Original

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A comparison of the efficacy of piperacillin-tazobactam and cefoperazone-sulbactam therapies in the empirical treatment of patients with febrile neutropenia

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ABSTRACT

Introduction. Empirical antibiotic therapy in neutropenic patients presenting with fever plays a significant role in reducing mortality related to infection. Empirical therapies with broad-spectrum intravenous bactericidal, anti-pseudomonal antibiotics are accepted treatments for febrile neutropenic patients. The aim of this study was to compare the efficacy of piperacillin-tazobactam (PIP-TAZO) and cefoperozone-sulbactam (CS) therapies in adult patients with haematological malignancies presenting with neutropenic fever in a prospective study design.

Methodology. Patients with haematological malignancies (leukaemia, lymphoma, multiple myeloma, and myelodysplastic syndrome) were recruited from June 2010–May 2013. Participants were over 18 years old, with an absolute neutrophil count (ANC) of less than 500/mm^3 following chemotherapy or expected to have an ANC less than 500/mm^3 in the first 48 h post-chemotherapy, and with an oral body temperature ≥ 38.3°C at a single measurement or 38.0°C after 1-h monitoring. Patients were randomised to the two treatment groups. The initial empirical therapy comprised PIP-TAZO (4.5 g/6 h/day, IV) and CS (2 g/8 h/day, IV).

Results. The overall success rate was 61% with CS and 49% with PIP-TAZO (p =0.247). Factors affecting the treatment success included a neutrophil count <100/mm^3, being in the relapse/refractory stage of malignancy, and the presence of a microbiologically documented infection (p <0.05).

Conclusion. PIP-TAZO and CS monotherapies are equally effective and safe for the empirical treatment of febrile neutropenic patients.

KEYWORDS: Cefoperozone-sulbactam; febrile neutropenia; haematological malignancy; monotherapy; piperacillin-tazobactam.

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Eficacia de piperacilina-tazobactam y cefoperazona-sulbactam en el tratamiento de pacientes con neutropenia febril

RESUMEN

Introducción. El tratamiento antibiótico empírico en pacientes neutropénicos con fiebre juega un papel importante en la reducción de la mortalidad asociada a la infección. El tratamiento empírico con antimicrobianos intravenosos de amplio espectro y antipseudomonas es el tratamiento aceptado para pacientes neutropénicos febriles. El objetivo de este estudio prospectivo fue comparar la eficacia de piperacilina-tazobactam (PIP-TAZO) y cefoperazona-sulbactam (CS) en pacientes neutropénicos febriles adultos con alteraciones hematológicas.

M**étodos.** Pacientes con alteraciones hematológicas (leucemia, linfoma, mieloma múltiple y síndrome mielodisplásico) fueron reclutados desde junio 2010 a mayo 2013. Todos los pacientes fueron mayores de 18 años de edad, presentaban un recuento absoluto de neutrófilos (RAN) menor de 500/mm^3 tras la quimioterapia o la expectativa de tener un RAN menor de 500/mm^3 en la primeras 48 h después de la quimioterapia, una temperatura corporal oral ≥ 38,3°C o 38,0°C después de 1 h de monitorización. Los pacientes fueron aleatorizados en los dos grupos de tratamiento empírico inicial PIP-TAZO 4,5 g/6 h/día IV o CS 2 g/8 h/día IV.

Resultados. La tasa de éxito total fue de 61% con CS y 49% con PIP-TAZO (p =0,247). Los factores que afectaron el éxito de tratamiento fueron un recuento de neutrófilos <100/mm^3 y la presencia de una infección documentada microbiológicamente (p <0,05).

Conclusión. El tratamiento en monoterapia de PIP-TAZO y CS son igual de eficaces y seguro para el tratamiento empírico de pacientes neutropénicos febriles.

Palabras clave: Cefoperazona-sulbactam; neutropenia febril, alteraciones hematológicas, monoterapia, piperacilina-tazobactam.

INTRODUCTION

Survival rates have increased in cancer patients due to the development of multi-drug chemotherapy protocols, the use of higher dosages, and improvement in supporting therapies for haematological malignancies. However, cytotoxic chemotherapy regimens, immunosuppression, and particularly neutropenia secondary to underlying bone marrow involvement in these patients result in increased infection rates. Initiating an empirical antibiotic therapy in neutropenic patients presenting with fever plays a significant role in the reduction of mortality related to infection[1].

Empirical therapies with broad-spectrum intravenous bactericidal, anti-pseudomonal antibiotics are the commonly accepted treatment approaches in febrile neutropenic patients. Knowledge of the specific infectious pathogens, their prevalence, and antibiotic resistance patterns guides application of empirical therapies to reduce mortality.

Several broad-spectrum antibiotics are used in the treatment of febrile neutropenia. Regimens approved by many clinical centres include cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam (PIP-TAZO), and cefoperazone-sulbactam (CS). Combinations of beta-lactam and beta-lactamases including PIP-TAZO and CS are successfully administered during febrile neutropenic episodes[2].

The objective of this study was to compare the efficacy of PIP-TAZO and CS therapies in adult patients with haematological malignancies presenting with neutropenic fever, in a prospective study design.

PATIENTS AND METHODS

Patients. Patients with haematological malignancies (leukaemia, lymphoma, multiple myeloma, and myelodysplastic syndrome) were recruited from June 2010–May 2013. Participants were over 18 years old, with an absolute neutrophil count (ANC) less than 500/mm³ following chemotherapy or expected to have an ANC below 500/mm³ in the first 48 h post-chemotherapy, and with an oral body temperature ≥38.3°C at a single measurement or 38.0°C after 1-h monitoring.

Evaluation and follow-up before treatment. Prior to treatment, a medical history was obtained, a detailed physical examination was performed, and at least two blood cultures were obtained from the peripheral vein and central venous catheter. If these were positive, a urine culture and other cultures deemed necessary from the clinical symptoms and signs were obtained, and a lung x-ray, complete blood count, and hepatic and renal function tests were performed. Daily follow-up patient visits were performed after the initiation of an appropriate antibiotherapy, and any fever, ANC, bacteria in cultures, newly developed infections, clinical improvements or deterioration, changes in the antibiotic regimen, decreases in fever, end of neutropenia, and side effects of antibiotics were recorded.

Antibacterial regimens. Empirical antibiotherapy was initiated immediately after the initial culture samples were taken. Patients were randomised to the two the treatment groups. Patient has been selected and randomized double-blinded by computerized system. Patients who had completed the treatment cycle at least 1 week prior were re-randomised. The initial empirical therapy consisted of PIP-TAZO (4.5 g/6 h/day, IV) and CS (2 g/8 h/day, IV). The antibiotic regimen was shifted to carbapenem in cases in which the fever persisted for more than 3-5 days during the initial antibiotic therapy, or if a resistant organism was documented or clinical deterioration was observed. However, on-going antibiotic therapy continued if the fever regressed, clinical improvement was observed despite the persistence of fever, no infectious foci were documented, or neutropenia tended to improve. Antifungal agents were added to the regimen of patients with fever persisting beyond 5-7 days. Treatment was stopped after 5 days without any signs of fever, after the disappearance of any infectious signs in patients whose neutropenia (ANC>500) or overall clinical condition improved. Treatment was administered until the improvement of clinical infection, if present, or the attainment of negative culture results modified by the antimicrobial sensitivity of the specific pathogen in cases of microbiologically documented infections, or after 10-14 days.

Evaluation of the treatment response. The treatment responses were classified as, 'successful treatment', 'successful with modification', and 'unsuccessful'. Successful treatment was defined as a complete improvement in all infectious signs and symptoms at 72 h and after 7-10 days of treatment with the initial antibiotics. Successful with modification treatment was defined as the need for treatment modification due to a recurrence of fever because of a viral, fungal, or parasitic infection not covered by the initial empirical antibiotic, or the addition of a glycopeptide antibiotic to the treatment regimen upon determination of a gram-positive infection. Unsuccessful treatment was defined as the development of a new infection, documented treatment-resistant pathogen, persistence of bacteraemia despite treatment, lack of clinical improvement, deterioration in clinical signs, death due to primary infection, the need to change the antibacterial therapy for another antibiotic with the same spectrum, shift to carbapenems or the addition of another antibiotic with the same spectrum to eradicate the primary infection after at least 72 h of therapy.

Classification of febrile neutropenia episodes. Febrile neutropenia episodes were aetiologically classified into the following three groups: clinically defined infection (CDI), microbiologically determined infection (MDI), and fever of unknown origin (FUO). CDI was defined when the pathogen could not be demonstrated (e.g. pneumonia, perianal infection, etc.); MDI was defined as a blood-culture-positive infection in the absence of any clinical foci, or infection with a microbiologically determined pathogen in a clinical focus with either positive or negative blood culture results; and FUO was defined as an isolated fever without any clinical or laboratory signs of infection.

Statistical analysis. Statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Distribution of data was determined by Kolmogorov-Smirnov test. Continuous variables were expressed as median (minimum-max-

Table 1 **Characteristics of febrile neutropenia episodes treated with two different antibiotic regimens.**

Total number of episodes	Cefoperazone-sulbactam (n=82)	Piperacillin-tazobactam (n=118)	p-value
Age [years, median (range)]	46 (20-69)	48 (20-79)	0.830
Sex [n, (%)]			
Male	45 (54.9)	73 (61.9)	0.323
Female	37 (45.1)	45 (38.1)	
Primary disease [n, (%)]			
AML	59 (72)	75 (63.6)	0.375
ALL	11 (13.4)	19 (14.1)	
Lymphoma	10 (12.2)	17 (14.4)	
MDS	2 (2.4)	4 (3.4)	
MM	0	3 (2.5)	
Remission status [n, (%)]			
In remission	59 (72)	90 (76.3)	0.600
Not in remission	23 (28)	28 (23.7)	
Comorbidity [n, (%)]			
No	36 (43.9)	51 (43.2)	0.924
Yes	46 (56.1)	67 (56.8)	
Comorbidity [n, (%)]			
HT	12 (26.1)	16 (23.9)	
DM	10 (21.7)	17 (25.4)	
Solid tumours	7 (15.2)	11 (16.4)	
Others*	17 (37)[a]	23 (34.3)[b]	
Neutrophil count [cells/mm^3, n, (%)]			
<100	44 (53.7)	61 (51.7)	0.390
100-500	20 (24.4)	22 (18.6)	
>500	18 (22)	35 (29.7)	
Type of infection [n, (%)]			
MDI	33 (40.2)	56 (47.4)	0.232
CDI	24 (29.3)	23 (19.5)	
FUO	25 (30.5)	39 (33.1)	

AML (Acute myeloid leukaemia), ALL (Acute lymphoblastic leukemia), MDS (Myelodysplastic syndrome), MM (Multiple myeloma), HT (Hypertension), DM (Diabetes mellitus), MDI (microbiologically determined infection), CDI (clinically defined infection), FUO (fever of unknown origin).

*** Others: Coronary artery disease, =5[a],7[b]; Chronic lung disease =6[a],5[b]; Thyroid disease =3[a],4[b]; Chronic HBV / HCV infection =2[a], 5[b]; Chronic kidney disease =1[a],2[b]**

imum), categorical variables as frequency and percent. Continuous variables were compared with the Mann-Whitney U test and categorical variables were compared using Pearson's Chi-square test for two groups. P value of less than 0.05 was considered statistically significant for all tests.

RESULTS

A total of 200 febrile neutropenic episodes in 157 patients hospitalised at the Department of Adult Hematology, Kocaeli Medical Faculty Education and Research Hospital, between June 2010 and May 2013, were included in the study.

Treatment with CS was administered to 82 (41%) patients and PIP-TAZO was administered to 118 (59%) study patients. There was no significant difference between the groups in terms of age, gender, malignancy, malignancy stage, neutrophil count, duration of neutropenia, and comorbidities (p >0.05) (table 1).

The aetiology of febrile neutropenia episodes was defined as a fever of unknown origin in 32%, clinically determined

Table 2 **Infections in neutropenic episodes.**

Total number of episodes	Cefoperazone-sulbactam (n=82)	Piperacillin-tazobactam (n=118)
Fever of unknown origin [n, (%)]	25 (30.5)	39 (33.1)
Clinically documented [n, (%)]	24 (29.3)	23 (19.5)
Oral mucositis	7	6
LRTI	6	5
GITI	4	5
Skin soft-tissue infection	3	3
Perianal cellulitis	3	2
CVAD-related cellulitis	1	2
Microbiologically documented [n, (%)]		
All cases	33 (40.2)	56 (47.4)
Bacteraemia	30 (36.5)	52 (44)
GPO, total	10	19
Staphylococcus epidermidis	4	4
Staphylococcus haemolyticus	3	5
Staphylococcus hominis	2	7
Staphylococcus aureus (MRSA)	0	2(0)
Enterococcus faecium	1	1
GNO, total	19	31
Escherichia coli (ESBL)	5 (3)	7(3)
Klebsiella pneumoniae (ESBL)	4(2)	10(6)
Pseudomonas aeruginosa (MDR)	1 (0)	2(0)
Enterobacter cloacae	2	1
Stenotrophomonas maltophilia	1	2
Proteus mirabilis	2	1
Acinetobacter baumannii (MDR)	0	1(0)
Serratia marcescens	1	1
Achromobacter xylosoxidans	0	1
Polymicrobial bacteraemia	3	5
GPO+GNO	3[a]	5[b]
Candidemia		
Candida albicans	1	2
Nonbacteraemic infections	3[c]	4[d]

LRTI= lower respiratory tract infections; GITI= gastrointestinal tract infections; CVAD= central venous access device; GPO= gram-positive organism; GNO= gram-negative organism.
[a]Infections with the following: (1) *E. coli* + *E. faecium*, (2) *E. coli* + *S. epidermidis*, (3) *K. Pneumoniae* + *E. faecium*.
[b]Infections with the following: (1) *E. coli* + *E. faecium*, (2) *E. coli* + *S. epidermidis*, (3) *K. pneumoniae* + *S. epidermidis*, (4) *K. pneumoniae* + *S. epidermidis*, (5), *K. pneumoniae* + *S. haemolyticus*
Nonbacteraemic infections:
[c][(3) perianal cellulitis-abscess: (2) *S. hominis*, (1) *E. coli*.]
[d][(2) perianal cellulitis-abscess: (2) *E. faecium*], [(2) skin soft-tissue infection (2) *S. hominis*]

infections in 23.5%, and microbiologically documented infections in 44.5% of cases. Microbiologically documented infections included bacteraemia and fungaemia in 41% of cases; these consisted of 56% gram-negative bacteria, 41% gram-positive bacteria, and 3% yeast cells (table 2).

Table 3 lists the results of the two treatment regimens. The overall success rate was 61% with CS and 41% with PIP-TAZO. Factors affecting treatment success included: a neutrophil count ?100/mm^3, being in a relapse/refractory stage of malignancy, and the presence of microbiologically documented infection ($p < 0.05$). No treatment-related side effects were observed (table 4).

Adverse events. A cutaneous allergic reaction was observed in 14 and 10 patients in the PIP-TAZO and CS group. In these cases treatment was continued with antihistaminic drugs. Gastrointestinal intolerance was observed in 16 and 17 patients in PIP-TAZO and CS group. Hepatotoxicity and other side effects were not noticed in our patients. There was no significant difference in diarrhoea and hypoprothrombinaemia.

DISCUSSION

Monotherapy is gradually becoming more popular in the treatment of febrile neutropenic patients, despite previous recommendations for the use of broad-spectrum anti-pseudomonal beta-lactam antibiotic and aminoglycoside combinations. Recent studies have demonstrated no differences between the two treatment protocols in terms of clinical results, and combination therapies carry a higher risk of side effects[3]. Empirical treatment regimens should be broad-spectrum, covering both gram-positive and gram-negative microorganisms. Anti-pseudomonal cephalosporins, including cefepime[4] and ceftazidime[5,6]; and carbapenems including imipenem-cilastatin[7-9], meropenem[10,11], beta-lactam/beta-lactamase inhibitor combinations including PIP-TAZO[10,12] and CS[13-17] have been used in monotherapies.

Although PIP-TAZO and CS have been investigated previously, few studies have compared the efficacy of PIP-TAZO and CS monotherapies. In a prospective study of paediatric cancer patients, CS and PIP-TAZO therapies were compared in the empirical treatment of febrile neutropenic cases. Fifty-two patients were recruited for the PIP-TAZO treatment, and 50 patients were recruited in the CS treatment, with resulting treatment success rates of 56% and 62% for CS and PIP-TAZO, respectively ($p > 0.05$)[17].

Others have reported different rates of success

Table 3 **Outcomes of treatments of neutropenic episodes in cancer patients.**

Total number of episodes	Cefoperazone-sulbactam (n=82)	Piperacillin-tazobactam (n=118)	p-value
Duration of neutropenia [(days), n, (%)]			
<7	14 (17.1)	22 (18.6)	0.922
≥7	68 (82.9)	96 (81.4)	
Duration of fever [(days), n, (%)]			
<7	48 (58.5)	83 (70.3)	0.084
≥7	34 (41.5)	35 (29.7)	
The results of treatment [n, (%)]			
Successful	22 (26.8)	27 (22.9)	0.247
Successful with modification	28 (34.1)	31 (26.2)	
Unsuccessful	32 (39.1)	60 (50.8)	
The agents used for modification			
Glycopeptides	9	16	
Antifungals	13	18	
Glycopeptides + antifungals	28	49	
Change in the empirical treatment	32	60	
Death [n, (%)]	12 (14.6)	20 (16.9)	

with different treatment regimens. Ozyilkan et al. (1999) compared a combination of CS and amikacin with imipenem and determined a 60% success rate for both treatments[14]. Bodey et al. (1993) investigated the efficacy of CS therapy in 673 neutropenic and non-neutropenic cancer patients and reported a treatment success rate of 76% with CS[18]. Winston et al. compared CS and imipenem empirical monotherapies in febrile neutropenic patients and reported success rates of CS and imipenem of 88% and 81%, respectively[13]. Bow et al. (2006) compared PIP-TAZO and cefepime and reported rates without modification of 26.8% and 20.5%, respectively[4]. Viscoli et al. (2006) evaluated febrile neutropenic cancer patients and reported a 51% success rate of the PIP-TAZO monotherapy[11]. Success rates of treatment without modification were reported to be 53% and 55% for PIP-TAZO and ceftazidime, respectively, and 77% and 74% after modification with vancomycin by Harter et al. (2006)[5]. The latter was a prospective study and no significant difference was determined between the efficacies of PIP-TAZO and CS in the empirical treatment of febrile neutropenic patients. Although the treatment success rate of CS was higher than that of PIP-TAZO (61% and 49%), this was not a statistically significant finding (p =0.247). These results are in agreement with those in previous studies, but are lower overall compared to the values reported. The lower success rates could be explained by the absolute neutrophil counts <100 mm^3 in 53% of the patients, neutropenia lasting longer than 7 days in 82% of the patients, treatment modification aimed at the specific pathogen in the presence of microbiologically documented infection, and the classification of this modification as a treatment failure.

The microorganisms present in febrile neutropenic patients have changed over the last 20-30 years. Since the mid-1980s, gram-positive microorganisms have been a more common cause of infection[19]. This is probably due to the increased use of central venous catheters (CVC), treatments that have little effective on gram-positive microorganisms in the initial empirical antibiotic regimens, prophylactic use of quinolones, and the use of chemotherapeutic medications that cause severe oral mucositis and diarrhoea[20]. The prevalence rates of gram-positive and gram-negative bacteria were comparable by the end of the 1990s, but there was a further peak in gram-negative infections in 2000, together with an increase in the prevalence of resistant gram-negative bacteria[21]. Gram-negative bacteria are predominant at centres where CVC is not common. Klastersky et al. (2007) reported a rate of bacteraemia of 23% in febrile neutropenic patients, and examination of 499 bacteraemic FN patients revealed gram-positive bacteria in 56%, gram-negative bacteria in 33%, and a polymicrobial aetiology in 9%[22]. Gupta et al. (2010) investigated 347 febrile neutropenic episodes and determined bacteraemia in 92 patients (27%), consisting of gram-negative bacteria in 64% and gram-positive bacteria in 36%[23]. In the study by Paul et al. (2007) of febrile neutropenic patients between 1988-2004, ≥50% of the infections resulted from gram-negative bacteria[24] We determined that bacteraemia and fungaemia were present in 41% (CS %36.5, PIP-TAZO %44) of the patients; Gram-negative bacteria accounted for 48% of cases, gram-positive bacteria for 41%, and yeast for 3%. Compared with data from the literature, the present rates are high. This situation can be explained by majority of the participants in the present study had acute leukaemia and ANC values were <100 mm^3. Blood circulation infections develop mostly in patients with acute leukaemia and underlying haematological malignancy is known to increase the development of bacteraemia. In addition, the state of neutrophil count below 100/mm3 and its duration over days increases the rates of serious infections and bacteraemia. The lower rates of gram-positive bacterial infection could be due to the early use of glycopeptide combinations, reduced use of CVC, the frequent use of beta-lactam antibiotics, and the reproduction of hospital-acquired resistant gram-negative bacteria. The rate of CVC use is lower in the Kocaeli Medical Faculty Education and Research Hospital because of the known complications, poor CVC control, and socio-economic factors; this intervention was maintained only for patients with severe venous route problems. Only 14 patients had a CVC in this study.

Table 4 **Factors affecting the success of treatments in febrile neutropenic episodes.**

	Successful (n=49)	Successful with modification (n=59)	Unsuccessful (n=82)	p-value
Antibiotics				
Cefoperazone-sulbactam	22 (44.9)	28 (47.5)	32 (34.8)	0.247
Piperacillin-tazobactam	27 (55.1)	31 (52.5)	60 (65.2)	
Sex [n, (%)]				
Male	32 (65.3)	32(54.2)	54 (58.7)	0.506
Female	17 (34.7)	27 (45.8)	38 (41.3)	
Primary disease [n, (%)]				
AML	29 (59.2)	41 (69.5)	64 (69.6)	0.248
ALL	6 (12.2)	7 (11.9)	17 (18.5)	
Lymphoma	9 (18.4)	10 (16.9)	8 (8.7)	
MDS	3 (6.1)	1 (1.7)	2 (2.2)	
MM	2 (4.1)	0	1 (1.1)	
Remission status [n, (%)]				
In remission	43 (87.8)	49 (83.1)	57 (62)	0.001
Not in remission	6 (12.2)	10(16.9)	35 (38)	
Neutrophil count [cells/mm^3, n, (%)]				
<100	21 (42.9)	36 (61)	48 (52.2)	0.001
100-500	16 (32.7)	14 (23.7)	12 (13)	
>500	12 (24.5)	9 (15.3)	32 (34.8)	
Duration of neutropenia [(days), n, (%)]				
<7	32(65.3)	51 (86.4)	81 (88)	0.002
≥7	17 (34.7)	8 (13.6)	11 (12)	
Type of infection [n, (%)]				
MDI	11 (22.4)	24 (40.7)	54 (58.7)	0.001
CDI	10 (20.4)	19 (32.2)	18 (19.6)	
FUO	28 (57.1)	16 (27.1)	20 (21.7)	

AML (Acute myeloid leukaemia), ALL (Acute lymphoblastic leukemia), MDS (Myelodysplastic syndrome), MM (Multiple myeloma), MDI (microbiologically determined infection), CDI (clinically defined infection), FUO (fever of unknown origin).

In summary, we concluded that PIP-TAZO and CS monotherapies were equally effective and safe for the empirical treatment of febrile neutropenic patients. There was no difference between CS and PIP-TAZO for the treatment and side effect. But compared with used CS only three time per a day in the treatment, maybe seen to advantaged according to PIP-TAZO.

CONFLICT OF INTEREST

None to declare

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