Published in final edited form as:

Pediatr Blood Cancer. 2013 May ; 60(5): 806–809. doi:10.1002/pbc.24467.

The Safety of Cefepime and Ceftazidime in Pediatric Oncology Patients

James M. Hoffman, PharmD^{*,‡}, Jamie Frediani, BSc[†], Michael Herr, BSc[†], Patricia M. Flynn, MD^{†,¶,§}, and Elisabeth E. Adderson, MD^{†,¶,||}

^{*}Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, U.S.A

[†]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, U.S.A

[‡]Department of Clinical Pharmacy, University of Tennessee College of Medicine, Memphis, TN, U.S.A

[¶]Department of Pediatrics, University of Tennessee College of Medicine, Memphis, TN, U.S.A

[§]Department of Preventative Medicine, University of Tennessee College of Medicine, Memphis, TN, U.S.A

^{||}Department of Molecular Sciences, University of Tennessee College of Medicine, Memphis, TN, U.S.A

Abstract

Background—Concern has been raised about possible increased mortality associated with the use of cefepime. There are limited data available on the pragmatic use of beta-lactam antibiotics, especially in children.

Procedure—This retrospective study included 532 pediatric oncology patients. The outcomes of patients treated with cefepime for suspected serious bacterial infections were compared to those of patients treated with ceftazidime. Primary outcomes included 30- and 90-day all-cause mortality.

Results—The demographic and clinical characteristics of 337 patients treated with ceftazidime were similar to those of 195 patients receiving cefepime. Thirty-day and 90-day all cause mortality rates were comparable (30-day OR for cefepime: 3.48, 95% CI 0.31 to 38.84, $P=0.3$; 90-day OR: 0.99, 95% CI 0.29 to 3.42, $P=1.0$). There were also no differences in infection-related mortality rates, secondary infections, or adverse drug events. Deaths occurring within 30 days of hospitalization were judged to be attributable to infection, but not the result of treatment failure or adverse drug events. Deaths occurring between 30 and 90 days were associated with progressive or new malignancy. Secondary infection was significantly associated with mortality.

Conclusions—The use of cefepime in pediatric oncology patients is not associated with increased mortality when compared to ceftazidime, however the small number of deaths in this

Address for correspondence: Elisabeth Adderson, Mailstop 320, 262 Danny Thomas Place, Memphis, TN, 38105; phone – 901-595-3459; fax-595-3099; elisabeth.adderson@stjude.org.

Conflict of Interest: Nothing to declare.

study limits the strength of this conclusion. Previous associations between antimicrobial therapy and increased all-cause mortality may have been confounded by patients' demographic characteristics and co-morbid conditions. All-cause mortality may be an insensitive outcome for studies examining the efficacy and safety of these agents.

Keywords

cefepime; ceftazidime; pediatric; oncology; drug safety

Introduction

Cefepime is a fourth generation cephalosporin with a broad-spectrum of activity against both Gram-negative and Gram-positive bacteria [1]. The drug's broad spectrum and resistance to degradation by many beta-lactamases makes it an appealing choice for the empiric therapy of serious bacterial infections, but concern has been raised about possible increased mortality associated with its use, particularly in patients with cancer, and there is limited data available on the safety and effectiveness of cefepime in children.

In 2006, Paul et al. published a systematic review of empiric antibiotic monotherapy for febrile neutropenia that reported higher all-cause mortality at 30 days with the use of cefepime than with other β -lactam antibiotics (RR 1.44, 95% CI 1.06 to 1.94; 3,123 participants), including a statistically insignificant increase in mortality in the subset of 3 trials in pediatric patients that compared cefepime to ceftazidime (RR 2.28, 95% CI 0.53 to 9.79; 3 studies, 263 children) [2]. Overall, bacterial secondary infection and infection-related mortality were also more common in patients treated with cefepime [2]. Yahav et al. subsequently analyzed trials in adults and children that compared cefepime with another β -lactam, and again associated cefepime with a higher 30-day all-cause mortality rate overall [Mantel-Haenszel adjusted risk difference (ARD) per 1000 population, 17.02; 95% CI, 5.54 to 28.5; 41 trials, 4,545 participants] and in the subgroup of patients treated for febrile neutropenia (ARD 1.42, 95% CI 1.09 to 1.84; 19 trials, 3,871 participants [3].

In November 2007 the United States Food and Drug Administration stated they were evaluating the safety of cefepime [4]. As part of this inquiry, Kim et al. analyzed trial and patient-level data from 88 clinical trials in adults and children and concluded that there was no significant increase in mortality among patients treated with cefepime relative to other antibacterials (trial-level ARD 5.38, 95% CI -1.53 to 12.28; 17,755 participants) [5]. Cefepime had a lower increased risk of mortality in trials that were omitted from preceding meta-analyses (ARD -2.8, 95% CI -11.47 to 5.80). A Bayesian re-analysis of the FDA data, however, found an overall 71% probability that the risk of death is increased with cefepime compared with alternative antimicrobial agents [6].

Concerns surrounding the design of the clinical trials and the systematic reviews that included these studies have not been resolved. Treatment failure was the primary outcome of most clinical trials comparing cefepime to other antimicrobials but, in some cases, information on mortality was not systematically collected [2,3]. A range of antimicrobial doses was used, including some now considered suboptimal, and mortality rates were

generally higher in those studies that used low doses of cefepime [2]. The quality of some clinical trials included in published systematic reviews has also not been ideal [2,3,7].

The safety and effectiveness of cefepime therapy in children may differ from that in adults. A systematic review of clinical trials for pediatric patients found no significant difference in all-cause mortality rates between cefepime and comparators (RD 0.00, 95% CI, -0.01 to 0.02; 16 trials, 1,827 patients) [7]. A second meta-analysis of data from both observational studies and randomized clinical trials of regimens containing third- and fourth-generation cephalosporins, with or without an aminoglycoside, reported comparable overall and infection-related mortality rates in pediatric patients with febrile neutropenia [7,8].

Finally, the outcomes of treatment with antimicrobial agents in everyday use may differ from those reported in clinical trials because of increased demographic and clinical heterogeneity, the use of other treatments and other factors.

For all of the above reasons, the safety and effectiveness of cefepime for the treatment of serious infections in children and children with cancer may be better or worse than suggested by published reports. St. Jude Children's Research Hospital's (SJCRH) Department of Infectious Diseases has produced standardized institutional guidelines for the empiric treatment of fever and neutropenia in children since 1987. Most non-neutropenic patients admitted to hospital for empirical therapy of suspected serious bacterial infections are also managed according to these guidelines, which were revised in October 2001 to recommend the use of cefepime instead of ceftazidime. The purpose of our retrospective study was to compare the outcomes of patients treated with ceftazidime with those treated with cefepime in this period.

Methods

Patients hospitalized for treatment of suspected or proven bacterial infections and who were treated with ceftazidime or cefepime between January 1, 2000 and December 31, 2002 were identified by review of pharmacy databases. Other antimicrobial agents were used at the discretion of treating physicians. Subjects' demographic and clinical data were abstracted from medical records. Patients without an underlying malignant disease and those who had received a hematopoietic stem cell transplant within the preceding year were excluded. For subjects with more than one episode, only the first inpatient exposure was included because it is conceivable that therapy of the initial episode might alter the outcomes of subsequent infections, e.g., by altering microbial flora or causing persistent adverse drug effects. There were no other major changes in the institutional protocol for the management of febrile neutropenia, or treatment protocols for the most common forms of cancer, including acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML) and medulloblastoma]. No significant change in the antimicrobial resistance patterns of bacterial pathogens isolated from patients was observed. The SJCRH Institutional Review Board approved the study with waiver of informed consent.

The primary outcomes assessed were 30 and 90-day all-cause mortality. Secondary outcomes included infection-related mortality, secondary infections and adverse drug events.

One investigator (EA), who was not involved in data collection, assessed the relationship between infection and mortality retrospectively, taking patients' therapy, medical comorbidities, clinical course and the results of diagnostic tests into consideration. Mortality was considered infection-related if an infection caused or contributed significantly to the patient's death. Secondary infections were identified retrospectively by investigators and defined as fever or other new symptoms associated with the isolation of a new pathogen or clinical or radiological evidence of a new site of infection. Since this was a retrospective study, only adverse drug events reported by health care providers in the patients' medical records were included.

Data were analyzed using the Stata V9.2 software package (Stata, College Station, TX). Demographic and clinical characteristics were compared using Student's *t* test, Chi-square and Fisher's exact tests, as appropriate. Risk factors for adverse outcomes were identified by univariate and multivariable logistic regression and OR or RD reported. Final models were based on backward selection with a predetermined cutoff of *P* 0.10 for inclusion in the model. *P* values <0.05 (2-tailed) were considered statistically significantly different. Results were not adjusted for multiple comparisons.

Results

A total of 532 patients meeting inclusion criteria received at least one dose of ceftazidime (n=337) or cefepime (n=195) during the study period. Ceftazidime was used routinely in from 1/1/2000 until 10/18/2001 (approximately 22 ½ months) and cefepime was used from 10/12/2001 through 12/29/2002 (approximately 13 ½ months). Thus, on average, ceftazidime was prescribed 15.0 times and cefepime 14.4 times per month during the study period. Groups were similar with respect to mean age (8.6 vs. 8.2 yrs, *P*=0.4), gender (58% male in each group, *P*=0.9), race (78% vs. 79% white, *P*=1.0) and type of malignancy (58% vs. 59% hematological malignancy, 29% vs. 28% solid tumor, 12% brain tumor in each group; *P*=1.0) (Table I). Similar numbers of patients in each group required intensive care at the time of hospitalization (4 vs. 2%, *P*=0.1) and had microbiologically-confirmed infections (10 vs. 12%, *P*=0.3), suggesting that the type and severity of illness did not change over the relatively short duration of the study. The mean duration of cephalosporin treatment in each group (5.3 vs. 5.5 days, *P*=0.6) and use of additional antimicrobials (56 vs. 54%, *P*=0.6) were also comparable.

One patient treated with ceftazidime and 2 patients treated with cefepime died within 30 days of hospitalization and were the only infection-related deaths [OR 30-day all-cause mortality for cefepime 3.48, 95% CI 0.31 to 38.65, *P*=0.3; risk difference (RD) for cefepime 0.01, 95% CI -0.01 to 0.2, *P*=0.3] (Table II). No patient who died within 30 days of hospitalization required intensive care at the time of hospital admission. An 18-year-old with ALL was hospitalized with severe colitis. He received 2 doses of ceftazidime before vancomycin, meropenem and tobramycin were prescribed. He died of multi-organ failure on the 14th hospital day. *Clostridium* sp., *Bacteroides* sp. and coagulase-negative *Staphylococcus* were isolated from culture of cerebrospinal fluid (CSF) obtained at postmortem; blood was sterile. A 7-year-old with metastatic hepatocellular carcinoma, initially admitted for a febrile illness, developed massive intraperitoneal hemorrhage and

multi-organ failure on the 5th hospital day. He was treated with cefepime for 2 days, after which, vancomycin, meropenem and tobramycin were prescribed. Despite the institution of antifungal therapy, he died on the 23rd hospital day of *Candida albicans* pneumonia. A 4-year-old with ALL whose induction chemotherapy was complicated by fever and neutropenia was treated with cefepime for 10 days. He was readmitted 4 days later and died within hours of refractory septic shock caused by *Bacillus cereus*.

All patients who died within 30 days were male, had leukemia or solid tumors and had microbiologically-confirmed infections, but the small number of deaths within 30 days precluded a comprehensive analysis of risk factors for 30-day all-cause mortality. An additional 6 patients treated with ceftazidime and 2 treated with cefepime died between 30 and 90 days after beginning cephalosporin therapy (90-day mortality OR for cefepime 0.99, 95% CI 0.29 to 3.42, $P = 1.0$; RD 0.00, 95% CI -0.03 to 0.02). All these deaths were attributed to progression of the patient's underlying malignancy ($n=7$) or a new secondary malignancy ($n=1$).

Secondary infections developed in 22 patients, and were microbiologically confirmed in 15 cases (6 invasive fungal infections, 1 polymicrobial bacterial and fungal infection). The odds of secondary infection were not increased in patients receiving cefepime (OR 2.14, 95% CI 0.91 to 5.08, $P=0.08$). Rashes attributed to study drugs were reported in 6 patients receiving ceftazidime and 3 receiving cefepime and were the only adverse drug events attributed to these agents. Cefepime was not associated with an increased risk of adverse drug events (OR 1.30, 95% CI 0.32 to 5.29, $P=0.7$).

Secondary infection was significantly associated with 90-day all-cause mortality (OR 25.3, 95% CI 6.7 to 95.1, $P < 0.001$) in a convergent multivariable logistical regression model adjusted for sex, ICU admission, use of other antimicrobial agents and the duration of cephalosporin therapy. The association of sex with 90-day all-cause mortality bordered on statistical significance (OR of death for females 0.1, 95% CI 0.0 to 1.07, $P=0.06$). When controlled for use of additional antimicrobial agents and treatment duration, duration of hospitalization remained the only statistically significantly predictor of secondary infection (OR 1.03, 95% CI 1.01 to 1.05, $P=0.001$) in a multivariable regression model.

Discussion

The association of an increased risk of mortality in cancer patients who received cefepime relative to treatment with other β -lactam drugs has been debated. Although the most comprehensive systematic reviews suggest that any risk of excess mortality with cefepime is low, using multiple types of data is useful when evaluating drug safety concerns. Active surveillance of the comparative outcomes of licensed antimicrobial agents is a valuable adjunct to data from randomized trials, since patients enrolled in randomized clinical trials may differ in important respects from the overall patient population with a particular condition and because study protocols may not reflect usual clinical care (particularly with respect to duration of therapy and the use of additional antimicrobials). Rapid and widespread acceptance of the recommendation to use cefepime for empiric therapy of suspected serious bacterial infections allowed us to compare the outcomes of treatments

with these agents in a heterogeneous pediatric oncology practice during a relatively short study period when the demographic characteristics, severity of illness and average duration of antimicrobial therapy remained constant.

We found no statistically significant difference in the risk of 30- or 90-day mortality in pediatric oncology patients treated with cefepime in this study, although low mortality rates and, especially, low infection-attributable mortality rates (0.56% at 30 days in this report, 10-fold lower than reported in many clinical trials included in previous analyses) limit the strength of any conclusions [2,3,5]. Indeed, a retrospective analysis suggests that a sample size of over 2,300 patients in each group would be required to reject the null hypothesis that the 1.0% and 0.3% 30-day mortality rates observed in the cefazidime and cefepime-treated groups, respectively, were the same, with 80% power ($\alpha = 0.05$, 2-tailed). These data are consistent with the Fisher et al. report that pediatric patients with newly diagnosed AML who received cefepime had no statistically significant difference in the risk of in-hospital mortality compared to those who received other β -lactams [9] and with Manji et al., who reported comparable mortality and secondary infection rates in a recent meta-analysis of observational and randomized studies of febrile neutropenic patients treated with third- or fourth-generation cephalosporin-containing regimens [8].

A criticism of systematic reviews of cefepime has been that mortality has not been a primary outcome of all included randomized clinical trials and, therefore, not been reported in all studies or not completely reported. A strength of this study is that ascertainment of the primary outcomes was possible for all patients and it was possible to infer that infection directly contributed to mortality in only 3 patients. These poor outcomes, however, could not be reasonably attributed to cefepime treatment failure or to adverse drug effects. In each of the 3 cases, either more broad-spectrum antimicrobials were substituted for cefepime many days before the patients' demise, the illness was fulminant, or death resulted from a secondary or concurrent infection that would not be anticipated to be adequately treated by cefepime. These observations suggest that all-cause mortality is not a sensitive measure of the adverse effects of antimicrobials, particularly if potential confounding factors are not considered.

Some previous meta-analyses found that febrile neutropenic patients treated with cefepime were more likely to have bacterial secondary infections than those treated with comparators [2]. We found no difference in secondary infection rates in patients treated with cefepime relative to those treated with ceftazidime, but that the development of a secondary infection was an independent risk factor for mortality. It seems plausible that secondary infections may make a direct, but subtle, contribution to mortality or that these infections may be a marker for patients who are more immunocompromised or debilitated and, therefore at higher risk of death. If this is the case, different rates of secondary infection in groups treated with cefepime and those treated with comparators may have contributed to the excess mortality attributed to cefepime in early systematic reviews. Risk factors for mortality were not specifically examined in these studies and an alternative biologically plausible explanation for the increased mortality of patients treated with cefepime has not been identified [2,3].

Despite the limited power of this study, and the inherent limitations of any retrospective analysis, it is reassuring that we found both very low mortality rates and no increased risk of mortality, infection-attributable mortality, secondary infection or adverse drug events in patients treated with cefepime. Our experience evaluating the safety of cefepime in our patient population provides broader lessons when evaluating other drug safety concerns. Drug safety risks are increasingly identified through meta-analysis. The cefepime experience illustrates the importance of concerns identified through meta-analysis be replicated and updated by other meta-analyses and that other data sources, including the local evaluation of frequently used drugs, may provide important insights into adverse drug effects and clinical outcomes.

Acknowledgments

This study was supported by National Institutes of Health [Grant CA21765] and the American Lebanese Syrian Associated Charities (ALSAC).

References

1. Cunha BA, Gill MV. Cefepime. *Med Clin North Am.* 1995; 79:721–732. [PubMed: 7791419]
2. Paul M, Yahav D, Fraser A, et al. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2006; 57:176–189. [PubMed: 16344285]
3. Yahav D, Paul M, Fraser A, et al. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007; 7:338–348. [PubMed: 17448937]
4. United States Food and Drug Administration. [September 30, 2009] Early communication about an ongoing safety review: cefepime (marketed as Maxipime). 2009. 2007 September 30(Updated 06/18/2009). <www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070496.htm>.
5. Kim PW, Wu YT, Cooper C, et al. Meta-analysis of a possible signal of increased mortality associated with cefepime use. *Clin Infect Dis.* 2010; 51:381–389. [PubMed: 20624065]
6. Kalil AC. Is cefepime safe for clinical use? A Bayesian viewpoint. *J Antimicrob Chemother.* 2011; 66:1207–1209. [PubMed: 21471137]
7. Adderson EE, Flynn PM, Hoffman JM. Efficacy and safety of cefepime in pediatric patients: a systematic review and meta-analysis. *J Pediatr.* 2010; 157:490–495. 495 e491. [PubMed: 20434167]
8. Manji A, Lehnbecher T, Dupuis LL, et al. A meta-analysis of antipseudomonal penicillins and cephalosporins in pediatric patients with fever and neutropenia. *Pediatr Infect Dis J.* 2012; 31:353–358. [PubMed: 22173145]
9. Fisher BT, Aplenc R, Localio R, et al. Cefepime and mortality in pediatric acute myelogenous leukemia: a retrospective cohort study. *Pediatr Infect Dis J.* 2009; 28:971–975. [PubMed: 19859014]

Table I

Demographic and clinical features of 532 pediatric patients treated with ceftazidime or cefepime.

	Overall (n=532)	Ceftazidime (n=337)	Cefepime (n=195)	P
Age (yr)				
Mean (SD)	8.4 (5.8)	8.6 (5.9)	8.2 (5.8)	0.4
Median (Range)	7.4 (0–20.8)	7.7 (0.1–20.8)	7.2 (0–20.7)	
Male (%)	309 (58)	195 (58)	114 (58)	0.9
Race (%)				
White	419 (79)	264 (78)	155 (79)	1.0
Black	99 (19)	64 (19)	35 (18)	
Other	14 (3)	9 (3)	5 (3)	
Malignancy (%)				
Hematological	313 (58)	197 (58)	116 (59)	1.0
Solid tumor	154 (29)	99 (29)	55 (28)	
Brain tumor	65 (12)	41 (12)	24 (12)	
ICU Admission (%)	17 (3)	14 (4)	3 (2)	0.1
Microbiologically - confirmed infection (%)	56 (11)	32 (10)	24 (12)	0.3
Duration of therapy (days)				
Mean (SD)	5.4 (3.9)	5.3 (4.0)	5.5 (3.8)	0.6
Range	0 – 31	0 – 31	0 – 30	
Use of additional antimicrobials (%)	295 (55)	190 (56)	105 (54)	0.6
Type of additional antimicrobial (%)				
Vancomycin	236 (44)	148 (44)	88 (45)	0.8
Anti-fungal	46 (9)	27 (8)	19 (10)	0.5
Other	143 (27)	92 (27)	51 (26)	0.8

Abbreviations: ICU, intensive care unit; SD, standard deviation

Table II

Treatment outcomes.

	Overall (n=532)	Ceftazidime (n=337)	Cefepime (n=195)	Odds Ratio (95% CI)	P
Mortality (%)					
30-day	3 (0.6)	1 (0.3)	2 (1.0)	3.48 (0.31-38.65)	0.3
90 day	11 (2.1)	7 (2.1)	4 (2.1)	0.99 (0.29-3.42)	1.0
Infection-attributable mortality (%)	3 (0.6)	1 (0.3)	2 (1.0)	3.48 (0.31-38.8)	0.3
Secondary infection (%)					
Any	22 (4.1)	10 (3.0)	12 (6.2)	2.14 (0.91-5.08)	0.08
Bacterial	13 (2.4)	5 (1.5)	8 (4.1)		
Fungal	8 (1.5)	4 (1.2)	4 (2.1)		
Bacterial + Fungal	1 (0.2)	1 (0.3)	0 (0.0)		
Adverse effects (%)	9 (2.0)	6 (1.9)	3 (2.4)	1.30 (0.32-5.29)	0.7