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Piperacillin–tazobactam Versus Carbapenem Therapy With and Without Amikacin as Empirical Treatment of Febrile Neutropenia in Cancer Patients: Results of an Open Randomized Trial at a University Hospital

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Objective: Empirical beta-lactam monotherapy has become the standard therapy in febrile neutropenia. The aim of this study was to compare the efficacy and safety of piperacillin–tazobactam versus carbapenem therapy with or without amikacin in adult patients with febrile neutropenia.

Methods: In this prospective, open, single-center study, 127 episodes were randomized to receive either piperacillin–tazobactam (4×4.5 g IV/day) or carbapenem [meropenem (3×1 g IV/day) or imipenem (4×500 mg IV/day)] with or without amikacin (1 g IV/day). Doses were adjusted according to renal function. Clinical response was determined during and at completion of therapy.

Results: One hundred and twenty episodes were assessable for efficacy (59 piperacillin–tazobactam, 61 carbapenem). Mean duration of treatment was 14.8 ± 9.6 days in the piperacillin–tazobactam group and 14.7 ± 8.8 days in the carbapenem group ($P > 0.05$). Mean days of fever resolution were 5.97 and 4.48 days for piperacillin–tazobactam and carbapenem groups, respectively ($P > 0.05$). Similar rates of success without modification were found in the piperacillin–tazobactam (87.9%) and in the carbapenem groups (75.4%; $P > 0.05$). Fungal infection occurrence rates were 30.5 and 18% in piperacillin–tazobactam and carbapenem groups, respectively ($P = 0.05$). Antibiotic modification rates were 30.5 and 13.1% ($P = 0.02$) and the addition of glycopeptides to empirical antibiotic regimens rates were 15.3 and 44.3% for piperacillin–tazobactam and carbapenem groups, respectively ($P = 0.001$). The rude mortality rates were 14% (6/43) and 29.3% (12/41) in piperacillin–tazobactam and carbapenem groups, respectively ($P = 0.08$).

Conclusions: The effect of empirical regimen of piperacillin–tazobactam regimen is equivalent to carbapenem in adult febrile neutropenic patients.

Key words: febrile neutropenia – granulocytopenia – empirical therapy – piperacillin/tazobactam – carbapenem – mortality

INTRODUCTION

Febrile neutropenia continues to represent a major cause of morbidity, mortality and cost in patients receiving cancer chemotherapy. The risk of febrile neutropenia increases in direct relationship with the duration and severity of neutropenia (1). Infections are the important causes of morbidity and mortality in febrile neutropenic (FN) patients, especially in patients with severe and prolonged neutropenia following

intensive chemotherapy for malignancies (2). Fever is the major sign of infection in neutropenic patient and commonly may be the only evidence of infection (3).

Since early institution of broad-spectrum antibiotic treatment reduces mortality in FN patients, empirical antibiotic therapy remains the basis of treatment for these patients (4–7). The guidelines and authors recommend cefepime, ceftazidime, carbapenem (C) monotherapy or dual therapy with an antipseudomonal β-lactam in combination with an aminoglycoside as the empirical antimicrobial therapy in FN patients (4,8,9).

Piperacillin is a broad-spectrum ureido-penicillin and tazobactam is a beta-lactamase inhibitor, active against many Gram-positive pathogens, and most Gram-negative pathogens, including *Pseudomonas aeruginosa* and anaerobic pathogens (10). Imipenem and meropenem are effective for most of the bacteria responsible for infections in neutropenic patients. They are the most common antimicrobials used as monotherapy in these patients (11,12). They have excellent microbiological activity against both Gram-negative and Gram-positive bacteria and are the treatment of choice for extended spectrum beta-lactamase (ESBL) producing Gram-negative bacterial infections (13).

Studies on the effectiveness of piperacillin–tazobactam (PT) or C monotherapy for empirical treatment of FN episodes from USA and European countries are mainly reported, whereas studies from around the world is missing (5,10,14–17). In this prospective, randomized trial, we aimed to evaluate the efficacy of PT therapy compared with C therapy with or without amikacin for the empirical treatment of Eurasian FN patients.

PATIENTS AND METHODS

Study Design and Criteria for Eligibility

This open, comparative, prospective, randomized, single-center study was conducted between July 2006 and January 2009 in Zonguldak Karaelmas University Teaching and Research Hospital (ZKUTRH), a 350-bed tertiary care center. Patients over 16 years of age who received chemotherapy for hematological malignancies or solid tumors were enrolled in order to evaluate the efficacy of PT or C therapy with or without amikacin in the empirical treatment of FN patients. Local ethical committee approvals were received for the study. Patients were evaluated during the therapy period and at completion of therapy. Patients were classified for staging of primary disease either in remission or non-remission.

Patients were included in the study, if they had fever attributable to neutropenia and presumed infection. In our study the sample size was taken as the episode number and the duration of fever was accepted as the primer variable for the sample size determination. We hypothesized that 3 days difference in the duration of fever in each treatment arm would be clinically significant. According to the power analysis result in order to achieve 5% type I error probability and 80% prior power, sample size should be at least 45 episodes in each arm. However, for better subgroup analysis we increased the sample size since there were no ethical and economical problems in the study period regarding this issue. As a result we evaluated 120 episodes (59 in the PT group and 61 in the C group) in this study.

The eligibility criteria were: (i) diagnosis of hematological malignancies or solid tumors, (ii) age $\geq$16 years, (iii) presence of neutropenia [which was defined as an absolute neutrophil count (ANC) $<$500 cells/mm^3 or if count $<$1000 cells/mm^3 expected to fall $<$500 cells/mm^3 within 24–48 h because of preceding chemotherapy], (iv) having an axillary temperature $\geq$38°C on two occasions at least 1 h apart or $\geq$38.5°C on one occasion in 24 h in the absence of any other obvious cause of fever, (v) not receiving any antimicrobial therapy within 1 week prior to admission and (vi) having no known allergy or other incompatibility to one of the study drugs. Only patients with presumed infectious causes of fever were included in the trial.

Exclusion criteria included the following: (i) presence of fever attributable to malignancy or transfused blood products or other medications, (ii) the administration of any systemic antibiotics within 1 week prior to enrollment, (iii) having a history of hypersensitivity reaction to PT or C regimen, (iv) hepatic or renal insufficiency, (v) protocol violation (non-adherence to protocol, early discontinuation secondary to severe adverse effects) and (vi) pregnant or lactating women.

Randomization and Antibiotic Treatments

Patients were randomly assigned to one of the treatment arms according to a computer-generated random-number program. Patients could be randomized more than once if they had completed the previous treatment cycle at least 1 week ago.

Patients received either IV PT (4 g/500 mg every 6 h) or IV C [meropenem (1 g every 8 h) or imipenem (500 mg every 6 h)]. The risk evaluation of patients was performed according to the criteria of 'The Multinational Association for Supportive Care in Cancer (MASCC)' (18). High-risk group was defined as MASSC risk index $\leq$20, low-risk group as MASCC risk index $\geq$21. If a patient was in high-risk group, we added amikacin (1 g/day) to the treatment groups. Doses were adjusted according to renal function. Glycopeptide antibiotics (vancomycin or teicoplanin) were added if indicated; such as mucositis, suspicious catheter related bloodstream infection or isolation of resistant Gram-positive microorganisms in cultures of blood, urine and other body fluids.

Antibiotic therapy was continued for a minimum of 7 days or at least 5 days beyond their last day of fever. Therefore antibiotic therapy could be stopped only after fever had subsided and a neutrophil count of $\geq$500/mm^3 was attained and/or after eradication of microbiological and/or clinical infection.

Clinical and Laboratory Evaluation

Before the start of antibiotic therapy, a complete medical history and physical examination were performed. Complete blood cell and differential counts, routine biochemistry, at least two sets of blood cultures (from two different peripheral veins and all lumens of central venous catheter), urine and sputum or tracheal aspirate cultures and a chest X-ray were obtained before starting antibiotic treatment. One set of blood culture consisted two bottles with 10 ml of blood added to each. Cultures of other sites of infection were performed as clinically indicated. Cultures were repeated during therapy if fever persisted or to isolate the causative pathogen or to document the eradication of the isolated pathogen. During febrile episode chest X-ray and computerized tomography or abdominal ultrasonography were obtained. Patients were monitored daily for clinical signs and symptoms and adverse events during antibiotic therapy. Complete blood cell counts, coagulation and biochemistry parameters and urine analysis were performed at least once a week.

Bacteriological isolates were identified by standard techniques and susceptibility tests were determined by disk diffusion method according to the recommendations of the Clinical Laboratory Standards Institute. All causative pathogens were tested for their susceptibility to the study drugs. PT resistance was defined for all microorganisms as a zone diameter $\leq$17 mm, according to diffusion susceptibility testing and as minimal inhibitor concentration (MIC) $\geq$128 mg/ml for Gram-negative microorganisms and MIC $\geq$16 mg/ml for staphylococci, according to MIC testing.

Classification of Febrile Episodes

Microbiologically documented infection (MDI) was defined as the isolation of 10^3 cfu/ml microorganisms. Bacteremia, a kind of MDI, was defined as the isolation of bacterial pathogen from blood. Clinically documented infection (CDI) was considered when there was a focus of infection on physical examination, without microbiological documentation. Fever of unknown origin (FUO) was considered when there was no clinical or microbiological evidence of infection in a febrile episode.

Evaluation of Response

Response was assessed during therapy and at completion of therapy. Response was categorized as 'a success' if all of the following criteria were found: patient's being a febrile ($<38^{\circ}$C) for at least five consecutive days, clearance of signs and symptoms of infection, eradication of the previously isolated infectious microorganism, no recurrence of primary infection within 1 week after discontinuation of treatment. Therapy modification was defined as all changes made to the initial empirical antibiotic therapy after the first 72–96 h.

Duration of fever, neutropenia and hospitalization, mortality rate, the need to modify initial empirical antibiotic therapy, the need to add antifungal therapy were compared between the two treatment arms.

Treatment Modification

Initial empirical therapy was modified according to susceptibility testing results in patients with a MDI. CDI was treated as appropriate. If the patient still had fever beyond the first 72–96 h of empirical therapy and the initial treatment did not include amikacin, it was added. Otherwise the antibiotic used in the initial empirical regimen was substituted with another antipseudomonal agent. Antifungal therapy (conventional amphotericine-B at a dose of 0.5 mg/kg/day) was started due to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) criteria (19). It is also started if the patient was still febrile on the fourth to sixth day of antibiotic therapy despite treatment modification.

Treatment Failure

Occurrence of one of the following events was considered as treatment failure: infection-related death, persistence of bacteremia or documented breakthrough bacteremia, fever still persisting after 72–96 h prompting modification of the initial therapy.

Statistical Analysis

Objective of this study was to compare the clinical success rates of the study-drug regimens. All analyses were performed using SPSS version 11.0 (Chicago, IL, USA). The significance of difference between groups was evaluated by χ^2 test with correction done when appropriate and using *t*-test as indicated. The significance level was accepted as $P < 0.05$, but multiple logistic regression analysis was used for determination of risk factors of mortality and in this analysis the significance level was accepted as $P < 0.10$. The study is not supported by the drug companies.

RESULTS

Characteristics of the Study Population

A total of 127 febrile neutropenia episodes of 84 adult patients were randomized between July 2006 and January 2009 in ZKUTRH. Seven episodes were excluded because of protocol violation. Response to therapy was evaluated in 120 episodes (59 in the PT group, 61 in the C group). The use of amikacin in each group was similar (8 in PT group, 11 in C group). Table 1 shows the most of the clinical characteristics of the patients were similar in two treatment group. Overall, 70% of the patients had hematological malignancy and 30% had solid tumors in both study groups ($P = 0.31$). About 17.5% of the patients had diabetes. The

Table 1. Characteristics of the piperacillin–tazobactam (PT) and carbapenem (C) groups

	Piperacillin–tazobactam	Carbapenem	*P* value
Number of episodes	59	61	–
Patients (*n*)	43	41	
Mean age, years (SD)	52.20 (15.31)	50.15 (15.95)	0.473
Sex, girls, *n* (%)	25 (58.1)	21 (51.2)	0.524
Mean duration of hospitalization, day (SD)	27.27 (22.4)	29.84 (23.2)	0.539
Mean duration of hospitalization before FEN, day (SD)	8.69 (14.9)	6.64 (10,1)	0.377
Underlying disease (%)			
Acute myelogenous leukemia	25 (42.4)	26 (42.6)	0.978
Acute lymphoblastic leukemia	4 (6.8)	8 (13.1)	0.243
Lymphoma	8 (13.6)	8 (13.1)	0.943
Multiple myeloma	2 (3.4)	1 (1.6)	0.536
Solid tumors	20 (33.8)	17 (27.8)	0.474
MDS	0	1 (1.6)	0.243
Antibiotic usage in last one month, *n* (%)	8 (13.6)	28 (45.9)	<0.0001
Hospitalization in last one month, *n* (%)	22 (37.3)	31 (50.8)	0.135
Chemotherapy in last one month, *n* (%)	46 (78.0)	45 (73.8)	0.591
Stage, *n* (%)			
Remission	2 (3.4)	6 (9.8)	0.148
Non-remission	57 (96.6)	55 (90.2)	
Classification of episodes, *n* (%)			
MDI, *n* (%)	15 (25.4)	18 (29.5)	0.063
CDI, *n* (%)	12 (20.3)	22 (36.1)	
FUO, *n* (%)	32 (54.2)	21 (34.4)	
Mucositis, *n* (%)	15 (26)	35 (57.5)	<0.0001
Central venous catheter	15 (25.5)	20 (32.5)	0.374
ANC $<100/mm^3$ at onset, *n* (%)	40 (67.7)	48 (78.6)	0.177

ANC, absolute neutrophil count; MDS, myelodysplastic syndrome; MDI, microbiologically documented infection; CDI, clinically documented infection; FUO, fever of unknown origin.

number of patients with chronic renal failure and/or chronic cardiac failure and/or chronic obstructive lung disease was similar in both groups ($P = 0.12$). There were mucositis in 42% of the patients.

The median age of the patients was 52.79 (range: 17–83). The mean MASCC risk index was 22.15 (range: 11–26). In the C group the MASCC risk indexes were lower than the patients in the PT group ($P = 0.02$). About 73.3% of the patients included in the study were severely neutropenic (ANC $< 100/mm^3$) patients ($P = 0.26$) and the duration of neutropenia was longer than 21 days in 27.5% of the patients ($P = 0.24$).

In the C group more patients were treated with antibiotics during the last month prior to the therapy ($P = 0.0001$) and there were more high-risk group patients (MASCC risk index ≤ 20; $P = 0.018$). But previous chemotherapy receiving rates and hospitalization rates during the last month prior to the therapy were similar for each group ($P = 0.51$). Also central venous catheter usage rates were similar for each group ($P = 0.32$). Mechanical ventilation and total parenteral nutrition (TPN) were needed for 6.7 and 2.5% of patients, respectively ($P = 0.07$).

Type of Infection and Distribution of Microorganisms

There were 53 (42.2%) FUO, 34 (28,3%) CDI and 33 (27.5%) MDI episodes. There was no statistically significant difference between the two treatment groups in terms of infection type ($P = 0.52$). But in the C group there were more patients with evident infection site on admission ($P = 0.03$). Causative microorganisms were isolated from 40 episodes; 29 from blood, 7 from urine, 2 from catheter and 2 from sputum. Most common blood isolates were *Escherichia coli* and *P. aeruginosa* (Table 2). Four *E. coli* (two of them were ESBL-producing), one *Enterococcus faecalis* (penicillin sensitive), one *Klebsiella pneumoniae* were isolated from urine cultures. There were one methicillin resistant *Staphylococcus epidermidis* (MRSE) and one methicillin sensitive *Staphylococcus aureus* (MSSA) in central venous catheter cultures; one *Stenotrophomonas maltophilia* and one *Pneumococcus pneumoniae* isolates in sputum cultures.

Gram-negative bacilli (*E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp.) were isolated from 18 patients (9 with acute leukemia, 8 with solid tumors and 1 with non-hodgkin lymphoma). Gram-positive microorganisms (*S. aureus*, *S. epidermidis*) were isolated from 11 patients (6 with acute leukemia, 3 with solid tumors, 1 with chronic lymphoblastic leukemia and 1 with non-hodgkin lymphoma).

Oropharyngeal herpes virus infection occurred in 11 episodes (9.2%); 5 in the PT group, 6 in the C group ($P = 0.53$). Fungal infections occurred in 29 episodes (24.2%). There were 23 fungal lower respiratory tract infections, three oropharyngeal candidiasis, one fungal arthritis, one candidial esophagitis and one vaginal candidiasis. Fungal infection occurrence rate in the PT and C groups were 30.5 and 18%, respectively.

Clinical Response and Following Antibiotic Modification

The clinical outcomes of the patients in two treatment arms are shown in Table 3. Mean duration of treatment was 14.8 ± 9.6 days in the PT group and 14.7 ± 8.8 days in the C group ($P = 0.12$). Mean duration of fever resolution was 5.97 and 4.48 days for the patients in the PT and C groups, respectively ($P = 0.23$). Febrile episodes were classified as FUO in 53 episodes (32 in the PT and 21 in the C group). No significant differences in success rates due to different types of infections were observed between treatment groups.

Table 2. Susceptibility of blood isolates in study groups

Microorganism	Number of isolates, sensitive/tested			
	Piperacillin–tazobactam	Carbapenem	Amikacin	Glycopeptide
Staphylococcus aureus	3/3	3/3	–	3/3
Staphylococcus epidermidis	4/8	4/8	–	8/8
Escherichia coli	7/7	7/7	7/7	–
Klebsiella pneumoniae	3/5	5/5	5/5	–
Pseudomonas aeruginosa	5/6	4/6	6/6	–
Acinetobacter	0/2	0/2	1/2	–

Table 3. Clinical outcomes of the patients of PT and C groups

	Piperacillin–tazobactam ($n = 59$)	Carbapenem ($n = 61$)	*P* value
Persistent response to therapy, *n* (%)	51 (86.4)	46 (75.4)	0.07
Duration of fever, mean days (SD)	5.97 ($\pm$6.8)	4.48 ($\pm$6.7)	0.23
Duration of neutropenia, mean days			
1–7 days, *n* (%)	31 (52.5)	29 (47.5)	0.34
8–20 days, *n* (%)	13 (22.1)	14 (22.9)	
21 days and more, *n* (%)	15 (25.4)	18 (29.5)	
Duration of hospitalization, mean days (SD)	27.3 ($\pm$22.4)	29.8 ($\pm$23.2)	0.60
Duration of therapy, mean days (SD)	14.8 ($\pm$9.6)	14.7 ($\pm$8.8)	0.12
Number of episodes with modification, *n* (%)			
Change in the empirical treatment	12 (30.5)	8 (13.1)	0.02
Only glycopeptide	9 (15.3)	27 (44.3)	0.001
Only antifungal	2 (3.4)	1 (1.6)	0.53
Both glycopeptide and antifungal	18 (30.5)	12 (19.7)	0.17
Mortality, *n* (%)	6 (10.2)	12 (19.7)	0.14

Success rates for the PT and C groups without any treatment modifications were 87.9 and 75.4%, respectively ($P = 0.06$). Therapeutic failure was observed in 22 episodes (%18.3). The overall response rate with or without modification of the assigned treatment was 80.1% occurring in 97 episodes.

Treatment modification was necessary in 30.5 and 13.1% of the episodes in the PT and C groups, respectively ($P = 0.02$). Glycopeptide antibiotic addition to the empirical antibiotic regimen was needed in 15.3 and 44.3% of the episodes in the PT and C groups, respectively ($P = 0.001$). Eleven patient (18%) in the C group and 18 patients (30.5%) in the PT group received antifungal therapy ($P = 0.53$). Empirical therapy in the PT group needed to be changed more frequently, but the need for glycopeptide addition to the empirical therapy was higher in the C group. In 25% of the patients both glycopeptides and antifungal therapy addition was required ($P = 0.17$).

Adverse Events

A cutaneous allergic reaction was observed in two patients in the PT group. In these cases treatment was continued with antihistaminic drugs. Gastrointestinal intolerance was observed in two patients in C group. Seizure was observed in one patient in C group. Hepatotoxicity and other side effects were not noticed in our patients.

Mortality

The overall mortality rate was 21.42% (18/84). Mortality rates in the PT and C groups were 14 and 29.3%, respectively ($P = 0.08$). Nine patients died within the first week of therapy (one in the PT and eight in the C group), five additional patients died on the 30th day of therapy (two in the PT and three in the C group) and four additional patients died after the 30th day (three PT and one C). Mortality rate within the first week of therapy was higher in the C group ($P = 0.05$). The median age and mean MASCC risk index of the patients who died within the first month of therapy were 56.9 and 20, respectively. The median age and median MASCC risk index of the patients who died after the first month of therapy were 53.25 and 23, respectively.

Rude mortality rates of patients with a low MASCC risk index ($\leq$20) were higher ($P = 0.04$). Rude mortality rates increased with the presence of severe neutropenia (ANC $<$ 100/mm^3; $P = 0.028$). Higher mortality rates were observed among patients for whom invasive methods such as mechanical ventilation or TPN were needed ($P = 0.0001$). Mortality rates also increased as the duration of neutropenia got longer ($P = 0.03$), therapy modification such as addition of glycopeptides or antifungals were needed ($P = 0.007$) and if there was no persistent response to the empirical therapy ($P = 0.0001$). The multivariate analysis of mortality risk factors are shown in Table 4.

DISCUSSION

The standard therapy of FN patients has changed over the past 40 years in response to the emergence of new pathogens, recognition of different types of neutropenic patients. The empirical antibiotic approach to managing febrile episodes in these patients continues to evolve. A recent meta-analysis of 29 randomized clinical trials pooling data from 4795 febrile episodes were set out to compare the efficacy of antibiotic monotherapy with that of combinations

Table 4. Multivariate analysis of mortality risk factors

Risk factor	Odds ratio	95% CI	*P*
No persistent response to therapy	0.047	0.005–0.444	0.008
Low MASCC risk index	0.827	0.68–1	0.05
Carbapenem therapy	0.143	0.017–1.22	0.05

including an aminoglycoside for empirical treatment of febrile neutropenia (20). The results of this analysis evidenced that monotherapy can be considered as effective as aminoglycoside-containing combinations.

Our study showed that PT or C (imipenem or meropenem), with and without combination of amikacin, were equally effective for the initial empirical management of FN cancer patients. And the response rates of both treatment arms were similar to the reported response rates (4,5,10,14,16,17,21–27). However, Sanz et al. (15) reported that the response rates were low both in the PT and C groups (31 and 42%, respectively).

Paul et al. (4) reported that an advantage for C was observed with regard to treatment failure, any antibiotic modification and glycopeptide addition and addition of antifungals was more common with C. However, in our study, empirical therapy in the PT group needed to be changed more frequently ($P = 0.02$) and the need for glycopeptide addition to the empirical therapy was higher in the C group ($P = 0.001$). Fungal infections mostly occurred in PT group ($P = 0.05$).

The rude mortality rate was higher the C group in our study ($P = 0.08$). However, significant advantage was observed with regard to infection-related mortality, microbiological failure and super infections (4).

The most common isolated pathogen in MDIs was *S. epidermidis*, causing bacteremia. In contrast Hamidah et al. (10) reported that predominantly Gram-negative organisms were isolated in neutropenic cancer patients.

Sharma et al. (3) reported that patients with acute leukemia have increased risk of Gram-negative bacterial infections as a result of quantitative or functional neutropenia. Similarly in our study Gram-negative bacilli such as *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* were most commonly isolated from acute leukemia patients. However, low rates of resistance to PT and Cs were detected during the period that our study was conducted. The majority of resistant bacteria in our study were *Acinetobacter baumanii* and *P. aeruginosa*. Because bacteria can rapidly mutate, institutions should continually monitor for changing patterns of resistance and adjust empirical antibiotic regimens as needed.

The analysis of safety data from our study revealed that both the PT and C with or without amikacin combinations were well tolerated. In two patients cutaneous allergic reaction was observed in PT group as a drug related adverse event. Gastrointestinal intolerance was observed in two patients and seizure was observed in one patient in C group. It is reported that C was associated with significantly more frequent pseudomembranous colitis (4). However, hepatotoxicity and other side effects were not noticed in our patients. The limitation of this study was that we enrolled small number of patients.

In conclusion, PT is as effective as C therapy for the empirical treatment of febrile neutropenia in hematological malignancies. In both treatment arms toxicity was low and did not limit antibiotic therapy.

Conflict of interest statement

None declared.

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