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Cefoperazone-sulbactam plus amikacin empirical therapy for febrile neutropenia in children with cancer

Aim: To determine the efficacy and safety of cefoperazone-sulbactam combined with amikacin in the treatment of febrile neutropenia in children with cancer.

Materials and Methods: The study included 20 cancer cases with 26 febrile neutropenia (FEN) episodes. Patient selection criteria were defined according to the guidelines issued by the Infectious Disease Society of America (IDSA).

Results: Patients diagnosed with acute leukemia (58%) and solid tumors (42%) were recorded. Twelve (46.2%) of the primary disease cases were refractory. The number of infection episodes identified microbiologically and clinically was 10 (38.5%) and 12 (46.1%), respectively. Fever of unknown origin was observed in only 4 cases (15.4%). The success rate of the empirical treatment without additional modification was 42.3% (11 FEN episodes). Four episodes (15.4%) needed a replacement for sulbactam/cefoperazone because of persistent fever, adverse reactions, and/or clinical deterioration. Three patients died because of relapse or because they were refractory. As 15 (57.7%) of the patients deteriorated clinically and had fever, glycopeptide antibiotics were given after 48-72 h. The overall response rate at the end of the therapy was 80.8%, with/without modification.

Conclusions: The combination of sulbactam/cefoperazone plus amikacin was effective and safe in the treatment of febrile episodes in neutropenic pediatric cancer patients.

Key words: Neutropenic fever, childhood, cefoperazone/sulbactam, amikacin

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Kanserli çocuklardaki ateşli nötropenik hastalar için sefoperazon-sulbaktam + amikasin ampirik tedavisi

Amaç: Bu prospektif çalışmanın amacı kanserli çocuklardaki febril nötropenin cefaperazone-sulbactam ve amikasin kombinasyonunun etkinliğini saptamaktır.

Yöntem ve Gereç: Bu çalışmaya, toplam 26 febril nötropeni gelişmiş olan 20 hasta dahil edildi. Hasta seçimi; Amerika İnfeksiyon Hastalıkları Topluluğu tarafından yayınlanmış olan kılavuzdaki tarif edilmiş olan kriterlere uygun yapıldı.

Bulgular: Teşhis edilen ve kayıt yapılan hastalar akut lösemi (% 58) ve solid tümörlü (% 42) hastalardır. Primer hastalığa refrakter olgu sayısı 12 (% 46,2) idi. Mikrobiyolojik ve klinik olarak saptanan infeksiyon sayısı sırasıyla 10 (% 38,5) ve 12 (% 46,1) idi. Nedeni bilinmeyen ateş sadece 4 vakada (% 15,4) vardı. Ampirik tedavinin başarısı diğer modifikasyon olmaksızın % 42,3 (11 FEN olayı). 4 FEN'li (% 15,4) hastada ateşin devam etmesi, yan etki ve/veya klinik olarak bozulma meydana gelmesi nedeniyle ampirik tedavi değiştirilme ihtiyacı oldu. Relaps yada tedaviye cevap vermediği için üç hasta kaybedildi. Klinik olarak durumu bozulan ve ateşi olan 15 hastaya (% 57,7) 48-72 saat sonra glikopeptid antibiyotik verildi. Tedavinin sonundaki tam cevap oranı, modifikasyonlu ve modifikasyonsuz olarak % 80,8'dir.

Sonuç: Sulbactam/sefoperazon ve amikasin kombinasyonu çocuk kanser hastalarındaki febril nötropeni olaylarının tedavisinde etkili ve emniyetlidir.

Anahtar sözcükler: Nötropenik ateş, çocukluk çağı, sefoperazon/sulbaktam, amikasin

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Introduction

The use of intensive chemotherapeutic regimens produces severe and prolonged neutropenia in many cancer patients. Neutropenia is known as a major predisposing factor for the development of infection in these patients. Management of febrile neutropenic episodes with early and effective empiric broad-spectrum bacterial antibiotic therapy decreases morbidity and mortality, and is now standard practice in treating cancer patients with febrile neutropenia (FEN). Various empiric regimens have been recommended for therapy (1-4).

B-lactam/B-lactamase inhibitor combinations are a good choice for empirical antimicrobial therapy in FEN patients, because their antibacterial spectrum covers both gram-negative and gram-positive pathogens, and the addition of the B-lactamase inhibitor overcomes resistance to B-lactam alone. Sulbactam is one of several currently available B-lactamase inhibitors that have intrinsic activity against both gram-positive and gram-negative bacteria. The addition of sulbactam to cefoperazone enhances cefoperazone's activity against B-lactamase, producing some anaerobes, including *Bacteroides fragilis* and many aerobic gram-negative bacilli, and enhances its activity against cefoperazone-susceptible pathogens (5-7).

Aminoglycosides play an important role, especially in the treatment of gram-negative rod bacteremia in granulocytopenic patients. Many investigators have shown that antibiotic combinations of aminoglycoside and B-lactam, used synergistically to avoid emergencies caused by resistant bacteria, are more effective than monotherapy in the treatment of FEN patients (8,9). Sulbactam/cefoperazone plus amikacin therapy has not been studied as extensively as the other combinations, but is reported to be effective and safe for the empirical treatment of episodes of fever in neutropenic patients (10).

The purpose of the present prospective study was to determine the efficacy and safety of cefoperazone/sulbactam combined with amikacin in the treatment of FEN in children with cancer.

Materials and methods

We reviewed the medical records of pediatric cancer patients that experienced episodes of fever and chemotherapy-induced neutropenia between June 2004 and March 2005. Patient selection criteria were determined according to the guidelines of the Infectious Disease Society of America (IDSA): neutropenia was defined as an absolute neutrophil count < 500 mm^3 or a count < 1000/mm^3, but expected to fall to < 500/mm^3 within 48 h; fever was defined as either a single axillary temperature of at least 38.5 °C or axillary temperature exceeding 38.0 °C for ≥ 1 h or twice within a 12-h period (11).

All patients were hospitalized. After complete history taking, comprehensive clinical and laboratory evaluations were performed for all patients. Chest radiographs were obtained. Blood, urine, throat, and stool cultures were taken before beginning antibiotic treatment. At least one blood sample was drawn through the catheter and peripheral vein from each patient with an indwelling venous catheter. An antibiogram profile of isolates was made for commonly used antibiotics. Patients received sulbactam/cefoperazone 100 mg/kg/day intravenously over 60 min every 8 h (recommended maximum daily dose of sulbactam was 4 g). This antibiotic was combined with amikacin 15 mg/kg/day in a single dose.

Each patient and/or parent provided informed consent prior to inclusion in the study. The study followed the guidelines of the Helsinki declaration concerning medical research with humans and received approval of the local ethics committee. No support was obtained from the drug manufacturers. Patients were monitored daily for clinical symptoms. All patients were assessed 48-72 h after the start of the empirical therapy, or earlier if clinically indicated. In cases of unresponsiveness to the therapy, adverse reactions, a resistant pathogen, or clinical deterioration, antibiotic treatment was changed or modified. Vancomycin was added when staphylococci were grown in culture. The addition of systemic antifungal therapy was usually considered in cases unresponsive to broad-spectrum antibiotic therapy and when clinical symptoms and fever continued for more than 5 days. Culture samples were repeated during therapy until fever ceased. Additional chest radiography was performed in patients that remained clinically febrile. Invasive diagnostic procedures were performed on a case-by-case basis. Therapy generally continued until the granulocyte count increased to > 1000/mm^3 or the patient was free of symptoms of infection for 5 days.

Data processing

Data are expressed as means (± standard deviation, SD) or as medians (range). The effects of risk factors on the duration of treatment and the response to the therapy were compared using the Mann-Whitney U test.

Results

The study included 20 patients (male/female: 10/10) with a mean age of 6.24 ± 2.8 years (range: 1-15 years) that had different malignancies (58% acute leukemia and 42% solid tumors) and 26 FEN episodes during a 10-month period. Clinical characteristics of the patients are shown in Table 1. Five patients were enrolled on more than one occasion (4 patients were enrolled twice and one patient was enrolled 3 times). In all, 12 (46.2%) of the patients were unresponsive to the chemotherapeutic regimens. The initial granulocyte count in 5 (19.2%) patients was < 100/mm^3. Antimicrobial prophylaxis was not used as an initial treatment. Two of the patients were given a central indwelling venous catheter. In all, 10 (38.5%) and 12 (46.1%) of the infection episodes were identified microbiologically and clinically, respectively. Fever of unknown origin was observed in 4 (15.4%) patients (Table 1).

Table 2 provides a list of the microorganisms identified in the patients. The results of therapy are summarized in Table 3. The empirical treatment's rate of success without modification was 42.3% (11 episodes). Four episodes (15.4%) required replacement of sulbactam/cefoperazone with another antibiotic because of persistent fever, adverse events, and/or clinical deterioration. Modification of the initial antibiotic therapy was used in 11 episodes by the addition of a glycopeptide, antifungal (fluconazole in 2 episodes and amphotericin B in 4 episodes), antiviral (acyclovir for herpes labialis in 2 episodes), metronidazole (in 1 episode), or cotrimoxazole (in 2 episodes).

Table 1. Characteristics of the patients/episodes.

	Number (%)
Number of patients	20
Number of episodes	26
Underlying malignancy	
Solid tumor	11 (42)
Acute leukemia	15 (58)
Age (median/range) (years)	6.24 ± 2.8 (1-15)
Sex (male/female)	10/10
Status of cancer	
Remission	14 (53.8)
Refractory	12 (46.2)
Entry ANC[a] severity	
< 100/mm^3	5(19.2)
> 100/mm^3	21 (80.8)
Central indwelling venous catheter[b]	2 (7.6%)
Patients receiving G-CSF[a]	14 (53.8%)
Diagnosis of infection episode	
Fever of unknown origin (FUO)	4 (15.4)
Microbiologically documented infection (MDI)	10 (38.5) [d]
Clinically suspected infection (CDI)	12 (46.1)
Pneumonia	2
Upper respiratory tract infection	2
Gastroenteritis	3
Mucositis	5

[a]ANC: Absolute neutrophil count
[b]One bacteremia case was catheter related
[c]G-CSF: Growth colony stimulating factor
[d]Multiple microorganisms were identified in 4 patients

Table 2. Microorganisms identified in the patients.

	Pathogens	Number
Blood	*Staphylococcus aureus*	1
	Staphylococcus hominis	1
	Escherichia coli	1
	Burkholderia spp.	1
Urine	*Escherichia coli*	1
	Non-hemolytic staphylococcus	2
	Proteus mirabilis	1
Respiratory tract	*Pseudomonas aeroginosa*	1
Stool	*Enterococcus* (vancomycin resistant)	2
	Candida albicans	1
	Rotavirus	1
	Enteamobea histolytica	1
Total		14

Multiple microorganisms were identified in 4 patients
* Case 1: 2 sites of infection; ∞ Case 2: 2 sites of infection
∈ Case 3: 2 sites of infection; § Case 4: 3 sites of infection

Table 3. Results of empirical therapy.

	Number (%)
Continuing without modification*	11 (42.3)
Continuing with modification*	11 (42.3)
Glycopeptide	11 (42.3)
Antifungal	6 (23)
Antiviral	2 (7.7)
Others	3(11.5)
Change of initial study antibiotic	4 (15.4)
Results of treatment	
Success at 72 h	1(3.8)
Success in 7 days	15 (57.7)
Success with modification	10 (38.5)
Overall success	21 (80.8)
Failure	5 (19.2)[a]
Duration of treatment	9.4 ± 6.1 days (range: 2-27 days).

*Status at early evaluation (72 h)
[a]3 patient that died and 2 that survived needed change of antibiotics

The overall mortality rate was 8.3%; all 3 cases were refractory. Because of clinical deterioration in patients (both patients' initial granulocyte counts were < 100/mm^3) the antibiotic regimens were changed on day 3 and they died due to the progression of malignancy (primary disease in 1 case was MDS-RAEB I and was AML in the other). The third patient (primary disease was medulloblastoma) died as a

result of bacteremia due to *Staphylococcus aureus* (catheter infection), although initiation was early and there was no resistance to glycopeptides (initial granulocyte count was > 100/mm^3).

Mean duration of treatment was 9.4 ± 6.1 days (range: 2-27 days). The duration of hospitalization increased in episodes with bacteremia and in episodes with modification of the therapy (Table 3). The differences between duration of treatment and some patient features, such as age, cancer type, and gender, were not significant.

The effect of different parameters on the response to the therapy was analyzed; disease status, severity of neutropenia, presence of bacteremia, and antibiotic modification had an effect. Additionally, 3 factors had significant prognostic impact on the timing of response to treatment: presence of mucositis (ulcers of the oral mucous membrane), gastroenteritis, and tonsillopharyngitis (hyperemia of the tonsilla and pharynx associated with rhinitis). All other factors, such as age, cancer type, and gender, were not significant predictors of successful treatment of solid or hematologic malignancies. The status of the underlying disease affected the length of treatment ($P < 0.005$). Skin rash during 1 episode and nausea/vomiting during 2 episodes were observed; hepatic side effects were not observed after antibiotic treatment.

Discussion

The prompt initiation of empirical antibiotics in FEN has been the most important advancement in the protection of cancer patients from sudden death; therefore, antibiotic regimens that are effective against the major known pathogens must be selected and drug resistance should be taken into account while FEN protocols are prepared. More than 50% of neutropenic patients with fever have fever of unknown origin (FUO). In the present study the FUO rate was 15.4%. In the present study 38.5% and 46.1% of cases had microbiologically and clinically confirmed episodes, respectively (Table 1).

Although some recent studies that analyzed the spectrum of organisms involved in pediatric FEN cases report that there was a shift from gram-negative pathogens to gram-positive pathogens, in particular those caused by *Staphylococcus* spp. and *Streptococcus* spp. gram-negative bacilli, especially *P. aeruginosa*, *Escherichia coli*, and *Klebsiella* spp., remain prominent causes of infection and must be treated with selected antibiotics (12). In the present study the number of gram-positive and gram-negative organisms isolated in cultures was equal. This might have been due to the rare presence of indwelling central venous catheters and the absence of pre-therapy prophylaxis in our patients. We observed that low ANC and refractoriness were risk factors for prognosis in our study population. Solid tumors (except hematological malignancy) and short duration of neutropenia (< 7 days) were risk-assessment factors used for determining low risk of FEN; however, patients diagnosed with hematological malignancy and FEN received combined antibiotic rather than monotherapy. Although the duration of FEN was not statistically significant, it was longer in hematological malignancy patients.

β-lactam/β-lactamase inhibitor combinations are a good choice for empirical antimicrobial therapy in FEN patients, because they have an additive or synergistic bacterial effect with a very broad spectrum of activity against most pathogens. Sulbactam/cefoperazone is effective for empirical monotherapy in febrile granulocytopenic patients (13,14). The increased cost effectiveness of sulbactam/cefoperazone treatment, as compared to imipenem/cilastatin, is emphasized (10). Another advantage of sulbactam/cefoperazone is in the treatment of anaerobic infection. The overall response rate of sulbactam/cefoperazone plus amikacin was 38% within 72 h of beginning treatment in the present study. A 57.7% response rate was obtained in less than 7 days with this combination. The overall response rate was 80.8%, with/without modification, at end of the therapy. These results confirm both the safety and efficacy of this treatment protocol, and are in agreement with previously reported results from other studies on sulbactam/cefoperazone, with/without the use other agents (13-20).

Only a few controlled trails evaluating the efficacy of sulbactam/cefoperazone in a large number of febrile granulocytopenic patients have been reported. El Haddad compared sulbactam/cefoperazone with piperacillin plus amikacin; the response rates were 77% for sulbactam/cefoperazone and 44% for piperacillin plus amikacin (14). Bodey et al. (17) reported there was no significant difference in the

overall rates of response to sulbactam/cefoperazone plus vancomycin (74%) and imipenem plus vancomycin (73%) in febrile granulocytopenic patients. In another randomized trial comparing sulbactam/cefoperazone to imipenem as a monotherapy for febrile granulocytopenia, Bickers et al. (19) reported low rates of response to sulbactam/cefoperazone (44%) and imipenem (33%), because of the frequent addition of empirical amikacin therapy to both antibiotic regimens. Toxicity related to antibiotics was minimal in the present study.

In conclusion, the present study shows that the combination of sulbactam/cefoperazone plus amikacin was effective and safe in the treatment of febrile episodes in neutropenic cancer patients.

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