Monotherapy with meropenem versus combination therapy with piperacillin plus amikacin as empiric therapy for neutropenic fever in children with lymphoma and solid tumors

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SUMMARY: Düzova A, Kutluk T, Kanra G, Büyükpamukçu M, Akyüz C, Seçmeer G, Ceyhan M. Monotherapy with meropenem versus combination therapy with piperacillin plus amikacin as empiric therapy for neutropenic fever in children with lymphoma and solid tumors. Turk J Pediatr 2001; 43: 105-109.

The purpose of this study was to compare meropenem monotherapy with combination therapy for empirical treatment of neutropenic fever in children with lymphoma and solid tumors. Ninety episodes of neutropenic fever in children (0.7-16.0; mean age 7.7 years) with solid tumors in a single center were randomized to receive either meropenem (50 mg/kg/dose-maximum 1 g, every 8 hours) or piperacillin (200 mg/kg/dose, every 6 hours) plus amikacin (15 mg/kg daily). Failure was defined as treatment modification. Non-Hodgkin's lymphoma (NHL) accounted for 62.2 percent of all episodes, and solid tumors (37.8%) for the rest. Blood cultures were positive in 23 percent of all episodes. Sixty-seven percent of all isolated microorganisms stained Gram-positive. Overall success was 70.0 percent (63/90). The success with meropenem was comparable to that seen with piperacillin plus amikacin: 76.6 versus 64.6 percent ($p = 0.25$). The failure rate was 33 percent with Gram-positive culture and 78 percent with Gram-negative or mixed cultures. The solid tumor group had significantly less bacteremia (4/34 versus 17/56; $p < 0.05$) and treatment failure (3/34 versus 24/56; $p < 0.001$) than the NHL group. No serious drug-related adverse event was noticed. Meropenem monotherapy was as effective as piperacillin plus amikacin combination in the empirical treatment of neutropenic fever in children with lymphoma and solid tumors.

Key words: neutropenic fever, children, meropenem, monotherapy.

Empirical broad-spectrum antibiotic therapy has reduced the risk of death in patients with neutropenic fever. During the past two decades combination therapy with betalactams and aminoglycosides has been standard therapy[1-4]. The invention of extended spectrum cephalosporins and carbapenems offered single-agent therapy. Although studies conducted by De Pauw et al.[5] and Pizzo et al.[6] showed that ceftazidime, the most widely used cephalosporin monotherapy, was as effective as combination therapy, its lack of activity against some Gram-positive organisms and increasing Gram-negative resistance against ceftazidime may limit its use[5,6]. Carbapenems, with their microbiological activity against both Gram-positive and Gram-negative bacteria, were promising candidates for empirical therapy in neutropenic fever. The Meropenem Study Group revealed that meropenem monotherapy was as effective as ceftazidime monotherapy[7]. The European Organization for Research and Treatment of Cancer Study showed that monotherapy with meropenem was equivalent to combination therapy with ceftazidime plus amikacin[8].

The present study was a single center, prospective, randomized trial to compare meropenem monotherapy versus combination therapy for empirical treatment of neutropenic fever in children with lymphoma and solid tumors.

Material and Methods

Patient Eligibility: This trial was conducted in a single center, Pediatric Oncology and Infectious Diseases Units of Hacettepe University, İhsan Doğramacı Children's Hospital, Ankara, Turkey. Patients (≤ 16 years of age) with lymphoma and solid tumors were eligible for randomization if they had fever (defined as a single oral temperature above 38.3 °C or a temperature of 38.0 °C or greater taken on two occasions at least 1 hour apart), neutropenia (absolute neutrophil count, ANC ≤ 500/mm³) and were without an apparent infection. Patients with leukemia were not included in this study since they were treated in another department. Patients were excluded if they had received antibiotics within the last four days, had blood or blood product infusion or had been given colony stimulating factor within the last six hours. None of our patients had a known allergy to any of the antibiotics prescribed in the protocol.

Initial Evaluation: A complete history was taken from each patient, and a detailed physical examination was performed. Complete blood count, peripheral blood smear, CRP, erythrocyte sedimentation rate, routine chest X-rays, urinalysis, urine culture and blood cultures (two sets, from different venipunctures at 30-minute intervals; two additional sets from central venous line if the patient had any), and other cultures (when indicated) were performed.

Study Design and Procedure: A total of 90 consecutive neutropenic fever episodes were evaluated. Episodes were randomized to receive either meropenem (50 mg/kg/dose-maximum 1 g, every 8 hours, infused over 20-30 minutes) or piperacillin (200 mg/kg/dose, every 6 hours) plus amikacin (15 mg/kg daily) in this one-side blinded study. Treatment modification was done after 72-96 hours (depending on the clinical condition) if the patient still had fever and neutropenia. The minimum duration of treatment was seven days, four of which were consecutive without fever. Failure was defined as treatment modification.

Statistical Analysis: All data were entered into a computerized data base and analyzed using SPSS programs. Chi-square (Fisher's exact tests for small samples) and Mann-Whitney U tests were used for comparison.

Results

The mean age was 7.7 years for the whole group (0.7-16.0; ± 4.46). The characteristics of the 90 episodes are given in Table I. Non-Hodgkin's lymphoma (NHL) (56 episodes) made up 62.2 percent of all episodes, and solid tumors the remainder (37.8%): rhabd-myosarcoma (8), Ewing's sarcoma (6), neuroblastoma[6], medulloblastoma (3), nasopharynx carcinoma (2), germ cell tumor (2), PPNET (2), and Hodgkin's disease, mesothelioma, Wilms's tumor, retinoblastoma, hepatoblastoma (1 episode each). Patients had central venous line in only 10 episodes (11%). The two treatment groups were comparable according to the parameters given in Table I.

Table I. Characteristics of 90 Episodes

Characteristics	Treatment groups	
	Meropenem	Piperacillin + Amikacin
Episodes (n)	45	45
Age [mean (range)]	7.0 (1.0-15.0)	8.4 (0.7-16.0)
Male/Female	27/18	21/24
Lymphoma (n)	27	29
Solid tumor (n)	18	16
Central line (yes/no)	5/40	5/40
Radiotherapy (yes/no)	13/32	12/33
Antimicrobial prophylaxis	None	None
Status of the disease		
Progression and relapse	10	14
Other status	35	31
Interval with the last chemotherapy (days) mean (range)	10 (2-16)	10 (3-19)
Hemoglobin (gr/dl) [mean (range)]	7.9 (4.0-13.0)	8.2 (5.2-12.1)
WBC (/mm³) [mean (range)]	805 (300-1600)	882 (100-2100)
Platelet (/mm³) [mean (range)]	68000 (9000-321000)	72000 (5000-444500)
ESR (mm/hour) [mean (range)]	82 (4-145)	92 (5-150)
CRP p(mg/dl [mean (range)]	6.9 (0.1-22.0)	8.7 (0.2-25.3)
ANC		
mean (range) (/mm³)	148 (0-500)	155 (0-450)
episodes with ≤ 100/mm³ at entry	19	23
Duration of ANC (median days)		
≤ 100/mm³	1	1
≤ 500/mm³	3	3
≤ 1500/mm³ (/mm³)	5	4
Success rate (%)	76.6	64.6

Duration of Neutropenia and Fever: The mean duration of neutropenia was 4.1 days (1-20); the difference between groups was not statistically significant. Neutropenia duration in episodes with progression and relapse was longer than in ones without active disease: four days (1-13) versus three days (1-21); $p < 0.05$). The mean duration of fever was 3.8 days (1-20). Although fever subsided earlier in the meropenem group, the difference between groups was not statistically significant (meropenem 3.4 days; piperacillin plus amikacin 4.3 days; $p = 0.27$).

Bacteremia: Blood cultures were positive in 23 percent of all episodes (21/90, 6 of them were polymicrobial: 1 double Gram-positive, 5 mixed). The distribution of 27 microorganisms isolated in 21 episodes is shown in Table II [single Gram-positive 44% (12/27), single Gram-negative 15% (4/27), mixed 41% (11/27)]. Gram-positives constituted 67 percent of all isolated microorganisms. One-third (4/12) of staphylococci were methicillin-resistant (MRSA). The stage of disease seemed to increase the risk of bacteremia: the risk was higher in cases of progression and relapse (38% versus 18%, $p = 0.055$). If the patient still had fever after 96 hours, the risk of bacteremia increased to 42 percent (vs 17%, $p < 0.05$).

Table II. Gram Staining of Blood-Isolated Microorganisms

Gram staining	Single (n)	Polymicrobial (n)	n (%)
Gram-positive	11	7	18 (66.7)
S. coagulase (-)	7	3	10 (37.0)
S. aureus	1	1	2 (7.4)
α-hemolytic Streptococcus	3	2	5 (18.5)
S. pneumoniae	–	1	1 (3.7)
Gram-negative	4	5	9 (33.3)
E.coli	1	3	4 (14.8)
P. aeruginosa	1	–	1 (3.7)
S. maltophilia	1	1	2 (7.4)
Klebsiella	–	1	1 (3.7)
Acinetobacter	1	–	1 (3.7)
Total	15	12	27 (100.0)

Mortality: The proportion of episodes ending in death was 2.2 percent (2/90). The first patient was a 13.5-year-old boy, stage III, abdominal NHL, with partial response to LMB-B chemotherapy. E. coli and MRSA had been isolated from blood culture. He had been given amphotericin B starting on the 7th day, and died on the 21st day when his ANC was still < 100/mm^3 and platelet count was < 50,000/mm^3. The second one was a 13.8-year-old girl, stage IV NHL, with relapsed disease. S. maltophilia and MRSA had been isolated from blood culture. She had been given amphotericin B starting on the 7th day, and died on the 9th day when her ANC was still < 100/mm^3 and platelet count was < 50,000/mm^3. The underlying disease was in terminal stage in this patient.

Non-Hodgkin's Lymphoma Versus Solid Tumors: The differences between the non-Hodgkin's lymphoma and solid tumor groups was striking. The solid tumor group had significantly less bacteremia (4/34 versus 17/56; $p < 0.05$) and treatment failure (3/34 versus 24/56; $p < 0.001$) than the NHL group.

CRP, ESR: Neither the CRP nor ESR level was associated with the risk of bacteremia, type of microorganism isolated, treatment failure, or amphotericin B use. No serious drug-related adverse event was noticed.

Discussion

With intensive chemotherapy, the five year disease-free survival rate in childhood cancer is 75 percent[1]. Neutropenic fever is one of the leading causes of morbidity and mortality either directly or indirectly by causing a delay or dose reduction in the chemotherapy regimen. Continuous monitoring of parameters (characteristics of patients, isolated microorganisms, causes of treatment failure, etc.) is crucial for determining a policy for treating neutropenic fever in an oncology center. Monotherapy leads to fewer adverse effects; morover, it reduces the amount of time and supplies needed for administering the antibiotics.

The median duration of neutropenia was three days in our study (1-21) compared to 11 days, 10 days (1-68) and nine days in studies conducted by EORTC and GIMEMA[8], Lucas et al.[3] and Petrilli et al.[4], respectively. The absence of leukemia and bone marrow transplantation patients in our trial very likely resulted in this difference.

Bacteria were isolated from blood cultures in 23 percent of all episodes, which was consistent with recent trials (24%, EORTC and GIMEMA; 24.4%, Lucas et al.)[8,3]. The significant difference between NHL and solid tumor groups (30.4% vs 11.8%) that we detected was also noticed by Lucas et al.[3] (24.4% in leukemia/lymphoma vs 3.1% in solid tumors)[3]. This fact probably contributed to less antibiotic modification in episodes with solid tumors in our study (3/34

vs 24/56; $p < 0.01$). With their shorter duration of neutropenia, and lesser culture positivity and requirement of antibiotic modification, neutropenic fever patients with solid tumors are promising candidates for early discharge, outpatient management and oral treatment.

Gram-positives constituted 67 percent of isolated microorganisms, as is the case in most centers[7-11]. In many centers 80 to 90 percent of patients have intravenous catheters. Lindblad[9] reported that 25 percent of patients with a central venous line had bacteremia (69% Gram-positive) compared to 14 percent of patients without a central venous line (40% Gram-positive)[9]. Although central venous lines were present in only 10 episodes (11%), Gram-positives still constituted two-thirds (67%) of isolated microorganisms (63% even if episodes with central venous line are excluded). Some factors other than increased use of intravenous device (such as hand washing and resistance to β-lactam antibiotics) may explain Gram-positive predominance.

Success against Gram-positive bacteremia without antibiotic modification was much higher in our center [67% vs 29% (Behre et al.[11]) and 28% (EORTC GIMEMA)[8]]. On the other hand, we had a much lower success rate against Gram-negative and mixed bacteremia [22% vs 47% (EORTC GIMEMA)[8]] irrespective of the antibiotic group.

Because there has been a considerable reduction in Gram-negative bacteremic episodes over the last 10 years, some authors believe that the need for aminoglycoside-containing regimens should be reassessed. Meropenem, which is highly stable to inactivation by renal dehydropeptidase, does not require cilastatin; moreover, its spectrum covers most Gram-positive, Gram-negative and anaerobic bacteria. It is successfully used in intraabdominal infections, meningitis, urinary tract infections and lower respiratory tract infections as an alternative to some combination therapy[12]. It does not increase the risk of seizure and has a lower incidence of nausea and vomiting than does imipenem/cilastatin.

Previous clinical studies with meropenem monotherapy in neutropenic fever were conducted in adult patients[7-11]. Only the EORTC GIMEMA trial included both children and adult patients[8]. Success rates varied between 45-60 percent. It is well known that neutropenia is shorter in duration in children than in adult patients[13]. The absence of leukemia and bone marrow transplantation patients and shorter duration of neutropenia very likely contributed to a higher success rate in our study. We also strictly avoided early modification before 96 hours (compared to 72 hours in other studies) unless the patient deteriorated clinically.

There are limited studies concerning meropenem monotherapy for neutropenic fever in children. Our study showed that meropenem monotherapy was well tolerated and was as effective as piperacillin plus amikacin combination therapy. The success rates of both groups were comparable with other empirical regimens. We conclude that meropenem monotherapy can be used in the empirical treatment of neutropenic fever in children with lymphoma and solid tumors.

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