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Original Paper

Randomised Comparison of Ceftazidime and Imipenem as Initial Monotherapy for Febrile Episodes in Neutropenic Cancer Patients*

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With the availability of new, broad-spectrum antibiotics, initial therapy with a single agent has become an alternative to classic combinations in the management of febrile, neutropenic cancer patients. The aims of this study were to compare the efficacy of ceftazidime and imipenem as empirical monotherapy of febrile episodes in neutropenic patients, and to examine the frequency with which second-line antibiotics (amikacin, vancomycin, or both) were required. A prospective clinical trial was carried out in a single centre. Eligible patients with solid tumours or lymphoma were randomised to receive monotherapy with ceftazidime or imipenem. In the event of no response, amikacin and/or vancomycin were added in 48–72 h intervals (sequentially, or according to clinical or microbiological data). Efficacy was evaluable for 111 assessable episodes. Median neutrophil count at entry was 100 cells/μl and median duration of neutropenia was 4 days. Febrile episodes were classified as microbiologically (34%) or clinically documented (42%), and fever of unknown origin (24%). Gram-negative infections (57%) predominated over gram-positive isolates (30%). The overall success rate with monotherapy (69% versus 70%), or with modification (20% versus 23%) were equivalent for ceftazidime and imipenem ($P = 0.75$). The mortality in this series was 5%. Single-agent therapy with either ceftazidime or imipenem is effective for the empirical treatment of febrile episodes in neutropenic patients with solid tumours. Early addition of amikacin and/or vancomycin resolves most failures of the first step.

Key words: febrile neutropenia, empirical antibiotic therapy, monotherapy, ceftazidime, imipenem
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INTRODUCTION

BACTERIAL INFECTIONS still represent the main cause of morbidity and mortality in cancer patients undergoing cytoreductive chemotherapy. The rapid institution of broad-spectrum antibiotics has become the gold standard of treatment when these patients develop fever and neutropenia. The classical approach includes combination regimens, such as antipseudomonal beta-lactam antibiotics plus aminoglycosides that offer a success rate of more than 80% [1]. Chemotherapy for solid tumours generally induces granulocytopenia of shorter duration and depth than that observed in treatment of acute leukaemia or after high-dose myeloablative chemotherapy. Alternatively, the use of aminoglycosides may enhance the toxicity (mainly nephrotoxicity) of cisplatin, a commonly employed agent in these patients. Thus, with the availability of new broader-spectrum antibiotics in the last decade, the interest in monotherapy has re-emerged [2]. Monotherapy has the advantages of decreased cost and easier handling compared with multidrug combinations.

Early studies have shown that single-agent therapy with either third generation cephalosporins or carbapenems [3–5] is as effective as combined treatment for febrile episodes, especially for those considered of low risk (mild neutropenia, no microbiological documentation, no haemodynamic deterioration) [6]. The most commonly used antibiotics for monotherapy are ceftazidime, cefoperazone and imipenem.

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The antimicrobial spectrum of ceftazidime includes most gram-negative bacteria (including *Pseudomona aeruginosa*), but has only a modest potency against gram-positive and anaerobic organisms. Imipenem shows significant activity against many gram-negative, gram-positive and anaerobic pathogens, thus representing the broadest known antibacterial coverage [7].

The aims of this prospective, randomised study were: (1) to compare the efficacy of ceftazidime and imipenem as empirical monotherapy for febrile neutropenic cancer patients receiving standard chemotherapy; and (2) to quantify the percentage of episodes in which antibiotic additions (amikacin, vancomycin, or both) are needed for each initial monotherapy in a sequential antibiotic protocol.

PATIENTS AND METHODS

Adult cancer patients undergoing systemic chemotherapy for solid tumours or lymphoma at the Department of Medical Oncology, Hospital La Fe (Valencia) were included if they met all the following criteria: fever (a single axillar temperature greater than 38.5°C or three measurements greater than 38°C in a 24 h period); neutropenia (a peripheral blood count of less than 500 neutrophils/μl); and clinically suspected infection (fever unrelated to progressive cancer, drug administration or blood product transfusion). Criteria for exclusion were any of the following: known hypersensitivity to any of the antibiotics in this protocol, significant renal failure (serum creatinine >3.5 mg/dl), or antibiotic treatment within the preceding 48 h. Patients with either advanced age or poor performance status were not excluded from the study.

Following admission, clinical history and physical examination were performed in all patients. Complete blood counts, standard serum chemistry, coagulation tests, and chest X-ray films were routinely obtained. Microbiological studies included at least one urine and three blood cultures, as well as cultures of any clinically suspicious focus. Thereafter, blood counts were repeated ever 2 days until neutrophil recovery (more than 1000/μl), and chest radiographs were conducted every 7 days while fever persisted or until resolution of infection-related lung images. New blood cultures were performed if the patient developed new temperature rises and before any antibiotic modification.

After registration, patients were randomly assigned to receive initial monotherapy (first step) with either ceftazidime (2 g intravenous every 8 h) or imipenem (500 mg i.v. every 6 h). In case of renal failure, with serum creatinine levels between 2 and 3.5 mg/dl, ceftazidime dosage was reduced to 1 g every 8 h while imipenem doses were unmodified. This treatment was maintained for 48–72 h according to clinical response and patient status. If fever and infectious signs resolved, patients remained on that regimen, irrespective of microbiological cultures. If not, then empirical amikacin (500 mg i.v. every 12 h, second step) and vancomycin (500 mg i.v. every 6 h, third step) were sequentially added in 48–72 h intervals. If cultures were positive or there was strong clinical suspicion of infection, then the appropriate antibiotic was selected: amikacin for gram-negative bacteraemia; vancomycin for catheter-related infections or gram-positive bacteraemia; and other agents not included in the protocol when appropriate (anti-anaerobes, antifungal or antiviral). Minimal duration of antimicrobial therapy was either: (1) 4 days after the patient became apyretic; (2) 2 days after neutrophil recovery (>1000/μl); or (3) until clinical signs of infection disappeared and cultures were negative, whichever was the longest.

Febrile episodes were classified, according to known criteria [8], as documented infections (either clinically or microbiologically proven) or fever of unknown origin. Categories of therapeutic response were: (1) success with monotherapy (complete resolution of the episode without modification of the initially assigned antibiotic); (2) success with modification (when addition of second and/or third step antibiotics—amikacin and/or vancomycin—was required for cure); (3) failure (when other antibiotics, not included in the study protocol, were needed, or the patient died from infection during the neutropenic episode); and (4) not evaluable (documented non-bacterial infection, significant protocol violation, or death unrelated to infection).

Comparison of proportions between the two groups was made by the chi-squared or Fisher's exact test, when appropriate. For continuous variables, the *t*-test was used. Probabilities below 0.05 were considered statistically significant.

RESULTS

From July 1991 to July 1994, 118 episodes of fever and neutropenia occurring in 102 cancer patients were randomised to receive treatment with either ceftazidime or imipenem. Main clinical features were similar (i.e. not significantly different) in both arms (Table 1).

Forty (34%) febrile episodes were classified as microbiologically documented infections, 49 (42%) as clinically documented infections and 29 (24%) as fever of unknown origin (possible or doubtful infections). In the first group, pathogens most frequently isolated were gram-negative bacteria (57%), especially *Escherichia coli* (eight episodes) and *P. aeruginosa* (8 episodes). Among gram-positive infections (30%), *Staphylococcus epidermidis* (7 cases) was the most common microorganism. Anaerobic, fungal and protozoal infections were rare. No significant differences between both study arms were encountered for these variables (Table 2). Infections located in the head and neck (including mucositis) accounted for a quarter of documented episodes. Systemic infections were more frequent among patients who received imipenem, whereas respiratory tract infections (including pneumonia) predominated in the ceftazidime group (not statistically significant). The distribution of other primary sites of infection for either microbiologically or clinically documented episodes was similar in both groups (Table 2).

Seven episodes (6%) were considered not evaluable, 3/58 in the ceftazidime arm (two cases of *Pneumocystis carinii* pneumonia (PCP), 1 fungaemia by *Candida parapsilosis*) and 4/60 in the imipenem arm (two protocol violations one of which was due to toxicity, 1 PCP, 1 case of sepsis by *Candida sp*). Thus, the final study population included 111 assessable episodes occurring in 95 patients. The overall percentages of success with monotherapy (69 versus 70%), success with modification (20 versus 23%), and failure (11 versus 7%) were superimposable for ceftazidime and imipenem, respectively ($P = 0.75$). 5 patients (5%) died during febrile neutropenia, 3 in the ceftazidime arm and 2 in the imipenem arm. Table 3 shows the distribution of responses by treatment group and type of infection.

The antimicrobial treatment was maintained for a median of 8 days in both arms (range 1–15). Antibiotic additions within the protocol consisted of amikacin (5 cases in each group), vancomycin (3 cases in the ceftazidime group and 1

*Table 1. Characteristics of patients and febrile episodes**

Characteristic	Cetazidime	Imipenem	Total
Episodes randomised	58 (49)	60 (51)	118 (100)
Patients	49 (48)	53 (52)	102 (100)
Age (years)			
Median	59	57	58
Range	15–75	16–75	15–75
Gender			
Male	27 (55)	32 (60)	59 (58)
Female	22 (45)	21 (40)	43 (42)
Indwelling catheters	17 (35)	19 (36)	36 (35)
Primary tumour			
Lymphoma/Hodgkin's	15 (31)	15 (28)	30 (29)
Lung cancer	11 (22)	12 (23)	23 (23)
Sarcoma	6 (12)	6 (11)	12 (12)
Breast cancer	6 (12)	4 (8)	10 (10)
Multiple myeloma	4 (8)	4 (8)	8 (8)
Other solid tumours	7 (14)	12 (23)	19 (19)
Leucocyte count at entry (cells/μl)†			
Median	735	535	585
Range	70–2060	70–2550	70–2550
Neutrophil count (cells/μl)‡			
Median	110	50	100
Range	0–500	0–500	0–500
Days in neutropenia			
Median	4	4	4
Range	1–15	2–10	1–15

* Results are expressed as number of patients (%). † $P = 0.22$. ‡ $P = 0.19$.

in the imipenem group), and amikacin plus vancomycin (3 and 7 cases, respectively). Of the 10 failures, five episodes were ultimately fatal due to septic shock, bleeding or both. The other five cases required protocol modifications: association of amphotericin B in two episodes randomised to imipenem, clindamycin or metronidazole in 2 patients assigned to ceftazidime, and change from ceftazidime to imipenem (due to resistance) in one.

Clinically significant toxicity was negligible, except for a single case of myoclonic encephalopathy secondary to imipenem that required discontinuation of treatment. Self-limited nausea, vomiting or diarrhoea were occasionally seen in both arms.

DISCUSSION

In the last decade, single agent therapy with broad-spectrum antibiotics has become an alternative choice to classic antimicrobial combinations in the management of febrile neutropenic episodes. Ceftazidime and imipenem are both useful in this context [9, 10]. According to clinical response and microbiological isolates, the addition of more selective, second-line antibiotics, such as amikacin or vancomycin, may be necessary. This delayed introduction does not compromise the chance of response [11]. Controlled clinical trials have compared both ceftazidime and imipenem to antibiotic combinations. Ceftazidime was as effective as several multidrug regimens [3, 4, 12, 13], except in an EORTC study. In the latter, subsequent modifications of the initial monotherapy were required with sufficient frequency for the authors to warrant empiric treatment with two-drug combination [14]. Imipenem has shown its clinical efficacy, even against ceftazidime combinations [5, 15, 16]. Winston and colleagues [16] found that, despite significant differences in *in vitro* activity, monotherapy with imipenem was associated with a similar response rate and less cost than double beta-lactam therapy with either cefoperazone plus piperacillin or ceftazidime plus piperacillin.

Prior to the present study, at least four randomised trials have compared ceftazidime and imipenem monotherapy [17–20]. Both drugs were equivalent in a study of severe, nosocomial infections occurring in non-oncological patients [19]. Nonetheless, ceftazidime was superior in pneumonial episodes. Liang and coworkers [17] reported favourable responses in 77% of patients treated with imipenem and 56% receiving ceftazidime ($P = 0.04$). Imipenem was more effective than ceftazidime for treatment of both gram-positive and gram-negative infections in these febrile neutropenic cancer patients. In another study with four treatment arms [18], the overall response rates were 76% with imipenem plus amikacin, 72% with imipenem alone, 71% with ceftazidime plus amikacin, and 59% with ceftazidime alone ($P = 0.009$ for ceftazidime versus all other regimens). More than two-thirds of these patients had haematological malignancies as the underlying disease. Multivariate logistic-regression analysis showed that neutrophil recovery was the most favourable prognostic factor for response, whereas gram-positive infection, acute leukaemia and pulmonary or enteric infection were unfavourable factors. Freifeld and associates [20] failed to show significant differences between ceftazidime and imipenem in both the overall response rate or the need for anti-

*Table 2. Distribution of infections and microbial isolates by treatment group**

Characteristic	Ceftazidime (n = 58)	Imipenem (n = 60)	Total (n = 118)
Type of infection			
Fever of unknown origin	13 (22)	16 (27)	29 (25)
Clinically documented	24 (41)	25 (42)	49 (42)
Microbiologically documented	21 (36)	19 (32)	40 (34)
Site of infection†			
Head and neck	11 (24)	12 (27)	23 (26)
Respiratory tract	13 (29)	8 (18)	21 (24)
Blood	7 (16)	12 (27)	19 (21)
Skin	5 (11)	5 (11)	10 (11)
Urinary tract	5 (11)	3 (7)	8 (9)
Catheter-related	2 (4)	2 (5)	4 (4)
Gastrointestinal	2 (4)	2 (5)	4 (4)
Microbial isolates‡			
Gram-negative	13 (57)	13 (57)	26 (57)
P. aeruginosa	4	4	8
E. coli	3	5	8
Enterobacter sp.	2	1	3
Klebsiella pneumoniae	2	1	3
Serratia sp.	1	0	1
Haemophilus influenzae	1	0	1
Acinetobacter sp.	0	1	1
Proteus mirabillis	0	1	1
Gram-positive	7 (30)	7 (30)	14 (30)
S. epidermidis	4	3	7
S. aureus	2	1	3
Streptococcus sp.	1	2	3
Corynebacterium D2	0	1	1
Anaerobes	0 (–)	2 (9)	2 (4)
Propionibacterium sp.	0	2	2
Not bacterial	3 (13)	1 (4)	4 (9)
P. carinii	2	0	2
Candida sp.	1	1	2

* Results are expressed as number of patients (%). † Includes both clinically and microbiologically documented infections. ‡ Some patients had multiple microbial isolates.

*Table 3. Response to therapy by type of infection and treatment arm**

	Response to treatment					
	Ceftazidime (n = 55)			Imipenem (n = 56)		
Type of infection	Success with monotherapy	Success with modification	Failure	Success with monotherapy	Success with modification	Failure
Microbiologically documented†	10	5	3	9	6	2
Clinically documented‡	16	5	3	14	7	2
Fever of unknown origin§	12	1	0	16	0	0
Total‖	38 (69)	11 (20)	6 (11)	39 (70)	13 (23)	4 (7)

* Results are expressed as number of episodes (%). † $P = 0.85$. ‡ $P = 0.72$. § $P = 0.45$. ‖ $P = 0.75$.

biotic modifications. Anti-anaerobic agents were more frequently added to ceftazidime, while imipenem therapy was more often complicated by gastrointestinal toxicity. The majority of the patients studied had solid tumours, and less than half had leukaemia or lymphoma.

The data of the present study confirm our preliminary results showing the effectiveness of monotherapy with either ceftazidime or imipenem for febrile neutropenic episodes [21].

Our results compare well with two recent randomised studies employing both drugs [19, 20]. The apparent superiority of imipenem over ceftazidime in terms of antimicrobial spectrum and clinical efficacy, that has been observed in other trials [17, 18], may be understated in febrile episodes of less risk. In fact, cancer patients with fever and neutropenia form a heterogeneous group with various risk of infection-related morbidity and mortality [22]. Hence, they should not be treated in a

uniform manner. Further studies should consider predictive factors for the development of bacteraemia [23], and prognostic features for response to therapy [18] or for poor patient outcome [24, 25] when comparing antimicrobial agents. These factors must also be used to individualise the therapy. We conclude that ceftazidime and imipenem are both effective for the management of febrile, neutropenic cancer patients with solid tumours undergoing standard chemotherapy. If any of the high-risk conditions are present (profound and prolonged neutropenia, documented bacteraemia, acute leukaemia, history of prior hospitalisation for febrile neutropenia, active underlying disease, hypotension, altered mental status, respiratory failure, dehydration, poor oral intake, or gross bleeding) [18, 23–25] other approaches should probably be investigated (two-drug therapy, use of granulocyte-colony stimulating factors, or both).

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