RESEARCH ARTICLE

Meropenem Versus Piperacillin-Tazobactam as Empiric Therapy for Febrile Neutropenia in Pediatric Oncology Patients

Gulay Sezgin*, Can Acipayam, Ayse Ozkan, Ibrahim Bayram, Atila Tanyeli

Abstract

Background: Infection is a serious cause of mortality in febrile neutropenia of pediatric cancer patients. Recently, monotherapy has replaced the combination therapy in empirical treatment of febrile neutropenia. Since there has been no reported trial comparing the efficacy of meropenem and piperacillin-tazobactam (PIP/TAZ) monotherapies, the present retrospective study was conducted to compare safety and efficacy in febrile neutropenic children with cancer. Materials and Methods: Charts of febrile, neutropenic children hospitalized at our center between March 2008 and April 2011 for hemato-oncological malignancies were reviewed. Patients received PIP/TAZ 360 mg/kg/day or meropenem 60 mg/kg/day intravenously in three divided doses. Duration of fever and neutropenia, absolute neutrophil count, modification, and success rate were compared between the two groups. Resolution of fever without antibiotic change was defined as success and resolution of fever with antibiotic change or death of a patient was defined as failure. Modification was defined as changing the empirical antimicrobial agent during a febrile episode. Results: Two hundred eighty four febrile neutropenic episodes were documented in 136 patients with a median age of 5 years. In 198 episodes meropenem and in 86 episodes PIP/TAZ were used. Duration of fever and neutropenia, neutrophil count, sex, and primary disease were not different between two groups. Success rates and modification rate between two groups showed no significant differences (p>0.05). Overall success rate in the meropenem and PIP/TAZ groups were 92.4% and 91.9% respectively. No serious adverse effects occurred in either of the groups. Conclusions: Meropenem and PIP/TAZ monotherapy are equally safe and effective in the initial treatment of febrile neutropenia in children with cancer.

Keywords: Pediatric febrile neutropenia - meropenem - piperacillin-tazobactam - childhood cancer - monotherapy

Asian Pac J Cancer Prev, **15 (11)**, 4549-4553

Introduction

Despite advances in treatment of cancer with chemotherapy and supportive care, febrile neutropenia (FEN) is a common complication after chemotherapy with a mortality between 2% to 6%. FEN should be managed efficiently and empiric antimicrobial treatment should be started immediately (Santaloya et al., 2007) . FEN management has changed in the recent years and patients have been treated due to some risk factors. There are a few studies in pediatric age group to determine risk factors for febrile neutropenia (Santaloya et al., 2002; Hartel et al., 2007). Initial antibiotic treatment for FEN should have a wide spectrum, be bactericidal and have anti-pseudomonal activity. Institutional bacterial resistance patterns should also be used to guide selection of first-line antibiotics (Hughes et al., 2002; Koh and Pizzo, 2010). Initially, beta-lactam and aminoglycoside combination have been used in the empiric treatment of febrile neutropenia (Cometta et al., 1995; Aksoylar et al., 2004). Recently, monotherapy with broad spectrum and bactericidal antibiotics replaced combination therapy. Effective monotherapies include anti-pseudomonal cephalosporins, carbapenems, ureidopenicillins, and cephalosporins combined with beta lactamase inhibitors (Agaoglu et al., 2001; Corapcioglu et al., 2006; Erbey et al., 2009; Uygun et al., 2009; Erbey et al., 2010; Vural et al., 2010; Demir et al., 2011; Ichikawa et al., 2011; Karaman et al., 2012).

Piperacillin/tazobactam (PIP/TAZ) is a beta-lactam/beta-lactamase inhibitor combination that has a wide range of activity against Gram-positive, Gram-negative, and anaerobic pathogens (Jones et al., 1989). Meropenem is a member of carbapenems, possesses the broadest antibacterial spectrum of any class antibiotic and has the advantage of having activity against extended-spectrum beta-lactamase-(ESBL) producing organisms. Recently, a meta-analysis found that for initial treatment of neutropenic fever, PIP-TAZ resulted in lower all-cause mortality than other beta-lactam antibiotics, including carbapenems in adult cancer patients (Paul et al., 2006). Pediatric data about this issue are very limited. To our knowledge, there is no study comparing meropenem to PIP/TAZ in pediatric hemato-oncology patients with febrile neutropenia. The aim of this retrospective clinical

*Division of Pediatric Oncology and BMT Unit, Cukurova University Medical School, Adana, Turkey *For correspondence: gulaysezgin@yahoo.com*

study is to compare the efficiency and toxicity of PIP/TAZ and meropenem monotherapy for the empirical treatment of pediatric cancer patients with fever and neutropenia.

Materials and Methods

Patients

Between March 2008 and April 2011, all children with FEN who had been treated for hemato-oncological malignancies, who were <18 years of age were identified. Fever was defined as either a single axillary temperature of ≥38.3˚C or sustained temperature over 1h of ≥38.0˚C. Neutropenia was defined as an absolute neutrophil count (ANC) ≤500 cells/mm^3 or ≤1,000 cells/mm^3, which was expected to be ≤500 cells/mm^3 within 24-48h (Hughes et al., 2002). Patients were identified more than once if they had a distinct episode of FEN and prior antibiotic treatment that had been completed at least 2 weeks earlier. Exclusion criteria were; presence of hypotension and multi-organ failure and intravenous antibiotic treatment within 48 hours of admission. Prophylactic antibiotics were not administered in any of the patients before or during antibiotic treatment.

Electronic and paper records were reviewed. Blood (both peripheral blood and central venous catheter (CVC) if present) and urine cultures, and cultures from any local site suspected to be infected were collected before antibiotic administration. The remission status, the presence of mucositis, the ANC, the duration of neutropenia and fever were recorded.

Classification of the febrile episodes

Infections were defined as fever of unknown origin (FUO) if the infection focus could not be defined, microbiologically documented infection (MDI, microorganism is isolated) and clinically documented infection (CDI, if typical signs of infection were found in physical examination despite no culture growth).

Antibiotic treatment

All patients received treatment on an inpatient basis. PIP/TAZ 360 mg/kg/day or meropenem 60mg/kg/day was started intravenously in three divided doses. Divisional policy was to evaluate the patients after 72 hr of treatment. If fever persisted >38.0˚C at 72 hr, and there was no microbiologically documented infection, amikacin at 15 mg/kg/day was added; if the patient still remained febrile at 96 hr, a glycopeptide (teicoplanin) at 10 mg/kg/day was added. In case of MDI and no clinical improvement, the antibiotic therapy was adjusted according to the antibiogram results. Empirical Amphotericin B at 3 mg/kg/day was started in patients with persistent fever on the 7th day of the febrile episode. Antibiotic therapy was continued until fever subsided and the neutrophil count was over 500 cells/mm^3 for 2 days. GCSF was used (5 μcg/kg/day, sc) as secondary prophylaxis when needed. Adverse events were recorded.

Evaluation of the treatment

Modification was defined as change in the initial empirical antimicrobial agent. The treatment was regarded as a success if fever and clinical signs of infection resolved without treatment modification. The treatment was regarded as a failure if another antibiotic or antifungal agent was added or the patient died due to infection during febrile neutropenia.

Statistical evaluation

Statistical analysis was performed using SPSS, version 11.5 (SPSS Inc., Chicago, IL). The data was evaluated using descriptive statistical methods. Statistical differences between study groups were assessed by chi-square test for categorical variables and student t-test for continuous variables. Two-tailed p values were used and p values of <0.05 were defined as significant.

Results

Patient quality

During the study period, 284 episodes in 136 patients (51 female, 85 male; median age 60 months, range, 4-231 months) were documented. Table 1 shows the characteristics of the episodes. There was no statistical difference for sex, underlying disease, number of initial ANC, duration of febrile neutropenia, remission status, grade 3-4 mucositis and number of patients receiving GCSF between the two treatment groups. Patients in the meropenem group were younger than the patients in the PIP/TAZ group (p=0.04).

Characteristics of the febrile attacks

Ninety eight episodes were seen in patients with leukemia 186 episodes were in patients with solid tumors. The mean ANC for the whole group was 108±200 cells/mm^3. In 70% of episodes, the neutrophil count was under 100 cells/mm^3. The median neutropenia duration was 7 days (range 0-80 days). The period of neutropenia was over 10 days in 20% of episodes. There was no difference between groups in terms of gender, remission status,

Table 1. Characteristics of the Febrile Neutropenic Episodes Treated with Two Different Antibiotics

Number of episodes	Meropenem (n=198)	PIP/TAZ (n=86)	Total (n=284)	p value
Age (months)				
Median	57	83	60	0.04
Range	4-231	5-228	4-231	
Sex				
Female	73 (37%)	35 (41%)	108 (38%)	0.54
Male	125 (63%)	51 (59%)	176 (62%)	
Primary disease				
Leukemia	127 (64%)	59 (69%)	186 (65%)	0.47
Solid tumors	71 (36%)	27 (31%)	98 (35%)	
Absolute neutrophil count, cells/mm^3				
Mean±SD	99±176	130±245	108±200	0.29
Episodes <100	143 (50%)	57 (20%)	200 (70%)	
Duration of febrile neutropenia (days)				
Median	7	6	7	
Range	0-80	2-30	0-80	0.28
Episodes >10d	41 (21%)	16 (19%)	57 (20%)	
Remission status				
In remission	43 (22%)	12 (14%)	55 (19%)	0.13
Grade 3-4 mucositis				
Yes	70 (35%)	36 (42%)	106 (37%)	0.29
GCSF use	147 (74%)	67 (78%)	214 (75%)	0.51

*GCSF: Granulocyte colony stimulating factor

Table 2. Clinically Documented Infections in Febrile Neutropenic (FEN) Episodes

Infection	Meropenem		PIP/TAZ		Total	
	n	%	n	%	n	%
FUO	58	29.3	28	32.6	86	30.3
URTI+oral cavity	33	16.7	20	23.3	53	18.7
Pneumonia	53	26.8	19	22.1	72	25.7
UTI	6	3.0	1	1.2	7	2.5
Typhilitis	1	0.5	1	1.2	2	0.7
Soft tissue infection	7	3.5	2	2.3	9	3.2
GIS infection	10	5.1	5	5.8	15	5.3
Port infection	5	2.5	0	0	5	1.8
Sepsis syndrome	22	11.1	10	11.6	32	11.3
Others	3	1.5	0	0	3	1.1
Total	198	100	86	100	284	100

*FUO: Fever of unknown origin; URTI: Upper respiratory tract infection; UTI: Urinary tract infection; GIS: Gastrointestinal system

Table 3. Microbiologically Documented Infections in FEN Episodes

Sample	Organism	Meropenem	PIP/TAZ	Total
No isolation		158	72	230
Catheter				
	E.Coli	1	1	2
	Klebsiella pneumonia	2	0	2
	Klebsiella oxytoca	1	0	1
	Pseudomonas aeroginosa	1	0	1
	Enterococcus fecalis	1	0	1
	Citrobacter sedlakii	1	0	1
	Staphylococcus haemolyticus	1	0	1
	Candida albicans	1	0	1
	Candida pelliculosa	1	0	1
	Candida tropicalis	0	1	1
Urine	E.Coli (ESBL+)	1	0	1
	Klebsiella pneumonia	0	1	1
Wound	Pseudomonas aeroginosa	0	1	1
Peripheral blood				
	E.Coli	5	0	5
	E.Coli (ESBL+)	0	1	1
	Klebsiella pneumonia	3	1	4
	Klebsiella spp	1	1	2
	Klebsiella spp (ESBL+)	0	1	1
	Pseudomonas aeroginosa	3	1	4
	Pseudomonas spp	0	1	1
	Staphylococcus aerus	1	0	1
	Staphylococcus epidermidis	6	0	6
	Staphylococcus hominis	4	2	6
	Staphylococcus haemolyticus	1	0	1
	Streptococcus spp	0	1	1
	Streptococcus mitis/oralis	1	0	1
	Streptococcus parasanguinis	1	0	1
	Streptococcus viridans	1	0	1
	Acinetobacter lwoffii	0	1	1
	Aeromonas hyrofiliacaviae	1	0	1
	Citrobacter freundii	1	0	1
	Enterobacter cloacea	0	1	1
	Stenotrophomonas maltophilia	1	0	1
Total		40	14	54

Table 4. Treatment Outcomes in FEN Episodes

	Meropenem n=198	PIP/TAZ n=86	Total n=284	p value
Duration of hospitalization(days)				
Median	8	8	8	0.43
Range	1-80	3-38	1-80	
Adverse effects	None	None	None	
Success without modification	76(68%)	36(32%)	112(39%)	0.58
Success with modification	122(71%)	50(29%)	172(61%)	0.58

Table 5. Effects of Patients and Episodes Characteristics on Modification

		Episodes without modification (n=112)	Episodes with modificaton (n=172)	Total (n=284)	p value
Antibiotics	Meropenem	76(68%)	122(71%)	198(70%)	0.58
	PIP/TAZ	36(32%)	50(29%)	86(30%)	
Sex	Female	39(35%)	69(40%)	108(38%)	0.37
	Male	73(65%)	103(60%)	176(62%)	
Diagnosis	Leukemia	39(35%)	59(34%)	98(35%)	0.93
	Solid tumors	73(65%)	113(66%)	186(65%)	
Remission	Yes	21(19%)	34(20%)	55(19%)	0.83
	No	91(81%)	138(80%)	229(81%)	
Duration of FEN					
	≤10days	87(78%)	140(81%)	227(80%)	0.45
	>10days	25(22%)	32(19%)	57(20%)	
ANC	<100	70(63%)	130(76%)	200(70%)	0.02
(cells/mm^3)	≥100	42(37%)	42(24%)	84(30%)	
Mucositis	Yes	79(71%)	99(58%)	178(63%)	0.03
	No	33(29%)	73(42%)	106(37%)	

*FEN: Febrile neutropenia; ANC: Absolute neutrophil count

primary disease, neutrophil count, neutropenia duration, or presence of grade 3-4 mucositis (p>0.05) (Table 1). Nineteen percent of the episodes were documented microbiologically. 70% of the infections were clinically documented and 30% of the episodes were fever of unknown origin (Table 2). One patient had rhinomaxillary mucormycosis, five patients had invasive aspergillosis infection of the lungs, three patients had CMV pneumonia and two had H1N1 pneumonia (data not shown). In 54% of the microbiologically documented episodes gram negative, in 41% gram positive microorganisms and in 5% fungi were isolated (Table 3). In 35 of the episodes patients had an indwelling catheter; four in the PIP/TAZ and thirty one in the meropenem group (data not shown).

Treatment and response to therapy

Outcome of treatment with two different regimens are presented in Table 4. Meropenem was used in 198 and PIP/TAZ was used in 86 of 284 episodes. There was no significant difference in duration of hospitalization between the two groups. No modification was done in 39% (n=112) of the episodes. Modifications were necessary in 61% of the episodes (172 episodes). The modification rate was not statistically different between the two groups (p=0.58). Success rate without modification was 68% in meropenem group and 32% in PIP/TAZ group (p=0.58). There were twenty two deaths in total during febrile neutropenic episodes and there was no statistical difference betweeen the two groups (p=0.87) (Table 4). The episodes in which patients had neutrophil count less than 100 cells/mm^3 and grade 3 or 4 mucositis, the modification rate was found to be higher (p<0.05) (Table 5).

No adverse effects due to treatment were observed. No patients were admitted with recurrent fever in the 10-day follow-up period.

Discussion

Infection is the main cause of mortality in neutropenic patients with cancer. Infections can be documented

microbiologically and clinically in 50% of the neutropenic febrile episodes. As the documentation of infection is difficult, broad spectrum antibiotics should be instituted as soon as possible (Rossi et al., 1996; Hahn et al., 1997; Hughes et al., 2002; Koh and Pizzo, 2010). Before the early introduction of empirical antibiotics, the mortality rate of Gram-negative infections, especially due to Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae, was about 80%. Many studies suggest that antibiotics used in the empirical treatment of neutropenic patients should be bactericidal, broad-spectrum and have antipseudomonal activity (Rossi et al., 1996; Koh and Pizzo, 2010). Combinations of beta-lactam and aminoglycosides have been used in pediatric febrile neutropenia for many years (Cometta et al., 1995; Aksoylar et al., 2004). Several studies have shown that combination therapy was not superior to monotherapy. Paul et al. (2010) have shown that ceftazidime, cefepime, PIP/TAZ, and carbapenems were effective as monotherapy in their meta-analysis. The results were in agreement with recent studies including pediatric cancer patients, reporting that cefozopran, cefepime, meropenem,imipenem, sulperazon and piperacillin–tazobactam were effective and safe for empiric treatment of febrile neutropenic episodes (Agaoglu et al., 2001; Corapcioglu et al., 2006; Erbey et al., 2009; Uygun et al., 2009; Vural et al., 2010; Demir et al., 2011; Erbey et al., 2010; Ichikawa et al., 2011; Karaman et al., 2012). Vural et al. (2010) compared PIP/TAZ versus imipenem in pediatric febrile neutropenia and reported that both antibiotics can be used safely as monotherapy. In a study with adult participants comparing PIP/TAZ with meropenem both antibiotics were found to be effective equally similar to our study (Oztoprak et al., 2010).

In adult patients febrile neutropenic episodes were stratified according to risk groups and there is a tendency to use monotherapy in low-risk groups. Although many studies have reported risk factors in febrile neutropenia in children, a universal scoring system for risk stratification is not available in children. Most important factors for risk groups are severity and duration of neutropenia, and presence of complications. Not being in remission, using high-dose chemotherapy protocols, the presence of severe mucositis, multiorgan failure shock,leukemia are also considered high-risk factors (Blot et al., 1997; Paesmans et al., 2000; Chindaprasirt et al., 2013). Recently, satisfying results with monotherapy in high-risk groups were also informed (Viscoli et al., 2006). In our study, all patients with hemato-oncological malignancies without multiorgan failure or shock received monotherapy regardless of other risk factors. In this study, leukemia constituted 35% of the febrile episodes and there was no statistical difference between the modification rate of solid tumors and leukemia (p=0.97). In 70% of episodes, neutrophil count was under 100/mm^3, in 20% of them, duration of neutropenia was more than 10 days and in 37% there was severe mucositis which are usually accepted as high-risk factors. The modification ratio was reported to be 20%-50% in several studies and our results were slightly higher than the published work. Factors affecting modification were neutrophil count less than 100 cells/mm^3 and the presence of severe mucositis which is consistent with previous reports ($p<0.05$) (Uygun et al., 2009; Karaman et al., 2012). Duration of neutropenia and remission status did not have an influence on modification ratio ($p>0.05$). There was no statistical difference without modification in the meropenem and the PIP/TAZ group.

The microorganisms isolated in febrile neutropenic episodes have changed in the last three decades. In the last decade Gram positive pathogens have been isolated more frequently than Gram negative pathogens (Duncan et al., 2007; Paul et al., 2007). There is an increase of Gram positive pathogens reported recently from pediatric hematology and oncology centers in Turkey (Kebudi et al., 2005). The use of central venous catheters and severe mucositis due to treatment may be the cause for this change (Herwaldt et al., 1992; Koh and Pizzo, 2010). There is still a predominance of Gram negative pathogens where central venous catheters are not frequently used. In our center, central venous catheters are not used routinely. In this study, 19% of febrile episodes were documented microbiologically and Gram negative pathogens were isolated more often than Gram positive pathogens.

In conclusion, in this retrospective study monotherapy with meropenem or PIP/TAZ was found to be equally effective and safe for the initial treatment of febrile neutropenia.

References

Agaoglu L, Devecioglu O, Anak S, et al (2001). Cost-effectiveness of cefepime+netilmicin or ceftazidime+amikacin or meropenem monotherapy in febrile neutropenic children with malignancy in Turkey. *J Chemother*, **13**, 281-7.

Aksoylar S, Cetingul N, Kantar M, et al (2004). Meropenem plus amikacin versus piperacillin-tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. *Pediatr Hematol Oncol*, **21**, 115-23.

Blot F, Guiguet M, Nitenberg G, et al (1997). Prognostic factors for neutropenic patients in an intensive care unit: respective roles of underlying malignancies and acute organ failures. *Eur J Cancer*, **33**, 1031-7.

Cometta A, Zinner S, de Bock R, et al (1995). Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The international antimicrobial therapy cooperative group of the European organization for research and treatment of cancer. *Antimicrob Agents Chemother*, **39**, 445-52.

Corapcioglu F, Sarper N, Emine Z, et al (2006). Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. *Pediatr Hematol Oncol*, **23**, 177-86.

Demir HA, Kutluk T, Ceyhan M, et al (2011). Comparison of sulbactam/cefoperazone with carbapenems as empirical monotherapy for febrile neutropenic children with lymphoma and solid tumors. *Pediatr Hematol Oncol*, **28**, 299-310.

Duncan C, Chisholm JC, Freeman S, et al (2007). A prospective study of admissions for febrile neutropenia in secondary paediatric units in South East England. *Pediatr Blood Cancer*, **49**, 678-81.

Erbey F, Bayram I, Yilmaz S, Tanyeli A (2009). Imipenem in the treatment of febrile neutropenic children. *Asian Pac J*

Cancer Prev, **10**, 921-4.
Erbey F, Bayram I, Yilmaz S, Tanyeli A (2010). Meropenem monotherapy as an empirical treatment of febrile neutropenia in childhood cancer patients. *Asian Pac J Cancer Prev*, **11**, 123-6.
Hann I, Viscoli C, Paesmans M, et al (1997). A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol*, **99**, 580-8.
Hartel C, Deuster M, Lehrnbacher T, Schultz C (2007). Current approaches for risk stratification of infectious complications in pediatric oncology. *Pediatr Blood Cancer*, **49**, 767-73.
Herwaldt LA, Hollis RJ, Boyken LD, Pfaller MA (1992). Molecular epidemiology of coagulase-negative staphylococci isolated from immunocompromised patients. *Infect Control Hosp Epidemiol*, **13**, 86-92.
Hughes WT, Armstrong D, Bodey GP, et al (2002). 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*, **34**, 730-51.
Ichikawa M, Suzuki D, Ohshima J, et al (2011). Piperacillin/tazobactam versus cefozopran for the empirical treatment of pediatric cancer patients with febrile neutropenia. *Pediatr Blood Cancer*, **57**, 1159-62.
Jones RN, Pfaller MA, Fuchus PC, et al (1989). Piperacillin/tazobactam (YTR 830) combination: Comparative antimicrobial activity against 5889 recent aerobic clinical isolates and 60 Bacteroides fragilis group strains. *Diagn Microbiol Infect Dis*, **12**, 489-94.
Karaman S, Vural S, Yıldırmak Y, et al (2012). Comparison of piperacillin/tazobactam and cefoperazone sulbactam monotherapy in treatment of febrile neutropenia. *Pediatr Blood Cancer*, **58**, 579-83.
Kebudi R, Vural S, Anak S (2005). Pediatric febrile neutropenia activities in Turkey. *Pediatr Blood Cancer*, **45**, 513.
Koh AY, Pizzo PA (2010). Infectious complications in the pediatric cancer patient. In: Pizzo PA, Poplac DG, editors. Principles and practices of pediatric oncology, 6th edition. Philadelphia, PA: Lippincott Williams & Wilkins, pp.1190-1242.
Oztoprak N, Piskin N, Aydemir H, et al (2010). Piperacillin/tazobactam versus carbapenem therapy with and without amikacin as empirical treatment of febrile neutropenia in cancer patients: results of an open randomized trial at a university hospital. *Jpn J Clin Oncol*, **40**, 761-7.
Paul M, Yahav D, Fraser A, et al (2006). Empirical antibiotic monotherapy for febrile neutropenia: Systemic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*, **57**, 176-89.
Paul M, Gafler-Gvili A, Leibovici L, et al (2007). The epidemiology of bacteremia with febrile neutropenia: experience from a single center, 1988-2004. *Isr Med Assoc J*, **9**, 424-9.
Paesmans M (2000). Risk factors assessment in febrile neutropenia. *Int J Antimicrob Agents*, **16**, 107-11.
Chindaprasirt J, Wanitpongpun C, Limpawattana P, at al (2013). Mortality, length of stay, and cost associated with hospitalized adult cancer patients with febrile neutropenia. *Asian Pac J Cancer Prev*, **14**, 1115-9.
Rossi C, Klastersky J (1996). Initial empirical antibiotic therapy for neutropenic fever: analysis of the causes of death. Support. *Care Cancer,* **4**, 207-12.
Santolaya ME, Alvarez AM, Aviles CL, et al (2007). Admission clinical and laboratory factors associated with death in children with cancer during a febrile neutropenic episode. *Pediatr Infect Dis J*, **26**, 794-8.
Santolaya ME, Alvarez AM, Aviles CL, et al (2002). Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. *Clin Infect Dis*, **35**, 678-83.
Uygun V, Karasu GT, Ogunc D, et al (2009). Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. *Pediatr Blood Cancer*, **53**,610-4.
Viscoli C, Cometta A, Kern WV, et al (2006). International antimicrobial therapy group of the European organization for research and treatment of cancer. Piperacillin–tazobactam monotherapy in high-risk febrile and neutropenic cancer patients. *Clin Microbiol Infect*, **12**, 212-6.
Vural S, Erdem E, Gulec SG, et al (2010). Imipenem/cilastatin versus piperacillin/tazobactam as monotherapy in febrile neutropenia. *Pediatr Int*, **52**, 262-7.