.o. therapy and had a response rate of 74.4% indicates that the rate of relapse after an initial response does not increase under p.o. therapy com-
pared to that with continued standard i.v. therapy. On the
other hand, serum drug levels after p.o. intake among patients who did not have mucositis were found to be in the expected range, but with rather delayed and prolonged peaks.

The death rates were similar (5%) in the two treatment groups either during treatment or at the follow-up period, which is a rather low percentage for similar high-risk popula-
tions of patients. The tolerability of both study regimens was good. The reported adverse events in three patients who were receiving p.o. ciprofloxacin necessitated discontinuation of drug in only one patient, who had pseudomembranous colitis (Table 6).

In this study the number of febrile patients who were suc-
cessfully treated without modification with high-dose cipro-
floxacin alone was comparable to the number of patients who were successfully treated with the standard antibiotic combi-
nation regimen. However, it is very important for the appro-
priate selection of empirical treatment in the febrile neutropenic host that each hospital determine bacteriologic predominance and perform resistance surveillance. A monotherapy approach with ciprofloxacin may not be recommended in centers in which infections caused by gram-positive cocci are clearly dom-
inant or in centers with significant numbers of infections caused by ciprofloxacin-resistant gram-negative organisms. There is no doubt that the standard combination of cefaza-
dime plus amikacin should also not be used in centers with significant numbers of infections caused by cefazidime-resis-
tant gram-negative organisms.

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