Oral Ciprofloxacin in the Management of Children with Cancer with Lower Risk Febrile Neutropenia

A Randomized Controlled Trial

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BACKGROUND. Recent reports and a previous randomized trial conducted at the authors' institution suggested that a lower risk subset of children with febrile neutropenia under chemotherapy might benefit of an oral antibiotic outpatient approach.

METHODS. The objective of this study was to test the efficacy of oral ciprofloxacin in the treatment of lower risk febrile neutropenia (LRFN) in children treated for malignant diseases. From November 1998 to December 1999, 93 episodes of LRFN in 87 children (median age, 5.5 years; range, 0.9–15.8 years) were included in a prospective randomized controlled single institution trial. Inclusion criteria included fever ($>$ 38 °C), severe neutropenia (absolute neutrophil count, $<$ 500/mm^3), and lower risk features (e.g., absence of severe comorbidity factors, good clinical condition, negative blood cultures, control of local infection, prediction of a period of neutropenia less than 10 days after admission, and compliant parents). After 24 hours of a single intravenous ceftriaxone (100 mg/kg) plus amikacin (15 mg/kg) and completed risk assessment workup, patients were discharged and randomly allocated to two groups. Group A (48 episodes) received ciprofloxacin 20 mg/kg/day orally (p.o.) every 12 hours for 6 days. Group B (45 episodes) received intravenous ceftriaxone plus amikacin for 2 days more followed by cefixime (8 mg/kg/day p.o.) every 24 hours for 4 additional days. Failure was defined as the need of a second hospitalization during the same episode.

RESULTS. Most of the patients (59% in Group A and 52% in Group B) were treated for malignant solid tumors. Fifteen (31%) children in Group A and 15 (33%) in Group B presented with fever of unknown origin (*P* value was not significant). No significant differences were found in sites of initial infection between both groups. Overall results in this study were excellent. Only one patient with respiratory failure was detected in Group B, who did well with secondary treatment.

CONCLUSIONS. In febrile neutropenic children after anticancer therapy and lower risk features, oral ciprofloxacin for 6 days after 24 hours of intravenous ceftraxione plus amikacin appears to be as efficacious as intravenous ceftriaxone plus amikacin for 2 days more followed by cefixime for 4 additional days. These results contribute to strengthen the concept of LRFN. ***Cancer* 2001;91:1563–7.**

KEYWORDS: fever, neutropenia, ciprofloxacin, lower risk, children.

An early inpatient therapy with broad-spectrum intravenous antibiotics for cancer patients with neutropenia and fever clearly has proved to reduce infection morbidity and mortality and has been considered the standard of care.[1–3]

It has been demonstrated that febrile neutropenic patients do not represent an homogeneous group.[4] Features that help to define pa-

tients at lower risk during hospitalization include early signs of bone marrow recovery, short duration of fever, absence of comorbidity factors, and a predictive period of neutropenia of less than 10 days.[4]

Recent advances, such as the availability of oral antibiotics with activity against most of the common pathogens isolated in these patients (e.g., ciprofloxacin, ofloxacin, cefixime), have made it possible to study the feasibility of outpatient management of lower risk episodes of fever and neutropenia.[5,6] Trials on this strategy are scarce in children.[7–11]

Children with cancer and their families often experience hospitalization as additional psychosocial and financial burdens, and devising safe outpatient strategies for carefully selected lower-risk patients with fever and neutropenia is an important goal in cancer treatment.[10]

We previously have proved that oral cefixime after 3 days of parenteral ceftriaxone plus amikacin was equally effective than a 7-day parenteral antibiotic therapy for lower risk febrile neutropenia in children.[11]

This single-center, randomized clinical trial was designed to assess the efficacy of oral ciprofloxacin for children with lower risk febrile neutropenia.

PATIENTS AND METHODS

Between November 1998 and December 1999, we conducted a prospective, randomized, controlled study to evaluate the efficacy of intravenous ceftriaxone plus amikacin given for 24 hours followed by oral ciprofloxacin in children with febrile neutropenia after chemotherapy and lower risk of bacteremia, who were hospitalized at the Hospital de Pediatría Professor Dr. J.P. Garrahan, Buenos Aires, Argentina. This hospital is a 450-bed tertiary care pediatric center, with special assistance on oncology and hematology patients and solid-organ recipients, as well as children undergoing cardiac surgery or neurosurgery. This study was conducted following the guidelines of the Declaration of Helsinki and received the approval of the Hospital Ethics Committee. An informed consent was obtained from the children guardians before enrollment.

Inclusion criteria were 1) age younger than 18 years old with neutropenia after chemotherapy for primary malignant disease, 2) absolute neutrophil count (ANC) less than 500/mm^3 or less than 1000/mm^3 with a predicted decline to less than or equal to 500/mm^3, 3) 1 episode of fever higher than 38.5 °C or 2 records higher than 38 °C within 24 hours, and 4) family ability to administer oral medications reliably. Exclusion criteria were 1) severe comorbidity factors (e.g., incoercible bleeding, refractory hypoglycemia, and hypocalcemia, hypotension, altered mental status, renal insufficiency [estimated glomerular filtration rate of $< 50\%$ normal for age], hepatic dysfunction [evidence by serum alanine aminotransferase > 4 times normal or bilirubin > 3 mg% at the time of the preceding chemotherapy cycle]), 2) respiratory failure, 3) poor clinical condition, 4) fascial, perineal, or catheter-associated cellulitis, 5) evidence of enteritis or severe mucositis, 6) uncontrolled local infection, 7) positive blood cultures within the first 24 hours, 8) neutropenia predicted to last more than 10 days after the onset of fever, 9) parents/caregivers deemed by the medical staff to be less than absolutely reliable, 10) infection with microorganisms known to be resistant to ceftriaxone or ciprofloxacin, 11) allergy to ceftriaxone or ciprofloxacin, 12) currently undergoing bone marrow transplantation. Positive blood cultures found after inclusion in the trial was be a cause to withdraw the patient from the study.

Peripheral blood and urine cultures and chest X-ray were performed for all patients at the onset of the study. Blood samples from port catheters and from peripheral veins for quantitative differential cultures also were taken in all cases. Also, when skin and soft tissue infections, diarrhea, pharyngitis, or any infection was suspected, cultures of the involved source were obtained.

After the initial workup was conducted, patients were registered and allocated by random number generation produced by a computer spreadsheet program to receive either ceftriaxone (100 mg/kg/day intravenously [i.v.], single-dose, maximum 2 g) plus amikacin (15 mg/kg/day i.v., single dose) the first day, followed by ciprofloxacin (20 mg/kg/day orally [p.o.] every 12 hours) for 6 days (Group A), or ceftriaxone plus amikacin for 3 days followed by cefixime (8 mg/kg/day p.o., every 24 hours) for 4 additional days (Group B).

Patients who had been receiving prophylactic acyclovir continued to receive this agent. Usage of hemopoietic growth factor did not hinder the enrollment, and the attending oncologist decided their administration in each case.

The patients were discharged after 72 hours of hospitalization and examined every 24 hours as outpatients by clinical examination and a differential leukocyte count every 48 hours when persistent neutropenia was observed.

Treatment success was defined as the resolution of the episode of fever and neutropenia and no readmission due to a new fever infection event within 7 days of discharge or a new febrile episode during the same period of neutropenia.

The Epi Info system (Centers for Disease Control, Atlanta, GA) was used for statistical analysis. Outcome rates were compared by the Fisher exact test or chi-

TABLE 1
Demographic and Clinical Characteristics of Two Groups of Studied Patients

Characteristic	Group A (ceftriaxone + ciprofloxacin) (%)	Group B (ceftriaxone + cefixime) (%)	*P* value
Episodes treated	48 (52)	45 (48)	NS
Patients	44 (50)	43 (50)	NS
Age (mos)			
Median	60	72	NS
Range	14–180	11–190	NS
Gender (male/female)	27/21	23/22	NS
Malignancy			
Leukemia	18 (37)	20 (44)	NS
Lymphoma	2 (4)	2 (4)	NS
Solid tumors	28 (59)	23 (52)	NS
Distribution of ANC at presentation			
0–100	11 (23)	14 (31)	NS
101–500	35 (73)	27 (60)	NS
> 500 with predicted decline	2 (4)	4 (9)	NS
Prophylactic G-CSF	27 (56)	17 (38)	NS
Endovascular catheter	16 (33)	21 (47)	NS

ANC: absolute neutrophil count; NS: not significant; G-CSF: granulocyte-colony stimulating factors.

TABLE 2
Clinical Course and Outcome of the 93 Episodes of Fever and Neutropenia

Characteristic	Group A (ceftriaxone + ciprofloxacin)	Group B (ceftriaxone + cefixime)	*P* value
No. of episodes	48	45	
Median duration of fever (days [range] ± SD)	1 (1–5) ± 1.1	1 (1–8) ± 3.2	NS
Median duration of neutropenia (days [range] ± SD)	4 (1–8) ± 2.1	4 (1–8) ± 2.1	NS
No. of episodes discharged with neutropenia (%)			
Neutropenia	31 (64)	26 (58)	NS
Fever of unknown origin	15 (31)	15 (33)	NS
Upper respiratory tract	28/33 (85)	25/30 (83)	NS
Gastrointestinal	0	2 (7)	
Skin	0	2 (7)	
Lower respiratory tract	4 (12)	1 (3)	NS
Urinary tract	1 (3)	0	
Success	48 (100)	44 (98)	NS
Failure	0	1	
Death	0	0	NS
ICU admission	0	0	

ICU: intensive care unit; SD: standard deviation; NS: not significant.

square test, Yates-adjusted. Numeric data are presented as an arithmetic mean. A *P* value less than or equal to 0.05 was assumed as significant.

RESULTS

One hundred ninety patients presented 237 consecutive episodes of febrile neutropenia, but only 93 episodes (from 87 patients; 39.2%) who fulfilled the inclusion criteria were included in the study. Forty-eight were randomized to be allocated to Group A and 45 to Group B. One hundred forty-three children who did not fulfill the entry criteria were excluded from this study at time of presentation. One child initially enrolled in the trial developed positive blood cultures due to a catheter-related bacteremia by coagulase negative *Staphylococcus* at 48 hours of admission. This was the only one episode of lower risk febrile neutropenia who was withdrawn from the study. The patient received 10 days of intravenous vancomycin with a favorable outcome.

Table 1 shows the comparative demographic and clinical characteristics of both groups. No significant differences in gender, age, intravenous catheter device, use of hemopoietic growth factors, or underlying disease were observed. The median duration of granulocytopenia after randomization was 4 days (range, 1–8 days; *P* value not significant). Eleven children (23%) in Group A and 14 (31%) in Group B had severe neutropenia (< 100 ANC) at the onset of fever (*P* value not significant). Thirty-seven (77%) children in Group A and 35 (78%) in Group B had greater than 500 ANC/mm^3 at the time of discontinuation of antibiotics. Thirty-one (64%) episodes in Group A and 26 (58%) in Group B were still neutropenic (≤ 500 absolute neutrophil count/mm^3) at the time of discharge (*P* value not significant; Table 2). The median duration of fever was 1 day in both groups of treatment (*P* value not significant). Thirty-two (66%) children in Group A and 24 (53%) in Group B had fever during only 1 day.

The origin of approximately one-third of all febrile episodes could not be determined. Infection was documented in 69% of the episodes in Group A and 67% of the episodes in Group B (*P* value not significant). Most documented infections were localized and mild. The most common were upper respiratory infections in both groups (*P* value not significant; Table 2). Four patients had microbiologically documented infections: urinary tract infection and acute diarrhea caused by *Escherichia coli*, *Streptococcus pyogenes* in one child with impetigo, and syncytial respiratory virus in another patient with pneumonitis.

A favorable outcome occurred in all episodes in Group A and in 44 (98%) in Group B. There was one respiratory failure in Group B. This child had a pneumonitis caused by syncytial respiratory virus lower respiratory infection with prolonged fever and neutropenia (more than 6 days). He did well after a second-

ary treatment, which included intravenous ceftazidime and amikacin, without further complications. One patient in Group B, the only case withdrawn from the study, needed the addition of another antibiotic. No child had an infection with microorganisms known to be resistant to ceftriaxone, cefixime, or ciprofloxacin. No patient had untoward effects. All children were discharged at 72 hours.

DISCUSSION

The management of patients with neutropenia and fever has been the subject of major changes over the last few years. Until recently, all febrile neutropenic patients were hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy.[3] In recent years, the concept of risk assessment during the initial phases of a febrile episode has been introduced and evaluated.[4,11] The identification of different risk categories of patients with neutropenia and fever, the recognition of a lower risk subgroup with a low incidence of serious infection-related complications during the episode, and the availability of new oral broad-spectrum antibiotics are of special interest because they made it possible to investigate new treatment strategies for this population.

The overall outcome for our lower risk children with febrile neutropenia was excellent, irrespective of the oral antibiotic employed in each randomization arm. In only one case, the strategy failed. This was an 8-year-old male patient allocated to the cefixime arm who developed a viral pneumonitis and persisted febrile during 8 days. He did well with secondary treatment.

This study demonstrates that febrile neutropenic children who meet certain low risk criteria might be safely managed using daily intravenous ceftriaxone plus amikacin followed by oral ciprofloxacin for 6 additional days. We previously had proved that oral cefixime after 3 days of parenteral ceftriaxone plus amikacin was equally effective than a 7-day parenteral antibiotic therapy for lower risk febrile neutropenia in children.[11] Both are suitable alternatives to conventional treatment for children who are at lower risk.

In compliant patients, with this lower risk criteria, the treatment could be changed after 1 day of intravenous therapy to an oral drug, such as cefixime, ciprofloxacin, ofloxacin, clindamycin, or quinolone associated with amoxicillin/clavulanic acid, and the patient could be discharged earlier from the hospital, with close and careful observation.[3,5,6,12] Reports of oral treatment in children with febrile neutropenia are scarce.[10,12,13] Ciprofloxacin was selected for evaluation in this study based on its bactericidal activity, optimal oral pharmacokinetics, lack of serious adverse events, and wide spectrum of activity against gram-negative bacteria.[14–16] The addition of gram-positive agents to the initial coverage remains a matter of controversy.[3] Ciprofloxacin has been shown to be effective in the outpatient management of adults with lower risk neutropenia and fever. Recently, Mullen et al. demonstrated its efficacy in children.[10] In their report, 40 children did well without untoward effects.

We used simple criteria to identify lower risk patients. We excluded patients who had received allogeneic bone marrow or peripheral blood stem cell transplants, and secondary or recurring neoplasia, granulocytopenia expected to last longer than 10 days, sepsis, poor clinical condition, bacteremia, severe clinical foci, or any other condition that required intravenous antibiotics or supportive therapy and hospitalization.[3,17,18] The careful selection of a lower risk population was a crucial factor in the success of the regimens. Other studies have used similar criteria, affirming their predictive value in the setting of fever and neutropenia.[6,10]

In our study, as in the studies by Kern et al.[6] and Freifeld et al.,[13] most of the patients had solid tumors, but the mean duration of neutropenia was shorter (3.4 days in the oral therapy group and 3.8 days in the intravenous therapy group).

In febrile neutropenic children after anticancer therapy and with lower risk features, oral ciprofloxacin for 6 days after 24 hours of intravenous ceftraxione plus amikacin appears to be as efficacious as intravenous ceftriaxone plus amikacin for 2 days longer followed by cefixime for 4 additional days.

Our results give support to the finding that a lower risk subset of patient with febrile neutropenia may be spared from an aggressive approach. There is no need to emphasize the advantages of an oral ambulatory strategy compared with a prolonged inpatient antibiotic therapy for the patients, their families, and the institutional savings. We believe that to define a safe, very low risk febrile neutropenic subset, each patient's initial blood cultures should be negative. In this trial, we refined the selection criteria of clinical and laboratory data to define clear-cut lower risk febrile neutropenia groups. A strict selection of children with very low risk febrile neutropenia may allow discontinuation of any further oral therapy once blood cultures and initial features are assessed. This will be the main hypothesis to be tested in our next randomized trial.

REFERENCES

1. Pizzo PA, Rubin M, Freifeld A, Walsh TJ. The child with cancer and infection. I. Empiric therapy for fever and neutropenia, and preventive strategies. *J Pediatr* 1991;119:679–94.

2. Pizzo PA, Commers J, Cotton D, Gress J, Hathorn J, Hiemenz J, et al. Approaching the controversies in antibacterial management of cancer patients. *Am J Med* 1984;76:436–49.
3. Hughes WT, Armstrong D, Bodey G, Brown AE, Edwards JE, Feld R, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997;25:551–3.
4. Buchanan GR. Approach to treatment of the febrile cancer patients with low-risk neutropenia. *Hematol Oncol Clin North Am* 1993;5:919–35.
5. Malik IA, Khan WA, Karim M, Aziz Z, Khan A. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. *Am J Med* 1995;98:224–31.
6. Kern WV, Cometta A, de Bock R, Langenaeken J, Paesmans M, Gaya H, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; 341:312–8.
7. Aquino V, Buchanan G, Tkaczewski I, Mustafa MM. Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. *Med Pediatr Oncol* 1997;28:191–5.
8. Bash RO, Katz JA, Cash JV, Buchanan GR. Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. *Cancer* 1994;74:189–96.
9. Aquino V, Tkaczewski I, Buchanan GR. Early discharge of low-risk febrile neutropenic children and adolescents with cancer. *Clin Infect Dis* 1997;25:74–8.
10. Mullen CA, Petropoulos D, Roberts M, Rytting M, Zipf T, Chan KW, et al. Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer* 1999;86: 126–34.
11. Paganini H, Sarkis C, De Martino M, Zubizarreta P, Casimir L, Fernández C, et al. Use of oral cefixime in lower-risk febrile neutropenic children with cancer. *Cancer* 2000;88: 2848–52.
12. Klaasen RJ, Allen JJ, Doyle T. Randomized placebo-controlled trial of oral antibiotics in low risk paediatric oncology patients with fever and neutropenia. *J Pediatr Hematol Oncol* 1999;21:334.
13. Freifeld A, Marchigiani D, Walsh T, Chanock S, Lewis L, Hiemenz J, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999;341:305–11.
14. Jick S. Ciprofloxacin safety in a pediatric population. *Pediatr Infect Dis J* 1997;16:130–4.
15. Freifeld A, Pizzo P. Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. *Pediatr Infect Dis J* 1997;16:140–6.
16. Patrick CC. Use of fluoroquinolones as prophylactic agents in patients with neutropenia. *Pediatr Infect Dis J* 1997;16: 135–9.
17. Paganini H, Bologna R, Debbag R, Casimir L, Gomez S, Rosanova M, et al. Neutropenia and fever in child in one single institution in Argentina. *Pediatr Hematol Oncol* 1998; 5:1–9.
18. Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PP. Predicting the risk of bacteremia in children with fever and neutropenia. *J Clin Oncol* 1996;14:919–24.