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Oral Ciprofloxacin vs. Intravenous Ceftriaxone Administered in an Outpatient Setting for Fever and Neutropenia in Low-Risk Pediatric Oncology Patients: Randomized Prospective Trial

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Background. Infections are one of the major complications in children undergoing chemotherapy. Monotherapy with either ciprofloxacin or ceftriaxone is safe and efficient in low-risk patients (solid tumors and stage I/II lymphomas). The same drugs may be used in an outpatient setting, decreasing costs and the risk of nosocomial infections. ***Procedure.*** Low-risk patients (N = 70) with episodes of fever and neutropenia (N = 116) were randomized to receive either oral ciprofloxacin or intravenous ceftriaxone as outpatients. Only one patient had a central venous catheter. ***Results.*** Episodes of fever and neutropenia were classified as fever of unknown origin (41% vs. 32%) or clinically documented infection (56% vs. 63%) in the ciprofloxacin and ceftriaxone groups, respectively. Most of these infections were of upper respiratory tract, skin, or gastrointestinal origin. The mean duration of neutropenia was 5 vs. 6 days. Fever persisted for 1–9 days (mean 2 vs. 3 days). Therapy was successful with no modifications in 83% vs. 75% of the episodes. Patients were admitted in 7% vs. 4% of the episodes. No bone or joint side effects were seen in either group. All patients survived. ***Conclusions.*** Outpatient therapy with either oral ciprofloxacin or intravenous ceftriaxone for fever and neutropenia is effective and safe in pediatric patients with solid tumors and stage I/II non-Hodgkin lymphoma (low-risk patients). Med. Pediatr. Oncol. 34:87–91, 2000.

Key words: ciprofloxacin; ceftriaxone; infections; fever; neutropenia

INTRODUCTION

Infection is one of the most serious complications of cancer therapy. Neutropenia is the single most important risk factor for infections [1]. Fever is a known medical emergency in neutropenic patients, requiring immediate broad-spectrum antibiotic treatment [2]. Antibiotic combinations that include third-generation cephalosporins have been quite successful.

Patients can be divided into low-risk and high-risk categories for severe infections [3–5]. Solid tumor patients undergoing conventional therapy and non-Hodgkin lymphoma patients with stage I or II disease have a low-risk for infectious complications. Most of these patients, in our hands, do not have central venous catheters. Ceftriaxone and amikacin are widely used in the treatment of fever and neutropenia [6,7]. In low-risk patients, monotherapy with ceftriaxone or ceftazidime has also been used with good results [8–12].

Although effective in the therapy of fever and neutropenia in adults, monotherapy with quinolones has not been utilized in pediatric patients because of experiments in young animals showing articular damage [13–16]. However, numerous recent reports have shown that ciprofloxacin is safe in children [13–16]. Quinolones have been included in antibiotic regimens for the treatment of fever and neutropenia in children with good results [16].

Outpatient therapy with quinolones for low-risk neutropenic patients has been successfully used in adults but, to our knowledge, has not been used in children. We randomized low-risk pediatric oncology patients with episodes of fever and neutropenia to receive intravenous ceftriaxone or oral ciprofloxacin as outpatients to compare the efficacy and safety of both regimens.

MATERIALS AND METHODS

All patients with solid tumors and non-Hodgkin lymphoma undergoing chemotherapy or radiation therapy who presented with fever and neutropenia were eligible for this study. Patients had to be between 3 and 20 years of age. Fever was defined as an axillary temperature of

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38°C or axillary temperature between 37.5°C and 38.0°C three times in a 24 hr period, each of the measurements at least 4 hr apart. Neutropenia was defined as bands plus segmented cells <500 cells/mm^3. Patients with neutrophils between 500 and 1,000/mm^3 within the first days after chemotherapy were also eligible to enter this study. All patients were thoroughly examined. Only hemodynamically stable patients were eligible for this study. Each episode was independently randomized to receive either intravenous ceftriaxone, 100 mg/kg/day as a single daily infusion, or oral ciprofloxacin, 25 mg/kg/day in two divided doses. No patient had Hickman-type indwelling catheters, although this was not an exclusion criteria. No statistical adjustments were adopted for multiple entries.

Initial evaluation included history, physical examination, chest and sinus X-rays, blood and urine cultures, hemogram, chemistries (sodium, potassium, BUN, creatinine, AST, ALT), and urinalysis. Patients who were randomized to receive ciprofloxacin had bilateral knee X-rays performed. Other cultures and cerebral spinal fluid examination were performed as clinically indicated. All patients returned daily to the clinic for evaluation, which included history, physical examination, blood cultures (if fever persisted), chest X-ray (weekly if fever persisted), and other tests as necessary. Patients receiving ceftriaxone had the drug infused daily in the clinic. Patients receiving ciprofloxacin had written orders about how to take and store it (sunlight-protected) and were asked to bring the medication daily for pill count.

Follow-up evaluation included a hemogram on alternate days, weekly chemistries, and, when indicated, a chest X-ray. On the third day of treatment patients were classified as having fever of unknown origin or clinically and/or microbiologically documented infections. Episodes with persistent fever, clinical status deterioration, or isolation of resistant organisms led to the addition of other antibiotics to the initial schema. Amphotericin B was added to the initial regimen if fever and neutropenia persisted for more than 7 days or if a fungal infection was suspected at any time. Patients were admitted if other antibiotics, with more than once per day infusion schedules, were associated or whenever clinically indicated.

Therapeutic success was defined as survival of the fever and neutropenia episode. Therapeutic success was defined as 'with modification' whenever another antibiotic, antiviral, or antifungal agent was added to the initial monotherapy.

Antibiotics were discontinued after the second consecutive afebrile day in patients having white blood cell counts >500 neutrophils/mm^3 and who had no identifiable source of infection. Clinically or microbiologically documented infections were treated for as long as necessary with ciprofloxacin. Ceftriaxone was switched to appropriate oral antibiotics after the resolution of both fever and neutropenia. All antibiotics were discontinued in patients with persistent fever but no identifiable source of infection and neutrophil count above 1,000/mm^3. The patients were then evaluated for fever of unknown origin. Bilateral knee X-rays were repeated at the end of ciprofloxacin therapy and monthly thereafter for 3 months to evaluate possible joint abnormalities.

TABLE I. Patient Demographics

	Ciprofloxacin	Ceftriaxone	*P*
Age (years); mean (range)	10.3 (3–20)	9.8 (3–20)	0.48
Sex (M/F)	46/22	56/14	0.14
Diagnosis			
Non-Hodgkin lymphoma	2	1	
Hodgkin disease	2	1	
Osteosarcoma	14	6	
Wilms tumor	3	5	
Neuroblastoma	21	25	
CNS tumors	10	19	
Ewing sarcoma	3	2	
Rhabdomyosarcoma	3	6	
Retinoblastoma	2	1	
PNET	4	1	
Others	4	3	
Total number of episodes	70	68	

The *t*-test was used to evaluate the difference between two means (duration of neutropenia, duration of fever, and age). The difference between proportions was used to evaluate the classification of the febrile episodes (fever of unknown origin, clinically or microbiologically documented infections, and admissions). χ^2 with Yates correction was used to evaluate difference in the sex distribution and treatment outcome.

RESULTS

From November, 1993, to December, 1995, 138 episodes of fever and neutropenia in 70 low-risk pediatric oncology patients were evaluated. For each episode of fever and neutropenia, patients were independently randomized to receive either ciprofloxacin or ceftriaxone. Patients were 3–20 years of age (mean 9.8 years), 45 male and 25 female, with underlying diagnosis of non-Hodgkin lymphoma stages I/II or solid tumors (Table I). All patients were neutropenic because of chemotherapy. Patients receiving high-dose chemotherapy were considered high-risk and therefore were not eligible for this study.

One hundred sixteen episodes were considered evaluable (Table II). Among the 22 nonevaluable episodes, 9 received ciprofloxacin and 13 received ceftriaxone ($P = 0.53$). The most important reason for exclusion was a nadir higher than 500 neutrophils/mm^3 (6 vs. 10 patients with ciprofloxacin and ceftriaxone, respectively). These patients were initially included because of fever criteria and white count between 500 and 1,000/mm^3 within the first days postchemotherapy. One patient in each group received nontransplant high-dose chemotherapy includ-

TABLE II. Randomized Episodes of Fever and Neutropenia

	Ciprofloxacin (%)	Ceftriaxone (%)	Total (%)	*P*
Evaluable episodes	59 (42.7)	57 (41.3)	116 (84.0)	0.53
Nonevaluable episodes	9 (6.5)	13 (9.4)	22 (15.9)	
Reason for exclusion				
Neutrophils nadir >500	6 (27.3)	10 (45.4)	16 (11.6)	
High-risk patients	1 (4.5)	1 (4.5)	2 (1.4)	
Allergic reaction	1 (4.5)	0	1 (0.7)	
Questionable fever	0	2 (9.0)	2 (1.4)	
Lost to follow-up	1 (4.5)	0	1 (0.7)	
Total	68 (49.3)	70 (50.7)	138 (100)	

TABLE III. Source of Infection

	Ciprofloxacin (%)	Ceftriaxone (%)	Total (%)	*P*
Fever of unknown origin	24 (40.6)	18 (31.6)	42 (36.2)	0.27
Clinically documented	33 (55.9)	36 (63.2)	69 (59.5)	
HEENT	24 (40.7)	23 (40.3)	47 (40.5)	
Mucosa	10 (17.0)	10 (17.5)	20 (17.2)	
Urinary tract	2 (3.4)	2 (3.5)	4 (3.4)	
Gastrointestinal	2 (3.4)	7 (12.3)	9 (7.8)	
Skin	2 (3.4)	6 (10.5)	8 (6.9)	
Soft tissue	4 (6.8)	1 (1.7)	5 (4.3)	
Lung	1 (1.7)	3 (5.3)	4 (3.4)	
Blood	0	1 (1.7)	1 (0.9)	
Joint	1 (1.7)	0	1 (0.9)	
Microbiologically documented	2 (3.4)	3 (5.3)	5 (4.3)	
Throat	1 (1.7)	2 (3.5)	3 (2.6)	
S. aureus				
K. pneumoniae				
Gr. B *Streptococcus*				
Skin (*S. viridans*)	0	1 (1.7)	1 (0.9)	
Urine (*P. mirabilis*)	1 (1.7)	0	1 (0.9)	
Blood (*Aeromonas hydrophila*)	0	1 (1.7)	1 (0.9)	
Total	59 (99.9)	57 (100.1)	116 (100)	

HEENT = head, eyes, ears, nose, throat.

ing cyclophosphamide. These patients were considered high-risk patients and were treated empirically with a combination of ceftriaxone and amikacin. One patient had hypersensitivity to ciprofloxacin and discontinued the drug, and one abandoned therapy. Two patients had questionable fever at the time of admission and remained afebrile during therapy.

The most common diagnosis (Table III) was clinically documented infection (56% vs. 63% of the episodes treated with ciprofloxacin and ceftriaxone, respectively; $P = 0.27$), followed by fever of unknown origin (41 vs. 32%). Sites of infection were upper respiratory tract (HEENT; 40.5%), mucosa (17.2%), gastrointestinal (7.8%), skin (6.9%), joint (6.9%), soft tissue (4.3%), urinary tract (3.4%), lung (3.4%), joint and blood (0.9% each), with similar distribution between the two groups. Upper respiratory infections included sinusitis (74.0%), tonsillitis (12.7%), and otitis media (12.7%). Some patients had more than one clinically documented site of infection. Microbiologically documented infections were identified in 3% vs. 5% of the episodes in the ciprofloxacin and ceftriaxone groups respectively. Isolates were *S. aureus, K. pneumoniae*, group B *Streptococcus, S. viridans*, and *P. mirabilis* from throat (3), skin (1), and urine (1). The only positive blood culture grew *Aeromonas hydrophila* (Table 3). Granulocytopenia (<500 cells/mm^3) lasted 1–15 days after randomization, with a mean of 5 vs. 6 days ($P = 0.0446$), and fever lasted for 1–9 consecutive days (mean 2 vs. 3; $P = 0.0134$) in the ciprofloxacin and ceftriaxone groups, respectively (Table IV).

Most patients received exclusive outpatient therapy (93.2% vs. 96.5%). The reason for admission was clinical status deterioration (1.7% in both groups), more than once per day antibiotic schedule, or both. Success was achieved without modification in 83.0% of the ciprofloxacin-treated episodes compared to 75.4% of those treated with ceftriaxone. The most frequently added antibiotic was amikacin (10.2% vs. 24.5% in the ciprofloxacin and ceftriaxone groups, respectively), followed by ceftriaxone (6.8% of ciprofloxacin-treated episodes). Ceftazidime, clindamycin, vancomycin, amoxicillin, amphotericin B, and acyclovir were added in fewer than 2% of the episodes. The only side effects observed were gastrointestinal and occurred in five ciprofloxacin-treated episodes (nausea and vomiting in four, diarrhea in one, epigastric pain in one; Table V). All knee X-rays were normal prior to and after the ciprofloxacin therapy. No patient died of infection.

DISCUSSION

Infections are one of the leading causes of death among immunosuppressed patients [17,18]. Fever is a known medical emergency in neutropenic patients demanding immediate broad-spectrum antibacterial coverage. Efforts have been made to identify low-risk patients who might be treated as outpatients [8–12]. Many drug combinations have proved efficient in the setting of fever and neutropenia. The feasibility of monotherapy increased with the introduction of the third-generation cephalosporins and, more recently, the quinolones [19]. Outpatient oral therapy benefits include patient satisfaction, low cost, and low risk of nosocomial infections. However, this therapy is indicated only for patients with low risk for clinical complications.

Patients may be divided into low- and high-risk categories for infectious complications based on their underlying diagnosis and the chemotherapy regimen [3,4]. Solid tumor and stage I/II non-Hodgkin lymphoma pa-

TABLE IV. Clinical Outcome

	Ciprofloxacin (%)	Ceftriaxone (%)	Total (%)	*P*
Duration of neutropenia (after admission)				
Number of days	5.0	5.9	5.45	0.04
Range	1–12	1–15	1–15	
Resolution of fever (number of days)				
Mean	2.0	3.0	2.5	
Range	1–9	1–9	1–9	
Therapy				
Exclusively outpatient	55 (93.2)	55 (96.5)	110 (94.8)	0.38
Admission	4 (6.8)	2 (3.5)	6 (5.2)	
Causes of admission				
Clinical deterioration	1 (1.7)	1 (1.7)	2 (1.7)	
Frequent schedule antibiotics	1 (1.7)	0	1 (0.9)	
Both	2 (3.4)	1 (1.7)	3 (2.6)	
Results				
Failure	0	0	0	
Success				
Without modification	49 (83.0)	43 (75.4)	92 (79.3)	0.43
With modification	10 (17.0)	14 (24.6)	24 (20.7)	
Additional therapy				
Amikacin	6 (10.2)	14 (24.5)	20 (1.7)	
Ceftriaxone	4 (6.8)	0	4 (3.4)	
Ceftazidime	1 (1.7)	1 (1.7)	2 (1.7)	
Clindamycin	1 (1.7)	1 (1.7)	2 (1.7)	
Vancomycin	1 (1.7)	0	1 (0.9)	
Amphotericin B	0	1 (1.7)	1 (0.9)	
Amoxicillin	1 (1.7)	0	1 (0.9)	
Acyclovir	1 (1.7)	1 (1.7)	2 (1.7)	
Total	59 (99.9)	57 (100.1)	116 (100)	

TABLE V. Adverse Effects*

	Ciprofloxacin (%)	Ceftriaxone (%)
Nausea and vomiting	4	0
Diarrhea	1	0
Epigastric pain	1	0
Total number of episodes	5	0

*A total of six adverse effects were observed in five episodes.

tients are considered to carry a low risk, as opposed to leukemia and stage III/IV lymphoma patients, who are at a higher risk for complications [4,5]. We have previously shown differences between the two groups regarding the length of granulocytopenia (10.5 days vs. 6.7 days in the high- and low-risk groups, respectively), proportion of positive blood cultures (21% vs. 9%), and superinfection (23.5% vs. 5.7%) [3]. Based on this experience, low-risk pediatric patients were treated with once-daily ceftriaxone as monotherapy [9]. Ceftriaxone yielded 97.5% therapeutic success owing to its broad-spectrum coverage, low toxicity, and long half-life. No modifications in therapy were made in 86.7% of the episodes. Amikacin was the most frequently added antibiotic.

In this study, we compared outpatient intravenous ceftriaxone, our standard approach to low-risk neutropenic patients, to oral ciprofloxacin. Quinolones have been widely used in recent years owing to oral formulation availability and broad-spectrum coverage [13–16]. Despite good tolerance in adults, the drug has not been widely used in children because of severe joint events observed in young animals. Hampel et al. in 1997 [14] studied 1,795 children receiving either oral ciprofloxacin (25 mg/kg/day) or intravenous ciprofloxacin (8 mg/kg/day). Thirty-one (1.5%) patients had arthralgia, mostly of moderate intensity, which resolved with no interventions. Sixty percent of the patients with arthralgias had underlying cystic fibrosis, which may be associated per se with this side effect. Other recent studies have also concluded that joint events associated with ciprofloxacin are rare and occur mostly in children with cystic fibrosis [20]. Chysky et al. [13] reviewed the clinical data from 634 children and adolescents who were treated with ciprofloxacin. The patients were 3 days to 17 years of age and were treated with either oral or intravenous ciprofloxacin for an average of 22.8 days. Sixty-two percent of the cases consisted of respiratory tract infections, mostly severe pulmonary complications of cystic fibrosis. The total incidence of side effects was 12.6%; 8 patients (1.3%) developed arthralgia, which resolved when the treatment was discontinued.

Considering the extensive knowledge about the use of ciprofloxacin in children, we decided to evaluate its efficacy in the treatment of fever and neutropenia in pediatric oncology patients. We treated 116 evaluable episodes of fever and neutropenia in 70 patients with low-

risk malignant disease. Although the difference in the duration of both fever and neutropenia after entering the protocol between the two groups achieved significance, we do not believe 1 extra day would have any clinical significance.

Fever of unknown origin and upper respiratory tract infections were the most frequent diagnosis. The distribution of episodes of unexplained fever (FUO) and clinically documented infections was similar between the two groups and comparable to that in other studies. Both drugs were well tolerated. Gastrointestinal side effects of mild to moderate intensity occurred in 8% of the patients treated with ciprofloxacin. No arthropathy was detected by either clinical or radiological (knee X-ray) examination. The efficacy was excellent, and there were no deaths in either group.

We should emphasize that all patients appeared well and were hemodynamically stable. Ciprofloxacin is *not* the therapy of choice if gram-positive organism infection is suspected. Only one patient had an indwelling catheter. We concluded that oral ciprofloxacin is as effective as intravenous ceftriaxone and, therefore, can be considered an adequate alternative for initial empirical therapy for neutropenic febrile children with solid tumors and stage I/II lymphomas.

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