

Research Article**Monotherapy using Cefepime in Comparison to Dual Therapy (PIP/TAZO plus Amikacin) for Febrile Neutropenic Pediatric Patients with Solid Tumors**Ahmad Kamel^{1*}, Lobna Shalaby, Walaa El Sayed¹, Hadir El Mahalawy²¹Pediatric Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt²Clinical Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt***Corresponding author**

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Abstract: Infectious diseases are important causes of morbidity and mortality in patients with cancer. Neutropenia has been recognized from any decades as a major risk factor for the development of infections in cancer patients undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic cancer patients have led to improved outcomes. The aim of this study was to compare the efficacy and safety of Cefepime monotherapy versus dual therapy with PIP/TAZO plus Amikacin for empirical treatment of neutropenic fever in children with solid tumors. Data of one hundred and thirty episodes in 80 patients treated with monotherapy as well as one hundred and twenty one episodes in 62 patients treated with dual therapy were analyzed. These episodes occurred in patients with solid tumors who were admitted to the pediatric oncology department at the National Cancer Institute, Cairo University between February 2012 and February 2013. Patients in the monotherapy arm received Cefepime 50 mg/kg/dose every 8 hours. Whereas, those of the dual therapy arm received PIP/TAZO 100mg/kg/dose every 8 hours plus Amikacin 15 mg/kg/day. Modification was defined as addition or shifting to other antimicrobials. Success without modifications was 87.6% & 86.7% in the monotherapy and dual therapy arms; respectively. The incidence of MDROs was lower among the monotherapy arm compared to dual therapy arm (p=0.013). Nephrotoxicity was higher among dual therapy arm (p=0.004). Glycopeptides were added slightly more in the dual therapy arm. The rate of gram positive bacteremia was higher than that of the gram negative in both treatment arms. There was no significant difference between the 2 arms regarding median duration of neutropenia, duration of hospitalization and crude mortality rate. Monotherapy was effective and safe for initial empirical treatment of febrile neutropenic episodes in children with solid tumors. Combination regimens that contain aminoglycosides did not improve treatment success, but it may increase nephrotoxicity, resistance, and cost.

Keywords: Febrile neutropenia, Monotherapy.

INTRODUCTION

Infections represent an important complication during chemotherapy for pediatric malignancies [1]. Fever during chemotherapy-induced neutropenia may be the only indication of an underlying infection, because signs and symptoms of inflammation typically are attenuated. It occurs in 10–50% of patients with solid tumors and 80% of those with hematologic malignancies, and usually develops after the first cycle of chemotherapy. Most patients have no documented infectious etiology, while, clinically documented infections occur in 20–30% of febrile episodes [2].

In the first week of neutropenia, hematogenous bacterial infections could be due to staphylococcus aureus, alpha hemolytic streptococcus, escherichia coli, enterobacteriaceae and pseudomonas aeruginosa. Indwelling intravascular devices, mucosal damage of the gastrointestinal and genitourinary tract, as well as

fluoroquinolone prophylaxis may also increase the risk of infection [3, 4].

All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (i.e., fever), to avoid mortality associated with serious infections [5]. Combination regimens (dual therapy) of a broad spectrum B-lactam antibiotic and amikacin have been the standard empirical treatment modality because of their synergistic effect on gram-negative bacteria and reduction in resistance, but there is evidence that monotherapy with a broad-spectrum cephalosporin such as ceftazidime, cefepime, or carbapenem is as effective as combination therapy. Monotherapy offers the advantages of decreased toxicity (mainly for patients treated with many nephrotoxic chemotherapy agents), lower cost, and easy administration compared to multidrug regimens [6].

Cefepime is a fourth-generation cephalosporin with activity against both methicillin-susceptible *S. aureus* and *P. aeruginosa*, and it has been extensively studied as monotherapy for febrile neutropenia, with good control of the disease. Therefore, it has been approved by the US Food and Drug Administration (FDA) to be used as empirical monotherapy for treating patients with febrile neutropenia [7].

We aim at exploration of the efficacy and safety of monotherapy using Cefepime given prospectively to febrile neutropenia (FN) patients treated for solid malignancies in comparison to combination therapy; Piperacillin/Tazobactam (PIP/TAZO) plus Amikacin during a period of 6 months for each group.

METHODOLOGY

This is an observational comparative study that carried out at the Pediatric Oncology Department, National Cancer Institute, Cairo University to investigate the efficacy and safety of monotherapy, Cefepime prospectively in FN pediatric patients treated for solid malignancies from September 2012 to February 2013 in comparison to combination (dual) therapy, PIP/TAZO plus Amikacin from February 2012 to July 2012. Local ethical committee approval was received for the study.

Patients with solid malignancies were included in the study if they developed neutropenia; defined as an absolute neutrophil count (ANC) < 500 cells/mm or if count < 1000 cells/mm expected to fall < 500 cells/mm within 24-48 hours because of preceding chemotherapy. Fever is confirmed if an axillary temperature $\geq 38^{\circ}\text{C}$ on two occasions at least 1 hour apart or $\geq 38.5^{\circ}\text{C}$ on one occasion in 24 hour in the absence of any other obvious cause of fever. Patients with fever attributable to malignancy or transfused blood products or other medications, were excluded. Patients had no history of receiving any antimicrobial therapy within 1 week prior to admission.

The following work-up was done for every patient:

- Complete blood picture, liver and kidney functions, and blood cultures (initial). Symptoms of urinary tract infection should be evaluated with a urine analysis and culture, if necessary. Vascular access, sites of inflammation or drainage should be cultured (if present). Biopsy with microbiologic and pathologic evaluation should be considered for new or undiagnosed skin lesions.
- Cultures were repeated during therapy if fever persisted or to isolate the causative pathogen or to document the eradication of the isolated pathogen. Bacteremia was defined as the isolation of bacterial pathogen from the blood. Clinically documented infections (CDI) were considered when there was a focus of infection on physical examination, without microbiological documentation. Fever of unknown

origin (FUO) was considered when there was no clinical or microbiological evidence of infection in a febrile episode.

In our study, we used BACTEC™ 9050 system, which is one of the BACTEC™ 9000 series. BACTEC™ blood culture system is a fully automated microbiology growth and detection system designed to detect microbial growth from blood specimens. BACTEC™ 9000 systems feature the BACTEC™ 9000 fluorescent sensor technology that allows for fully-automated, walk-away testing using a continuous-monitoring instrument that agitates and incubates BACTEC/F blood culture bottles, resulting in early detection of positives. The BACTEC 9050 System; accommodates 50 test vials, features an extremely small footprint, only 4.25 square feet of tabletop is needed and no external computer is required (BD Bactec 9050 Blood Culture System Manual). Culture specimens should be collected during or immediately after completing the examination. Two blood samples should be cultured. When obtaining blood cultures, there are 3 options; 1) One set can be obtained peripherally and one can be obtained from a central venous catheter (if present), 2) Both sets can be obtained peripherally, and 3) Both sets can be obtained through the catheter. In the absence of lesions or clinical signs and symptoms, routine cultures of the anterior nares, oropharynx, urine, stool, and rectum are rarely helpful. Diarrheal stools felt to be infectious should be tested for the presence of *Clostridium difficile*. In patients with diarrhea, consider testing for Rotavirus and Noro virus in winter months and during outbreaks.

- Diagnostic imaging include: CT Chest and echocardiography.

Initial Empiric Antibiotic Therapy

- All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (that is, fever). Patients received IV Cefepime monotherapy (50 mg/kg every 8 hours) or combination regimen of PIP/TAZO (100 mg/kg every 8 hours) plus Amikacin (15 mg/kg every 24 hours).
- Response was assessed during therapy and at completion of therapy. Response was categorized as (a success) if all of the following criteria were found: patient became afebrile ($< 38^{\circ}\text{C}$) for at least 3 consecutive days, clearance of signs and symptoms of infection, eradication of the previously isolated infectious microorganism.
- Duration of fever, neutropenia, hospitalization, mortality rate, the need to modify initial empirical antibiotic therapy and the need to add antifungal therapy were compared between the two treatment arms.

- Vancomycin should be considered in the following clinical situations:
 - a) Clinically apparent, serious, intravenous catheter-related infections. Many of these infections are caused by coagulase-negative staphylococcal isolates, which are usually beta-lactam antibiotic resistant.
 - b) The patient's blood cultures are positive for Gram-positive bacteria before final identification and susceptibility testing.
 - c) Known colonization with penicillin /cephalosporin resistant pneumococci or MRSA.
 - d) Hypotension or septic shock develops in the patient without an identified pathogen (clinically unstable).
 - e) Soft tissue infection.
 - f) Risk factors for viridans group streptococcal bacteremia: severe mucositis (for example, associated with cytarabine) and prophylaxis with ciprofloxacin or TMP/SMX.
 - g) If empiric Vancomycin is initiated in any of these situations, its use should be re-assessed within 2 to 3 days of initiation. If a resistant Gram-positive pathogen cannot be identified and if clinically appropriate, empiric Vancomycin therapy should then be discontinued.
- Initial empiric therapy for patients who are clinically unstable:

Sepsis is suggested by signs of clinical instability including hypotension, tachypnea, new or worsening tachycardia, mental status changes, decreased urine output, and organ dysfunction. Initial therapy for sepsis should broadly covers pathogens that are likely to cause sepsis while minimizing the potential for inadequate treatment. The antibiotic regimen should be modified, if necessary, after culture results and susceptibility are known. The initial empiric regimen for the neutropenic patient with clinical instability may include a broad spectrum beta-lactam (for example, imipenem, meropenem, or piperacillin-tazobactam) plus aminoglycoside and vancomycin. Addition of fluconazole or an echinocandin should be strongly considered in patients not receiving antifungal prophylaxis.
- Initial empirical therapy was modified according to susceptibility testing results in patients with bacteremia. CDI was treated as appropriate. Antifungal therapy (conventional amphotericin-B at a dose of 1 mg/kg/day) was added if the patient was still febrile in absence of an obvious cause whether clinically or microbiologically.

Statistical Methods

Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL).

Numerical data of scores were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). A p-value < 0.05 was considered significant.

RESULTS

During the period from September 2012 to February 2013, 130 episodes of febrile neutropenia in 80 patients with solid tumors treated by monotherapy. On the other hand, 121 episodes of febrile neutropenia in 62 patients of the same group treated by dual therapy in the period from February 2012 to July 2012 at the Pediatric Oncology Department, National Cancer Institute, Cairo University. Thirty three of the patients in the monotherapy arm had more than one febrile episode and 34 of the patients in the dual therapy arm had more than one febrile episode. Twenty four of the patients were enrolled in both arms.

Table 1 showed the different diagnoses of patients enrolled into the study. Monotherapy arm included 49 patients who were in remission, while, 31 patients were not in remission. On the other hand, dual therapy included 39 patients who were in remission and 23 patients were not in remission. The difference between the two arms wasn't statistically significant ($p= 0.79$). Relapse was encountered in 12 cases enrolled in monotherapy arms, but not in the remaining 68 patients. Sixteen cases were in relapse and enrolled in dual therapy arm, and the remaining 46 cases were not.

Clinical picture of the studied patients

Monotherapy arm; all episodes presented with fever, 28/130 episodes with mucositis, 3/130 with diarrhea, 5/130 with abdominal pain, 5/130 with documented infections, and 2/130 patients were admitted to ICU.

Dual therapy arm; all episodes presented with fever, 30/121 episodes with mucositis, 5/121 with diarrhea, 7/121 with abdominal pain, 11/121 with documented infections, and 3/121 patients were admitted to ICU.

In the two arms; the duration of 1st attack of fever ranged from 24 to 72 hours with a median of 24 hours. The two groups were comparable regarding the clinical picture of the febrile episodes. Mucositis encountered in monotherapy arm were of grade I/II in 75% of patients and of grade III/IV in 25% of patients. In dual therapy, grade I/II mucositis were encountered in 93.3% of patients, and grade 6.7% of patients.

Initial Evaluation

CBC Findings

Monotherapy arm; Total leucocytic count (TLC) ranged from 0.0 to 1.9 with a median of 0.4 ($\times 10^3$), Absolute neutrophilic count (ANC) ranged from 0.0 to

1.00 with a median of 0.02 ($\times 10^3$), HB level ranged from 4.4 to 15 with a median of 8 (mg/dl) and platelet count ranged from 3 to 447 with a median of 69.5 ($\times 10^3$).

Dual therapy arm; Total leucocytic count (TLC) ranged from 0.0 to 1.9 with a median of 0.3 ($\times 10^3$), Absolute neutrophilic count (ANC) ranged from 0.0 to 1.00 with a median of 0.02 ($\times 10^3$), HB level ranged from 4 to 12 with a median of 8 (mg/dl) and platelet count ranged from 1.00 to 358 with a median of 50 ($\times 10^3$). The two groups were comparable regarding the CBC findings ($p=0.452$).

Monotherapy arm; 101/130 episodes had baseline ANC less than 100, 20/130 episodes had baseline ANC from 100-499 and 9/130 episodes had baseline ANC from 500-1000.

Dual therapy arm; 97/121 episodes had baseline ANC less than 100, 13/121 episodes had baseline ANC from 100-499 and 11/121 episodes had baseline ANC from 500-1000. The difference between the two arms wasn't statistically significant ($p=0.486$).

Liver functions

Monotherapy arm; ALT ranged from 5 to 639 with a median of 20.5, AST ranged from 7 to 1014 with a median of 32, and total bilirubin ranged from 0.1 to 3.4 with a median of 0.5.

Dual therapy arm; ALT ranged from 5 to 1344 with a median of 24, AST ranged from 9 to 3911 with a median of 30, and total Bilirubin ranged from 0.1 to 6 with a median of 0.5. The two groups were comparable regarding the liver function tests.

Blood cultures

The 1st blood culture and sensitivity

Monotherapy arm; it showed no growth in 110 episodes, gram positive organisms in 15 episodes and gram negative organisms in 5 episodes. Gram positive organisms were mainly Coagulase Negative Staph. (CONS), *Staph. aureus*, *Staph. epidermidis*, alpha hemolytic *streptococci*, *Staph. hemolyticus* and *micrococcus* species while gram negative organisms were *E. coli*, *Pseudomonas* and *Kelbsiella pneumoniae*.

Dual therapy arm; it showed No growth in 104 episodes, gram positive organisms in 12 episodes and gram negative organisms in 5 episodes. Gram positive organisms were mainly Coagulase Negative Staph. (CONS), *Staph. aureus*, *Staph. epidermidis*, *Staph. hominis* while gram negative organisms were *Pseudomonas*, *Enterobacter* and *Acientobacter*. There were no cases of (MRSA) or (ESBLs) in the two arms. Total gram positive cultures were 17.88%, while, total gram negative cultures were 6.62%.

Multi-drug resistant organisms (MDROs) were observed in monotherapy arm in 10 patients (50%) of the positive 1st blood culture, while in dual therapy arm; they were observed in 15 (88.2%) of the positive 1st

blood culture. The difference between the two groups was statistically significant ($p=0.013$).

The 2nd and 3rd blood culture and sensitivity

Table 2 showed the results of 2nd and 3rd blood culture and sensitivity. In the 2nd blood culture and sensitivity, 2 organisms were found to be MDROs in each arm. In the 3rd blood culture and sensitivity, 2 organisms were found to be MDROs in the monotherapy arm and 1 organism was found to be MDRO in dual therapy arm.

CT chest

In monotherapy arm; it was not done in 94/130 episodes, was free in 20/130 episodes, showed patchy infiltrations in 5/130 episodes, showed nodular infiltrations in 10/130 episodes and showed diffuse infiltrations in 1/130 episode. In dual therapy arm; it was not done in 83/121 episodes, was free in 23/121 episodes, showed patchy infiltrations in 2/121 episodes, showed nodular infiltrations in 12/121 episodes and showed diffuse infiltrations in 1/121 episode. The two groups were comparable regarding the results of the CT chest ($p=0.6$).

ECHO

In monotherapy arm; ECHO was not done in 94/130 episodes, found to be compromised in 8/130 episodes and not compromised in 28/130 episodes. In dual therapy arm; ECHO was not done in 92/121 episodes, found to be compromised in 6/121 episodes and not compromised in 23/121 episodes. The difference between the two groups wasn't statistically significant ($p=0.88$).

Causes and management of fever

Monotherapy arm; 5/130 (3.85%) episodes showed clinically documented infections, 20/130 (15.38%) episodes showed microbiologically documented infections and 105/130 (80.77%) showed unexplained fever. Dual therapy arm; 11/121 (9.09%) episodes showed clinically documented infections, 17/121 (14.05%) episodes showed microbiologically documented infections and 93/121 (76.86%) showed unexplained fever. The two groups were comparable regarding the cause of fever. The rate of bacteremia in both arms was 14.74%. Patients enrolled in monotherapy arm were initiated on cefepime, while those in dual therapy arm were initiated on PIP/TAZO +Amikacin. Sixteen episodes in each arm needed modification of the initial empiric regimen. Modification of therapy was totally done in 32/251 (12.75%). In monotherapy arm; modification of therapy was done in 16/130 (12.31%) episodes; 3/130 episodes were modified due to vital instability, 10/130 episodes were modified due to positive blood culture, 2/130 episodes were modified due to documented infections and 1/130 episode was modified due to unclear reason. On the other hand, in dual therapy arm; modification was done in 16/121 (13.22%) episodes; 5/121 episodes

were modified due to vital instability, 9/121 episodes were modified due to positive blood cultures, 1/121 episodes was modified due to documented infections and 1/121 episode was modified due to unclear reason. Glycopeptide was added in 3 episodes in monotherapy arm, while, it was added in 12 episodes in dual therapy arm. The difference between the 2 arms was statistically significant ($p= 0.014$). Addition of an empiric antifungal therapy was done in 34/130 (26.15%) episodes in monotherapy arm and in 31/121 (25.62%) episodes in dual therapy arm, with no significant difference ($p= 1$). Table 3 showed criteria with multi-drug resistant organisms.

The duration of neutropenia in monotherapy arm ranged from (3-18 days) with a median of 8 days, while in dual therapy arm; it ranged from (2-17 days) with a median of 7 days. The difference between the two groups wasn't statistically significant ($p= 0.5$). The duration of hospitalization in monotherapy arm ranged from 3 to 18 days with a median of 7 days, while, in dual therapy arm; it ranged from 2 to 17days with a median of 7 days. The difference between the two groups wasn't statistically significant ($p= 0.5$).

At the end of febrile episode

Serum Creatinine in monotherapy arm ranged from 0.1 to 1.8 with a median of 0.3, while in dual therapy arm; it ranged from 0.2 to 2.5 with a median of 0.4. The difference between the two arms was statistically significant ($p= 0.004$) that indicates higher nephrotoxicity with patients who received aminoglycosides in combination regimen.

In monotherapy arm; 114/130 episodes didn't need change of the empiric antibiotic regimen, while, in dual therapy arm; 105/121 episodes didn't need change of the empiric antibiotic regimen. The crude mortality rate at the end of each episode of febrile neutropenia in monotherapy arm was 1.5% ($n=2$ cases); one case was relapsing RMS with lung metastasis and the other one was medulloblastoma. In dual therapy arm; it was 1.7% ($n=2$ cases); one case was relapsing RMS and the other one was relapsing Ewing's sarcoma. Mortality in the cases under investigation was disease related rather than due to infection.

Table 1: Diagnoses of patients enrolled in monotherapy and dual therapy arms

Diagnosis	Monotherapy		Dual Therapy	
	No.	%	No.	%
Ewing sarcoma	9	11.2	12	19.3
Neuroblastoma	20	25	12	19.3
Wilms' tumor	8	10	9	14.5
Osteosarcoma	13	16.2	11	17.7
Brain tumors	8	10	9	14.5
Rabdomyosarcoma	13	16.2	6	9.6
Yolk sac tumors	5	6.2	1	1.6
Clear cell sarcoma of the kidney	2	2.5	-	-
Miscellaneous	2*	2.5	2**	3

*Miscellaneous tumors include; desmoplastic small round cell tumor and infantile fibrosarcoma.

**Misscellaneous tumors include; unclassified sarcoma and desmoplastic small round cell tumor.

Table 2: Diagnoses of patients enrolled in monotherapy and dual therapy arms

Culture	Organisms	Monotherapy		Dual Therapy	
		No.	%	No.	%
2 nd Culture and Sensitivity	No growth (NG)	43	87.8	37	90.2
	E.Coli	1	0.8	1	0.8
	α hemolytic streptococci	1	0.8	1	0.8
	CONS	0	-	2	1.7
	Staph.epidermidis	2	1.5	0	-
	streptococcus	1	0.8	0	-
	Mixed bacilli	1	0.8	0	-
3 rd Blood Culture and Sensitivity	NG	14	82.4	19	95
	CONS	0	-	1	0.8
	Staph.epidermidis	2	1.5	0	-
	Enterobacter	1	0.8	0	-

Table 3: Criteria of episodes with multi drug resistant organisms (MDROs) in the two arms (25 episodes)

Type of growth	Age	gender	diagnosis	Disease status	ICU admission	Fate
CONS	4 years	female	NB	Non remission	Not needed	Alive
	3 years	male	NB	Non remission	Not needed	Alive
	4 years	female	NB	Non remission	Not needed	Alive
	6 years	female	RMS	Non remission	Not needed	Alive
	4 years	female	NB	Remission	Not needed	Alive
	4 years	female	MB	Remission	Not needed	Alive
	6 years	female	RMS	Non remission	Not needed	Alive
<i>Staph. aureus</i>	1 year	male	YST	Non remission	Not needed	Alive
	3 years	male	NB	Non remission	Not needed	Alive
	6 years	female	RMS	Non remission	Not needed	Alive
	18 years	male	OS	Non remission	Not needed	Alive
	1 year	male	YST	Non remission	Not needed	Alive
<i>Staph. epidermidis</i>	6 years	male	MB	Remission	Not needed	Alive
	1 Year	male	RMS	Remission	Not needed	Alive
<i>Staph. hemolyticus</i>	4 years	male	RMS	Remission	Not needed	Alive
	4 years	male	RMS	Remission	Not needed	Alive
Enterobacter	1 year	male	NB	Non remission	Not needed	Alive
	1 year	male	YST	Non remission	Not needed	Alive
Actienobacter	13 years	male	OS	Remission	Not needed	Alive
Alpha hemolytic sterpt.	13 years	male	OS	Remission	Not needed	Alive
<i>Pseudomonas aurogenosa</i>	7 years	female	ES	Non remission	Not needed	Alive
Non aurogenosa pseudomonas	3 years	male	RMS	Non remission	Not needed	Alive
Micrococcus	4 years	female	WT	Non remission	Not needed	Alive
<i>K. pneumoniae</i>	17 years	female	ES	Remission	Not needed	Alive
<i>Staph. hominis</i>	1 year	female	NB	Non remission	Not needed	Alive

NB: Neuroblastoma, RMS: Rhabdomyosarcoma, MB: Medulloblastoma, YST: Yolk Sac Tumor, OS: Osteosarcoma, ES: Ewing Sarcoma, WT: Wilms' Tumor

DISCUSSION

Infectious diseases are important causes of morbidity and mortality in patients with cancer. Neutropenia has been recognized from any decades as a major risk factor for the development of infections in cancer patients undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic cancer patients have led to improved outcomes [8]. Therefore, we attempted to investigate the efficacy and safety of monotherapy; Cefepime prospectively in FN pediatric patients with solid malignancies in comparison to group received combination therapy, PIP/TAZO + Amikacin during a period of 6 months for each group.

In the present study; ANC at baseline in the both groups ranged from (0 to 1000 cells/ μ L) with a median of 20 cells/ μ L. This is coinciding with Zengin *et al.* [11] who reported that ANC at randomization ranged from (0-1000 cells/ μ L) with a median of 54 cells/ μ L and from (0-983 cells/ μ L) with a median of 100 cells/ μ L in the monotherapy and dual therapy arms; respectively. The ANC in our study was less than 100 cells/ μ lin 77.7% and 80.2% of the episodes in the monotherapy and dual therapy arms; respectively. This is higher than what was reported by Tamura *et al.* [7], who found that the ANC was less than 100 cells/ μ l in 56.8% and 56.4% of the episodes in the monotherapy and dual therapy arms;

respectively. This may be attributed to the efficacy of preventive measures they followed such as -----????

In the present study; the episodes of the monotherapy arm showed 3.85% clinically diagnosed infections, 15.38% bacteremia and 80.77% unexplained fever. Whereas, in dual therapy arm, 9.09% of the episodes showed clinically diagnosed infections, 14.05% bacteremia and 76.86% unexplained fever. This is different from what was observed by Tamura *et al.* [7] who reported that in the monotherapy arm; 62.5% of the episodes showed clinically diagnosed infections, 25% bacteremia and 50.6% unexplained fever. Whereas, in the dual therapy arm; 58.3% of the episodes showed clinically diagnosed infections, 42.9% bacteremia and 58.5% unexplained fever.

In the present study; the overall rate of bacteremia was 14.74% which is similar to that of Sarper *et al.* [9] study, which was 12% and higher than that of Chuang *et al.* [10] that was 8.7%. The overall rate of gram positive bacteremia was higher than that of the gram negative (17.88% versus 6.62%). This was similar to results reported by Sarper *et al.* [9], Kebudi *et al.* [11], Yildirim *et al.* [12] and Oztoprak *et al.* [13]. Le Guyader *et al.* [14] evaluated 148 febrile neutropenic children with hematological malignancy and showed gradual increase of gram positive pathogens, especially coagulase-negative

staphylococci in the succeeding years (76.8%, 84.5%, and 87% in 1996-1997, 1998, and 1999, respectively). Dominance of gram-positive organisms was also reported between 2004 and 2006 in the studies from North America and Japan; 63.6% and 59%; respectively [15, 16]. On the contrary, Hamidah *et al.* [17] and Sharma *et al.* [18] reported predominance of Gram negative organisms in their neutropenic cancer patients.

Because bacteria can rapidly mutate, institutions should continually monitor for changing patterns of resistance and adjust empirical antibiotic regimens as needed [13]. The increasing frequency of antibiotic-resistant organisms is a major concern. In the present study; the incidence of bacterial resistance among patients received monotherapy was lower than that among patients received dual therapy with statistical significant difference ($p=0.013$). This is not coinciding to Bliziotis *et al.* [19] who found no difference in the emergence of antimicrobial resistance between the two groups among their non-neutropenic patients. The higher incidence of bacterial resistance in our patients may be due to repeated attacks of febrile neutropenia following subsequent cycles of chemotherapy.

Possible indications for the first-line glycopeptides therapy include local predominance of resistant gram positive bacteria (methicillin-resistant *Staph. aureus* or penicillin-resistant streptococci), severe sepsis, shock, or skin and soft tissue infections, including catheter tunnel infection [21]. In the present study; glycopeptide was added in 6% of the episodes which is nearly similar to what was mentioned by Kebudi *et al.* [11] who added glycopeptides in 8% of the episodes. The incidence of glycopeptide administration in our study was lower in the monotherapy arm compared to that in the dual therapy arm ($p=0.014$) and this was similar to Sarper *et al.* [9]. Advantages of less addition of glycopeptides include lesser toxicity, lesser cost and possibly lesser development of resistance.

Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4-7 days of antibiotics and whose overall duration of neutropenia is expected to be > 7 days [2]. In the present study; the percentage of episodes needed addition of an empiric antifungal was nearly equal between the two treatment arms. It was added in 26.15% and 25.62% of the episodes in the monotherapy and dual therapy arms; respectively. Different findings were reported by other researchers. Sarper *et al.* [9] and Paul *et al.* [20] reported higher percentage in the dual therapy arm compared to the monotherapy arm, while, Zengin *et al.* [6] reported higher percentage in the monotherapy arm compared to the dual therapy arm.

Antimicrobial modifications were required in 12.75% of all episodes in the study. In contrast, Kebudi *et al.* [11]

reported higher rate of modification (38%), although there was high percentage of the episodes with severe neutropenia. The rate of treatment modification in this study was 12.31% in the monotherapy arm and 13.22% in the dual therapy arm. Sarper *et al.* [9] reported lower rate of modifications in the monotherapy arm compared to the dual therapy arm.

We found no difference between monotherapy arm and dual therapy arm regarding the success rate without modification of the antimicrobial; 87.6% versus 86.7%; respectively. Same finding was reported by Zengin *et al.* [6] who reported success rate without modification in 45.9% and 42.9% in the monotherapy and dual therapy arms; respectively. This highlights that monotherapy was as reliable as dual therapy in cure of the FN episodes without modifications of the antimicrobial regimen.

In addition, statistical significant difference was achieved when comparing between serum creatinine level in monotherapy and dual therapy (range 0.1-1.8 with median 0.3 versus range 0.2-2.5 with median 0.4); $p=0.004$. This was also emphasized by the reports of ECIL-1, whereas, in aminoglycoside comprising treatments, nephrotoxicity and ototoxicity are more frequent [21]. This result was also similar to the study of Zengin *et al.* [6] in which the serum creatinine ranged from (0.1 – 0.7) with a median of 0.4 and from (0.2 – 4) with a median of 0.4 for the patients in the monotherapy and dual therapy arms; respectively. Thus, it is evident from the present study as well as similar studies, that monotherapy carries lesser risk of nephrotoxicity.

In the present study; the median duration of neutropenia was 8 days and 7 days in the monotherapy and dual therapy arms; respectively ($p=0.5$). This was similar to the results of Sarper *et al.* [9] study, where the median duration of neutropenia was 7.5 days and 8 days in the monotherapy and dual therapy arms; respectively. Zengin *et al.* [6] reported that the median duration of neutropenia was 10 days and 12 days in the monotherapy and dual therapy arms; respectively ($p= 0.72$). In the latter study the median duration of neutropenia was higher than what was reported in our study because patients included in their study had acute leukemia.

Our study did not show any difference in the crude mortality rate; 1.5% in the monotherapy arm ($n=2$) versus 1.7% in the dual therapy arm ($n=2$). In addition, mortality in most of the cases under investigation was disease related rather than due to infection. In Zengin *et al.* [6] study, the infection related mortality was zero. Also Sarper *et al.* [9] reported mortality rate of zero.

CONCLUSION

We conclude that monotherapy antibiotic can be used effectively and safely in the febrile neutropenic episodes of pediatric patients and it is not inferior at all to combination regimens. No difference was appreciated regarding the need for treatment modification, addition of glycopeptide,

addition of empiric antifungal therapy, the success rate without modification, the duration of hospitalization, the duration of neutropenia, and the crude mortality rate. In addition, monotherapy offers lesser risk for nephrotoxicity and ototoxicity.

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