RESEARCH COMMUNICATION

Meropenem Monotherapy as an Empirical Treatment of Febrile Neutropenia in Childhood Cancer Patients

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Abstract

Introduction: Chemotherapy related neutropenia developing in oncologic patients is a significant condition and major cause of morbidity and mortality. Febrile neutropenic attacks without complications can be successfully treated with wide-spectrum anti-pseudomonal cephalosporins or carbapenems. Objective: We investigated the efficacy and safety of meropenem in the treatment of febrile neutropenia (FN) in children with cancer. Materials and Methods: Twenty four patients who had a febrile neutropenic episodes followed by initiation of empirical meropenem therapy were included in the study. Results: Of all the patients, 13 (54.2%) had solid tumors, while 11 (45.8%) were diagnosed to have acute leukemia. Among all, 7 (29.2%) and 15 (62.5%) infections were identified microbiologically and clinically, respectively. Fever of unknown origin was observed in 2 (8.3%) patients. The mean duration of neutropenia was 7.2 ± 3.1 (4-14) days in patients with solid tumors, and 9.3 ± 4.7 (2-17) days in the group with leukemia. This difference was not statistically significant (log rank, p=0.063). Average time of stay in hospital was 10.1 ± 6.4 (4-21) days for patients with solid tumors, and 15.9 ± 11.7 (5-37) days for patients with leukemia (log rank, p=0.041). FN duration was observed to be significantly longer in patients with an absolute neutrophil count (ANC) of less than 100/mm^3 and even those with an ANC of less than 200/mm^3, and in children who were not in remission for the underlying malign disease (p<0.05). While 22 (91.7%) of the patients were discharged from the hospital, 2 (8.3%) died. The success rate of empirical therapy started with meropenem was 87.5%. Conclusion: Meropenem is effective and safe for treatment of FN in pediatric cancer patients.

Key Words: Choldhood cancer - febrile neutropenia - meropenem treatment

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Introduction

Patients with an abnormally low neutrophil count of < 500/mm^3, 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 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; Erbey et al., 2009).

The purpose of the present study was to determine the efficacy and safety of meropenem in the treatment of FN in children with cancer.

Materials and Methods

We reviewed medical records of pediatric cancer patients experiencing 24 episodes of fever and chemotherapy-induced neutropenia retrospectively in between April 2004 and March 2005. Patient selection criteria were determined according to the guidelines of Infectious Disease Society of America (IDSA); Neutropenia was defined as an absolute neutrophil count (ANC) of <500/mm^3 or a count of <1000/mm^3 but expected to fall <500/mm^3 within 48 hours; and fever was defined as either a single axillary temperature of at least 38.5 °C or axillary temperature of exceeding 38.0 °C for ≥1 h or two times within 12-h 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 cultures were taken before initiation of antibiotic treatment. At least one blood sample was drawn through catheter and from peripheral vein from patients who had indwelling venous catheters. Antibiogram profiles of isolates were determined for commonly used antibiotics. Patients received meropenem 60 mg/kg/day intravenously over 30-60 minutes, every 8 h.

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Each patient and/or parent gave informed consent before being included in the study. The study respected the guidelines of the Helsinki Declaration concerning medical research in humans, and received local ethics committee approval. No support was obtained from 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 clinical deterioration, antibiotic treatment was changed or modified. Glycopeptide was added when staphylococci grew in culture. Addition of systemic antifungal therapy was usually considered in patients with FN in case of unresponsiveness to broad-spectrum antibiotic therapy and the persistence of clinical symptoms and fever for more than 5 days. Cultures were repeated during therapy until fever ceased. Chest radiography was repeated 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 values (± 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 meropenem treatment (male/female:12/12) were included in our study. Patients had a mean age of 8.6 ± 3.8 (1.5-14) years. Of all the patients, 13 (54.2%) had solid tumors, while 11 (45.8%) had acute leukemia. In all, 7 (29.2%) and 15 (62.5%) of the infections were identified microbiologically and clinically, respectively. Fever of unknown origin was observed in 2 (8.3%) 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 8.1 ± 4.0 (2-17) days, and mean duration of hospital stay was 12.8 ± 9.5 (4-37) days. While mean duration of neutropenia was 7.2 ± 3.1 (4-14) days in children with solid tumors, it was 9.3 ± 4.7 (2-17) days in the group with leukemia. This difference was not statistically significant (log rank, p=0.063). Mean duration of hospital stay was 10.1 ± 6.4 (4-21) days in patients with solid tumors, while being 15.9 ± 11.7 (5-37) days in those with leukemia. This difference was statistically significant (log rank, p=0.041) (Figure 1).

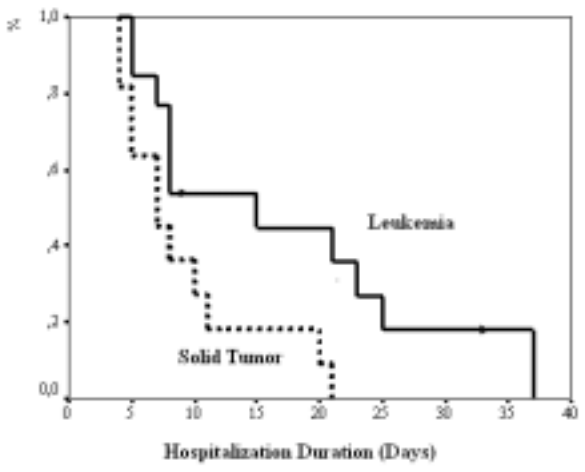

Figure 1. Hospitalization Duration Curves

Table 1. Characteristics of the Patients/Episodes

Age (median /range) (years)		8.6 ± 3.8 (1.5-14)
Sex (male/female)		12/12 (50/50)
Underlying malignancy	Solid tumor	13 (54.2)
	Acute leukemia	11 (45.8)
Status of cancer	Remission	11 (45.8)
	Nonremission	13 (54.2)
Entry ANC severity	≤100/mm^3	8 (33.3)
	>100/mm^3	16 (76.7)
Central indwelling venous cathether[a]		1 (4.2)
Patients receiving G-CSF		19 (79.2)
Mean receiving G-CSF		2.5 ± 1.4 (1-5 days)
Diagnosis of infection episode-fever		2 (8.3)
Microbiologically documented infection		7 (29.2)
Clinically suspected infection[b]		15 (62.5)
	Pneumonia	9 (62.5)
Upper respiratory tract infection		7 (29.2)
	Gastroenteritis	4 (16.7)
	Mucositis	11 (45.8)
	Urinary infection	6 (25.0)
Microorganisms established		
Blood	Klebsiella pneumonia	1 (4.2)
	Staphylococcus hominis	1 (4.2)
	Staphylococcus warneri	1 (4.2)
	Streptococcus mitis[c]	1 (4.2)
	Enterobacter cloacae[c]	1 (4.2)
Urine	Candida nonalbicans	1 (4.2)
Stool	Coagulase -ve Staphylococcus	1 (4.2)
	Candida albicans	1 (4.2)
	Rotavirus[c]	1 (4.2)
Ear	Pseudomonas aeruginosa[c]	1 (4.2)
Nose	Mucor mycosis[c]	1 (4.2)
Total		11 (45.8)
Results of empirical therapy		
Continuing without modification[d]		12 (50.0)
Continuing with modification [d]		
Glikopeptid		12 (50.0)
Antifungal		9 (62.5)
Antiviral		3 (12.5)
Change of initial study antibiotic		1 (4.2)
Results of treatment	Success at 72 h	1 (4.2)
	Success in 7 days	12 (50.0)
	With modification	12 (50.0)
	Overall success	21 (87.5)
	Failure	3 (12.5)

ANC, absolute neutrophil count; [a]One bacteremia case was catheter related; G-CSF: Granulocyte Colony Stimulating Factor; [b]Upper infections in a patient; [c]Multiple microorganisms identified in 2 patients; [d]Status at early evaluation (72 hours)

Investigation of the factors affecting duration of neutropenia and hospital stay revealed that patients with an ANC of 100/mm^3 and less, and even those 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. Duration of hospital

Table 2. Factors Affecting Febrile Neutropenia and Hospitalization Duration

		Mean duration (days)			ANOVA test
		FN	P value	Hospitalization	P value
Sex	Male	9.0 ± 4.1	0.29	14.3 ± 9.7	0.42
	Female	7.3 ± 3.9		11.2 ± 9.3	
Age	>Five	8.1 ± 4.2	0.84	21.3 ± 13.5	0.046
	≥Five	8.5 ± 3.1		11.1 ± 7.8	
Type	ALL	6.8 ± 2.9	0.054	10.0 ± 6.5	0.06
	AML	12.2 ± 5.1		23.0 ± 13.1	
ANC	>100	6.7 ± 3.2	0.009	11.0 ± 10.2	0.21
	≤100	11.0 ± 4.1		16.3 ± 6.9	
ANC	>200	6.6 ± 3.4	0.02	10.6 ± 10.6	0.19
	≤200	10.3 ± 3.9		15.8 ± 7.0	
Microorganism					
	(+)	9.1 ± 4.3	0.36	12.8 ± 8.0	1.00
	(-)	7.5 ± 3.8		12.7 ± 10.5	
Remission		5.9 ± 2.7	0.009	9.1 ± 6.7	0.081
Nonremission		10.0 ± 4.0		15.9 ± 10.6	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count

stay was detected to be significantly longer in patients 5 years old and younger (Table 2). Throughout the study period, meropenem treatment was supported with glycopeptid in 12 (50%) patients, with antifungal agents in 9 (37.5%) patients, and with acyclovir in 3 (12.5%) patients. In one patient, meropenem was replaced with ceftazidime, as the growing microorganisms proved sensitive to ceftazidime. While twenty-two patients (91.7%) were discharged from the hospital, 2 patients (8.3%) died. The success rate of empirical therapy started with meropenem was detected as 87.5%. During these episodes, we did not recognize any drug-related adverse events.

Discussion

Traditionally, a combination of an aminoglycoside plus an antipseudomonal β-lactam agent is the most widely 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; Erbey et al., 2009; Paulus and Dobson, 2009). Meropenem 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 (Baldwin et al., 2008). We started empirical meropenem monotherapy in patients included in the study, and achieved an 87.5% clinical success. During this study period we did not observe any drug-related adverse events. In other studies where meropenem was used as the first choice, Müller et al. (2005) reported a 72.9% success, while Kutluk et al. (2004) stated their success rate as 87.5%. While the causative microorganism remains unknown in 70-80% of all febrile episodes, 20-30% can be documented microbiologically (Müller et al., 2005). In this study period, the rate of our microbiologically documented infections (29.2 %) was similar to those reported in literature.

Müller et al (2005) have investigated 87 FN episodes developing in 55 pediatric patients, and detected mean neutropenia durations as 19.9 ± 6.6 days in AML, 14.9 ± 9 days in ALL, and 8.6 ± 3.5 days in patients with solid tumors. Similarly in this study, durations of neutropenia and hospital stay was found to be shorter in cases with solid tumors compared to leukemic patients. In another study, Oguz et al (2006) investigated 65 FN attacks in 37 patients with solid tumors, and detected the mean hospital stay as 11.5 ± 2.8 days and the mean neutropenia duration as 6.6 ± 3.3 days in the group which received meropenem. 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.

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 these patients.

In our previous study, we used empirical imipenem monotherapy in a similar study group. The overall success rate was 95.8%. 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. 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 (Erbey et al., 2009). This findings was similar to current study.

In conclusion, empirical meropenem therapy applied in our study was detected to be successful and safe. It was observed that duration of hospital stay was significantly shorter in patients with solid tumors compared to those with leukemia, and also that duration of FN was significantly longer in patients with an ANC of less than 100/mm^3 and even in those with an ANC of less than 200/mm^3, and in children who were not in remission for the malign disease.

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