

## Imipenem-Cilastatin versus Sulbactam-Cefoperazone plus Amikacin in the Initial Treatment of Febrile Neutropenic Cancer Patients

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*The treatment of infectious complications in cancer patients has evolved as a consequence of the developments in the chemotherapy of cancer patients. In this prospective, randomized study, we compared imipenem-cilastatin and sulbactam-cefoperazone with amikacin in the empiric therapy of febrile neutropenic (<1000/mm<sup>3</sup>) patients with liquids and solid tumours. Of 30 evaluable episodes, 15 were treated with imipenem-cilastatin and 15 were treated with sulbactam-cefoperazone plus amikacin. 73% of episodes were culture-positive; gram-positive pathogens accounted for 62% of the isolates. Bacteremia was the most frequent site of infection. The initial clinical response rate for both regimens was 60% (p>0.05). No major adverse effects occurred.*

*This study demonstrated that imipenem-cilastatin monotherapy and combination therapy of sulbactam-cefoperazone plus amikacin were equally effective empiric therapy for febrile granulocytopenic cancer patients.*

**Key words ;** Imipenem-Cilastatin, Sulbactam-Cefoperazone, Amikacin, Neutropenic fever

### INTRODUCTION

The increasing use of more intensive chemotherapeutic regimens to achieve maximal antitumour activity has produced severe and prolonged neutropenia in many patients<sup>1,2</sup>. Life-threatening infection is a significant complication in patients undergoing intensive myelosuppressive therapy for treatment of malignancy. Neutropenia was known almost 3 decades ago as a major predisposing factor for the development of infection in patients with cancer. Absolute neutrophil counts less than 1000 cells/mm<sup>3</sup> are associated with over 70% of septic episodes in neutropenic host. Fatality rates range from 30% to 70%, depending on the degree and the duration of neutropenia<sup>2,3</sup>. Early empiric therapy

with broad-spectrum bactericidal antibiotics is now standard practice in treating the cancer patients with febrile granulocytopenia<sup>1,4</sup>.

Imipenem is an antibacterial agent of the carbapenem class of beta-lactams with a very broad spectrum of activity that includes most gram-negative and gram-positive pathogens, including aerobes and anaerobes, and with marked activity against species producing beta-lactamases<sup>1,5,6</sup>. Sulbactam is a beta-lactamase inhibitor which has been combined with ampicillin and cefoperazone<sup>7</sup>. Sulbactam itself has limited antibacterial activity against some aerobic gram-negative bacilli (AGNB) which include non-aeruginosa *Pseudomonas* spp. and *Acinetobacter* spp.<sup>8,9</sup>. In combination with cefoperazone, it extends the spectrum of the latter antibiotic to some anaerobes, including *Bacteroides fragilis*, and many beta-lactamase-producing AGNB (10). Aminoglycosides have played an important role, especially in the treatment of gram-negative rod bacteremia in these granulocytopenic patients.

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Aminoglycosides are rapidly bactericidal and show concentration dependent killing, a feature that favors regimens that achieved high peak serum concentrations<sup>11, 12</sup>.

Several studies regarding imipenem-cilastatin and sulbactam-cefoperazone plus amikacin as initial therapy for febrile neutropenic cancer patients had been reported<sup>6, 13-16</sup>.

The purpose of our study was to compare the efficacy of empiric therapy with imipenem-cilastatin monotherapy and the combination of sulbactam-cefoperazone plus amikacin in the treatment of presumed bacterial infection in neutropenic cancer patients.

### PATIENTS and METHODS

We performed this study at Ondokuz Mayıs University Hospital, Samsun. Patients were eligible if they had liquids or solid tumours, neutropenia (<1000/mm<sup>3</sup>) and fever (defined by at least two oral temperature readings above 38.0 at least 4 h apart within a 24-h period, single oral temperature above 38.5 ) in the absence of an obvious noninfectious cause of fever, such as administration of blood products or cytotoxic drugs. The patients were informed about antibiotic regimens.

Initial assessment included history and physical examination, urinalysis, complete blood counts, absolute neutrophil counts, blood biochemistry and chest X-ray. Specimens for bacterial and fungal cultures were collected from nose, throat, urine, stool, sputum (if available), blood and any other appropriate sites before commencement of antibiotic treatment. The antimicrobial prophylaxis was not used before initial treatment. Fifteen

patients were randomly allocated to receive either imipenem-cilastatin (500 mg i.v. every 6 h) or a combination of sulbactam-cefoperazone (2 g i.v. every 12 h) plus amikacin (15 mg/kg/day, on average 500 mg i.v., every 12 h).

The response to empiric therapy was evaluated at 72 h and therapy was modified only if the patient did not respond, or deteriorated, if there were adverse reactions, or if a resistant pathogen was isolated. If fevers persisted after five days of antibiotic therapy, empirical antifungal therapy (fluconazole, 200 mg PO or IV every 24 hours) was started. Therapy was generally continued until the patient was free of symptoms of infection for 5 days or granulocyte count increased to >1000/mm<sup>3</sup>.

Antibiotic-related nephrotoxicity was diagnosed when the serum creatinine level increased to 0.5 mg/dl from baseline in the absence of other causes of renal dysfunction or other nephrotoxic drugs. Antibiotic-related hepatotoxicity was indicated when the serum aspartate and alanine aminotransferase increased 2-fold from baseline in the absence of other causes of hepatic dysfunction or hepatotoxic drugs.

### RESULTS

During a 12-month period, 30 patients with episodes of fever and granulocytopenia were enrolled in this study. Clinical characteristics of the evaluable patients are shown in table 1.

Of the 30 evaluable episodes, 15 were treated with an imipenem-cilastatin monotherapy and a combination of sulbactam-cefoperazone plus amikacin. Age and underlying disease were comparable. Numbers of culture-positive episodes were 10 and 11, respectively,

**Table 1. Clinical characteristics of the patients**

Parameter	Imipenem/cilastatin	sulbactam-cefoperazone with amikacin
Evaluable episodes	15	15
Mean age (range) years	41.6 (18-66)	49.6 (49-86)
Sex (MF)	13/2	5/10
Number of patients with underlying disease		
Leukemia	12	12
Lymphoma	1	2
Multiple myeloma	1	-
Solid tumour	1	1
Number of patients with culture positive	10	11
Mean granulocyte at study entre (range)	553 (110-900)	422 (35-900)

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in the two regimens and the overall rate of positive cultures was 73%. The sites of infection and the causative organisms are listed in table 2.

no major adverse effects requiring a change of antibiotics. However, two patients developed drug induced diarrhea and emesis in the group receiving the

**Table 2. Index infection by site in microbiologically documented**

	Imipenem/cilastatin	sublactam- cefoperazone with amikacin
Blood	9	8
Respiratory tract	2	1
Urinary tract	1	4
Oral cavity	3	5
Soft tissue/ skin	5	6
Gastrointestinal tract	-	2
Staphylococcus aureus	10	6
Pseudomonas spp.	1	3
Escherichia coli	1	3
Acinetobacter boumannii	-	1
Beta- haemo lytic streptococcus	1	1
Enterobacter spp.	-	2

**Table 3. Status at early evaluation (72 hr)**

	Imipenem/cilastatin	sublactam- cefoperazone with amikacin
Continuing without modification	9 (60%)	9 (60%)
Continuing with modification	6	6
Vancomycin	3	5
Fluconazole	2	5
Acyclovir	1	-

An early clinical evaluation after 72 h of empiric therapy showed that 60% of patients responded favorably to the initial empiric therapy. Table 3 shows the status at early evaluation. All of the patients in whom culture-negative episodes were observed were successfully treated with the initial regimen. One patient who had herpetic infection used acyclovir.

There were no statistically significant differences between the treatment groups in patient outcome for the microbiologically documented, clinically documented, or possible infection groups ( $p>0.05$ ).

In 9 (60%) of imipenem-cilastatin groups and 9 (60%) of sublactam-cefoperazone plus amikacin groups, an outcome of success without modification of therapy was achieved. The addition of vancomycin was the most frequently used modification in both groups. There were

imipenem-cilastatin. None of these was considered serious or severe.

## DISCUSSION

Granulocytopenia has been closely associated with cancer and its treatment<sup>4, 17)</sup>. Despite the poor inflammatory reaction in these patients, the onset of fever usually represents an infection in the body<sup>1, 13, 18)</sup>. Confirmation of infection usually involves a delay of some days before all the laboratory results are available. The primary objective of empiric antibiotic therapy is to protect many patients with cancer from the immediate cause of death<sup>2, 18)</sup>. In order to reduce infection-related morbidity and mortality, a number of treatment concepts have been utilized during the past 3 decades. Therefore,

the antibiotic regimens must be selected against the major known pathogens<sup>1, 3, 18, 19</sup>.

Since the 1970's, the most frequently used empiric antibacterial therapy has consisted of two or three-drug regimens, usually combining a cephalosporin, an antipseudomonal penicillin or both with an aminoglycoside<sup>1, 18</sup>. The rationale for this approach is based on the wide range of potential gram-positive and gram-negative organisms necessitating coverage and the evidence that combination therapy results in additive or synergistic bactericidal activity. The availability of newer, broader spectrum cephalosporins, carbapenems and monobactams has led to considerable controversy regarding the use of these agents as monotherapy for empiric antibacterial treatment of the febrile compromised host<sup>20, 21</sup>.

Most investigators have shown that antibiotic combinations of aminoglycoside with a beta-lactam for synergy and avoidance of the emergence of resistant bacteria are more effective than monotherapy in the treatment of febrile neutropenic patients<sup>22, 23</sup>. Monotherapy with imipenem-cilastatin has been previously demonstrated to be effective in noncomparative trials. Comparative studies with imipenem-cilastatin versus piperacillin plus amikacin and ceftazidime plus amikacin have shown that imipenem-cilastatin is equal to other combinations<sup>24, 25</sup>. These results have demonstrated that imipenem/cilastatin monotherapy could be a practical alternative regimen<sup>6, 13, 14, 24</sup>.

The incidence of infection due to gram-positive organisms has increased markedly in patients with cancer<sup>6, 27</sup>. In our study, 73% of the episodes had a positive culture; gram-positive pathogens accounted for 62% of the isolates. The response rate (60%) was the same for the two regimens. Each regimen covers the organisms most frequently isolated in neutropenic patients. Toxicity related to antibiotics were minimal in both groups.

In summary, this study demonstrated that monotherapy of imipenem-cilastatin and the combinations of sulbactam-cefoperazone with amikacin were equally effective in the treatment of febrile episodes in neutropenic cancer patients.

## REFERENCES

1. Young LS. *Infection in cancer patients*. In: Haskell CM. *Cancer treatment*. Philadelphia W.B. Saunders, 1995: 206-216.
2. Pizzo AP. *Infection in cancer patients*. In: Devita VT, Hellman S, Rosenberg S A. *Principles and practice of oncology Philadelphia J.B. Lippincott Company, 1993: 2292-2338*.
3. Link H, Maschmeyer G, Meyer p, Hiddemann W, Stille W, Helmerking M. *Interventional antimicrobial therapy in febrile neutropenic patients*. Study Group of the Ehrlich Society for Chemotherapy. *Ann Hematology* 1994; 69: 231-243.
4. Klastersky J. *Prevention and treatment of infections related chemotherapy*. In: Cviticovic E, Droz JP, Amand JP, Khoury S. *Handbook of chemotherapy in clinical oncology*. Paris , F.I.I.S. 1993, 477-481.
5. Akita H, Sato Y, Iwata S, Nita Y, Yokota T, Sunkawa K. *Bacteriological and clinical studies on meropenem in the pediatric field*. *Jpn J Antibiotics* 1992; 45: 744-755.
6. Miller J A, Butler T, Beveridge R A, Kales A N, Binder R A. *Efficacy and tolerability of imipenem-cilastatin versus ceftazidime plus tobramycin as empiric therapy of presumed bacterial infection in neutropenic cancer patients*. *Clin Therapeutics* 1993; 15: 486-499.
7. English AR, Retsema J A, Girard A E, Lynch J E, Barth W E. *CP-45,899, a beta-lactamase inhibitor that extends the antibacterial spectrum of beta lactams: initial bacteriological characterization*. *Antimicrob Agents Chemother* 1978; 14: 414-419.
8. Body G P, Miller P, Ho D H. *In vitro assessment of sulbactam plus cefoperazone in the treatment of bacteria isolated from cancer patients*. *Diag Microb Infect Dis* 1989; 2: 209-214.
9. Jacoby G A, Sutton L. *Pseudomonas cepacia susceptibility to sulbactam*. *Antimicrob Agents Chemother* 1978; 33: 583-584.
10. Moody J A, Fasching C E, Sinn L M, Gording D N, Peterson L R. *Comparative efficacy of cefoperazone, cefoperazone plus sulbactam, ciprofloxacin, clindamycin, metronidazole, and penicilline G against anaerobic bacteria in an animal model*. *J Lab Clin Med* 1990; 115: 190-195.
11. Gerber A U, Feller-Segessenmann C. *In vivo assessment of in-vitro killing patterns of pseudomonas aeruginosa*. *J Antimicrob Chemother* 1985; 15: 201-206.
12. Vogelman B S, Craig W A. *Kinetics of antimicrobial activity*. *J Pediatr* 1986; 108: 835-840.
13. Freifeld A G, Walsh T, Marshall D, Gress J, Steinberg S M, Hathorn J, Rubin M, Jarosinski p, Gill V, Young R C. *Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem*. *J Clin Oncol* 1995; 13: 165-176.
14. Au E, Tow A, Allen D M, Ang P T. *Randomised study comparing imipenem/cilastatin to ceftriaxone plus gentamicin in cancer chemotherapy-induced neutropenic fever*. *Ann Acad Med Sing* 1994; 23: 819-822.
15. Horiuchi A, Hasegawa H, Kageyama T, Yonezawa T, Kitani T, Masaoka T, Yasunaga K, Kawagoe H, Nagai

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- K. Efficacy of sulbactam/cefoperazone for the treatment of infections in patients with hematologic diseases. *Diagn Microbiol Infect Dis* 1989; 2: 215-219.
16. Bodey G P, Elting L S, Narro J, Koller C, O'Brien S, Estey E, Benjamin R. An open trial of cefoperazone plus sulbactam for the treatment of fever in cancer patients. *J Antimicrob Chemother* 1993; 32: 141-152.
17. Kim S K, Demetri G D. Chemotherapy and neutropenia. *Hematology/Oncology Clin N Am* 1996; 10: 377-395.
18. Pizzo P A. Management of fever in patients with cancer and treatment-induced neutropenia. *New Engl J Med* 1993; 18: 1323-1332.
19. Klastersky J. Empiric treatment of infection during granulocytopenia: a comprehensive approach. *Infection* 1989; 17: 59-64.
20. Rubin R H. Empiric antibacterial therapy in granulocytopenia induced by cancer chemotherapy. *Ann Intern Med* 1988; 108: 134-136.
21. Brown A E. Neutropenia, fever, and infection. *Am J Med* 1984; 76: 30-35.
22. Lowe LJ, Schimpf SC, Schiffer CA. Improved prognosis for granulocytopenic patients with gram-negative bacteremia. *Am J Med* 1980; 68: 643-648.
23. Klastersky J, Meunier-Carpentier F, Prevost JM. Significance of antimicrobial synergism for the outcome of gram-negative sepsis. *Am J Med Sci* 1977; 273: 157-167.
24. Norby SR, Vandercam B, Louis T. Imipenem-cilastatin versus amikacin plus piperacilin in the treatment of infections in neutropenic patients: a prospective randomized multi-clinic study. *Scand J Infect Dis* 1987; 52: 65-78.
25. Perez C, Sirham M, Ibarra J, Grebe G, Lira P, Oliva J, Duhalde M, Ocqueteau M, Acuna G. Imipenem/cilastatina versus ceftazidima-amikacina para el tratamiento de pacientes neutropenicos febriles. *Rev Med Chil* 1993; 123: 312-320.
26. Wade J C, Schimpf S C, Newman KA. *Staphylococcus epidermidis*: An increasing cause of infection in patients with granulocytopenia. *Ann Intern Med* 1962; 97: 502-508.
27. Rubin M, Hathan J W, Marshall D. Gram-positive infections and use of vancomycin in 350 episodes of fever and neutropenia. *Ann Intern Med* 1988; 108: 30-35.
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