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Cost-Effectiveness of Cefepime + Netilmicin or Ceftazidime + Amikacin or Meropenem Monotherapy in Febrile Neutropenic Children with Malignancy in Turkey

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Summary

Infection remains the major cause of morbidity and mortality in immunocompromised children with malignancy. In addition, the economic impact of antibiotic treatment should always be evaluated, especially in developing countries. In our center between January 1998 and January 1999, 73 children with hematological malignancies [acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML)]; 9 children with solid tumors (rhabdomyosarcoma, neuroblastoma) had 87 febrile neutropenic episodes (related to chemotherapy). These children were randomized prospectively into three treatment groups. The first group (n: 28) received cefepime plus netilmicin, while the second group (n: 29) was treated with ceftazidime plus amikacin and the third (n: 30) with meropenem as monotherapy. The aim of the study was to compare the success rates and cost of fourth generation cephalosporin plus aminoglycoside and monotherapy of meropenem with ceftazidime plus amikacin, which is the standard therapy for febrile neutropenia. Microbiologically documented infections were 29.9%, clinically documented infections were 9.2% and 60.9% of the febrile neutropenic episodes were considered to be FUO. Gram-positive microorganisms were the most commonly isolated agents from blood cultures [*MRSA* (*Methicillin Resistant Staphylococcus aureus*) in 6 patients and *MSSA* (*Methicillin Sensitive Staphylococcus aureus*) in 4 patients]. The success rates were 78.5%, 79.3% and 73.3 % for the 1st, 2nd and 3rd groups respectively. In 4 patients (4.5%) fever responded only to amphotericin-B therapy. There was no statistically significant difference between the three treatment regimens with respect to efficacy, safety and tolerance (χ^2 test, $p>0.05$),

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but while the third and fourth generation cephalosporins + aminoglycosides were comparable for cost, the monotherapy regimen was the most expensive. The main determining factors for the choice of treatment of febrile neutropenic children, especially in a developing country, are cost, presence of indwelling catheter and the bacterial flora of the unit, as well as efficacy.

Key words: **Febrile neutropenia, cefepime, netilmicin, ceftazidime, amikacin, meropenem, neutropenia, pharmacoeconomics.**

INTRODUCTION

Cancer patients who are treated with intensive myelosuppressive chemotherapy are at high risk of developing life threatening infections as a result of granulocytopenia [1]. If empiric antibiotic treatment is not instituted at the first sign of infection, infections in the neutropenic patient may be lethal. For the past 20 years, combinations of beta- lactams and aminoglycosides have been the standard therapy for febrile neutropenia, especially in those with profound, long-lasting granulocytopenia. The reason for the use of aminoglycoside-containing combinations was the possibility of synergistic bactericidal efficacy, which has been reported to improve the outcome in neutropenic patients with Gram-negative bacteremia [2].

The new broad-spectrum bactericidal antibiotics, such as broad-spectrum cephalosporins or carbapenems offer the advantage of single-agent therapy. Moreover, over the last 10 years there has been a shift in the type of microorganisms recovered from the blood of neutropenic patients with a reduction in Gram-negative bacteria, including *Pseudomonas aeruginosa*, and a significant increase in Gram-positive isolates [3]. Therefore, the need for the aminoglycoside-containing combination must be reassessed in view of this microbiological change. With excellent microbiological activity against both Gram-negative bacteria including *P. aeruginosa* and Gram-positive bacteria, with the exception of enterococci and methicillin resistant *Staphylococcus aureus* (MRSA), carbapenems are very good alternatives to broad-spectrum cephalosporins as empiric treatment of febrile neutropenia. Imipenem/cilastatin, the first available carbapenem, has been used in several studies, although its major complication at high doses is gastrointestinal toxicity [4]. Meropenem, a new carbapenem, is reported to be well tolerated and as effective as ceftazidime for empiric treatment of febrile neutropenic patients [5]. Cefepime is a broad-spectrum cephalosporin with good activity against Enterobacteriaceae, good antipseudomonal activity and Gram-positive bacteria with the exception of MRSA [6].

The present study was a prospective, randomized trial to test meropenem monotherapy and a fourth generation cephalosporin + aminoglycoside combination in comparison with ceftazidime + amikacin which is the standard combination for febrile neutropenia. The objectives of the present trial were to evaluate and compare the safety, tolerance, efficacy and cost of these treatment alternatives.

PATIENTS AND METHODS

Between January 1998 - January 1999, 87 febrile neutropenia episodes in 82 patients with hematological malignancies (48 acute lymphoblastic leukemia, ALL; 26 acute myeloid leukemia, AML) and in 13 patients with solid tumors (1 rhabdomyosarcoma, and 12 neuroblastoma) treated with intensive chemotherapy at the Department of Pediatric Hematology-Oncology and Our Children Leukemia Foundation Medical Center, were included in the trial. Median age was 7 years (range: 9 months-18 years) and M:F ratio was 1:8. Patients were eligible for randomization if they had fever (axillary $\geq$38.5°C on one occasion or >38°C on two occasions within 12 h), neutropenia (ANC $<1x10^9$/L) and a presumed infection (i.e. fever not likely to be due to a non-infectious cause such as drug or blood product transfusion).

Patients were excluded from the trial if they had received any intravenous antibiotic during

the neutropenic episode or during the preceding 96 h, had a known allergy to any of the protocol antibiotics and had renal or hepatic failure. All patients were on prophylactic treatment with ketoconazole (5 mg/kg/d) and trimethoprim-sulfamethoxazole (5 mg/kg/d, 3 days in a week).

Clinical and laboratory evaluation

When fever occurred in a neutropenic patient, a thorough history and physical examination was performed with special attention to the skin, venipuncture sites, intravenous catheters, oropharynx, sinus, lungs, abdomen and perianal region. Blood, urine and throat cultures were obtained immediately. Blood cultures were drawn both from a peripheral vein and from the catheter simultaneously. When necessary, lesion, stool and sputum cultures were also done. Empiric antibiotics were started according to randomization when these procedures were completed. Follow-up studies included repeated hematological analysis and biochemistry. Blood cultures were repeatedly taken daily for persistent fever or bacteremia until the cultures were negative.

Randomization procedure

Patients were randomized into three study groups: the first group (n: 28) was treated with cefepime (100 mg/kg/d i.v. in 3 doses) plus netilmicin (5 mg/kg/d i.v. in 2-3 doses), the second group (n: 29) with ceftazidime (100 mg/kg/d i.v. in 3 doses) plus amikacin (15 mg/kg/d i.v. in 2 doses), and the third group (n: 30) with meropenem alone (60 mg/kg/d i.v. in 3 doses).

Classification of febrile episodes and evaluation of response

Febrile episodes were classified as:

* Microbiologically documented infections with or without bacteremia
* Clinically documented infections
* Fever of unknown origin (FUO)

After the initiation of empiric therapy, patients were evaluated at 48-72 h (early evaluation) and at the completion of the treatment (overall evaluation). The response was evaluated as a success if fever and clinical signs of infection (whenever present) resolved and the infecting organisms (whenever isolated) were eradicated without change of the antibacterial therapy. Normalization of temperature had to be maintained for at least 5 consecutive days for qualification of treatment success. The response was evaluated as a failure if:

* The patient died of the primary infection
* Bacteremia persisted beyond the first 24 h of therapy
* The documented pathogen was resistant to the antibiotic regimen, regardless of the patient's clinical condition.
* No response was obtained after at least 48 h of empiric therapy, which usually prompted modification or addition of a glycopeptide to the protocol.

Early modification was allowed to occur before 48 h, and the results were considered as failure if shock, acute respiratory distress syndrome, disseminated intravascular coagulation or multiple organ failure developed, or with progression of the clinically documented infection and persistence of fever 48 h or more after initiation of empiric therapy and after the microbiological documentation of the primary infection as viral, fungal or mixed (bacterial plus viral or fungal).

If no response was seen after 96 h of empiric antibiotic treatment, antifungal therapy was initiated. In patients with microbiologically documented infection, if a pathogen was resistant to the antibiotic used, treatment was modified according to antibiotic susceptibility.

Data were analyzed using the chi-square method.

RESULTS

At randomization, there were no significant differences among the three treatment groups for any characteristics of the patients evaluated for response to therapy (*Table 1*). Groups were well balanced for stratification of underlying diseases, with leukemia being the most frequent diagnosis in all groups (85.7% in the first group, 89.6% in the second group, 80% in the third group).

Only 26.4% of febrile patients had positive

blood cultures, and 2.3% positive urine culture. In 26/87 (29.8%) of febrile neutropenia episodes, a pathogenic microorganism was isolated, with Gram-positive microorganisms being the most commonly (65.38%) isolated (*Table 2*) (11, (12.6%) MRSA, 5 (5.7%) MSSA and 1 (1.1%) alpha-hemolytic streptoccocus. Microbiologically documented infection was present in 10/28 (35.7%), 10/29 (34.4%) and 6/30 (20%) patients in the 1st, 2nd and 3rd groups respectively (*Table 3*).

There were 8 (9.19%) clinically documented infections in 1/28 (3.5%) patients in the 1st group, 4/29 (13.7%) in the 2nd group and 3/30 (10%) in the 3rd group. FUO was present in 17 (60.7%), 15 (51.7%), 21 (70%) patients in the 1st, 2nd and 3rd groups respectively. The success rates were 78.5%, 79.3% and 73.3 % for the 1st, 2nd and 3rd groups respectively. A comparison of antibiotic regimens with respect to leukocyte count was not possible because the patients in the groups were not similar. Empirically a glycopeptide was added to 21.25% of all randomized patients with persistent fever. In terms of success there was no difference among these three groups (p>0.05). In 4 patients (4.5%) fever responded only to amphotericin-B therapy.

TABLE 1 - *Characteristics of patients.*

	Cefepime + Netilmicin 1st group		**Ceftazidime + Amikacin 2nd group**		**Meropenem 3rd group**		**TOTAL**	
	n.	**(%)**	**n.**	**(%)**	**n.**	**(%)**	**n.**	**(%)**
Patients (n.)	27		28		27		82	
Febrile episode	28		29		30		87	
ALL	13	(46.4)	16	(55.1)	19	(63.3)	48	(55.2)
AML	11	(39.3)	10	(34.5)	5	(16.7)	26	(29.9)
Solid tumor	4	(14.3)	3	(10.4)	6	(20)	12	(14.9)
Median age (years)	9		7		6		7	
ANC(mm^3)/febrile episode								
<100	6	(21.4)	2	(6.9)	2	(6.7)	10	(11.5)
100-500	5	(17.9)	8	(27.6)	15	(50)	28	(32.2)
501-1000	17	(60.7)	19	(65.5)	13	(43.3)	49	(56.3)

TABLE 2 - *Organisms responsible for febrile neutropenic episodes.*

Microorganism	**1st group n. 28 (%)**		**2nd group n.29 (%)**			**3rd group n.30 (%)**	
	blood	**urine**	**blood**	**urine**	**throat**	**blood**	**urine**
MRSA	6 (21.4)	–	2 (6.8)	–	–	3 (10)	–
MSSA	1 (3.5)	–	4 (13.8)	–	–	–	–
alpha-hemolytic *Streptococcus* spp	–	–	–	–	–	1 (3.3)	–
Klebsiella spp.	1 (3.5)	–	–	–	–	–	–
Enterobacter spp.	–	–	–	–	–	2 (6.6)	–
Escherichia coli	1 (3.5)	–	–	1 (3.4)	–	–	–
P. aeruginosa	1 (3.5)	–	1 (3.4)	1 (3.4)	1 (3.4)	–	–
TOTAL	10 (35.7)	–	7 (24.1)	2 (6.8)	1 (3.4)	6 (20)	–

TABLE 3 - *Success rates according to the different empiric antibiotic treatment regimens.*

	1st group n.28	(%)	2nd group n.29	(%)	3rd group n.30	(%)
Microbiologically documented infection	10	(35.7)	10	(34.5)	6	(20)
Clinically documented infection	1	(3.6)	4	(13.8)	3	(10)
FUO	17	(60.7)	15	(51.7)	21	(70)
Success rate	22	(78.5)	23	(79.3)	22	(73.3)
Amphotericin B response	2	(7.1)	1	(3.4)	1	(3.3)

Adverse effects

In the meropenem arm, 3 patients had vomiting but no seizures. No adverse or allergic reactions were observed in the other treatment groups.

Cost

The daily costs of cefepime + netilmicin, ceftazidime + amikacin and meropenem for a 30 kg patient were $53.8, $46.2 and $121.4 respectively (*Table 4*).

TABLE 4 - *Costs associated with three different antibiotic regimens (US $ / 30 kg patient / day).*

Cefepime + Netilmicin	$53.8
Ceftazidime + Amikacin	$46.2
Meropenem	$121.4

DISCUSSION

Infection is a major cause of morbidity and mortality in neutropenic patients. When neutropenia is prolonged, the risk for febrile episodes increases. Only 20-30% of neutropenic febrile patients have positive blood cultures [1,7] and our rate is in agreement with 25.2% in this study. Early studies reported that infections during the neutropenic period were most likely to be caused by aerobic Gram-negative microorganisms, especially *P. aeruginosa* and associated with a high risk of mortality [8]. Since the early 1980s, this bacterial profile has changed to Gram-positive microorganisms. Our study also confirms this with 65.3% of the positive cultures revealing a Gram-positive microorganism. MRSA, MSSA and alpha-hemolytic streptococci were the main causes of infections, in agreement with the literature [1,3]. The reason for this change is the extensive use of indwelling central venous catheters, more severe cases of oral mucositis from intensive use of chemotherapeutic agents and empiric treatment of febrile episodes with antibiotics directed primarily against Gram-negative microorganisms. Despite the apparent decline in Gram-negative bacterial infections, rapid initiation of empiric antimicrobial treatment directed against these organisms at the onset of fever has been shown to decrease mortality [8,9]. Therefore, the combination of an antipseudomonal beta-lactam plus an aminoglycoside is commonly used in empiric therapy.

The development of new broad-spectrum bactericidal antibiotics, such as carbapenems and broad-spectrum cephalosporins has offered the prospect of single-agent therapy [6,7,10,11]. The question of whether combination therapy can be safely replaced with monotherapy in febrile neutropenia has arisen. Several studies suggest that monotherapy is sufficient in patients with possible infection or with short neutropenic periods [12]. The answer to this question remains controversial especially for patients with bacteremia and for those with persistent and profound neutropenia.

The present trial shows that meropenem monotherapy is as effective as the ceftazidime + amikacin or cefepime + netilmicin combination for the empiric treatment of fever in profoundly and persistently neutropenic patients.

Cometta *et al* also show in their study that meropenem monotherapy is as effective as ceftazidime + amikacin in 958 patients [13].

The success rate observed in our study is similar to that obtained in other trials [13]. The relatively low response rates achieved for all three groups are related to strict definitions of failure by the Immunocompromised Host Society consensus; in particular any change in the empiric antibiotic regimen was assessed as a failure [14]. According to this consensus the purpose of empiric therapy is to achieve a continuous normalization of temperature and resolution of all signs and symptoms of the infection without addition of other antibiotics. The term "success with modification" was introduced almost a decade ago. This term means the addition of new antibiotics to the initial treatment or alteration for a number of febrile episodes. This approach might double the success rates as this group believes empiric therapy is not designed to last but to prevent death in the early stage before a more specific antibiotic regimen is chosen, based on bacteriologic results and the patient's initial response. Modification is only needed in 20% of FUO patients while this might be as high as 60% in patients with clinically or microbiologically documented infections.

In other trials, adjustment of therapy in neutropenic patients with persistent fever has become a common clinical practice, despite the absence of clinical deterioration or of documentation of a microorganism resistant to the antibiotic regimen used [13]. In the present study, the most frequent modification was the addition of a glycopeptide which was most frequent (32%) in the cefepime + netilmicin arm, lowest (12%) in the meropenem monotherapy group and 27.2% in the ceftazidime + amikacin combination arm. Thus, a glycopeptide was added empirically in 21.25% of the randomized patients, mainly in those with persistent fever. Gram-positive microorganisms are less adequately covered by empiric antibiotic regimens. Although the mortality rate due to Gram-positive bacteremia is low (<%5), severe complications like septic shock may occur. MRSA and *Streptococcus viridans* are the most dangerous Gram-positive microorganisms. In the management of febrile neutropenia, vancomycin might be added to the empiric antibiotic treatment, especially in patients with indwelling catheters. It is our routine to add vancomycin to the antibiotic regimen used if fever does not subside at 48 h and culture results do not yield any pathogen.

The cost of pharmaceuticals must also be considered in a developing country like Turkey which has limited sources for health care [15]. The third and fourth generation cephalosporins + aminoglycosides were comparable for both efficacy and cost in our study, while the monotherapy had the highest cost. Although monotherapy required less modification, its high cost might limit its use as first-line treatment. Meropenem might be used as a second-line treatment and / or empiric therapy for very high risk, severely neutropenic patients. Therefore, in our next trial, we plan to use ceftazidime plus amikacin as first-line therapy for patients with an absolute neutrophil count (ANC) of 500 to 1000 /mm^3. For patients with severe neutropenia (ANC<500/mm^3), we wish to compare the efficacy of a carbapenem plus aminoglycoside with cefepime plus an aminoglycoside, to prevent emerging resistance to monotherapy.

In conclusion, different combinations might be considered for empiric therapy, depending on their efficacy, the nosocomial bacterial flora and resistance patterns and the cost, which is very important for developing countries with limited resources.

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