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Domiciliary treatment of febrile episodes in cancer patients: a prospective randomized trial comparing oral versus parenteral empirical antibiotic treatment

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Abstract Hospitalization and empirical broad-spectrum, intravenous antibiotics are the standard treatment for febrile cancer patients. Recent evidence supports the suggestion that febrile episodes in a low-risk population can be managed successfully in an outpatient setting, but the optimal drug regimen is unknown. In a prospective randomized clinical trial we compared ciprofloxacin 750 mg p.o. twice a day with ceftriaxone 2 g i.v. as a single daily dose for the empiric domiciliary treatment of febrile episodes in low-risk neutropenic and nonneutropenic cancer patients. A total of 173 patients, accounting for 183 febrile episodes, were enrolled in the study. Overall, successful outcomes were recorded for 76 of 93 (82%) febrile episodes in patients who were randomized to the oral regimen and for 68 of 90 (75%) febrile episodes in patients randomized to the i.v. regimen: this difference was not statistically significant. The success rate was similar in all subgroups of patients: neutropenic and nonneutropenic, with documented infection and with fever of unknown origin. There were 3 deaths in the group of patients treated with the parenteral regimen, and two of these were related to treatment failure. Both treatments were well tolerated, and the cost of the oral regimen was lower. This prospective study suggests that domiciliary antibiotic empiric monotherapy is feasible in febrile nonneutropenic or low-risk neutropenic outpatients in whom a bacterial infection is suspected, and that either an oral or a parenteral regimen can be used. A number of factors may influence the choice between an orally and an i.v.-administered antibiotic, but owing to the easier administration and lower cost, the oral regimen seems to be preferable.

Key words Cancer · Fever · Outpatient antibiotic therapy

Introduction

Bacterial infection is an important cause of morbidity and mortality in cancer patients [10]. Although patients with profound (<100) and prolonged (>10 days) neutropenia are at the greatest risk, serious infections also occur in low-risk neutropenic cancer patients [17] and in those with an adequate neutrophil count [9, 13]. In fact, besides neutropenia, there are many predisposing factors in infection, including local factors attributable to the tumor and specific deficiencies in host defense mechanisms as a result of certain malignant processes or secondary to cancer chemotherapy [2, 5, 6, 11]. Therefore initial therapy with broad-spectrum antibiotic therapy seems to be warranted in all these patients [4, 9, 14].

Recent evidence, albeit limited, supports the suggestion that febrile episodes in nonneutropenic or low-risk neutropenic patients can be managed successfully at home or in an outpatient setting [8, 15, 16], thanks to the availability of antibacterial compounds with favorable characteristics concerning their broad spectrum of activity, high bacteri-

Table 1 Patient characteristics

	Regimen	
	Oral ciprofloxacin	Ceftriaxone
No. of episodes	93	90
Gender ratio (M/F)	68/25	63/27
Age (years)		
Median	60	59
Range	20–74	24–80
Solid tumors [no. (%)]	50 (54)	48 (53)
Hematological malignancies [no. (%)]	43 (46)	42 (47)
Progressive cancer [no. (%)]	82 (88)	80 (89)
Neutrophil count <1,000 [no. (%)]	21 (23)	20 (22)
Nonneutropenic	72 (77)	70 (78)
Duration of therapy (days)		
Median	9	8
Range	2–44	1–20

Table 2 Febrile episodes and response to therapy [success/total episodes (%)]

	Oral regimen	IV regimen	Overall
No. of episodes	93	90	183
Documented infection	27/33 (82)	24/35 (69)	51/68 (71)
Microbiologically	16/20 (75)	12/18 (67)	28/38 (73)
With bacteremia	6/8 (75)	5/9 (55)	11/17 (65)
Without bacteremia	10/12 (83)	7/9 (77)	17/21 (80)
Clinically	11/13 (85)	12/17 (70)	23/30 (76)
Fever of unknown origin	49/60 (82)	44/55 (80)	93/115 (80)
Death from infection	0/93 (0)	2/90 (2)	2/183 (1)
Total	76/93 (81)	68/90 (75)	144/183 (78)

cidal effect, and favorable kinetic properties, which allow a convenient administration schedule such as oral or once daily parenteral administration. However, the most efficacious and convenient type of empiric antibiotic regimen to be administered to a febrile cancer patient at home is unknown.

Both parenteral and oral antibiotic regimens have been studied [1, 7, 15, 16,], but comparative data on these two routes of administration are lacking. Ciprofloxacin and ceftriaxone are two interesting options in this setting. All this prompted us to conduct a randomized clinical trial to compare ciprofloxacin administered p.o. with ceftriaxone given i.v. at home, for the empiric treatment of febrile episodes resulting from infection in low-risk neutropenic and nonneutropenic cancer patients.

Materials and methods

Patient population

All consecutive adult outpatients with cancer referred to the participating centers were eligible for the study. Criteria for inclusion were: fever ≥38°C in two measurements, lasting no more than 24 h and judged to be of infectious origin, residency within 20 miles of the participating centers, and signed informed consent. Criteria for exclusion were: severe chemotherapy-induced neutropenia (ANC ≤300) at entry; severe comorbidity requiring hospitalization [shock, respiratory failure (P_aO_2<60 mmHg)]; acute leukemia and bone marrow transplant within the last 2 years; antibiotic treatment within the previous 5 days; use of hematopoietic growth factors; positive history of intolerance to quinolone derivatives and/or beta lactams; renal failure (creatinine clearance <30 ml/min); age younger than 18 years; pregnancy or nursing state.

Study design and treatment protocol

The study protocol was approved by the Ethics Committees of the participating centers. All eligible patients were subjected to a baseline evaluation including: physical examination, complete blood count, urine analysis, assay of BUN, creatinine level, serum electrolyte levels and liver function tests. Blood cultures were carried out in all patients, while any possible sources of infection were cultured when appropriate. Blood cultures (one from the central venous catheter and one from a peripheral vein) were performed in duplicate (one sample for aerobes and the other for anaerobes), and this procedure was repeated within 1 h. Cultured infecting pathogens were identified by genus and species, and susceptibility to the antibiotics studied determined. Chest X-ray, blood gas analysis and serology for pneumonia were performed only in cases of respiratory tract infection. The complete blood count and laboratory biochemical tests performed on admission were repeated on the last day of treatment and whenever clinically indicated. Blood cultures were repeated if fever persisted and if initially positive, until they became negative or until the patient was classed as a treatment failure. After a check to see that all the criteria of inclusion and exclusion were met, the patients were randomly assigned to receive one of the treatment regimens, a computer-generated randomization list of blocks permutated by center being used. Patients were not eligible to re-enter the protocol until they were fully recovered from their last febrile episode. The treatments were: oral ciprofloxacin 750 mg (1 1/2 500 mg tablets) twice daily and 2 g of ceftriaxone i.v. as a single daily dose. The patients received their first dose in the hospital clinic, and if there were no adverse reactions they received a 10-day supply of drugs and were sent home. The patients were informed specifically about the dosage and schedule of whichever treatment they received, how to measure their body temperature correctly, the possible side-effects of the anti-infectious treatment, and what to do in case of an unfavorable outcome of therapy. The patients received the antibacterial treatment at home for at least 5 days after defervescence. The patients receiving the i.v. regimen were visited at home by a nurse for infusion therapy. The clinical monitoring was carried out by the investigators at 48, 72 and 96 h after the start of the antibacterial treatment at home according to the patients' needs. Patient's compliance with the oral regimen taken at home was assessed by counting the residual tablets at the end of therapy.

Classification of febrile episodes

The primary febrile episodes were classified as either clinically or microbiologically documented infections or fever of undetermined origin (FUO). Diagnosis of bloodstream infection required at least one positive blood culture, with the exception of infection with coagulase-negative staphylococci, for which at least two positive blood cultures were required.

Case review

To verify the patient's eligibility, classification of the infection, and evaluation of the response according to the protocol definitions, every Case Report Form was reviewed by two investigators (G.G.,G.B.), who were unaware of which antimicrobial regimen had been allocated.

Table 3 Site of documented infections and response to therapy [success/total episodes (%)]

	Oral regimen	IV regimen
Bacteremia	6/8 (75)	5/9 (55)
Pneumonia	13/16 (81)	12/17 (70)
Urinary tract	4/4 (100)	4/6 (66)
Skin/soft tissue	2/2 (100)	3/3 (100)
Others	2/3 (66)	–
Total	27/33 (82)	24/35 (69)

Table 4 Blood isolates and response to therapy [success/total episodes (%)]

Organism	Oral regimen	IV regimen
Gram-negative	4/4	1/2
Escherichia coli	1/1	1/2
Klebsiella pneumoniae	1/1	–
Enterobacter aerogenes	1/1	–
Aeromonas hydrophilus	1/1	–
Gram-positive	2/4	4/7
Staphylococcus aureus	–	1/1
Staphylococcus, coagulase-negative	1/1	2/4
Streptococcus viridans	0/1	–
Streptococcus pneumoniae	1/1	1/1
Streptococcus bovis	0/1	–
Streptococcus faecalis	–	0/1
Total	6/8 (75)	5/9 (55)

Evaluation of response

The responses to the antibiotic regimens were classified as success or failure. A success was recorded when fever and the clinical signs of infection disappeared and eradication of the infecting micro-organism was obtained without changing the allocated antibacterial therapy, and the response persisted for at least 4 days after the discontinuation of therapy. A failure was recorded when no response to the empirical therapy was obtained; that is, if the pathogen or fever persisted and the patient's clinical conditions did not improve, so that hospitalization and/or a change of antibacterial therapy had to be arranged, or when death occurred as a result of the primary infection.

Cost evaluation

A retrospective cost analysis was performed by evaluating all direct costs per patient concerning the empirical antibiotic treatment, the mean overall cost of failure, and the mean overall cost of side effects; the indirect or intangible costs were not evaluated. An average exchange rate of 1,600 Italian lire to 1 US dollar was used.

As far as the costs of failure are concerned two hypotheses were considered. According to the first (most costly) we assumed that all the patients in whom treatment failure was recorded needed hospitalization. The cost of each failure with hospitalization was calculated according to the Italian Disease Related Groups. According to the second hypothesis (least costly), we assumed the overall cost of failures to be the sum of the costs related to the patients actually admitted to hospital after treatment failure (9 for ciprofloxacin and 5 for ceftriaxone) plus the cost of an antibiotic rescue treatment for the patients who failed on treatment but did not require hospitalization. The cost recorded for each failure without hospitalization was that of 8 days' treatment with i.v. imipenem (1 g three times daily).

In the same way the costs related to side-effects were calculated. According to the most costly hypothesis we assumed each case of treatment interruption caused by a side-effect as a failure with hospitalization; according to the least costly hypotheses we assumed each case of treatment interruption caused by a side-effect as a failure without hospitalization (see above).

Statistical analysis

The objective of the trial was to assess whether ciprofloxacin is at least as effective as ceftriaxone. The main efficacy criterion was the clinical response to treatment at the end of therapy (already defined). On the assumption that the success rate of ceftriaxone treatment (standard) in febrile cancer inpatients is about 80%, the study was designed to enroll 99 patients per treatment, in an attempt to prove that the success rate of outpatient ciprofloxacin therapy would not be greater than 15% lower than that of the standard therapy at a level of significance of 0.05 and a power of 80% [12]. The difference in the success rates of ciprofloxacin versus ceftriaxone therapy had to be calculated with 95% (one-sided) confidence limits: if the lower limit was greater than –15% the hypothesis of nonequivalent efficacy could be rejected.

Baseline homogeneity of the treatment groups were compared by means of an ANOVA model for continuous variables and by means of the Mantel-Haenszel test for categorical ones; the center and treatment were included as main effects in the model. The calculated *P*-values had only descriptive meaning. All the analyses of efficacy were performed on an 'intention-to-treat' basis.

Results

From June 1991 to May 1996, 173 febrile patients, accounting for 183 febrile episodes, were enrolled in the study, and their characteristics are shown in Table 1. The two treatment groups were well matched with respect to age, gender, underlying disease and number of neutropenic patients.

At the initial evaluation 115 (63%) febrile episodes were FUO, 38 (21%) microbiologically documented infections and 30 (16%) clinically documented infection (Table 2). Lung and blood were the most frequent sites of infection (Table 3).

Overall, clinical success outcomes were recorded in 76 of the 93 (82%) febrile episodes of patients who were randomized to the oral regimen and in 68 of the 90 (75%) febrile episodes of patients randomized to the i.v. regimen; the difference in the success rate was 5.1% in favor of the oral regimen, and the lower 95% confidence limit was –6.0: since it is included in the defined equivalence region (–15%), the hypothesis of nonequivalence was rejected.

Success rate according to the type of infection was also similar between treatments. It was reported in 49 of 60 (82%) febrile episodes of patients with FUO treated with ciprofloxacin and in 44 of 55 (80%) febrile episodes of patients treated with ceftriaxone. Among febrile episodes in patients with clinically documented infections, 11 of 13 (85%) of those treated with the oral regimen, and 12 of 17 (70%) receiving the i.v. regimen responded successfully to therapy. A similar overall success rate was observed in the subgroup of neutropenic patients: 19 of 21 (90%) and 15 of 20 (75%) febrile episodes of patients randomized to the oral and to the i.v. regimens, respectively, responded to

Table 5 Mean total cost per febrile patient in US dollars according to treatment

	Outpatient treatment				Inpatient treatment
	Most costly hypothesis		Least costly hypothesis		
	IV	Oral	IV	Oral	
Direct cost [a]	313	80	313	80	
Mean cost of failures	687	514	300	349	
Mean cost of side effects	62	121	26	51	
Total cost	1062	715	639	480	2812

[a] Acquisition cost of drugs including, for ceftriaxone only, the administration cost (cost of both the materials used and the time spent by nursing staff in administering therapy). The prices of drugs and materials were those published in the 55th edition of L'Informatore Farmaceutico, OEMF (ed. L. Marini), Milan 1996. The mean times for a single administration of ceftriaxone were 2 min for preparation, and 5 min for administration and check during infusion. From data obtained from the Administrative Department (Local Health Unit, USL), the mean cost per hour per worker during the 1996 period was 33,600 lire (560 lire/min) for the nursing staff and 60,000 lire (1,000/min) for the medical staff

therapy. The microbiologically documented infections without bacteremia responded to therapy in 10 of 12 (83%) febrile episodes treated with ciprofloxacin and 7 of 9 (78%) febrile episodes treated with ceftriaxone. Blood isolates and response to therapy are shown in Table 4. Bacteremic infections responded in 6 of 8 (75%) patients treated with the oral regimen and in 5 of 9 (55%) patients treated with the i.v. regimen. Single Gram-negative bacteremias responded in 4 of 4 patients treated with ciprofloxacin and in 1 of 2 patients treated with ceftriaxone. Gram-positive bacteremias were prevalent (65% of all bacteremias), and single Gram-positive bacteremias responded in 2 of 4 patients treated with ciprofloxacin and 4 of 7 patients treated with ceftriaxone. Treatment failures occurred during the oral regimen in 2 patients with lung cancer who had bacteremia caused by resistant *Streptococcus bovis* and *Streptococcus viridans*. These two patients were subsequently successfully treated at home after the initial therapy had been changed.

Failure with the i.v. regimen occurred in 4 patients. One had *Escherichia coli* bacteremic pneumonia, two had bacteremia caused by methicillin-sensitive coagulase-negative *Staphylococcus*, which in both cases was treated at home after the antibacterial therapy had been changed. The last patient had *Streptococcus faecalis* bacteremia, which was successfully treated in hospital. Nonbacterial infections were equally distributed amongst the two treatment groups. *Candida* stomatitis was diagnosed in 10 patients (6 in the oral regimen arm and 4 in the i.v. regimen arm), and these were intercurrent infections in 5 of them. Herpes simplex infections were diagnosed in 6 patients (4 in the oral regimen arm and 2 in the i.v. regimen arm), and 4 of these were intercurrent infections.

Three patients died, all of whom were receiving the intravenous regimen, and 2 of these deaths were probably related to infection. One patient died in hospital, where he was admitted after 12 h of home treatment for clinical deterioration. He died 36 h after admission of a septic shock while profoundly neutropenic. Outpatient treatment thus did not delay intensive care in this case. The other patient died at home 24 h after starting treatment, from *E. coli* bacteremia and respiratory failure related to pneumonia. In this case the outpatient treatment could have delayed the start of intensive care. The last patient was promptly hospitalized and died in a surgical department because of problems related to the underlying disease. Seventeen patients receiving the oral regimen were admitted to hospital: 9 because of failure of the outpatient antibiotic therapy, and 8 because of problems related to the underlying disease. Thirteen patients receiving the i.v. regimen required hospitalization, 5 for failure of therapy and 8 for reasons not related to the febrile episode.

Only a few side-effects occurred, and they were equally distributed between the two groups of treatment. Moderate gastrointestinal (GI) disorders were reported in 2 patients in each group; mild to moderate rash in 2 patients treated with the oral regimen, and 1 rash of moderate intensity in a patient receiving the i.v. regimen. One patient receiving the oral regimen had mild crystalluria. The drug was discontinued in 2 patients treated with ceftriaxone (1 GI disturbance, 1 rash) and in 3 patients treated with ciprofloxacin (1 GI disturbance, 2 rashes). Compliance with the oral regimen was good.

The results of the cost evaluation analysis are illustrated in Table 5. With both the most costly and the least costly hypotheses it can be shown that the i.v. regimen was more expensive than the oral regimen; on the other hand, both outpatient treatments were less expensive than the treatment of fever in an inpatient setting.

Discussion

Infection remains a common serious problem in cancer patients, especially, but not exclusively, when the patient is granulocytopenic. When these patients are diagnosed as having an infection they are usually admitted to hospital for appropriate investigations and are started on a broad-spectrum parenteral antibiotic therapy during their time as inpatients. There is evidence from randomized trials that

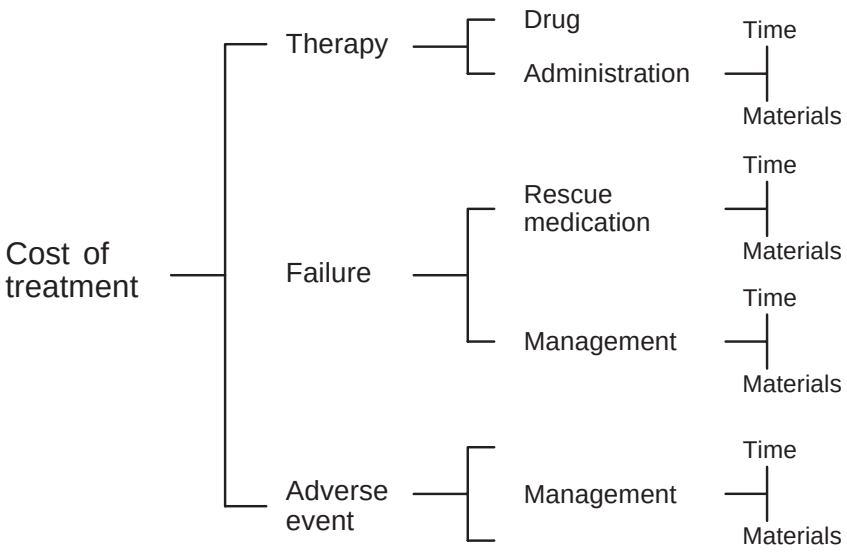

Fig. 1 Breakdown of the elements assessed in the analysis of costs incurred in both treatment arms, showing what was included in each of the different cost elements

empiric outpatient antibiotic therapy can be another safe and effective option besides hospitalization, at least for selected cancer patients [8, 15, 16]. There is less evidence suggesting the best initial choice for a home antibacterial treatment. This study shows that a single-agent oral antibacterial therapy can be regarded as effective and as safe as a broad-spectrum parenteral therapy. Previous experience with intravenous and a combination of oral antibiotics led to reports of a range of response rates for low-risk febrile neutropenic patients: 53% [18] to 95% [16]. The differences in response rates between these trials are probably due to the inclusion of patients with different prognostic factors, such as severity of illness, underlying disease and severity or duration of neutropenia. The 80% response rate found in our study may appear unimpressive if we consider that not all patients were neutropenic. However, we have to take into account that, despite a normal or near-normal neutrophil count, our patients suffered from serious infections [e.g. pneumonia (18% of patients), bacteremia (10%)] and the majority of them had a progressive uncontrolled cancer, which places them at a high risk of serious infectious complications [17].This fact justifies the use of an empirical treatment in our patients rather than the choice of the alternative approach to culture, with antibiotics held back until the culture results are available. Although our sample size may be too small to detect a minor difference, we observed a similar success rate in both nonneutropenic and neutropenic patients and in patients with solid tumors or hematological malignancies. Failure of therapy was observed in 18%/31% of documented infections and in 18%/20% of FUO, respectively, in the ciprofloxacin/ceftriaxone-treated patients; not unexpectedly, it was more frequent in Gram-positive than in Gram-negative bacteremias (5 vs 1). Only 1 patient receiving intravenous therapy died from Gram-negative infection. It has been suggested that ciprofloxacin is less effective in Gram-positive than in Gram-negative bacteremia [3] and our results, albeit derived from a small number of bacteremic infections, seem to confirm this finding. In fact, 100% (4/4) of Gram-negative bacteremias responded to oral ciprofloxacin, while only 50% (2/4) of Gram-positive bacteremias were successfully treated with the quinolone. The 2 patients who failed had S*treptococcus viridans or bovis* bacteremia and were successfully treated at home after changing the initial therapy. On the other hand, the response rate of Gram-positive bacteremic infections in patients receiving ceftriaxone was also not completely satisfactory (4/7, 57%). This result may suggest the need of a better coverage against Gram-positive bacteria, at least in patients not responding to the initial empirical treatment. The side-effects found with the two regimens ranged from mild to moderate, and we would like to stress that we did not find cases of nephrotoxicity such as were reported in a previous study by Rubenstein et al. [16] in patients treated with oral ciprofloxacin. However, in their study, oral ciprofloxacin was used at a higher dose (750 mg three times daily) and in combination with clindamycin.

When we designed this study, there were no data on the feasibility and safety of domiciliary oral treatment of febrile cancer patients. Therefore, to be on the safe side we excluded patients who had marked prolonged granulocytopenia and selected a ‘low-risk’ population for home therapy, admitting only nonneutropenic and moderately neutropenic patients. However, despite this limitation, our results are still deserving of attention, because they show the possibility of using domiciliary oral antibiotic empiric monotherapy in febrile cancer patients in whom a bacterial infection is suspected. However, we have to take into account that despite the success of antimicrobial therapy at home, a small number of patients (10%) still required hospital admission because of problems that were unrelated to the infection. Notwithstanding the limits of a retrospective cost evaluation analysis, as far as the economic evaluation

is concerned, the oral regimen was shown to be less expensive than the i.v. regimen; at the same time it must be underlined that both regimens were shown to be less expensive than inpatient treatment. Domiciliary treatments (i.v. or oral) cost about one-third of the total cost of inpatient treatment at most. Both oral and intravenous regimens may be clinically acceptable from the aspects of efficacy and tolerability, providing always that the patients undergo appropriate initial evaluations and are carefully followed up. A number of factors may influence the choice between oral and intravenous antibiotics, but owing to the easier administration and lower cost, the oral regimen seems to offer better advantages.

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