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Ceftriaxone Versus Latamoxef in Febrile Neutropenic Patients: Empirical Monotherapy in Patients with Solid Tumours

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121 patients with 132 febrile episodes were randomised to ceftriaxone or latamoxef monotherapy in order to compare antibiotic efficacy in neutropenic patients treated with cytotoxic chemotherapy for solid tumours. In 80 evaluable episodes no significant differences were observed between the two groups with respect to efficacy and fatal failure rates. Of episodes treated with ceftriaxone, 67% showed a favourable clinical response vs. 61% in the latamoxef group. The clinical response rates in episodes with documented bacterial infections were 67 and 56% in the two treatment groups. In 18% of the episodes with documented initial infections the patients died of presumably uncontrolled infection. The convenient once daily dosage schedule combined with fewer severe adverse reactions favours the use of ceftriaxone instead of latamoxef. Although a relative high degree of response was seen, empirical antibiotic monotherapy apparently does not offer a sufficient antibacterial cover in infections in this type of patient with defective host immunity.
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INTRODUCTION

BACTERIAL INFECTIONS in neutropenic patients treated with cytotoxic chemotherapy often initially present with fever alone. Untreated, the infections lead to a case fatality ranging from 25 to 61%, depending on the blood granulocyte count [1–4]. An important therapeutic improvement was the recognition that fever of ≥38°C, persistent for ≥2 h, should be considered the threshold for initiating empirical broad spectrum antimicrobial therapy.

The preferred standard combination for first-line treatment has been a beta-lactam agent and an aminoglycoside [5–7]. As cisplatin has become a cornerstone in the cytotoxic chemotherapy of solid tumours, the principal issue of avoiding nephrotoxicity raises the question of whether the use of a potent single antibiotic drug, particularly a newer cephalosporin, is a safe alternative to the usually preferred standard combinations [8, 10]. In recent trials where none or very few bacteriaemic infections were documented during short neutropenic periods, the patients responded irrespective of whether they received one or two antibacterial agents [9, 11, 12]. Accordingly, the use of the cephalosporin latamoxef alone was found to be at least as effective and safe as combined treatments in a previous trial when given to neutropenic patients with solid tumours [10]. However, latamoxef has some drawbacks; it has to be administered three times daily and it interferes with the production of vitamin K precursors in the intestine.

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The introduction of a new cephalosporin, ceftriaxone [13, 14], has one great advantage compared to other broad spectrum cephalosporins: a serum half-life of 8.5 h enabling once daily dosage. Accordingly, a prospective randomised multicentre study was initiated with the purpose of comparing the clinical and bacteriological efficacy plus the safety profile of ceftriaxone and latamoxef in febrile neutropenic patients with solid tumours. Furthermore, we wished to explore the possibility of identifying subgroups of patients with risk of poor outcome on single-agent empirical antibiotic therapy.

MATERIALS AND METHODS

The trial was an open, prospective, randomised, comparative study including three hospitals. Patients (aged >18 years) with solid tumours, undergoing cytotoxic chemotherapy, who were admitted to the participating departments because of fever and neutropenia, i.e. total white blood count (WBC) $<1.0 \times 10^9$/l, were included.

Fever was defined as rectal temperature between 38.0 and 38.5°C for 12 h, or temperature >38.5°C for 2 h. Informed consent was mandatory according to the rules of the Local Ethical Committees. Excluded from the study were patients with progressive tumour status [15], with jaundice, serum creatinine >150 μmol/l, known or suspected allergy to cephalosporins, infections due to organisms already well identified, treatment with anticoagulant therapy, systemic steroids, or other antibiotics within the preceding 3 days. Patients with septic shock, and patients having blood product transfusion within 24 h as the likely cause of fever were also excluded.

Before antibiotic therapy the following cultures were done: Blood (aerobic–anaerobic), midstream urine, throat swab for pathogenic bacteria and yeasts, sputum specimen from patients with expectoration, faecal specimen from patients with diarrhoea, and swabs from other suspected foci of infection. Furthermore, chest X-ray, serum creatinine and complete blood count were performed. Primary positive cultures were repeated after

48 h antibiotic treatment. Complete blood counts and clinical examination were performed every day. Cultures were regarded positive if the number of microorganisms in the urine was $\geq 10^5$/ml, or if a bacterium, considered a pathogen, dominated in a throat specimen or was found in representative areas in a sputum specimen. If a blood culture contained microorganisms from the normal skin flora, it was regarded as a contaminant unless found in at least two separate blood cultures.

The patients included were randomised to receive intravenously either ceftriaxone (Rocephin®) 50 mg/kg body weight /day; maximum 2 g administered once a day, or latamoxef (Moxalactam®) 90 mg/kg body weight/day; maximum 6 g administered every 8 h. Before the first dose of latamoxef, 10 mg vitamin K was given intravenously.

Protocol treatment was primarily given for 48 h unless imminent septic shock or deterioration of the patient's condition indicated supplementary antibiotic therapy. Temperature $\leq$38.5°C at 48 h indicated unchanged treatment until WBC increased to $>1.0 \times 10^9$/l and temperature remained below 37.5°C for at least 24 h. Temperature >38.5°C at 48 h or later resulted in cessation of protocol treatment and antibiotic therapy as indicated.

In order to evaluate final clinical outcome four categories were used:

(i) Complete resolution was defined as a temperature <37.5°C within 48 h, lasting until WBC was $>1.0 \times 10^9$/l.
(ii) Improvement was defined as at least 1°C decrease of temperature and temperature $\leq$38.5°C within 48 h and no change of antibiotics.
(iii) Failure included patients with change of antibiotics because of the temperature remaining >38.5°C, patients with change of antibiotics according to bacteriological findings, or death of patient related to infection.
(iv) Patients were classified as non-evaluable if WBC was $>1.0 \times 10^9$/l within 48 h, death not related to infection or death within 48 h, premature trial drug withdrawal, and other protocol violations.

Three categories were used in order to characterise the microbiological outcome:

(i) Qualified pathogen elimination was defined as elimination of causal pathogen from initially positive specimen(s) when re-examined after at least 48 h of antibiotic therapy.
(ii) Failure when the causal pathogen was not eliminated.
(iii) Non-evaluable when initial positive specimen(s) was not re-examined.

All clinical adverse reactions were registered. For statistical analysis Fisher's exact test and Mann–Whitney's two-sample rank sum test were used. Significance was defined as a P-value <0.05.

RESULTS

A total of 121 patients with 132 febrile episodes entered the study (Table 1). 52 of 132 episodes (39%) were non-evaluable, leaving 80 evaluable episodes in 72 patients. Premature increase of WBC, observed in 23% of all episodes, was the major reason for episodes being characterised as non-evaluable. The most common reasons for protocol violation were concomitant treatment with prednisolone, granulocyte–macrophage colony-stimulating factor, or other antibiotics (Table 1). Death within 48 h was due to septic shock in 3 cases and intestinal gangrene in 1 case.

Table 1. Number of episodes of fever and neutropenia

	Ceftriaxone	Latamoxef
Patients randomly assigned	60	61
Episodes randomly assigned	64 (100%)	68 (100%)
Evaluable episodes	36 (56%)	44 (65%)
Non-evaluable episodes	28	24
Premature increase of WBC	17 (27%)	13 (19%)
Excessive toxicity	1 (2%)	2 (3%)
Death within 48 h	4 (6%)	0
Protocol violation	6 (9%)	9 (13%)

There were no major differences between the two treatment groups with respect to clinical characteristics, including initial WBC (Table 2). The duration of neutropenia defined as WBC $<1.0 \times 10^9$/l was 4.4 days in the ceftriaxone group vs. 4.7 days in the latmoxef group. There was no significant difference in the mean duration of treatment, with the two drugs being 4.1 and 4.3 days, respectively. More evaluable episodes in the ceftriaxone group [18 of 36 (50%)] than in the latamoxef group [16 of 44 (36%)] had initially documented bacterial infections.

Clinical outcome

Table 3 shows the clinical outcome according to time of defervescence. In 78% (28/36) and 75% (33/44) of the episodes treated with ceftriaxone and latamoxef, respectively, the patients had a favourable outcome after 48 h therapy. Of these episodes with initial improvement the antibiotic regimen was changed due to increasing temperature in four episodes (14%) in the ceftriaxone group and five (15%) in the latamoxef group.

Table 4 lists the final clinical outcome with significant microbiological findings for the 80 episodes. There were 18 microbiologically documented infections in the ceftriaxone group and 16 in the latamoxef group. Yeasts were found as superinfections in 2 patients (6%) and 5 patients (11%) treated with ceftriaxone and latamoxef, respectively, during trial therapy. In no case was yeast the initial causative microorganism.

There were no significant differences between the two treatment arms with respect to complete resolution, improvement, failure or death rates ($P>0.50$). The failure rate was 33% (6/18) in the ceftriaxone group and 44% (7/16) in the latamoxef group in episodes with documented initial bacterial infections ($P>0.50$). The overall failure rate, 38% (13/34) among patients with documented infections was not significantly higher than the rate of 35% (16/46) among patients without documented initial infections ($P>0.50$). The failure rate was significantly lower in episodes with monomicrobial infections, 20% (5/25) compared to polymicrobial infections 89% (8/9) ($P<0.01$). An overall higher failure rate was found in patients with no-change status of tumour compared to patients having responding tumours, 51% (20/39) vs. 20% (5/25), respectively ($P<0.05$) (Table 2). Furthermore, a trend towards higher frequency of failures was found in patients with performance status 2–4 as compared to patients with performance status 0–1 (see Table 2 for definition), 42% (22/53) vs. 26% (7/27) ($P<0.3$).

7 of the 72 evaluable patients (10%) died within 15 days from the start of trial treatment of presumed initial infection or superinfection. 1 patient died on day 9 of pneumonia diagnosed on clinical and radiographic findings without bacteriological documentation. The types of infection and bacteriological find-

Table 2. Clinical characteristics of evaluable patients

Characteristic	Ceftriaxone	Latamoxef	Total
Evaluable patients	34 (12)	38 (16)	72 (28)
Evaluable episodes	36 (12)	44 (17)	80 (29)
Sex (male/female)	15/21 (6/6)	22/22 (9/8)	37/43 (15/14)
Age in years, median [range]	62 [18–74] (61 [26–68])	61 [18–77] (63 [24–77])	61 [18–77] (62 [24–77])
<61	17 (6)	21 (6)	37 (12)
61–70	18 (6)	19 (8)	37 (14)
>70	2 (0)	4 (3)	6 (3)
Tumour type			
Lung	12 (4)	17 (7)	29 (11)
Ovary	9 (5)	11 (5)	20 (10)
Testis	2 (1)	9 (3)	11 (4)
Breast	4 (0)	1 (0)	5 (0)
Others	9 (3)	6 (2)	15 (4)
Treatment			
Combination chemotherapy	32 (11)	32 (10)	64 (21)
Single-agent chemotherapy	3 (0)	11 (7)	14 (7)
Radiotherapy	7 (1)	5 (2)	12 (3)
Disease status			
NC	19 (10)	20 (10)	39 (20)
CR/PR	10 (2)	15 (4)	25 (5)
No information	7 (0)	9 (4)	16 (4)
Performance status*			
WHO 0–1	12 (1)	15 (6)	27 (7)
WHO 2–3	23 (10)	26 (9)	49 (19)
WHO 4	1 (1)	3 (2)	4 (3)
Initial WBC (10^9/l)			
Median	0.4 (0.5)	0.4 (0.4)	0.4 (0.4)
Range	0.0–0.9 (0.0–0.9)	0.1–0.9 (0.1–0.8)	0.0–0.9 (0.0–0.9)

Values in parentheses are failures.
CR = Complete remission; PR = partial remission; NC = no change.
*WHO performance scale. 0: capable of all normal activity without restriction; 1: ambulatory and able to carry out light work; 2: capable of all self-care, up and about more than 50% of waking hours; 3: capable of only limited self-care, confined to bed or chair more than 50%; 4: completely disabled, totally confined to bed or chair.

ings for the 6 other patients are given in Tables 4 and 5. The death rate, 17% (3/18) in the ceftriaxone group and 19% (3/16) in the latamoxef group, in episodes with documented initial infections did not differ significantly.

Microbiological outcome

The strains isolated and the final bacteriological outcome are shown in Table 5. A total of 53 strains was initially isolated in 34 episodes. Of these 33 (62%) were Gram-negative, and 20 (38%) Gram-positive. The elimination rate on antibiotic trial therapy was 95% (19/20) of the Gram-negative, and 75% (6/8) of the Gram-positive strains. The elimination rate did not differ significantly between the ceftriaxone- and latamoxef-treated patients, 82% (14/17) vs. 100% (11/11), respectively ($P>0.30$). In patients with bacteraemia the elimination rate was 89% (8/9) in the ceftriaxone group and 100% (7/7) in the latamoxef group.

Microbiological adverse reactions were seen in 10 episodes. Seven of these had upper airway superinfections with yeast and no initially documented infection. 1 patient with initial polymicrobial bacteraemia with *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* responding to trial therapy died on day 7 with *Pseudomonas aeruginosa* septicemia. In 1 patient with negative primary cultures, *P. aeruginosa* were found in the blood on the second day of treatment, and another patient also with negative initial cultures had intestinal *Clostridium difficile* infection on day 2. Twenty-five of the 53 initially positive cultures were not reevaluated, mainly because of clinical complete resolution resulting in discharge of the patient from the department. However, 3 ceftriaxone-treated patients and 6 latamoxef-treated patients with final clinical failure were without microbiological reexamination.

Clinical adverse events probably due to trial treatment were seen in 16 cases (Table 6).

DISCUSSION

This investigation did not reveal any significant differences between the two closely related antibiotic compounds, ceftriaxone and latamoxef, with regard to either clinical or bacteriological outcome in a group of patients with solid tumours, neutropenia, and fever. Furthermore, this study demonstrated that the microbial safety profile of giving a single-agent therapy once daily with ceftriaxone is as good as using latamoxef three

Table 3. Clinical outcome of 80 evaluable episodes

Clinical outcome	Evaluable episodes Ceftriaxone	Latamoxef
At 48 hours	36	44
Temperature <37.5°C	18	18
Temperature decreased 1°C and ≤38.5°C	10	15
Failure	8	11
Final	36	44
Complete resolution	18	18
Improvement	6	9
Failures	12 (3)*	17 (4)*
Initial improvement, change of antibiotic due to secondary rise in temperature	4	5
Initial improvement, change of antibiotic according to bacteriological findings	0	1
No improvement	8	11

*Death, presumably of infection, in parentheses.

times daily. The schedule of ceftriaxone is far more convenient for patients and the hospital staff. Of major concern is the high incidence (7%) of severe adverse reactions, such as anaphylactic reactions and overt bleeding seen after latamoxef whereas no severe side-effects were observed after ceftriaxone administration (Table 6). Overall, this favours the use of ceftriaxone instead of latamoxef for single-agent empirical antibiotic therapy in our patients. Severe bleeding episodes associated to latamoxef therapy have been reported earlier [16–19].

Our response rates, 67% for ceftriaxone and 56% for latamoxef, in episodes with documented bacterial infections do not differ from comparative trials where latamoxef was combined with an aminoglycoside or used in a double beta-lactam regimen giving response rates of 59–83% (median 69%) [20–25]. This is also evident when our results are compared to several single-agent studies with cefrazidime and imipenem showing response rates between 21 and 81%, median 43% [26–30]. Even in subgroups of patients with documented bacteraemia our response rates, ceftriaxone 62% and latamoxef 50%, fall within the observed range from earlier two-agent trials, 50 to 85%, median 73% [20–23]. Failure to eliminate the microorganism was documented in only two episodes in our study, both fatal, but 25 initially positive cultures were not reinvestigated (Table 5). In six (18%) of the episodes with documented initial infections the patients died presumably of uncontrolled infections during trial therapy. 3 of these patients had an initially favourable response, but modification of the original trial therapy was done because of increasing temperature or according to initial bacteriological findings. Interestingly, the subset of evaluable patients (46 episodes) without microbiologically documented initial infection did not have a better final outcome, but of major clinical importance is that only one (2%) died of presumed infection.

Although our response rates do not seem different from the response rates of other investigations, we must conclude that neither ceftriaxone nor latamoxef gives an entirely satisfactory result in our subset of patients with initially documented infections. Several reasons may account for this outcome. A direct

Table 4. Final clinical outcome according to type of primary infection and treatment in 80 episodes

Type of infection	Clinical outcome at the end of the protocol: Complete resolution CEF	Complete resolution LAT	Improvement CEF	Improvement LAT	Failure CEF	Failure LAT	Total CEF	Total LAT
Bacteraemia							8	6
Monomicrobial	4*	2*	1	0	0	0		
Polymicrobial	0	0	0	1	3 (1)†	3 (1)†		
Urinary infection							4	5
Monomicrobial	2	2	2	1	0	2 (1)		
Polymicrobial	0	0	0	0	0	0		
Airway infection							5	4
Monomicrobial	2	1	1	1	1 (1)	2 (1)		
Polymicrobial	0	0	0	0	1	0		
Other sites							1	1
Monomicrobial	0	1	0	0	0	0		
Polymicrobial	0	0	0	0	1 (1)	0		
Microbiologically undocumented primary infections	10	12	2	6	6	10 (1)	18	28
Total (n = 80)	18	18	6	9	12 (3)	17 (4)	36	44

CEF = Ceftriaxone; LAT = latamoxef.
*1 patient having another infection besides bacteraemia.
†2 patients having other infections besides bacteraemia.
Death, presumably due to infection, in parentheses.

Table 5. Microbiological findings in episodes with documented initial infections

Type of infection and organism	Bacteriological outcome No. of strains isolated and treatment					
	Elimination		Failure		Impossible to evaluate	
	CEF	LAT	CEF	LAT	CEF	LAT
Bacteraemia						
Escherichia coli	4	3 (1)	0	0	1	1
Klebsiella pneumoniae	1	1	0	0	1	0
Enterobacter cloacae	0	1	0	0	0	0
Pseudomonas aeruginosa	0	0	1 (1)	0	0	0
Salmonella paratyphi	0	1	0	0	0	0
Staphylococcus aureus	1	0	0	0	0	2
Staphylococcus epidermidis	1	0	0	0	0	0
Streptococcus pneumoniae	0	1	0	0	1	0
Haemolytic Streptococci, group A	1	0	0	0	0	0
Non-haemolytic Streptococci	0	0	0	0	0	1
Subtotal	8	7	1	0	3	4
Urinary tract infection						
Escherichia coli	3	1	0	0	1	3
Klebsiella pneumoniae	1	1	0	0	1	0
Streptococcus faecalis	0	0	0	0	0	2
Morganella morganii	0	0	0	0	0	1 (1)
Subtotal	4	2	0	0	2	6
Airway infection						
Enterobacter cloacae	0	0	0	0	1	0
Hemophilus influenzae	0	1	0	0	1	1 (1)
Streptococcus pneumoniae	1	0	0	0	1	1
Haemolytic Streptococcus, group A	0	0	0	0	1	1
Staphylococcus aureus	0	1	0	0	1	0
Branhamella catarrhalis	1 (1)	0	0	0	1	0
Subtotal	2	2	0	0	6	3
Other sites						
Bacillus sp.	0	0	1 (1)	0	0	0
Staphylococcus aureus	0	0	0	0	0	1
Staphylococcus epidermidis	0	0	1 (1)	0	0	0
Subtotal	0	0	2	0	0	1
Total no. of strains	14	11	3	0	11	14
in no. of episodes	11 (1)	7 (1)	2 (2)	0	1	10 (2)

CEF = Ceftriaxone; LAT = latamoxef.
*Death of superinfection with *Pseudomonas aeruginosa*.
Death, presumably due to infection, in parentheses.

Table 6. Adverse reactions, all episodes

	Ceftriaxone	Latamoxef
No. of episodes	64	68
Anaphylactic reactions	0	2
Dizziness	0	6
Bleeding (severe)	0	3
Diarrhoea	1	0
Erythema	1	0
Others (mild)	3	0
Total	5 (8%)	11 (16%)

comparison of the results in different trials is not possible as the efficacy and safety of an antibiotic regimen depends on (i) the isolated organisms and their antimicrobial susceptibility, (ii) the duration of persistent neutropenia, and (iii) the actual immunological status of the host. The frequency of Gram-positive bacterial strains was the same as in the previous study in the same geographic area 5 years ago [10]. The clinical failure rates in these subgroups were similar, 33 vs. 31%, when patients infected with *Streptococcus faecalis* were excluded.

There was no evidence of a decrease in antibiotic susceptibility from the previous to the present study regarding Gram-negative strains. Interestingly, in the present study six of 14 episodes with *E. coli* infection were clinical failures although all reinvestigated cultures showed qualified bacteriological elimination. The cause

of failure in two of these episodes was superinfection with *P. aeruginosa*. The discrepancy observed in the four other episodes between *in vitro* and *in vivo* susceptibility of *E. coli* to cephalosporins was not observed in our earlier study 5 years ago where all five episodes with *E. coli* demonstrated favourable clinical responses [10]. Lack of efficacy of beta-lactam single or combination therapy against *P. aeruginosa* infections is well known [21, 24, 30]. We found a relatively low incidence of *P. aeruginosa* infections. In one episode *P. aeruginosa* was the primary causative pathogen, in two other episodes it occurred as superinfection. In two of these three episodes the outcome was fatal. Similar resistant gram-negative superinfections were also seen in a study using ceftazidime as monotherapy for the same category of patients [31].

Presumably, most bacterial infections in neutropenic patients are caused by strains with which the patient is already colonised. These strains emerge as pathogens when host defence is compromised by neutropenia or underlying disease. In this study we have demonstrated a trend towards higher failure rates in patients with poor performance status and significantly higher failure rates in the subsets of patients with polymicrobial infections and non-responding tumours. These circumstances, together with the nature of the isolated strains in cases of fatality, suggest a defective line of defence due to host immune deficiency as the major cause of the poor outcome of empirical antibiotic therapy. A more aggressive systemic cytotoxic chemotherapy may have contributed to the disturbances of host immune integrity as a longer duration of neutropenia, median 4.5 vs. 3 days was found in this study compared to the previous study [10].

This study suggest that significantly supportive enhancement of the host immune system, such as the use of hemopoietic growth factors, might be of more clinical value than development of new antibiotic drugs in the treatment of infections in cytotoxic chemotherapy induced neutropenic patients [32, 33].

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