Randomized Trial of Cefepime Monotherapy or Cefepime in Combination with Amikacin as Empirical Therapy for Febrile Neutropenia

K. Tamura,[1] K. Imajo,[2] N. Akiyama,[4] K. Suzuki,[5] A. Urabe,[6] K. Ohyashiki,[7] M. Tanimoto,[3] T. Masaoka,[8] and the Japan Febrile Neutropenia Study Group[a]

[1]Fukuoka University Hospital, Fukuoka; [2]Okayama Citizen's Hospital and [3]Okayama University Hospital, Okayama; [4]Metropolitan Bokutoh Hospital, [5]Japan Red Cross Medical Center, [6]NTT Kanto Medical Center, and [7]Tokyo Medical University Hospital, Tokyo; [8]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.[a]

A multicenter open randomized trial was conducted to compare cefepime monotherapy with cefepime/amikacin combination (dual) therapy in treating febrile neutropenic patients with hematologic disorders. Among the 189 evaluable patients, 5.8% had microbiologically and 10.6% had clinically documented infections. Excellent response was seen in 32.6% and 45.7% of monotherapy and dual therapy recipients, respectively, at day 3 ($P = .065$). At day 3, patients with neutrophil counts of <500/μL receiving dual therapy had a better response than did those receiving monotherapy (45% vs. 27.6%; $P = .024$). The same was true for patients with leukemia. Adverse events were minimal, and early death was observed in 7 patients in the dual therapy group and 5 patients in the monotherapy group. Overall, cefepime monotherapy is as effective as dual therapy for the initial treatment of febrile neutropenic patients. Further study is warranted for patients with severe neutropenia and leukemia who may benefit from dual therapy.

Chemotherapy for hematologic malignancies is quite intensive and often complicated with severe neutropenia that sometimes induces life-threatening infection. Some features are distinctive of infections occurring during a neutropenic period. Fever is often the only major symptom, and signs and symptoms, if present, are so subtle that it is difficult for clinicians to determine causes of fever, even after obtaining a thorough history and performance of physical examination and laboratory testing, including imaging studies. Finally, the causative microorganisms are also rarely identified, and the clinical course is sometimes rapidly progressive to a lethal outcome. Therefore, clinicians should be aware of the above-mentioned nonspecific but important findings when a patient with neutropenia becomes febrile. Prompt initiation of empirical therapy with broad-spectrum antimicrobials is mandatory.

The combination of an aminoglycoside and an antipseudomonal β-lactam has been commonly used as empirical therapy for febrile neutropenia in Japan. Since the Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in neutropenic patients with fever were published in 1990 [1], investigators from the United States and Europe have reported that monotherapy with a single broad-spectrum cephalosporin or carbapenem is not worse, at least, than is therapy with well-established combination regimens.

Among cephalosporins, ceftazidime and cefepime can be used as single agents for treating febrile neutropenic patients, according to the IDSA guidelines. Ceftazidime has strong antimicrobial activity against *Pseudomonas aeruginosa,* whereas it has limited activity against methicillin-susceptible *Staphylococcus aureus* and streptococci. It is also suspected that monotherapy with third-generation cephalosporins, including ceftazidime,

[a] Investigators and institutions who participated in the study are listed at the end of the text.

Reprints or correspondence: Dr. K. Tamura, Department of Internal Medicine, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan (ktamura@fukuoka-u.ac.jp).

Clinical Infectious Diseases 2004;39:S15–24

1058-4838/2004/3901S1-0004$15.00

promotes the selection and spread of extended-spectrum β-lactamase–producing microorganisms and *ampC*-derepressed mutants. Cefepime is a fourth-generation cephalosporin with activity against both methicillin-susceptible *S. aureus* and *P. aeruginosa*, and it has been extensively studied as monotherapy for febrile neutropenia, with good control of the disease. Therefore, it has been approved by the US Food and Drug Administration to be used as empirical monotherapy for treating patients with febrile neutropenia.

Although monotherapy with cefepime is recommended by the IDSA guidelines, such an approach has never been discussed within the Japanese medical community. Experts from Japan and also from the United States and Europe who had dealt with malignant diseases and infectious complications gathered in Miyazaki, Japan, in 1998, for a consensus meeting to establish practical guidelines for the use of antimicrobial agents in patients with febrile neutropenia [2]. Subsequently, in 2000, the Japan Febrile Neutropenia Study Group was established and conducted a multicenter, randomized, controlled study to compare monotherapy with combination therapy and to validate the recommendation proposed in this consensus meeting.

METHODS

The study was an open, unblinded, prospective randomized trial. It was conducted according to the Evidence-Based Recommendations on Antimicrobial Use in Febrile Neutropenia in Japan proposed at the Miyazaki meeting [2].

Patient eligibility. Patients hospitalized in 1 of the 30 participating centers who had given written consent to participate in the study were eligible if they met the following criteria: they were≥16 years of age and they had malignant hematologic disease or severe aplastic anemia, chemotherapy-induced neutropenia with a polymorphonuclear neutrophil count of <1000/μL at enrollment, a temperature of ≥37.5°C, and a life expectancy of ≥3 months. Body temperature was measured at an axillary fossa after perspiration was wiped off, according to routine practice in Japan.

Patients were excluded if they had been taking systemic antibiotics during the 72 h prior to study entry because of a febrile episode, had a known history of hypersensitivity to cephalosporins or aminoglycosides, were undergoing a blast crisis in chronic myelogenous leukemia, were infected with HIV (although HIV testing was not a prerequisite for inclusion), or had renal failure. Pregnant or lactating women were also excluded.

Patients with septic shock, infection with coagulase-negative staphylococci, or infection with organisms resistant to cefepime were also excluded. Patients receiving nonabsorbable oral agents for prophylactic gut decontamination were eligible, as were those receiving prophylaxis with antivirals and antifungals, if these agents were used according to the protocol at the participating centers, except for intravenous amphotericin B, which is associated with a high frequency of pyretic adverse effects.

Randomization procedure. Patients were randomly assigned to receive either cefepime (1–2 g iv b.i.d.) or cefepime at the same dosage combined with amikacin (100–200 mg iv b.i.d.) as a first-line regimen when they developed neutropenic fever. Randomization was done automatically at the time of enrollment on the exclusive Web site located at the University Hospital Medical Information Network Center, the University of Tokyo Hospital, through the personal computer at each institution.

Clinical evaluation and classification of fever. Patients were evaluated clinically before randomization and then daily by the investigator at each center. Evaluation included obtaining a thorough history and performing physical examination, complete blood cell count, urinalysis, blood chemistry profiles, measurement of C-reactive protein, chest radiography, 1 or 2 blood cultures, and other appropriate cultures in case of a possible focus of infection. This evaluation was done before antibiotic therapy was instituted.

Clinical data were collected on day 0, day 3, day 7, the day the patient recovered from aplasia (neutrophil count of ≥1000/μL), day 4 after discontinuation of the study treatment, and at any time that a clinical event led to a modification of the antiinfective therapy. At least complete blood cell count and C-reactive protein determination were done serially until the end of the observation period or until 30 days after the start of initial antibiotic therapy.

Each febrile episode was classified as fever of unknown origin, clinically documented infection, or microbiologically documented infection, according to international guidelines [3]. New infections were defined as infections caused by a new pathogen from the original site of infection or by any pathogen from a new site of infection, either during the study treatment or within 4 days after discontinuation of study therapy.

Bacteriological studies. Samples for at least 2 sets of blood cultures were obtained from 2 different sites on day 0, before the study treatment was begun. Any isolate from culture of blood was considered to be a pathogen, except for coagulase-negative staphylococci (CNS). If 2 sets of cultures yielded results positive for CNS, it was considered a pathogen, if other clinical signs and symptoms were suggestive of bacteremia rather than contamination. A bacteriological sample was also obtained from any site of suspicion on day 0. These samples were collected again from all patients on day 3. Further bacteriological samples were obtained as necessary until eradication of the organism was documented or until the initial antibiotic treatment was changed.

Study drug administration and antibiotic treatment schedule. Cefepime at a dose of 1–2 g diluted in 50–100 mL of

sterile isotonic saline or 5% dextrose in water was infused over a 30-min period every 12 h. Amikacin was administered over 30 min immediately after infusion of cefepime was completed, for patients assigned to combination therapy. The drug therapy was started on day 0 and was given for 3 days, unless the patient's clinical condition worsened or microorganisms resistant to these antibiotics were isolated.

If the patient became afebrile within 72 h and a causative microorganism was not identified by day 4, the initial treatment was continued for ⩾4 additional days. If the etiology was established, the antibiotic therapy was adjusted according to the susceptibility profile of the isolate, and treatment with broad-spectrum antibiotics was maintained for ⩾7 days, irrespective of the neutrophil count.

If fever persisted for >72 h or recurred after an initial response, the causes of fever were reassessed with a thorough history and physical examination, serological testing for fungal antigens (e.g., β–D-glucan), and blood culture, in addition to the studies done on day 0.

If the etiologic agent was not identified, amikacin was added to the treatment regimen for patients in the monotherapy arm, and efficacy was reassessed after 48 h. For patients in the combination-therapy arm, cefepime was changed to another β-lactam. The use of a glycopeptide (vancomycin), an azole antifungal, or amphotericin B was considered according to the algorithm recommended in the Japanese guidelines [2] (figure 1).

Granulocyte colony-stimulating factor (G-CSF) was given to patients with severe neutropenia who did not show a response to the initial therapy for 3 days and had not been taking G-CSF. In contrast, human normal immunoglobulin preparations,

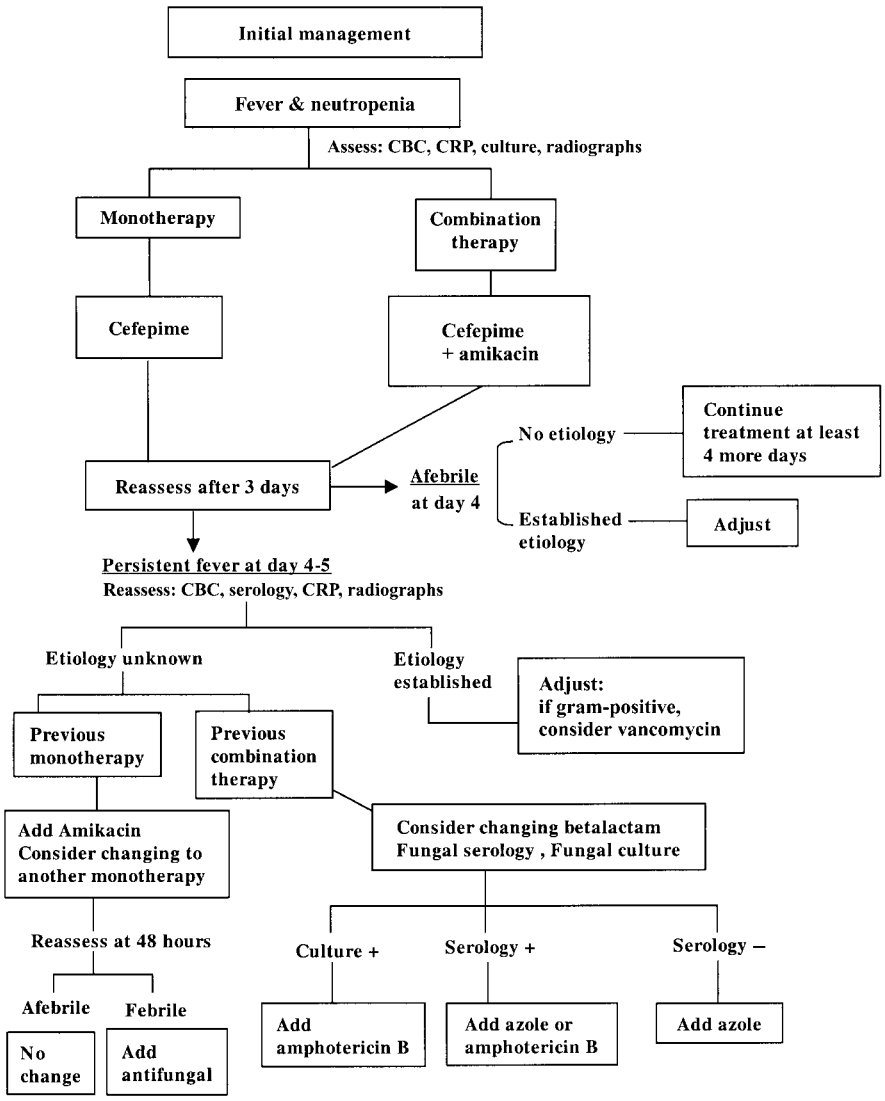

Figure 1. Treatment algorithm for febrile neutropenia. Patients were randomized to receive either monotherapy with cefepime or dual therapy with a combination of cefepime and amikacin. CBC, complete blood cell count; CRP, C-reactive protein; serology, serological test results.

corticosteroids, and antineoplastic agents were used only if therapy with these agents was started before or 4 days after institution of the initial antibiotic therapy.

Response to therapy. Patients were evaluated for the efficacy of therapy on day 3 to determine whether the initial antibiotics needed to be changed. The response criteria were as follows: excellent response was defined as occurrence of defervescence (<37.0°C) within 72 h after the start of the assigned empirical therapy, and no response was defined as a body temperature of >37°C by the end of the first 72 h, in which case the antimicrobials were changed. The final evaluation for treatment response was performed at day 7 and used the following criteria: excellent response was defined as defervescence (<37.0°C) that occurred within 3 days after the start of the initial therapy and lasted for >4 days with significant improvement of infection-related signs, symptoms, and abnormal laboratory values; good response was defined as complete defervescence (<37.0°C) that occurred by day 7 with improvement of infection-related symptoms and laboratory findings; and no response was defined as a therapeutic response other than those described above. The possibility of recurrence was considered if initial defervescence occurred by day 3 but fever recurred during treatment with the same antibiotics, in association with signs and symptoms of possible infection. Tumor fever was considered if the number of leukemic cells increased or the tumor began to grow again rapidly with no signs or symptoms or laboratory findings suggesting other causes of fever after the initial response to the study drug.

Toxicity. Patients were carefully monitored for side effects, and all intercurrent events were reported. Determinations of hematologic and biochemical parameters and urinalysis were done at least on days 0 and 3, as well as 7 and 4 days after the termination of study therapy. Renal function was assessed with serum creatinine levels, and hepatic function with serum bilirubin, transaminase, and alkaline phosphatase levels. All adverse effects were categorized according to the World Health Organization criteria for cancer treatment [4].

Statistical analysis. Data required to assess treatment response and adverse events were recorded through a computer at each institution on the Web page of the central registration office. The data were analyzed by the biostatistician in the central office. The comparability of treatment arms was analyzed by χ^2 *t* test or Wilcoxon rank-sum test for quantitative variables, and the degree of significance for success rates was evaluated by χ^2 test.

If there was no difference in treatment response between monotherapy and combination therapy, as other studies have reported [5–10], the number of patients required to detect a significant difference at the 95% confidence level had to be >77 patients in each arm. Therefore, we planned to accrue 100 patients in each arm for 1 year after each institutional review board approved the study. The preliminary analysis was scheduled for 1 year after patient accrual, if accrual was too slow to reach the number of patients expected.

RESULTS

Characteristics of the study population. Between 1 May 2000 and 1 February 2002, there were 201 patients from 30 institutes enrolled in this study and randomized to receive cefepime

Table 1. Demographic and clinical characteristics of patients in a study of monotherapy with cefepime or dual therapy with a combination of cefepime and amikacin.

Characteristic	Proportion or no. (%) of patients		
	Monotherapy (*n* = 95)	Combination therapy (*n* = 94)	Overall (*n* = 189)
Sex, male/female	57/38	57/37	114/75
Underlying disease			
Leukemia	45 (47.4)	45 (47.9)	90 (47.6)
Lymphoma	36 (37.9)	36 (38.3)	72 (38.1)
Myelodysplastic syndrome	5 (5.3)	7 (7.4)	12 (6.3)
Anaplastic anemia	2 (2.1)	3 (3.2)	5 (2.6)
Myeloma	4 (4.2)	1 (1.1)	5 (2.6)
Other	3 (3.2)	2 (2.1)	5 (2.6)
Neutrophil count at baseline, cells/μL			
100	54 (56.8)	53 (56.4)	107 (56.6)
100–499	22 (23.2)	27 (28.7)	49 (25.9)
500–999	19 (20.0)	14 (14.9)	33 (17.5)
Neutrophil count of <100 cells/μL for ⩾6 days	40 (42.1)	35 (37.2)	75 (39.7)
Previous G-CSF treatment	33 (34.7)	35 (37.2)	68 (36.0)

NOTE. G-CSF, granulocyte colony-stimulating factor.

Table 2. Antibiotics and other agents added on day 3 to the empirical regimen that might modify the clinical course.

Regimen, drug or drug class added	No. of patients, by day of therapy that drug was added to regimen					
	Day 3	Day 7	Day 10	Day 14	Day 30	Total
Cefepime						
Amikacin	19	1	0	0	0	20
G-CSF	29	2	1	1	0	33
Antibiotics	1[a]	1	1	2	0	5
Antifungals	7	5	1	2	0	15
Analgesics	1	0	0	0	0	1
Antivirals	0	0	0	0	0	0
γ-Globulin	0	2	0	1	0	3
Other	4	0	0	0	0	4
Any change	8[b]	13	7	2	0	30
Cefepime and amikacin						
Amikacin	0	0	0	0	0	0
G-CSF	34	1	0	0	0	35
Antibiotics	4[c]	4	1	0	0	9
Antifungals	7	3	1	3	0	14
Analgesics	1	0	0	0	0	1
Antivirals	1	0	0	0	0	1
γ-Globulin	1	0	0	0	0	1
Other	5	0	0	0	0	5
Any change	21[d]	7	3	4	1	36

NOTE. G-CSF, granulocyte colony-stimulating factor.

[a] Clindamycin.

[b] Meropenem, 4 patients; panipenem, 3; and cefoperazone/sulbactam, 1.

[c] Glycopeptide, 4 patients.

[d] Imipenem, 4 patients; meropenem, 6; panipenem, 6; other carbapenem, 2; ceftazidime, 2; and erythromycin, 1.

monotherapy ($n = 100$) or cefepime/amikacin combination therapy ($n = 101$). Twelve patients were not evaluable for the efficacy of therapy because of inclusion criteria violations, including body temperature of <37.5°C (3 patients) and neutrophil counts of >1000/μL (2 patients) at the start of treatment, tumor fever (1 patient), and early discontinuation other than treatment failure (6 patients).

Thus, the remaining 189 patients were evaluable for clinical response. The patients' demographic and clinical characteristics at enrollment are summarized in table 1. There were 95 patients in the cefepime arm and 94 in the cefepime/amikacin combination arm.

The 2 groups were comparable with respect to underlying malignancies, neutrophil counts on enrollment, use of G-CSF, and duration of neutrophil counts of <500/μL. The patients with leukemia and myelodysplastic syndrome accounted for >50% of each group.

Febrile episodes were analyzed and classified as fever of un-

Table 3. Clinical efficacy of initial empirical therapy as of day 3 and day 7 of therapy for patients in the 2 treatment arms.

Day after start of initial therapy	Response rate, by treatment arm				
	Cefepime ($n = 95$)		Cefepime and amikacin ($n = 94$)		
	Proportion[a]	Percentage	Proportion[a]	Percentage	*P*
3	31/95	32.6	43/94	45.7	.065
7	48/95	50.5	55/94	58.5	.269

NOTE. Patients whose initial empirical therapy was changed on day 3 were evaluated as having experienced treatment failure on day 7. $P \leq .05$ was considered significant.

[a] No. of patients with response/no. treated.

Table 4. Treatment response in the 2 treatment arms, by modified intent-to-treat analysis.

Day	No. (%) of patients, by treatment arm: Cefepime (n = 95)	Cefepime and amikacin (n = 94)	P
3	31 (32.6)	43 (45.7)	.065
7	61 (64.2)	72 (76.6)	.062
10	76 (80.0)	82 (87.2)	.179
14	78 (82.1)	87 (92.6)	.031
30	82 (86.3)	90 (95.7)	.023

NOTE. Patients who responded after day 7 include those whose empirical therapy was changed on day 3. $P \leqslant .05$ was considered significant.

known origin in 83.6% of the patients, clinically documented infection in 10.6%, and microbiologically documented infection in 5.8%.

Clinical response. A primary evaluation for clinical response was done on day 3. Table 2 summarizes the changes in antibiotics and other agents on day 3 and the subsequent observation days that might modify the clinical course. Seventy-four patients who responded to the initial antibiotic regimen within the first 3 days continued to receive the same regimen. Thirty-one patients (32.6%) treated with cefepime monotherapy and 43 patients (45.7%) treated with combination therapy achieved complete defervescence within the first 72 h. For the 115 patients who remained febrile after 72 h, therapy was changed according to the algorithm in figure 1. In the monotherapy arm, amikacin was added to the treatment regimen for 19 patients and cefepime was replaced by other antibiotics for 8 patients (meropenem for 4, panipenem for 3, and cefoperazone/sulbactam for 1). Antifungals were added to the treatment regimen for 7 patients. In the combination-therapy arm, cefepime was replaced by other antibiotics for 21 patients (ceftazidime for 2, a carbapenem for 18, and erythromycin for 1); glycopeptides were added to the regimen for 4 patients, and antifungals for 7.

Clinical results are summarized in tables 3 and 4. The rate of complete defervescence within 3 days was not different between the monotherapy and the dual-therapy arms (P = .065), although patients in the latter arm tended to have a quicker response to the initial therapy. The rate of significant improvement at day 7 rose to 50.5% from 32.6% in the monotherapy arm and to 58.5% from 45.7% in the combination-therapy arm (table 3). Again, there were no statistically significant differences in the rate of defervescence between the monotherapy and the dual-therapy arms.

The subset analysis showed that, among patients with neutrophil counts of <500/μL at the start of treatment, more patients in the combination-therapy arm than in the monotherapy arm had a clinical response (table 5). The same is true for patients with leukemia: patients receiving combination therapy had a better clinical response than did those treated with cefepime alone (48.9% vs. 24.4% at day 3 [P = .016]; 73.3% vs. 53.3% at day 7 [P = .049]) (table 6).

Of the 19 patients randomized to receive monotherapy who had amikacin added to their regimen on day 4, there were 6 (31.6%) who responded by day 7. Two (28.6%) of the 7 patients who had an antifungal added to their regimen on day 4 responded by day 7.

The number of patients with microbiologically or clinically documented infection was very small in this study (table 7).

Table 5. Clinical response according to baseline neutrophil count among patients in the 2 treatment arms.

Treatment arm, outcome	No (%) of patients with response, by day after initiation of therapy and baseline neutrophil count: Day 3, <500 cells/μL	Day 3, ⩾500 cells/μL	Day 3, Subtotal	Day 7, <500 cells/μL	Day 7, ⩾500 cells/μL	Day 7, Subtotal
Cefepime						
Effective	21 (27.6)[a]	10 (52.6)[b]	31 (32.6)	48 (63.2)[c]	13 (68.4)[d]	61 (64.2)
Not effective	55 (72.4)	9 (47.4)	64 (67.4)	28 (36.8)	6 (31.6)	34 (35.8)
Subtotal	76 (100)	19 (100)	95 (100)	76 (100)	19 (100)	95 (100)
Cefepime and amikacin						
Effective	36 (45.0)[e]	7 (50.0)[f]	43 (45.7)	60 (75.0)[g]	12 (85.7)[h]	72 (76.6)
Not effective	44 (55.0)	7 (50.0)	51 (54.3)	20 (25.0)	2 (14.3)	22 (23.4)
Subtotal	80 (100)	14 (100)	94 (100)	80 (100)	14 (100)	94 (100)
All patients						
Effective	57 (36.5)	17 (51.5)	74 (39.2)	108 (70.1)	25 (75.8)	133 (78.8)
Not effective	99 (63.5)	16 (48.5)	115 (60.8)	48 (29.9)	8 (24.2)	56 (21.2)
Total	156 (100)	33 (100)	189 (100)	156 (100)	33 (100)	189 (100)

NOTE. P values are as follows: a vs. b, P = .038; e vs. f, P = .729; a vs. e, P = .024; b vs. f, P = .881; c vs. d, P = .669; g vs. h, P = .382; c vs. g, P = .109; d vs. h, P = .252.

Table 6. Clinical efficacy as of day 7 of therapy for patients in the 2 treatment arms with leukemia and other hematologic disorders.

	Response rate, by treatment arm				
	Cefepime (n = 95)		Cefepime and amikacin (n = 94)		
Underlying disease	Proportion[a]	Percentage	Proportion[a]	Percentage	P
Leukemia	24/45	53.3	33/45	73.3	.049
Other hematologic diseases	37/50	74.0	39/49	79.6	.510

NOTE. $P \leq .05$ was considered significant.

[a] No. of patients with response as of day 7/no. treated.

Blood cultures yielded a pathogen for 11 patients, whereas 20 patients had clinically diagnosed infections. Treatment response was achieved in 36.4% of patients with microbiologically documented infections and in 60.0% of those with clinically diagnosed infections (tables 7 and 8). There were no statistically significant differences in the response rates between arms.

Seven early deaths occurred (on days 5, 6 [2 patients], 7, 11, 22, and 23) in the monotherapy arm, and 5 early deaths occurred (on days 8, 18 [2 patients], 22, and 24) in the combination-therapy arm. Of 4 patients who died within 7 days of therapy in the monotherapy arm, 1 died of septic shock on day 5 and another died of progression of leukemia and infection on day 6.

Adverse events. Adverse events possibly related to therapy occurred in 5 patients in the monotherapy arm and in 4 in the combination-therapy arm. These events, including skin rash in 3 patients, renal dysfunction in 1, and mild elevation of liver function test results in 5, were mild and did not require cessation of treatment with the study drug, except for 1 patient receiving combination therapy, who had skin rash.

DISCUSSION

There was no consensus regarding empirical antibiotic therapy for febrile neutropenic patients in Japan until recently. Since the early 1980s, comparative or randomized trials comparing monotherapy with a β-lactam and combination of a β-lactam and an aminoglycoside have been conducted in United States and Europe [5–9]. The results indicated that monotherapy was comparable in effectiveness to combination therapy and was considered to be even better because of less toxicity and lower costs. These results were extensively reviewed by the IDSA, who released the guidelines for the use of antimicrobials in the management of febrile neutropenic patients in 1990 [1] and revised them in 1997 [3] and 2002 [11]. The IDSA guidelines state that monotherapy can be considered a standard initial therapy for uncomplicated febrile episodes in neutropenic patients.

The US Food and Drug Administration and the IDSA Joint Committee also in 1992 published the guidelines for the evaluation of new anti-infective drugs for the treatment of febrile neutropenia [12]. Cefepime was approved by the US Food and Drug Administration for use as empirical monotherapy for febrile neutropenia after it was evaluated for the aforementioned guidelines [12].

In February 1998, the Japanese guidelines for the use of antimicrobials in treating febrile neutropenic patients were established during the consensus meeting held in Miyazaki, Japan. Japanese hematologists and distinguished experts from the United States and Europe who had made important contributions to this field attended this meeting. After this meeting, the Japan Febrile Neutropenia Study Group was established to

Table 7. Clinical response among patients with various causes of febrile neutropenia in the 2 treatment arms.

	Response rate, by treatment arm				
	Cefepime (n = 95)		Cefepime and amikacin (n = 94)		
Cause of fever	Proportion[a]	Percentage[b]	Proportion[a]	Percentage[b]	P
Bacteremia	1/4	25.0	3/7	42.9	.554
Clinically diagnosed infection	5/8	62.5	7/12	58.3	.852
Fever of unknown origin	42/83	50.6	45/75	60.0	.236
Total	48/95	50.5	55/94	58.5	.269

NOTE. Percentage of patients with good response to antibiotics at day 7. $P \leq .05$ was considered significant.

[a] No. of patients with response/no. treated.

[b] Percentage of patients with good response to antibiotics at day 7.

Table 8. Outcomes in the 2 treatment arms among patients with microbiologically documented infection.

Infecting microorganism	Outcome, by treatment arm	
	Cefepime (n = 5)	Cefepime and amikacin (n = 9)
Coagulase-negative staphylococci	…	Infection eradicated, 1; unknown outcome, 1
Enterococcus species	Unknown	…
Escherichia coli	Unknown	Eradicated
Enterobacter cloacae	Unknown	…
Pseudomonas aeruginosa	Unknown	Infection decreased, 1; no change, 1
Aeromonas hydrophila	Eradicated	…
Methicillin-resistant *Staphylococcus aureus*	…	Eradicated
Stomatococcus mucilaginosus	…	Eradicated
Candida species	…	Unknown
Candida inconspicua	…	Superinfection
Total no. of infections eradicated	1	4

conduct a randomized study designed to confirm the usefulness of the proposed guidelines in clinical practice in Japan.

The objective of the study was to compare the efficacy of cefepime monotherapy with that of the cefepime/amikacin combination therapy as an empirical treatment for febrile neutropenic patients who had hematologic malignancies or severe aplastic anemia as underlying diseases. On the basis of the literature, a response rate as high as 50% was expected with both regimens. The efficacy of the combination therapy was 45.7%, as expected, but that of the monotherapy was rather low, 32.6%, although the difference was not statistically significant. Also, 4 patients in the monotherapy arm died during the first 7 days of treatment, 2 of them from infection-related complications. The subset analysis showed that the patients with leukemia and/or grade 4 neutropenia experienced a better response to the combination therapy.

There are possible reasons why treatment with cefepime alone (at a dosage of 1–2 g b.i.d.) tended to achieve complete defervescence less frequently than did combination therapy. First, the dosages used in this study were low. The 1–2 g b.i.d. dosage of cefepime, as well as the 200–400 mg b.i.d. dosage of amikacin, are maximum dosages approved for use in treating patients with severe infection in Japan. The dosages used in Japan appear to be one-third to one-half those used in the United States or Europe, where cefepime is usually given at a dosage of 2 g t.i.d. and amikacin at a dosage of 7.5 mg per kg of body weight twice daily (e.g., 900 mg for a patient weighing 60 kg). On the other hand, another group of investigators from a southwestern district of Japan [10] who studied the same doses of antimicrobials as in the present study to treat similarly ill or even more seriously ill patients reported no differences in efficacy between monotherapy and dual therapy. The activity of cephalosporins is time dependent rather than concentration dependent, as is the case for aminoglycosides, so they are more effective when administered 3–4 times a day than they are at the twice-daily schedule used in the present study and approved in Japan. It is therefore suggested that cefepime, if used as a single agent, be given to patients with severe febrile neutropenia at 8-h intervals (i.e., 1–2 g iv q8h instead of 1–2 g iv q12h).

Another issue that should be discussed is the definition of treatment response. Our study protocol defined the response to treatment as a decline in body temperature, measured at the axillary fossa, to <37.0°C. The response criteria used in most US and European studies include significant improvements in fever, as well as in other clinical signs and symptoms. This does not necessarily mean complete defervescence. Urabe et al. [13] conducted a single-arm study with a protocol otherwise similar to ours. They started empirical therapy with cefepime as a single agent and added amikacin to the regimen if signs and symptoms failed to improve by day 3 of the empirical therapy. The response rate at day 6 was 56.9% for monotherapy and rose to 64.7% when amikacin was added to the treatment. The response criterion in this study was also complete defervescence.

In our study, the logistic regression analysis targeting the outcome on day 7 found that severity of illness was the only pretreatment variable that proved to be a strong predictor ($P < .001$). The number of patients with severe infection was greater in the monotherapy arm than in the combination-therapy arm ($P = .086$), and this might have favored the combination-therapy arm (data not shown).

The second objective of our study was to assess the validity of the guidelines [2]. Guidelines are meant to assist clinicians in decision-making related to the management of the conditions specified in each guideline [3, 11]. In this respect, when patients are treated according to the guideline recommendations, the outcome should be superior or at least comparable

to the outcomes achieved in current clinical practice. The overall response rates with monotherapy and combination therapy were similar, although the latter tended to be associated with a better response in patients with severe neutropenia and leukemia. There were no differences in the rates of complications, adverse events, and mortality between the 2 arms. This suggests that the recommendation proposed by the Miyazaki consensus meeting—that is, monotherapy with cefepime or a carbapenem—applies to most patients with febrile neutropenia, although combination with an aminoglycoside should be considered for patients with leukemia and neutrophil counts of $<500/\mu L$ that predictably last for >5–6 days.

In this respect, the 2002 IDSA guidelines [11] proposed that patients with febrile neutropenia be categorized into 2 risk groups: low risk and high risk. The purpose of this division is to allow low-risk patients to be treated with oral antimicrobials in an outpatient setting, to avoid unnecessary hospitalizations and long, expensive courses of parenteral antibiotic therapy. On the other hand, it is necessary to specify predictive factors for selecting high-risk patients, to prevent kidney-function alterations associated with the addition of an aminoglycoside to a single-agent regimen. Rubenstein et al. [14] investigated a similar cohort and reported a 32% prevalence of documented infections during a febrile episode, which were associated with worse outcomes, compared with patients with true fever of unknown origin.

In our study, the response rates on day 14 were 82.1% and 92.6% in the monotherapy and combination-therapy arms, respectively. Although the difference appears to be statistically significant, it is difficult to accept because many changes in management were made after day 7. Therefore, the discussion should be confined to the results obtained before day 10.

In conclusion, cefepime monotherapy, in general terms, is as effective as cefepime in combination with amikacin for the empirical treatment of febrile neutropenic patients, but a subset analysis suggests that the patients with acute leukemia and/or severe neutropenia might respond to the combination therapy better than to therapy with cefepime alone. Future studies should focus on the patients' background risk and treatment response.

Japan Febrile Neutropenia Study Group Members

Principal Investigators and locations of participating centers are as follows: M. Imamura, Hokkaido University Medical Hospital; Y. Niitsu, Sapporo Medical University Hospital; S. Aoki, Niigata University Medical Hospital; N. Nomoto, Niigata Kobari Hospital; S. Maruyama, Niigata South Hospital; K. Ozawa, Jichi Medical School Hospital; M. Bessho, Saitama Medical School Hospital; K. Oshimi, Juntendo University Hospital; K. Ohyashiki, Tokyo Medical University Hospital; H. Mizoguchi, Tokyo Women's Medical University Hospital; M. Kato, Toho University Omori Hospital; A. Urabe, NTT Kanto Medical Center; K. Suzuki, Japan Red Cross Medical Center; M. Higashihara, Kitasato University Hospital; T. Hotta, Tokai University Hospital; K. Ohnishi, Hamamatsu Medical University Hospital; H. Saito, Nagoya University Hospital; Y. Kobayashi and M. Taniwaki, University Hospital, Kyoto Prefectural University of Medicine; Y. Tomiyama, Osaka University Hospital; M. Hasegawa, Osaka Medical College Hospital; M. Hino, Osaka City University Hospital; S. Fukuhara, Kansai Medical University Hospital; A. Kanamaru, Kinki University Hospital; M. Tanimoto, Okayama University Hospital; K. Imajo, Okayama Citizen's Hospital; A. Kimura, Hiroshima University Research Institute for Radiation Biology and Medicine; T. Kyo, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital; M. Harada, Kyushu University Hospital; K. Tamura, Fukuoka University Hospital; and M. Sata, Kurume University Hospital.

Acknowledgments

We thank all physicians, microbiologists, and data managers involved in this trial, and the following expert consultants who made valuable suggestions in the preparation of the manuscript: Jean A. Klastersky (Institut Jules Bordet, Universite Libre de Bruxelles, Brussels), John Wingard (University of Florida, Shands Cancer Center, Gainesville), Juan Jose Picazo (University of Madrid), Kenneth Rolston (University of Texas M. D. Anderson Cancer Center, Houston), and Reuben Ramphal (University of Florida, Gainesville). We also thank the University Hospital Medical Information Network Center, the University of Tokyo Hospital, for their assistance in the computer-aided enrollment and randomization of the patients on the study Web site.

Financial support. National Institute of Radiological Sciences.

References

1. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis **1990**; 161:381–96.
2. Masaoka T. Conclusions and recommendations: evidence-based recommendations on antimicrobial use in febrile neutropenia in Japan. Int J Hematol **1998**; 68(Suppl 1):S39–40.
3. Hughes WT, Armstrong D, Bodey GP, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis **1997**; 25:551–73.
4. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, **1979**:16–21.
5. Ramphal R, Gucalp R, Rotstein C, Cimino M, Oblon D. Clinical experience with single agent and combination regimens in the management of infection in the febrile neutropenic patient. Am J Med **1996**; 100(Suppl 6A):83S–9S.
6. Klastersky JA. Treatment of neutropenic infection: trends towards monotherapy? In: Klastersky JA, eds. Febrile neutropenia. Berlin: Springer-Verlag, **1997**:47–52.
7. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N Engl J Med **1986**; 315:552–8.
8. Winston DJ, Ho WG, Bruckner DA, Champlin RE. Beta-lactam antibiotic therapy in febrile granulocytopenic patients: a randomized trial comparing cefoperazone plus piperacillin, ceftazidime plus piperacillin, and imipenem alone. Ann Intern Med **1991**; 115:849–59.
9. Leyland MJ, Bayston KF, Cohen J, et al. A comparative study of im-

ipenem versus piperacillin plus gentamicin in the initial management of febrile neutropenic patients with haematological malignancies. J Antimicrob Chemother **1992**; 30:843–53.
10. Tamura K, Matsuoka H, Tsukada J, et al. Cefepime or carbapenem treatment for febrile neutropenia as a single agent is as effective as a combination of 4th-generation cephalosporin + aminoglycosides: comparative study. Am J Hematol **2002**; 71:248–55.
11. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis **2002**; 34:730–51.
12. Hughes WT, Pizzo PA, Wade JC, Armstrong D, Webb CD, Young LS. Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. Clin Infect Dis **1992**; 15(Suppl 1): S206–15.
13. Urabe A, Toyama K, Asano S, et al. Efficacy of cefepime in the treatment of severe infections accompanying hematological diseases [in Japanese]. Antibiot Chemother **1999**; 15:103–11.
14. Rubenstein EB, Kim YJ, Legha R, Rolston K, Multinational Association of Supportive Care in Cancer. Documented infections in febrile neutropenic patients presenting with apparent fever of undetermined origin: a wolf in sheep's clothing [abstract 5]. In: Program and abstracts of the 12th International synposium on Supportive Care in Cancer (Washington, DC). Supportive Care Cancer **2000**; 8:242.