RESEARCH COMMUNICATION

Imipenem in the Treatment of Febrile Neutropenic Children

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Abstract

Introduction: Infection of neutropenic children treated with malignancies is even now the major cause of early morbidity and mortality. Febrile neutropenic attacks without complications are successfully treated with wide-spectrum anti-pseudomonal cephalosporins or carbapenems. Objective: To determine the efficacy and safety of imipenem in the treatment of febrile neutropenia in children with cancer. Materials and Methods: Twenty four patients who had a febrile neutropenic (FN) episodes followed by initiation of empirical imipenem therapy were included in the study. Results: Of the patients, 10 (41.7%) had solid tumors, while 14 (58.3%) were diagnosed to have acute leukemia. Among all, 5 (20.8 %) and 15 (62.5 %) of the infections were identified microbiologically and clinically, respectively. Fever of unknown origin was observed in 4 (16.7 %) patients. The mean duration of neutropenia was 6.3 ± 1.4 (4-8) days in patients with solid tumors, and 9.3 ± 7.4 (3-25) days in the group with leukemia. Average time of stay in hospital was 9.0 ± 4.1 (4-20) days for patients with solid tumors, and 14.4 ± 10.6 (4-33) days for patients with leukemia. FN duration was observed to be significantly longer in patients with an ANC of less than 200/mm^3, and in children who were not in remission for the underlying malignant disease. In addition, average time of stay in hospital was observed to be significantly longer in patients who were not in remission for the underlying malign disease. All of the patients were discharged. The success rate of empirical therapy started with imipenem was found be 95.8 %. Conclusion: Imipenem is effective and safe in the treatment of FN in pediatric cancer patients.

Key Words: Febrile neutropenia - imipenem - childhood - Turkey

Asian Pacific J Cancer Prev, **10**, 921-923

Introduction

Patients with an abnormally low neutrophil count of < 500/mm3, or those expected to have a decrease in their neutrophil count to under 500/mm^3 in 24 to 48 hours, are considered neutropenic. Chemotherapy related neutropenia developing in oncologic patients is a significant condition, and an oral temperature of 38.3°C at a single measurement or a fever of over 38°C detected at least two times in 12 hours in these patients is described as febrile neutropenia (FN) (Hann et al., 1997; Hughes et al., 2002). Disruption of the gastrointestinal system mucosa due to chemotherapy and impairment of tissue integrity due to frequent invasive interventions facilitates infection by opportunistic microorganisms (Jones et al., 1996; Yalcın, 1998). Empirical antibiotic treatment in FN should be selected according to the foci and type of infection, central venous catheter presence, and the clinical flora. Febrile neutropenic attacks without complications are successfully treated with wide-spectrum anti-pseudomonal cephalosporins or carbapenems (Paulus and Dobson, 2009).

The purpose of the present study was to determine the efficacy and safety of imipenem in the treatment of febrile neutropenic children with cancer.

Materials and Methods

We reviewed medical records of pediatric cancer patients experiencing with 24 episodes of fever and chemotherapy-induced neutropenia retrospectively in between November 2004 and May 2005. Patient selection criterias were determined according to the guidelines of Infectious Disease Society of America (IDSA); neutropenia was defined as an absolute neutrophil count of <500/mm^3 or a count < 1000/mm^3, but expected to fall <500/mm^3 within 48 hours; fever defined as either a single axillary temperature of at least 38.5 C° or axillary temperature of exceeding 38.0 C° for ≥1 hour or two times within 12-hours period (Hughes et al., 2002).

All patients were hospitalized. After complete history taking, comprehensive clinical and laboratory evaluations were done for all patients. Chest radiographs were performed. Blood, urine, throat and stool culture were taken before beginning of antibiotic treatment. At least one blood sample was drawn through the catheter and peripheral vein from the patient who had an indwelling venous catheter. Antibiogram profile of isolates was determined for commonly used antibiotics. Patients received imipenem-cilastatin 60 mg/kg/day, every 6 h intravenously in 30-60 minutes.

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Each patient and/or parent gave informed consent before including the study. The study respected the guidelines of the Helsinki declaration concerning mediacal research in humans and received local ethics Committee approval. No support was obtained by the drug manufacturers. Patients were monitored daily for clinical symptoms.

All patients were assessed after 48-72 h of empirical therapy or earlier if clinically indicated. In case of unresponsiveness to the therapy, adverse reactions, a resistant pathogen or deterioration clinically, antibiotic treatment was changed or modified. Glycopeptide was added when staphylococci was grown in culture. The addition of systemic antifungal therapy was usually considered in patients with febrile neutropenia in case of unresponsiveness to broad-spectrum antibiotic therapy and the continuing of clinical symptoms and fever for more than 5 day. Culture samples were repeated during therapy until fever ceased. Chest radiography was obtained again in patients remained clinically febrile. Invasive diagnostic procedures were performed case-by-case. Therapy was generally continued until granulocyte count increased to >1000/mm^3 and the patient was free of symptoms of infection for 5 days.

Statistical analyses were performed by SPSS 10.01 pack program. Data were expressed by mean (± standard deviation, SD) or as median (range). The duration of treatment affected by risk factors and the response to the therapy were compared by using Kaplan Meier and Anova test.

Results

Twenty four patients who experienced FN attacks and who were started empirical imipenem treatment (male/female:12/12) were included in our study. Patients had a mean age of 81,8 ± 46,4 (18-168) months. Of all the patients, 10 (41.7%) had solid tumors, while 14 (58.3%) were acute leukemia patients. In all, 5 (20.8 %) and 15 (62.5 %) of the infections were identified microbiologicaly and clinicaly, respectively. Fever of unknown origin was observed in 4 (16.7 %) patients. Clinical characteristics of the patients and FN episodes are shown in Table 1, along with the results of therapy.

Mean duration of neutropenia was 7.8 ± 5.4 (3-25) days, and of hospital stay was 11.7 ± 8.3 (4-33) days. While mean duration of neutropenia was 6.3 ± 1.4 (4-8) days in children with solid tumors, it was 9.3 ± 7.4 (3-25) days in the group with leukemia (p>0.05). Mean duration of hospital stay was 9.0 ± 4.1 (4-20) days and 14.4 ± 10.6 (4-33), respectively, again not significant (p>0.05).

Investigation of the factors affecting duration of neutropenia and hospital stay revealed that patients with an ANC of 200/mm^3 and less, and children who were not in remission for the underlying malign disease had a significantly longer duration of FN (p<0.05). In addition, average time of stay in hospital was observed to be significantly longer in patients who were not in remission for the underlying malign disease (p<0.05) (Table 2). Throughout the study period, imipenem treatment was supported with glycopeptid in 8 (33.3%) patients, with antifungal agents in 4 (16.7%) patients, and with acyclovir in 3 (12.5%) patients. In one patient, imipenem was replaced with ciprofloxacine, as the growing microorganisms proved sensitive to ciprofloxacin. All of patients were discharged from the hospital. The success rate of empirical therapy started with imipenem was detected as 95.8%. During these episodes, we did not recognize any drug-related adverse events.

Table 1. Characteristics of the Patients/Episodes

Characteristic		Number (%)
Age (median /range) (months)		81.8 ± 46.4 (18-168)
Sex (male/female)		12/12 (50/50)
Malignancy	Solid tumor	10 (41.7)
	Acute leukemia	14 (58.3)
Cancer Status	Remission	15 (62.5)
	Nonremission	9 (37.5)
Entry ANC[a]	≤100/mm^3	6 (25.0)
severity	>100/mm^3	18 (75.0)
Central indwelling venous cathether[b]		1 (4.2)
Patients receiving G-CSF[c]		16 (67.7)
Mean receiving G-CSF		3.6 ± 2.3 (1-8) days
Diagnosis of infection episode		
Fever of unknown origin		4 (16.7)
Microbiologically confirmed infection		5 (20.8)
Clinically suspected infection[d]		15 (62.5)
	Pneumonia	3 (12.5)
	Upper respiratory tract infection	10 (41.7)
	Gastroenteritis	3 (12.5)
	Mucositis	9 (37.5)
	Urinary infection	5 (20.8)
Identification of microorganisms established		
Culture	Pathogens	
Blood	Staphylococcus epidermitis	1 (4.2)
	Streptococcus viridans	1 (4.2)
Urine	Pseudomonas stutzeri	1 (4.2)
Stool	Entamoeba histolytica	1 (4.2)
	Candida albicans[e]	1 (4.2)
	Giardia lamblia[e]	1 (4.2)
	Rotavirus[e]	1 (4.2)
	Salmonella arizona[e]	1 (4.2)
	Total	8 (33.3)
Results of empirical therapy		
Continuing without modification[f]		6 (25.0)
Continuing with modification[f]		18 (75.0)
	Glikopeptid	8 (33.3)
	Antifungal	4 (16.7)
	Antiviral	3 (12.5)
	Others (ornidasole)	2 (8.3)
Change of initial study antibiotic		1 (4.2)
Results of treatment		
	Success at 72 h	1 (4.2)
	Success in 7 days	15 (62.5)
	Modified Success	8 (33.3)
	Overall success	23 (95.8)
	Failure	1 (4.2)

[a]Absolute Neutrophil Count; [b]one case of bacteremia was catheter related; [c]Granulocyte Colony Stimulating Factor; [d]2 and upper infections in a patient; [e]Multiple microorganisms were identified in 2 patients; [f]Status at early evaluation (72 hours)

Discussion

Traditionally, a combination of an aminoglycoside plus an antipseudomonal β-lactam agent is the most widely

Table 2. Factors Affecting FN and Hospitalization Duration (HD)

		n	FN	P value	HD	P value
Sex	Male	12	8.6 ± 6.9	0.49	12.3 ± 8.9	0.72
	Female	12	7.0 ± 3.5		11.1 ± 8.1	
Leukemia		14	9.3 ± 7.4	0.20	14.4 ±10.6	0.10
Solid Tumor		10	6.3 ± 1.4		9.0 ± 4.1	
ANC	>100	18	6.7 ± 4.8	0.094	10.3 ± 7.3	0.15
	≤100	6	11.0 ± 6.3		16.0 ± 11.7	
ANC	>200	15	5.7 ± 1.5	0.013	9.2 ± 4.8	0.055
	≤200	9	11.2 ± 7.7		15.9 ± 11.3	
Microorganism						
	(+)	5	6.2 ± 7.8	0.47	12.8 ± 11.7	0.75
	(-)	19	8.2 ± 6.0		11.4 ± 8.9	
Remission		15	5.6 ± 1.7	0.007	7.9 ± 4.1	0.002
Nonremission		9	11.4 ± 7.4		18.0 ± 10.0	

Data are days; ANC, absolute neutrophil count

used and accepted. Single agent therapy became a possibility when broad-spectrum antibiotics, such as third and fourth generation cephalosporins with anti-Pseudomonal activity (ceftazidime or cefepime), ureidopenicillins with β-lactamase inhibitors, and carbapenems, became available (Vandercam et al., 2000; Agaoglu et al., 2001; Paulus and Dobson, 2009). Imipenem is a broad spectrum antibacterial agent of the carbapenem family, indicated as empirical therapy prior to the identification of causative organisms, or for disease caused by single or multiple susceptible bacteria in both adults and children with a broad range of serious infections (Zhanel et al., 2007). We started empirical imipenem monotherapy in patients included in the study, and achieved an 95.8% clinical success. During this study period we did not observe any drug-related adverse events. In other studies where imipenem was used as the first choice, Riikonen and his colleagues (1991) reported a 82% success, while Freifeld and his colleagues (1995) stated their success rate as 98%.

While the causative microorganism remains unknown in 70-80% of all febrile episodes, 20-30% can be documented microbiologically (Müler et al., 2005). In this study period, our microbiologically documented infections rate (20.8 %) was similar to the literature.

Yildirim et al. (2008) have started empirical carbapenem therapy (imipenem + meropenem) in 41 of the 87 FN attacks they treated in leukemia patients, while initiating empirical piperacillin tazobactam plus amicasin therapy in 46 attacks, and reported mean neutropenia duration as 7.3 ± 5.2 and mean duration of hospital stay as 12.6 ± 5.3. In this study, durations of neutropenia and hospital stay was found to similar to the literature.

The underlying disease not being in remission, and an ANC of less than 100/mm^3 are among factors related to poor prognosis in FN (Santolaya et al., 2001). As we detected in our study also, duration of neutropenia and hospital stay were longer in children who were not in remission for the malign disease. On the other hand, it was observed that for patients with ANC of less than 200/mm^3 the duration of neutropenia was significantly longer. Even though in this study the differences were not significant for patients with ANC of less than 100/mm^3, our results support that severe neutropenia negatively affects prognosis.

In conclusion, empirical imipenem therapy applied in our study was detected to be successful and safe. It was observed that duration of FN was significantly longer in patients with an ANC of less than 200/mm^3, and in children who were not in remission for the malign disease. In addition, average time of stay in hospital was observed to be significantly longer in patients who were not in remission for the underlying malign disease.

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