Cefepime versus Ceftazidime as Empiric Therapy of Febrile Episodes in Neutropenic Patients

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Introduction

The last two decades have seen a number of changes in the medical management of neutropenic patients. The availability of new myelosuppressive chemotherapeutic agents, together with the increased use of both allogenic and autologous bone marrow transplantation (BMT), has resulted in a dramatic increase in the number of patients who are severely neutropenic. Similarly, the development of hematopoietic growth factors has allowed the use of more aggressive chemotherapeutic regimens. Therapeutic advances such as these have resulted in dramatic improvements in the outcome of many cancer patients. Today, cures can be expected for many patients with leukemia or lymphoma, and prolonged survival has been described for those diagnosed with a variety of solid tumors. The management of the neutropenic period, which is usually associated with an increased risk of morbidity, has thus become increasingly important.

Infectious complications are a major threat to neutropenic patients. While the risk of bacterial infection in these patients is probably of greatest immediate concern, both fungal and viral infections have become an increasingly serious problem. The various risk factors for infection in the neutropenic period have been well characterized in a number of historic epidemiologic observations. The depth and duration of neutropenia is the most important risk factor, with an absolute neutrophil count (ANC) of less than 100 cells/μl presenting the greatest risk [1]. The subject's underlying cancer, along with the type and intensity of treatment for that cancer, influence both the risk of infection and the spectrum of infecting organisms. Patients with leukemia usually have the highest rate of bacterial infection [2]. For some patients with leukemia or lymphoma, as well as for a selected group of patients with solid tumors, BMT has become a viable treatment option [3]. The neutropenia that follows BMT is usually severe and lasts 3–4 weeks [4, 5]. The number of patients undergoing this procedure is growing rapidly; it is estimated that more than 15 000 transplants are performed per year.

Focal signs of infection are frequently absent in the neutropenic patient population; fever may represent the earliest, and sometimes the only, sign of infection. In the late 1960s and early 1970s the majority of cases of fever in patients with neutropenia could be attributed to a microbiologically or clinically defined infection [6]. Over the course of the last two decades there has been an evolution in the trends of infection in this subject population. In the 1970s infections caused by gram-negative pathogens such as *Escherichia coli, Klebsiella pneumoninae*, and

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Pseudomonas aeruginosa predominated [7, 8]. Since the 1980s infections caused by gram-positive organisms have become more prevalent, particularly those due to *Staphylococcus aureus,* coagulase-negative staphylococci, and viridans streptococci [9, 10]. Interestingly, as the prompt initiation of therapy has become more routine, the likelihood of a definitive microbiologic diagnosis has decreased; the cause of fever may not be identified in as many as 70% of patients [11]. The increased use of broad-spectrum prophylactic antibiotics, targeted against a variety of bacterial, fungal, and viral pathogens, may also contribute to this phenomenon. The initiation of empiric antibiotic therapy is the cornerstone in the management of febrile episodes in neutropenic patients. It is well recognized that the prompt initiation of empiric antibiotics significantly reduces the morbidity and mortality associated with untreated infections in these patients [12].

The choice of empiric antibiotic regimens has evolved as well. Early studies demonstrated the utility of a combination of a β-lactam and an aminoglycoside [13, 14]. Such regimens, which have been well studied both in the United States and in Europe, have been effective at eradicating the spectrum of gram-negative pathogens that predominated at the time the studies were conducted. In recent years the changing epidemiology of these infections, together with the advent of new antibiotics, has prompted the evaluation of different empiric regimens. Monotherapy with a broad-spectrum agent, for example, has proved to be an effective alternative to combination therapy [15–18].

Cefepime is a new injectable cephalosporin developed by Bristol-Myers Squibb. Its activity encompasses a broad range of gram-positive and gram-negative bacteria, including *S. aureus, P. aeruginosa,* and the Enterobacteriaceae [19]. Other interesting characteristics of cefepime are its low affinity for chromosomal β-lactamases, its rapid penetration through the bacterial cell wall, and its affinity for penicillin-binding proteins [20]. The activity of cefepime has been demonstrated clinically in a number of indications that include pneumonia, complicated and uncomplicated urinary tract infections, skin and soft tissue infections, as well as bacteremia associated with these infections. Activity against these infections, together with its excellent safety profile, suggests that cefepime would be an appropriate choice for the empiric treatment of fever in neutropenic patients.

Material and Methods

Three trials comparing cefepime to ceftazidime were conducted at a total of 28 centers, 13 in the United States and 15 in Europe. The first study was an open randomized trial which accrued 90 patients who were treated for a total of 104 febrile episodes. The second study was a large randomized study conducted at 15 centers in Europe; 221 patients were treated for 324 febrile episodes. The last study, a double-blind randomized trial conducted in the United States, enrolled 276 patients treated for 315 febrile episodes. The design and conduct of these three studies were largely comparable; all data were therefore pooled for a meta-analysis including all 647 patients. All definitions and assessments presented in this analysis are in accordance with the guidelines published by the Immunocompromised Host Society (IHS) and the Infectious Diseases Society of America (IDSA).

Patient eligibility

Adult patients 18 years of age or older were eligible if they became febrile during a neutropenic episode. Fever was defined as a single temperature greater than 38.3°C, or as two or more measurements between 38.1° C and 38.3° C occurring over a 12-h period. Neutropenia was defined as an ANC below 500 cells/μl; patients with counts expected to drop below this level could also be enrolled. Neutropenia had to be related to an underlying malignancy or its treatment (chemotherapy and/or radiation therapy) or to bone marrow transplantation. Patients with neutropenia in the setting of hematologic disorders such as myelodysplasia were also eligible. All patients were informed of the investigative nature of the study before providing informed consent. Trials were conducted in accordance with the Declaration of Helsinki and all applicable national and local ethical requirements.

Clinical and Laboratory Evaluation

A complete history, physical examination, and routine chest X-ray, were performed on all patients prior to initiating study antibiotics. Laboratory examinations included a hematologic profile (white blood cell count with differential, hemoglobin and platelets), liver function tests (alkaline phosphatase, SGOT, SGPT, total bilirubin), renal function tests (BUN and serum creatinine), and electrolytes (sodium, potassium, calcium, and phosphorus). The initial microbiologic evaluation included two sets of blood cultures, a urine culture, and cultures of any potential site(s) of infection. All isolated bacteria were speciated and antibiotic susceptibility testing was performed using the Kirby-Bauer method or the equivalent MIC methods recommended by the National Committee for Clinical Laboratory Standards. Clinical and laboratory evaluations were repeated during the study and at the end of the antibiotic therapy. Follow-up was required, usually 5–7 days after the last dose of either cefepime or ceftazidime.

Classification of Febrile Episodes

Patients were classified as having one of four different diagnoses:

a) microbiologically documented infection (MDI),
b) clinically documented infection (CDI),
c) fever of unknown origin (FUO), or
d) noninfectious fever.

Evaluation of Response

Patients were evaluated after 72–96 h for early response, at the end of antibiotic administration, and during poststudy follow-up. A response was considered a success if both fever and any clinical signs of infection resolved, and the infecting organism, whenever isolated, was eradicated without a change in study

therapy. A response was to have been maintained for 5–7 days following completion of the initial antibiotic regimen. A failure was defined as no response to the empiric regimen and included the development of complications such as septic shock, adult respiratory distress syndrome, disseminated intravascular coagulation, or multiple organ failure. The persistence of fever for at least 96 h, persistent bacteremia (greater than 24 h on study therapy), or recurrent or breakthrough bacteremia also qualified as a treatment failure. Other criteria for failure included progression of primary infection, isolation of a pathogen resistant to study therapy, any death due to the primary infection, and any relapse of the primary infection during the immediate posttreatment period (within 7 days).

Therapeutic Regimens

In all three studies patients received either cefepime or ceftazidime, both of which were administered intravenously at a dose of 2 g every 8 h. Doses were adjusted for renal dysfunction according to the manufacturer's recommendation.

Duration of Therapy

Patients were to be treated for a minimum of 4 days after the resolution of fever (temperature < 38° C) and/or resolution of neutropenia (ANC > 500 cells/μl).

New Infections and Death

A new infection was defined as any infection, either clinically or microbiologically documented, for which the onset of signs and symptoms occurred during study therapy or during the follow-up period. Causes of death were classified as related to the infection (primary or secondary infection) or to the underlying disease.

Analysis

Data from these three studies were reviewed by an independent consultant who assessed each case for eligibility, evaluability, and response; the consultant was blinded to the assigned treatment. All data were entered and analyzed by Bristol-Myers Squibb Biostatistics and Data Management personnel.

Patients were considered unevaluable for our primary analysis in the following situations:

a) initial infection caused by a virus, fungus, parasite, or mycobacterium;
b) a noninfectious cause of fever;
c) early discontinuation of therapy, i.e., prior to the end of the third day of treatment, for any cause other than treatment failure;
d) absence of fever or neutropenia as previously defined;

e) a major protocol violation, such as the addition of a concomitant antimicrobial when not clinically justified;
f) being randomized but not treated; and
g) receiving pretreatment antibiotic for an established infection in the 3 days prior to randomization.

Comparability of the treatment groups was assessed using the Cochran-Mantel-Haenszel test for categorical data in a two way analysis of variants based on rank for continuous variables. Both tests adjusted for protocol. A stepwise logistic regression model was also used to identify independent prognostic factors. Prognostic factors included in this model were the protocol, the classification of infection, the underlying disease, the severity and duration of neutropenia, the use of hematopoietic growth factors, and a history of undergoing a bone marrow transplantation. In the outcome evaluation a 95% confidence interval around the difference in success rate was also constructed.

Results

A total of 647 adult patients were accrued in these three studies; 327 received cefepime and 320 received ceftazidime. At entry the two treatment groups were

Table 1. Pretreatment characteristics

	Cefepime (n=327)		Ceftazidime (n=320)	
	n	%	n	%
Age				
Median	52	—	53	—
Range	18–88	—	16–84	—
Sex (male/female)	176/151	—	180/140	—
Underlying cancer				
Leukemia	136	42	129	40
Lymphoma/myeloma	82	25	83	26
Solid tumors	105	32	94	29
Other	4	1	14	4
Bone marrow transplantation	28	9	33	10
Baseline neutrophil count < 100/μl	175	56	157	51
Neutrophil nadir < 100/μl	239	73	226	71
Days of neutropenia (< 500 μl)				
Median	7	—	7	—
Range	0–56	—	0–44	—
Antibacterial prophylaxis	108	33	110	34
Quinolones	67	20	65	20
Trimethoprim/sulfamethoxazole	25	8	26	8
Other	46	14	47	15
Antifungal prophylaxis	74	23	77	24
Antiviral prophylaxis	52	16	67	21

well balanced for all prognostic factors (Table 1). About two-thirds of the patients had an underlying hematologic malignancy, primarily leukemia. Severe neutropenia, defined as an ANC <100 cells/μl, was documented in over half of the patients at entry and in over 70% of patients during treatment. The duration of neutropenia was similar in the two groups. One-third of the patients received some form of antimicrobial prophylaxis; quinolones were the agents most frequently administered. The prophylactic use of antifungals and antivirals was similar in both treatment groups.

Treatment

The median duration of therapy was 7 days for both cefepime and ceftazidime (Table 2). A prolonged duration of antibiotic therapy was usually related to prolonged episodes of neutropenia. Modification of the empiric regimen to control the original infection was required in 45% of the cefepime-treated patients and in 48% of the ceftazidime-treated patients. These modifications most often consisted of the addition of an antibacterial, usually a glycopeptide such as vancomycin. The addition of a glycopeptide occurred more often in the ceftazidime group (27% versus 22% for cefepime, $p = 0.083$). This difference was particularly pronounced in patients with MDI, occurring in 26 of 122 (21%) cefepime patients and in 39 of 109 (36%) ceftazidime patients ($p = 0.056$). This difference was also seen among patients with CDI (9 of 15, 18% for cefepime and 15 of 51, 29% for ceftazidime). There was no difference noted among patients with FUO. In both treatment groups treatment modifications usually occurred between days 3 and 5. Compared to the other diagnostic categories, modifications occurred somewhat earlier among those with MDI.

Table 2. Therapy

	Cefepime		Ceftazidime	
	n	%	n	%
Duration of therapy (days)				
Median	7	—	7	—
Range	1–50	—	1–33	—
Treatment modification	147	45	153	48
Antibacterials	98	30	107	33
Glycopeptides	71	22	87	27
Antifungals	71	22	75	23
Antivirals	40	12	41	13

Response rates

A total of 249 cefepime-treated patients and 228 ceftazidime-treated patients were evaluable for response, representing evaluability rates of 76% and 71%, respectively.

The most common reason for unevaluability was early treatment modification, i.e. before 72 h of effective therapy, without adequate reason (Table 3). In the group of evaluable patients, the success rate was 53% for cefepime and 55% for ceftazidime ($p = 0.680$; 95% confidence interval -11, +7; Table 3). The reasons for treatment failure were similar in the two treatment groups. There were, however, a greater number of persistent or breakthrough bacteremias in the ceftazidime group and a greater proportion of persistent fever in the cefepime group.

Table 3. Outcome of therapy

	Cefepime n (n = 327)	%	Ceftazidime n (n = 320)	%
Patients not evaluable	78		92	
Early treatment modification	48		54	
Non-infectious fever	3		3	
Viral of fungal infections	6		10	
No documentation of fever and/or neutropenia	10		12	
Other	11		13	
Evaluable patients	249		228	
Outcome				
Success	133	(53)	126	(55)
Failure	116	(47)	102	(45)
Reason for failure				
Resistant pathogen	11		13	
Persistent/breakthrough bacteremia	5		13	
Progression	5		4	
Death	3		3	
Persistent fever	90		66	
Relapse	2		3	

Response to therapy was analyzed by diagnostic category (Table 4). For patients with MDI the response rate was 47% for cefepime and 43% for ceftazidime. In those with documented bacteremia the corresponding figures were 45% and 40%. Of the 142 MDIs 121 were due to single organisms; seventy-one (59%) were caused by gram-positive pathogens and 50 (41%) by gram-negative pathogens. The response rate for patients with gram-positive infections was somewhat higher for cefepime, while for those with gram-negative infections the response to ceftazidime was more favorable. Clinical outcome was most favorable in patients with solid tumors, those with the least severe degree of neutropenia, and in those with the shortest duration of neutropenia. In the various subgroups of prognostic relevance no difference between cefepime and ceftazidime was observed.

The efficacy analysis was repeated on all eligible patients (intent-to-treat analysis). Twenty-seven patients (13 in the cefepime group, 14 in the ceftazidime group) were excluded from this analysis because of either the absence of neutropenia (cefepime 8, ceftazidime 10), a noninfectious fever (cefepime 3, ceftazidime 3), poor

Table 4. Outcome by prognostic categories

	Cefepime		Ceftazidime	
	n	%	n	%
Overall	133/249	53	126/228	55
MDI	38/81	47	26/61	43
Bacteremia	26/58	45	19/47	40
Single gram-positive organism	15/38	39	10/33	30
S. aureus	3/5		1/2	
Staphylococcus coagulase-negative	5/14		4/13	
Viridans streptococci	6/11		5/12	
Other gram-positive		1/8		0/6
Single gram-negative organism	16/30	53	13/20	65
E. coli	4/8		8/10	
P. aeruginosa	3/8		1/2	
Klebsiella sp.	3/7		3/5	
Other gram-negative	6/7		1/3	
Polymicrobial	6/12	50	3/8	38
CDI	12/30	40	17/33	52
FUO	83/138	60	83/134	62
Cancer diagnosis				
Hematologic malignancy	73/169	43	66/148	45
Solid tumor	58/76	76	53/69	77
Baseline neutrophil count				
≤100/μl	75/134	56	71/120	59
>100/μl	50/101	50	49/101	49
Duration of neutropenia				
<10 days	99/159	62	85/136	63
≥10 days	33/89	37	40/90	44

antibiotics (cefepime 2, ceftazidime 0), or absense of fever (cefepime 0, ceftazidime 1). Thus 620 patients (96%) were included in this analysis. Patients with non-bacterial infections and those with inappropriate modification of the empiric regimen were considered treatment failures. The overall the response rate was 133/314 (42%) for cefepime and 126/306 (41%) for ceftazidime. Among patients with MDI the response rates were 36% for cefepime and 27% for ceftazidime. The corresponding figures among patients with CDI were 32% and 39%, and those with FUO 49% and 51%.

New infections

The incidence of new infections was higher in the ceftazidime group (35 episodes, 15%) than in the cefepime group (26 episodes, 10%). The majority of new infections were MDIs (cefepime 17, ceftazidime 22). There were 17 new episodes of bacteremia or fungemia, 6 in the cefepime group and 11 in the ceftazidime group.

These infections often occurred during the first week of therapy; there was no difference in time to development of a new infection in the two groups.

Mortality

Deaths occurred more often in the cefepime group (36 deaths, 11%) than in the ceftazidime group (23 deaths, 7%). The most frequent cause of death was underlying cancer; there were 20 such deaths in the cefepime group and 10 in the ceftazidime group. Mortality due to the presenting infection was similar in the two treatment arms (6 cefepime, 8 ceftazidime). Both groups had some deaths attributed to new infections.

Adverse Events

Both antibiotics were very well tolerated, as can generally be expected with cephalosporins. Overall the incidence of adverse events felt to be probably drug-related was very low (14% for cefepime and 10% for ceftazidime). The most frequent of these was rash, which was seen in 6% of cefepime patients and 4% of ceftazidime patients. The other most frequent adverse event was gastrointestinal intolerance; diarrhea, nausea, and vomiting were seen in 1–2% of patients. Changes in laboratory parameters were infrequent and usually of no clinical relevance.

Discussion

Several factors have contributed to changes in the management of neutropenic cancer patients over the last two decades. BMT and peripheral stem cell transfusions are among the treatment options for a variety of malignancies. The availability of hematopoietic growth factors has allowed the use of more aggressive chemotherapeutic regimens. With such regimens the risk of mucositis and other alterations in natural defense barriers is greater. This, coupled with the more widespread use of prophylactic antibiotics such as the quinolones, has contributed to changes in the microbiology of infections in this population. Infections caused by gram-negative pathogens have decreased in incidence, while those caused by gram-positive organisms have increased in frequency. The studies included in this report mirror these recent trends, with a predominance of infections caused by gram-positive organisms such as *S. aureus,* coagulase-negative staphylococci, and viridans streptococci.

Cefepime is a new cephalosporin with a broad spectrum of activity against both gram-positive and gram-negative organisms, including *S. aureus,* viridans streptococci, *P. aeruginosa,* and the Enterobacteriaceae. The drug provides coverage for a number of the organisms typically encountered in febrile neutropenic patients and thus can be considered a suitable candidate for monotherapy in this setting.

This report reviews the results of three randomized studies comparing cefepime, given at a dose of 2 g intravenously every 8 h, to ceftazidime given at the

same dose. These three studies accrued a total of 647 patients. Two of the studies, one of which was double-blind, were large trials adequately powered to demonstrate the equivalence of cefepime and ceftazidime. The studies accumulated a population of patients with a variety of underlying malignancies, as well as a broad range of severity and duration of neutropenia. Despite this apparent heterogeneity, the treatment groups were well-balanced for all prognostic factors, supporting the inclusion of the studies in a meta-analysis.

The evaluable subset of patients met current IDSA guidelines for definitions of fever, neutropenia, and diagnosis leading to neutropenia. All evaluable patients had fever above 38° C, a neutrophil count lower than 500/μl, and a cancer diagnosis of hematologic malignancy, solid tumor, or myelodysplastic syndrome. Neutropenia was generally severe, with nearly three-quarters of the patients having a neutrophil count lower than 100/μl at some time. The duration of neutropenia varied widely, ranging from 0 to 56 days, with a median of 7 days. Approximately one-third of the patients had neutropenia lasting 10 days or more.

The evaluation of outcome in these patients is particularly complex. Of particular importance is the addition of any new antimicrobials, as well as the timing of these changes. Two of the three studies were open – label trials in which biases in subject management could have occurred. To minimize the impact of any potential bias on the interpretation of outcome, efficacy data were reviewed in a blinded fashion by a consultant, who used outcome criteria based on IDSA and IHS guidelines. This blinded assessment provided consistency across the three studies and was a key aspect for justifying the use of a meta-analysis.

The primary measure of outcome was based on the analysis of the first febrile episodes in evaluable patients. Overall, cefepime and ceftazidime proved to be of comparable efficacy, with respective success rates of 53% and 55% ($p = 0.680$, 95% confidence interval -11, +7). In the subset of patients with MDI the success rate for cefepime was, again, comparable to that of ceftazidime (47% versus 43%). Further consideration of both the clinical outcome by pathogen and the reasons for treatment failure demonstrates two important features. First, patients treated with cefepime had the lower incidence of persistent/breakthrough bacteremia (5 cases versus 13 in ceftazidime-treated patients). Second, for patients with coagulase-negative staphylococcal infections, the success rate for cefepime was 5/14 versus 4/13 for ceftazidime; it was 3/5 versus 1/2 for *S. aureus*. The overall response rate for gram-positive infections was 39% for cefepime and 30% for ceftazidime.

An assessment of the modifications made to the empiric regimen reveals another potential advantage of cefepime; a glycopeptide was added in 22% of cefepime patients and 27% of ceftazidime patients. This trend toward better gram-positive activity was not associated with a loss of activity against gram-negative organisms. Moreover, the addition of antibiotics with targeted activity against gram-negative pathogens, such as the aminoglycosides, was infrequent (3%). Given the oft-cited trend toward gram-positive infections in the febrile neutropenic patient, these features would seem to favor cefepime as choice for empiric monotherapy.

The efficacy of cefepime in febrile neutropenia was substantiated by the "modified intent-to-treat" analysis, which corroborated the equivalence of cefepime and ceftazidime. In this analysis the outcome for patients with MDI

was even more impressive, with success rates of 36% for cefepime and 27% for ceftazidime. Finally, a logistic regression analysis of the most significant prognostic factors further supports the activity of cefepime in this population. In the subset analyses based on these prognostic categories cefepime was at least as efficacious as ceftazidime.

The safety analysis of these three studies is largely unremarkable. The incidence of adverse events, particularly probably-related adverse events, is low and in keeping with what is expected with a cephalosporin in this indication. Similarly, changes in laboratory parameters are consistent with our previous experience with cefepime.

In conclusion, the data presented here provide evidence of the activity of cefepime when used as empiric therapy for the treatment of febrile episodes in neutropenic patients. Both efficacy and safety data support its use as monotherapy at a dose of 2 g every 8 h.

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