Feasibility of Oral Ciprofloxacin for the Outpatient Management of Febrile Neutropenia in Selected Children with Cancer

Victor M. Aquino, M.D.
Larry Herrera, M.D.
Eric S. Sandler, M.D.
George R. Buchanan, M.D.

Department of Pediatrics, The University of Texas Southwestern Medical Center at Dallas, and the Center for Cancer and Blood Disorders, Children's Medical Center of Dallas, Dallas, Texas.

BACKGROUND. Children with cancer who develop an episode of chemotherapy-induced febrile neutropenia usually are admitted to the hospital for intravenous empiric antibiotic therapy. In the current study, the authors examined the use of ciprofloxacin as outpatient management in selected patients with fever during an episode of neutropenia.

METHODS. Febrile neutropenic patients with a diagnosis of cancer were eligible for outpatient management with oral ciprofloxacin if they appeared well and demonstrated the following characteristics: age 1–21 years, malignancy in remission, absolute phagocyte count $> 100/mm^3$, > 7 days since the initiation of the last course of chemotherapy, and reliable parents. Eligible children received a single dose of ceftazidime and were observed for 2–23 hours. Patients were discharged receiving oral ciprofloxacin (20/mg/kg/day divided in 2 doses) until the patient was afebrile for 24 hours, had sterile blood cultures, and had evidence of bone marrow recovery. Patients were admitted if they appeared toxic, had positive blood cultures, or were febrile for ≥ 5 days.

RESULTS. Forty-five evaluable episodes occurred in 32 children. Forty of the 45 patients (89%) were treated successfully in the outpatient setting. The 95% lower confidence bound on the proportion of successful outcomes was 70%. Five children required hospitalization: 2 due to noncompliance, 1 to receive intravenous acyclovir for herpes zoster, and 2 (4%) whose blood cultures were positive for *Streptococcus viridans* and *S. pneumoniae.* All had uncomplicated hospitalizations.

CONCLUSIONS. The current study demonstrates that very carefully selected, low risk patients with febrile neutropenia may be treated successfully without hospitalization using oral ciprofloxacin. Additional research is required to refine further the optimal criteria for the selection of appropriate patients for outpatient management. ***Cancer* 2000;88:1710–4.** © *2000 American Cancer Society.*

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Children who develop fever during an episode of chemotherapy-induced neutropenia traditionally are hospitalized and treated with broad-spectrum intravenous antibiotics until resolution of the neutropenia (i.e., recovery of the absolute neutrophil count [ANC] to $> 500/mm^3$).[1-7] Recently, investigators have shown that patients with febrile neutropenia who have evidence of early bone marrow recovery (rising ANC, absolute phagocyte count [APC], or platelet count) are at a relatively lower risk of bacteremia and can be discharged safely before complete recovery from neutropenia.[8-13] It may be possible that patients who exhibit these features at the time of

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Address for reprints: Victor M. Aquino, M.D., Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75235-9063.

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presentation with fever and neutropenia can be managed safely as outpatients.

Talcott et al.[14] demonstrated that healthy-appearing adult cancer patients with fever and neutropenia had a lower rate of incidence of subsequent clinical deterioration and might be candidates for outpatient therapy. Other studies[15-18] also have shown that selected patients can be managed safely as outpatients with either intravenous or oral broad-spectrum antibiotics. To our knowledge this management strategy has not been well studied in children with cancer. However, several retrospective reviews of children with cancer have identified the following features as being associated with a lower risk of bacteremia: temperature < 39.1 °C,[19] absolute monocyte count (AMC) $> 100/mm^3$,[19] and diagnosis of a solid tumor.[20]

We hypothesized that carefully selected pediatric patients with febrile neutropenia who demonstrate early evidence of bone marrow recovery can be treated safely as outpatients with oral ciprofloxacin. A clinical trial was conducted to test this hypothesis.

MATERIALS AND METHODS

Patient Population

All children and adolescents with cancer seen at the Children's Medical Center at Dallas between February 1996 and January 1998 who presented with febrile neutropenia were eligible for enrollment. The study was closed temporarily between January and May 1997 for preliminary analysis of the data prior to presentation at a scientific meeting. The study then was reopened to further patient accrual. These children were being treated according to a variety of Pediatric Oncology Group and local institutional chemotherapeutic protocols. Fever was defined as a single oral or axillary temperature of > 38.5 °C or 2 measurements of > 38.0 °C in a 24-hour period.[21] Neutropenia was defined as an ANC of < 500 cells/mm^3 (ANC $= 0.01 \times$ [% bands + % polymorphonuclear cells] $\times$ total leukocyte count). The study was approved by the institutional review board of the University of Texas Southwestern Medical Center at Dallas, and written informed consent was obtained.

Patient Eligibility

Patients were eligible for enrollment in the study if they were age > 12 months but < 21 years, had an APC (APC $= 0.01 \times$ [% bands + % polymorphonuclear cells + % monocytes]) $> 100/mm^3$, and were in disease remission. Patients with a solid tumor were eligible if they had responsive or stable disease at the time of their last radiographic evaluation. Patients receiving high dose pulse chemotherapy were required to be ≥ 7 days from the initiation of the last course of chemotherapy to assure that they were at or beyond the nadir of their neutropenia. Patients also were required to have reliable parents, a telephone in the home, adequate transportation, agreement to daily follow-up, and residence within 100 miles of the study institution. Patients were evaluated carefully for signs of sepsis (i.e., hypotension, shaking chills, etc.). Patients were ineligible if they appeared septic; had undergone bone marrow transplantation; were receiving high dose intermittent or continuous infusion cytarabine for acute myelogenous leukemia or Burkitt lymphoma; had a known allergy to ciprofloxacin, cephalosporins, or penicillin; were receiving oral antibiotics for a minor bacterial infection (e.g., pharyngitis, otitis media, cellulitis, etc.); or had another medical condition best managed in the hospital (e.g., severe mucositis, anemia requiring blood transfusion, diarrhea unresponsive to dietary manipulation, or dehydration requiring intravenous fluid administration).

Diagnostic Evaluation

Patients were evaluated carefully by one of the hematology-oncology staff at the time of presentation with febrile neutropenia. A complete blood count (CBC) with differential leukocyte count and blood cultures were obtained. The ANC, APC, and AMC (AMC = total leukocyte count $\times$ [0.01 $\times$ % monocytes]) were calculated. Other laboratory tests and imaging studies were obtained as clinically indicated. The patient then received a single dose of intravenous ceftazidime (50 mg/kg). If the child appeared clinically well after an observation period of 2–23 hours, the patient was offered enrollment. If patients presented during the night, they were hospitalized for a period of < 23 hours until the child could be evaluated by an attending physician. If patients were observed for > 8 hours, treatment with ciprofloxacin was initiated 8 hours after the first dose of ceftazidime.

Study Execution

After enrollment, the patient began treatment with ciprofloxacin (20 mg/kg/day divided into 2 doses, with a maximum dose of 500 mg). Families were advised to take the child's temperature every 4–6 hours at home and administer acetaminophen for fever. Parents were instructed to call the physician if the child appeared ill, developed shaking chills, or had persistent fever. Patients were seen in the outpatient unit daily for evaluation, including a CBC and blood culture. Ciprofloxacin was continued until fever was absent for 24 hours, blood cultures were sterile, and evidence of continued bone marrow recovery (APC rising on 2 consecutive days or a doubling of the admission APC) was apparent. A CBC then was obtained every other

TABLE 1
Characteristics of 45 Episodes of Lower Risk Febrile Neutropenia in Children with Cancer Treated as Outpatients with Oral Ciprofloxacin

Mean age (yrs) (range)	6.5 (2–20)
Gender	
Male	24 (53%)
Female	21
Underlying diagnosis	
Leukemia/lymphoma	31 (69%)
Solid tumor	14
Central venous catheter	
Yes	30 (67%)
No	15
Concomitant G-CSF therapy	13 (29%)

G-CSF: granulocyte-colony stimulating factor.

day until the ANC was $> 500/mm^3$. Patients with a defined focus of infection continued receiving an oral antibiotic (either ciprofloxacin or an alternate antimicrobial agent) when they met criteria to discontinue the ciprofloxacin. If a patient developed gram-positive bacteremia and appeared well, intravenous vancomycin was added to the outpatient regimen. Management of the febrile episode was considered successful if the child did not require hospitalization.

Patients were withdrawn from the study and immediately hospitalized if they appeared ill, had fevers that persisted for > 5 days, or developed gram-negative bacteremia.

Statistical Analysis

A total of 32 patients were managed according to the study protocol, with 8 patients being enrolled multiple times. A 95% lower confidence bound on the proportions of successful treatments was obtained using the number of patients treated successfully. For the analysis, a conservative decision was made to consider any unsuccessful episode for each of the eight patients who were enrolled multiple times as a "failure." With a sample size of 32 patients, the length of a 95% lower confidence bound would not exceed 15%. The 95% lower confidence bound was calculated using the binomial density function.

Stopping rules to alert the investigators of the presence of an unacceptably high number of positive cultures or hospitalizations were calculated based on a binomial probability law.[22] Patient outcomes were analyzed after every five patients completed the study for violation of the stopping rule.

RESULTS

Patient Characteristics

During the study period, a total of 235 episodes of febrile neutropenia occurred. Sixty-five of these (28%) met the criteria for study inclusion. Forty-five of the eligible episodes (69%) occurring in 32 patients were managed on the study protocol. The characteristics of the episodes of febrile neutropenia are summarized in Table 1. None of the 45 children enrolled on the study experienced clinical deterioration after the dose of intravenous ceftazidime.

TABLE 2
Results of Outpatient Management of 45 Episodes of Lower Risk Febrile Neutropenia in Children with Cancer Treated as Outpatients with Oral Ciprofloxacin

	Mean (range)
Absolute phagocyte count at study entry ($/mm^3$)	494 (117–1780)
ANC at study entry ($/mm^3$)	194 (0–462)
Platelet count at study entry ($\times 10^3$)	163 (18–528)
No. of days since the beginning of the last course of cytotoxic chemotherapy	11.5 (7–19)
Days febrile on study	2.2 (1–5)
Days neutropenic (ANC $< 500/mm^3$) on study	4.0 (1–8)
Maximal temperature at study entry (°C)	38.9 (38–40)
	No. of episodes (%)
Children with focal infections	6[a] (13%)
Admission for intravenous antibiotic therapy	5/45 (11%)
Positive blood culture	2/45 (4%)

ANC: absolute neutrophil count.
[a] Four with otitis media, one with Cryptosporidium enteritis, and one with herpes zoster.

Study Results

The results of outpatient management of these 45 episodes of febrile neutropenia are summarized in Table 2. The mean APC at study entry was $494/mm^3$, with a range of $117–1760/mm^3$. The mean ANC at study entry was $194/mm^3$, with a range of $0–462/mm^3$. Two children had an ANC of $0/mm^3$ and 18 had an ANC $< 100/mm^3$. Fourteen children (42%) had an AMC $< 100/mm^3$. The mean temperature at presentation was approximately 39.0 °C, and 16 patients (36%) had a temperature > 39.0 °C.

After enrollment, the mean duration of fever was 2.2 days and that of neutropenia was 4.0 days. Six children had evidence of a focal infection. Four (9%) had otitis media and 1 patient developed herpes zoster. One child presented with diarrhea and was diagnosed with Cryptosporidium enteritis. She completed a 5-day course of azithromycin with complete resolution of symptoms.

Forty of the 45 episodes (89%) were managed successfully in the outpatient setting. Stated more conservatively, 27 of 32 patients (84%) had successful outcomes. The 95% lower confidence bound on the

proportion of successful outcomes was 70%. Two children required admission due to inability to tolerate the ciprofloxacin. They both vomited several doses of the antibiotic. Both children remained clinically well during their hospitalization and all blood cultures were sterile. Each child was discharged after the third hospital day with the diagnosis of fever without source. One patient was admitted for treatment with intravenous acyclovir for severe herpes zoster that developed 2 days after study enrollment. All blood cultures from this patient were sterile. Two patients (4%) had positive blood cultures. One child appeared well on admission to the hospital but his initial blood culture was positive for viridans streptococcus. He could not receive home intravenous antibiotic therapy because he did not have a central venous catheter. Repeat cultures were sterile and the child was discharged 3 days later. A second patient was hospitalized with a high fever and persistent otitis media 2 days after study enrollment. Initial blood cultures taken at the time of study admission were sterile. A tympanotomy was performed. The middle ear and blood cultures performed at the time of admission to the hospital were positive for *Streptococcus pneumoniae*. The child was well throughout his admission without signs of sepsis. He was treated with a 10-day course of intravenous vancomycin.

A review of the 20 episodes of febrile neutropenia occurring in patients who were eligible for the study but not enrolled was conducted. The most common reason for a patient not to be enrolled was the on-call fellow or attending physician overlooking the fact that the patient was eligible for enrollment. All these episodes were managed in the hospital. None of these patients had positive blood cultures.

DISCUSSION

Outpatient antibiotic therapy has been shown to be a safe and effective alternative to hospitalization for the treatment of selected patients with a variety of infections.[23-26] In particular, experience continues to be gained in the outpatient management of cancer patients at relatively lower risk of bacteremia. Rubenstein et al.[15] randomized febrile neutropenic adults with cancer who were healthy-appearing to either an oral regimen of ciprofloxacin and clindamycin or intravenous antibiotics. The study demonstrated no statistically significant difference in efficacy between the two arms. However, 4 patients age $>$ 60 years receiving the oral regimen developed severe renal toxicity. In a more recent study from this group, amoxicillin and clavulanate potassium (Augmentin®; SmithKline Beecham, Philadelphia, PA) and ciprofloxacin showed a success rate similar to that of the original oral regimen with no evidence of renal toxicity.[16] Malik et al.[27] compared ofloxacin administered either in the hospital or on an outpatient basis and found no difference in success rates between the two arms. Mustafa et al.[18] demonstrated that selected children with febrile neutropenia could be treated safely as outpatients using intravenous ceftriaxone.

Ciprofloxacin is an oral antibiotic that might be efficacious in the empiric treatment of febrile neutropenia in lower risk children with cancer. Ciprofloxacin is a quinolone with activity against many common gram-negative bacterial pathogens, including *Enterobacteriaceae, Pseudomonas aeruginosa,* and some gram-positive organisms.[28-30] Ciprofloxacin is absorbed rapidly after oral administration, has good distribution to all body compartments, and is convenient to administer in view of its half-life of 3–6 hours.[31] For years, quinolone-induced arthropathy observed in juvenile animals was believed to represent a contraindication to the use of such agents in prepubertal patients.[32-34] However, published data regarding quinolone use in children now includes $>$ 1000 patients without evidence of arthropathy.[28,30]

The current study demonstrates that carefully selected febrile neutropenic children with cancer who meet certain low risk criteria can be treated safely as outpatients using oral ciprofloxacin. The overall success rate of 89% is similar to that reported previously in adult cancer patients treated on an outpatient basis.[15,16] Although 4% of the patients had bacteremia, both isolates were gram-positive bacteria. None of the children had evidence of sepsis or a complicated hospitalization.

Approximately 25% of patients with febrile neutropenia seen at the study institution were eligible for outpatient management using the low risk criteria described. Children with leukemia who received continuous low dose chemotherapy as well as patients receiving pulsed chemotherapy were treated safely on this protocol. We believe that the presence of any evidence of bone marrow recovery from a prior course of chemotherapy may identify a relatively lower risk population of febrile neutropenic children who might be appropriate candidates for outpatient management. Carefully designed studies are required to explore this issue further.

Outpatient therapy for febrile neutropenia with oral antibiotics offers several advantages over management in the hospital with parenteral antibiotics, including elimination of the need for a needle stick, reduced exposure to nosocomial pathogens, and improved quality of life by allowing children more time at home with their families. Additional research is required to refine further optimal criteria to be used for the selection of patients for the outpatient man-

agement of febrile neutropenia. Because the 95% lower bound confidence interval was 15%, larger studies are required to confirm the safety of the approach. We currently are planning a prospective study to evaluate whether the criteria used to identify lower risk children can be modified to allow a larger number of patients to be treated safely in the outpatient arena.

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