Outpatient Therapy with Oral Ofloxacin for Patients with Low Risk Neutropenia and Fever

A Prospective, Randomized Clinical Trial

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BACKGROUND. Hospitalization and treatment with broad-spectrum intravenous antibiotics is the standard care for patients with neutropenia and fever. This randomized clinical trial evaluated the feasibility and efficacy of ambulatory care with oral ofloxacin for patients with low risk, chemotherapy-induced neutropenia and fever.

METHODS. Patients with solid tumors who were treated with conventional dose chemotherapy, presented with fever (axillary temperature >38°C on 2 occasions or >38.5°C on a single occasion) and neutropenia (absolute neutrophil count, <500 cells/μL), and met low risk criteria were eligible for this study. They were randomized either to hospitalization and treatment with broad-spectrum intravenous antibiotics, which consisted of a combination of cefazidime and amikacin, or to outpatient treatment with oral ofloxacin. The definitions of fever of unknown origin, clinical and microbiologic infection, success, success with modification, and failure were the usual ones for this type of study.

RESULTS. One hundred episodes were randomized, and 95 were evaluable (47 were randomized to ceftazidime/amikacin and 48 to ofloxacin). Baseline characteristics, as well as the proportion of patients with microbiologic and clinical infections, were similar in the two groups. In 91% of episodes in the inpatient group and 89% in the ofloxacin group, patients recovered uneventfully ($P = 1$; 95% CI for the difference, -0.09 to 0.13), with 2 and 5 patients requiring modification of the antibiotics, respectively. Eight percent of episodes in the control group and 10.4% in the experimental group resulted in treatment failure. Eight patients (16%) in the outpatient group experienced failure with ambulatory care and were admitted to the hospital.

CONCLUSIONS. Outpatient oral antibiotic therapy with oral ofloxacin for patients with low risk neutropenia and fever is safe and similar in efficacy to hospitalization and treatment with broad-spectrum parenteral antibiotics. ***Cancer* 1999;85:213–9.**
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KEYWORDS: oral ofloxacin, low risk neutropenia and fever, outpatient therapy, bacteremia.

The rapid hospitalization and treatment with broad-spectrum intravenous antibiotics of cancer patients with neutropenia and fever has clearly been shown to reduce infectious morbidity and mortality and has been considered the standard of care.[1] However, there are a number of problems associated with prolonged hospitalization for patients with fever and neutropenia, including toxicities of the antimicrobial agents, costs, exposure to nosocomial pathogens, worsening of quality of life, and the deleterious financial and psychologic consequences derived from continuous absence from work or

home. On the other hand, it is well recognized that the majority of these patients have prompt defervescence and negative blood cultures and probably do not need such an aggressive approach.

In the last few years, it has been established that patients with fever and neutropenia are a heterogeneous population with a different risk of developing a serious infection-related complication during the episode. In a retrospective study, later validated in a prospective one, patients with neutropenic fever who were outpatient at the time of presentation of the febrile episode, had their tumor under control, and did not manifest any other significant associated acute, comorbid condition had a low risk (2–5%) of a serious complication during the episode of neutropenia and fever.[2,3] Recent advances, such as the availability of oral antibiotics with activity against most common pathogens isolated in this population, broad-spectrum intravenous antibiotics that are suitable for single daily dose administration, improvement in permanent access devices, and programmable computerized small volume infusion pumps, have made possible the performance of trials to study the feasibility of outpatient management of patients with low risk neutropenic fever.[4–6]

This single-center, randomized clinical trial was designed to assess the feasibility and efficacy of outpatient antibiotic treatment with oral ofloxacin for patients with low risk neutropenic fever, compared with a standard parenteral antibiotic combination given on an inpatient basis.

METHODS

Selection Criteria

Adult patients with solid tumors treated with conventional doses of chemotherapy were eligible for the study if they met all the following inclusion criteria: neutropenia (absolute neutrophil count [ANC] $<500/\mu L$, or $500–1000/\mu L$ expected to fall below $500/\mu L$ in the next 24 hours); fever (axillary temperature $>38°C$ on two occasions 4 hours apart in 1 day or $>38.5°C$ in a single record unrelated to the administration of pyrogenic agents); and an Eastern Cooperative Oncology Group [ECOG] performance status of 0–2. Patients were excluded if they had progression of their malignant diseases; signs or symptoms of a potentially severe infection (hypotension, oliguria, altered mental status, tachypnea, respiratory failure, clotting abnormality, or acidosis); a serious focal infection (pneumonia, extensive cellulitis, meningitis, or pyelonephritis); hypercalcemia; uncontrolled bleeding; cardiac, renal, or liver failure; or another comorbid condition that required admission to the hospital. Patients were also excluded from the trial if they were admitted at the time of the febrile episode, had taken antibiotics within the preceding 96 hours, had known hypersensitivity to any of the study drugs, were pregnant or in lactation, lived farther than 2 hours from the hospital, were unable to take oral medication, had a history of tumor fever, or presented with any other severe extrahematologic chemotherapy-related toxicity. Patients were required to have an optimal understanding of the study, to have a 24-hour home companion, and to give written informed consent.

Study Design and Treatment Strategy

Eligible patients gave a detailed medical history and underwent a thorough physical examination, complete blood count, urinalysis, measurement of serum creatinine, electrolytes, acid balance status, liver function tests, coagulation parameters, arterial oxygen saturation, and a chest X-ray. Two blood cultures were taken from patients with a temperature over 37.5°C; urine cultures and cultures from other body sites were taken if clinically indicated. Blood cultures were performed using BACTEC bottles (Becton-Dickinson, Towson, MD). Antibiotics susceptibility profiles were determined by a microdilution automatized assay. Patients were randomized by the consecutive drawing of sealed envelopes to receive either ofloxacin 400 mg every 12 hours orally (p.o.) or a combination of ceftazidime 2 g every 8 hours intravenously (i.v.) plus amikacin 500 mg every 12 hours i.v. Patients randomized to oral treatment were discharged immediately after administration of the first antibiotic dose and followed in the outpatient clinic every other day. They were instructed to maintain close telephone contact and to report to the hospital if their general condition deteriorated or they developed new signs or symptoms. Patients randomized to the intravenous combination were admitted to the hospital. Follow-up visit included a medical history, physical examination, and a blood count. Antibiotics were maintained until the ANC recovered over $500/\mu L$ and the patient had remained afebrile for 48 consecutive hours and for a minimum of 5 days. Patients with focal or microbiologic infections received individualized treatment.

Diagnostic Criteria

The episodes were classified as 1) fever of unknown origin if there were no signs or symptoms of infection and cultures were sterile; 2) clinically documented infection if there were signs or symptoms of a focal infection without any microbiologic isolate; or 3) microbiologic documented infection if a pathogen organism was isolated from blood, urine, or another body site along with clinical, radiographic, or laboratory evidence of infection at the same site. Coagulase

negative staphylococci and other common contaminant organisms required at least two consecutive positive blood cultures to be considered pathogens. Treatment outcome was considered either 1) a success without modification when the episode resolved with the allocated treatment; 2) a success with modification when the episode resolved but required additional treatment with an antibiotic, antifungal, or antiviral agent; or 3) treatment failure when fever persisted over 72 hours, a second febrile episode occurred, or the infection progressed within 72 hours as shown by worsening of an obvious source of infection, shock, continuing positive blood culture, or death. Patients who experienced treatment failure were withdrawn from the study and treated according to the discretion of the responsible physician. Patients who were randomized to ambulatory care and experienced failure were promptly admitted to the hospital.

Statistical Considerations

This study was designed as an equivalence therapeutic trial, the major endpoint of which was to prove the similar efficacy of both treatment regimens.[7] The sample size was calculated assuming a response rate of 90% for the inpatient group, according to our previous experience,[8] to ensure that outpatient therapy would not be 25% worse (i.e., 65%). With a statistical power of 80% and a significance level of 0.05 in a two-sided statistical test, and assuming 10% patients losses, a least 48 patients were required per arm and 50 were finally enrolled. Comparisons between proportions were made using the chi-square test or Fisher's exact test when appropriated, and the confidence interval of the differences between proportions were calculated. Comparison between continuous variables was made with Student's *t* test, using nonparametric tests for variables that did not adjust to the normal distribution.

RESULTS

One hundred seventy episodes of neutropenia and fever were seen at our institution during the study period, excluding bone marrow transplantation patients and episodes that occurred among hospitalized patients. One hundred episodes (58.8%) met trial selection criteria and were randomized, 50 to admission and treatment with intravenous cefatzidime/amikacin and 50 to ambulatory care and treatment with oral ofloxacin. Five episodes were not evaluable (3 in the inpatient group and 2 in the outpatient group) for the following reasons: 3 patients never had an ANC below 500/μL, 1 had an ECOG performance status of 3, and the other was a patient with nonsmall cell lung carcinoma who had a lung abscess. The remaining 95 episodes (47 in the ceftazidime/amikacin group and 48 in the ofloxacin group) were evaluable and constitute the basis of this report. The baseline characteristics of the patients are summarized in Table 1. Significant prognostic variables were well balanced between both groups. In 39 episodes (41%), the patients were profoundly neutropenic, with an ANC <100/μL. As was expected because of the study population and selec-

TABLE 1
Patient Characteristics

	Ceftazidime/amikacin (n = 47)	Ofloxacin (n = 48)
Median age, yrs (range)	56.3 (25–76)	55 (18–72)
Gender (male/female)	21/26	20/28
Tumor types		
Breast carcinoma	16	20
Nonsmall cell lung carcinoma	7	8
Small cell lung carcinoma	5	4
Non-Hodgkin's lymphoma	5	5
Soft tissue sarcoma	5	3
Ovarian carcinoma	3	5
Germ cell tumor	3	3
Gastric carcinoma	3	2
Others[a]	0	3
Chemotherapy regimen[b]		
CMF	8	5
FEC	4	5
Vinorelbine-cisplatin	4	6
VIP	3	6
Cyclophosphamide-carboplatin	3	4
Ifosfamide-doxorubicin	3	3
VM-26–cisplatin	6	4
EP	3	3
CHOP	3	3
Others[c]	13	11
Median ANC at inclusion (range)	120 (2–480)	175 (2–500)
No. (%) with ANC <100 cells/μL	20 (42.6%)	19 (39.6%)
Median no. of days since last chemotherapy course	12 (4–18)	12 (6–21)
Median no. of days with ANC <500 cells/μL	3 (1–7)	4 (1–12)

ANC: absolute neutrophil count.

[a] Colon carcinoma, unknown primary, head and neck cancer: 1 each.

[b] CMF: cyclophosphamide 600 mg/m^2, 5-fluorouracil (5-FU) 600 mg/m^2, methotrexate 40 mg/m^2. FEC: 5-FU 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2. Vinorelbine-cisplatin: vinorelbine 30 mg/m^2, cisplatin 100 mg/m^2. VIP: etoposide 500 mg/m^2, ifosfamide 1.2 g/m^2 × 5, cisplatin 100 mg/m^2. Cyclophosphamide-carboplatin: cyclophosphamide 750 mg/m^2, carboplatin 350 mg/m^2. Doxorubicin-ifosfamide: doxorubicin 75 mg/m^2, ifosfamide 5g/m^2. VM-26-cisplatin: tenitoposide 300 mg/m^2, cisplatin 100 mg/m^2. EP: etoposide 300 mg/m^2, cisplatin 100 mg/m^2. CHOP: cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, doxorubicin 50 mg/m^2, prednisone 50 mg/m^2 × 5.

[c] Bleomycin 15 mg/i.v./every 12 hrs × 10 doses, cisplatin 100 mg/m^2, etoposide 500 mg/m^2 (3). Vinorelbine 30 mg/m^2, 5-FU 750 mg/m^2/day × 5 (3). Doxetaxel 100 mg/m^2 (2). Paclitaxel 175 mg/m^2, doxorubicin 50 mg/m^2 (3). Paclitaxel 175 mg/m^2, cisplatin 100 mg/m^2 (3). Dexamethasone 40 mg, cytarabine 2 g/m^2 every 12 hours × 2, cisplatin 100 mg/m^2 (1). Vincristine 2 mg/m^2, doxorubicin 30 mg/m^2, cyclophosphamide 600 mg/m^2 (3). Etoposide 300 mg/m^2, 5-FU 500 mg/m^2, leucovorin 300 mg/m^2 (1). Topotecan 1.5 mg/m^2 × 5 days (3). 5-FU 1 g/m^2 × 5 days (2).

TABLE 2
Type of Episode by Treatment Arm

	Ceftazidime/amikacin (n = 47)	Ofloxacin (n = 48)
Fever of unknown origin	31 (65.9%)	34 (70.8%)
Clinical infection	10 (21.3%)	8 (16.6%)
Microbiologic infection		
Bacteremia	4 (8.5%)	4 (8.3%)
Other	2 (4.3%)	2 (4.1%)

TABLE 3
Characteristics of Bacteremias by Treatment Arm

Bacteremia	Ceftazidime/amikacin (n = 40)	Ofloxacin (n = 38)
Staphylococcus epidermidis	1	2
Streptococcus viridans	1	—
Pseudomonas aeruginosa	—	1
Bacillus spp	1	—
Fusobacterium spp	—	1
Polimicrobial[a]	1	—
Total	4 (8.5%)	4 (8.3%)

[a] *Citrobacter freundii* and *Escherichia coli.*

tion criteria, the duration of Grade 4 neutropenia was short (median number of days with an ANC $<500/\mu L$, 3 and 4, respectively). Grade 4 neutropenia lasted longer than 7 days in only 5 patients. Three patients had permanent subcutaneous venous access devices and 1 were receiving granulocyte-colony stimulating factor.

The proportions of patients with fever of unknown origin, clinically documented infection, and microbiologically documented infections were similar in the two treatment arms (Table 2). Clinical infections were mild and included mucositis (2), culture negative dysuria (7), diarrhea (2), perianal inflammation (3), folliculitis (2), cellulitis (1), and gingivitis (1). Four patients had a positive urine culture (3 *Escherichia coli* and 1 *Proteus mirabilis*), and all of them were susceptible to quinolone antibiotics. There were eight episodes of bacteremia, five with gram positive organisms, two with gram negative rods (including a polymicrobial episode with a *Citrobacter freundii* and *E. coli*) and one with anaerobic bacteria. None of these episodes occurred in the 3 patients with permanent venous catheters. All gram negative rods and 1 coagulase negative staphylococcus were susceptible to quinolones antibiotic (Table 3). There were no episodes of breakthrough bacteremias in this study.

Ninety-one percent of the patients treated in the hospital responded to the antibiotics, compared with 89.5% of those treated with oral ofloxacin as outpatients ($P = 1$; 95% CI of the difference, -0.09 to 0.13). Table 4 summarizes patients' outcomes according to type of episode. Patients with clinically or microbiologically documented infections required more treatment modifications, irrespective of the treatment group. The majority of patients (90%) became afebrile within the first 24 hours after antibiotics were started. Two episodes in the inpatient group and 5 in the ambulatory group required modification of the initial antimicrobial regimen. All modifications were changes or additions of antibacterial agents, with no patients requiring antifungal or antiviral drugs. Overall, there were 9 treatment failures, 4 among the patients treated with cefatzidima/amikacin and 5 among the patients treated with ofloxacin. Failures in the inpatient arm were due to persistence of fever over 72 hours (2), the appearance of a second febrile episode (1), and the development of septic shock (1). This last patient had a polymicrobial bacteremia with *E. coli* and *Citrobacter freundii* susceptible to ceftazidime and amikacin, but developed progressive shock with multiorgan failure and died. This was the only death in this study. Patients treated with ofloxacin experienced failure due to persistent of fever (2), reappearance of fever (1), and clinical deterioration (2). One of these last 2 patients had mild diarrhea and the other had a fever of unknown origin; both of them were febrile in the first outpatient visit 48 hours after starting antibiotics and were admitted to the hospital. Overall, 8 patients randomized to outpatient care had to be admitted to the hospital, 3 because of a positive blood culture that required an intravenous antibiotic (*Fusobacterium* spp [1], *Pseudomonas aeruginosa* [1], and *Staphylococcus epidermidis* [1]) and 5 because of failure of the outpatient regimen. These patients had more prolonged neutropenia (median, 6 days), required more days on antibiotics (median, 6 days), and had a longer hospital stay (median, 7 days). None of them died or had serious infection-related complications.

DISCUSSION

The management of patients with neutropenia and fever has been the subject of major changes over the last few years. The identification of different risk categories of patients with neutropenia and fever, the recognition of a low 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 have made it possible to investigate outpatient treatment strategies for that population. The current study demonstrates that ambulatory care with oral

TABLE 4
Treatment Outcomes

	Ceftazidime/amikacin (n = 47)			Ofloxacin (n = 48)		
Outcome	FUO	Clinical infections	Microbiologic infections	FUO	Clinical infections	Microbiologic infections
Success	29	9	3	30	5	3
Success with modification	0	0	2	0	2	3
Failure	2	1	1	4	1	0
Overall success		43 (91.4%)			43 (89.5%)	
Overall failures		4 (8.5)			5 (10.4%)	

FUO: fever of unknown origin.

ofloxacin is a suitable alternative to conventional treatment for patients with solid tumors treated with conventional dose chemotherapy who are at low risk for neutropenia and fever. Several aspects of this trial deserve further comment.

Patients were categorized as low risk based on the prediction model proposed by Talcott et al.[2,3] This model accurately identified the medical risk of patients with neutropenia and fever using only clinical information available on the first day of their medical course. Patients who were ambulatory at the time of the episode of neutropenia and fever, had their tumor under control, and did not have any other comorbid condition comprised the low risk category in this classification. This subgroup rarely developed serious complications (3%) and had no mortality. Based on their risk assessment model, Talcott et al. performed a pilot study of early discharge and home antibiotic therapy for the low risk group after a short inpatient treatment period of 48 hours. Patients with focal infection and those older than 65 years were not included. The results of this experience were disappointing; only 53% of the patients responded to the original antibiotic regimen, and 30% had to be readmitted for different reasons.[6] The unfavorable outcome of this preliminary trial could be attributed to the high number of patients with acute leukemia and neutropenia lasting longer than 7 days. This study did not include patients with acute leukemia or those who were receiving high dose outpatient chemotherapy; both of these factors probably explain the short duration of Grade 4 neutropenia in this trial (with a median of 3 and 4 days, respectively) and only 5 patients' having neutropenia for longer than 1 week. The duration of neutropenia strongly influences the outcome of patients with neutropenic fever.[9] This factor probably explains the high success rate (90%) in the current study and in other studies that included patients with solid tumors who had neutropenia for less than or equal to 7 days.[4,5] It is possible that, to develop more accurate risk models that effectively select the patients who would most benefit from this approach, other variables (such as the underlying malignancy and expected duration of neutropenia) should be incorporated.

Ofloxacin was selected for evaluation in this study based on its bactericidal activity, optimal oral pharmacokinetics, lack of serious adverse affects, and wide spectrum of activity against gram negative bacteria.[10,11] More importantly, in a randomized study, oral ofloxacin was demonstrated to be as effective as a combination broad-spectrum intravenous regimen in the treatment of hospitalized patients with neutropenia and fever.[12] It has also been shown to be effective in the outpatient management of patients with low risk neutropenia and fever in a similar designed trial.[4] One of the potential problems with the use of quinolones monotherapy for patients with neutropenia and fever is its limited activity against gram positive organisms. For this reason, quinolones antibiotics have been commonly used in combination with gram positive targeted antibiotics in this setting.[5] However, although the spectrum of bacterial isolates in patients with neutropenia and fever is changing, and gram positive bacteria are now the most common isolates in major cancer centers (50% of isolates in our study were gram positive), the addition of gram positive agents to the initial coverage remains a matter of controversy.[13,14] Most gram positive isolates are coagulase negative staphylococci that normally have a mild clinical course and whose treatment can be delayed until cultures become positive.[15] Of major concern is the isolation of more pathogenic organisms, such as *Streptococcus viridans*.[16] These agents are more common in patients with extensive mucositis who are treated with cytosine arabinoside and receive quino-

lones prophylaxis. None of these patients were eligible for this trial. Nevertheless, one patient with mild mucositis in this study developed an *S. viridans* bacteremia, and this incident emphasizes that this strategy should be applied with caution in treating patients at risk for bacteremia due to aggressive gram positive organisms. A second potential problem with the use of oral quinolones in the treatment of patients with neutropenia is the emergence of resistant gram negative rods in patients exposed to these antimicrobial agents.[17,18] This might limit the treatment of patients who have more than one episode of neutropenia and fever and have received quinolones previously. Similar to other reports, we did not find differences in outcome for patients randomized twice who therefore had received quinolones previously.[4] However, the low number of patients who were randomized twice in our trial makes it difficult to have a clear understanding of the importance of this problem.

The type of infectious episode strongly influenced the likelihood of a favorable response in this study. Patients with fever of unknown origin were more likely to respond to treatment than those with clinical or microbiologic infections in both treatment arms. The comparisons, however, are difficult because of the low number of patients in the last categories. It is possible that patients with negative cultures may have fever of noninfectious etiology and may not require antibiotic treatment. The study of markers of bacteremia in serum, such as protein C, interleukins, and others, may help in sparing some patients from antibiotic treatment.[19,20] The majority of patients randomized to oral ofloxacin successfully recovered from the episode of neutropenia and fever and avoided hospitalization, with its social, practical, and economic inconveniences. Only 8 patients had to be admitted to the hospital after failure of ambulatory management. The clinical courses of these patients were optimal; none of them had any serious complications. The insistence in reporting any new symptom or complication, the requirement of a 24-hours companion, living a short distance from the hospital, the availability of physicians trained in the management of this syndrome, and the rapid admission and initiation of intravenous broad-spectrum antibiotics probably explain the favorable outcome of this group. It cannot be overemphasized that these aspects should be seriously considered before this strategy can be recommended for widespread use.

In summary, the selection criteria employed in this trial efficiently enabled the selection of a group of patients with low risk neutropenic fever. In our experience, most (58%) of adult patients with solid tumors treated with conventional dose chemotherapy belong to this category. Outpatient therapy for these patients with oral ofloxacin was a safe and attractive strategy, with results comparable to those achieved with a conventional intravenous inpatient regimen. These results, along with data from other clinical trials that have explored the suitability of outpatient management with oral antibiotics for patients with neutropenia and fever, suggest that the standard approach to treating this patients should be redefined.

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