Journal of Research in Applied and Basic Medical Sciences 2025; 11(2): 227-234

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

Urmia University of Medical Sciences

Comparison of clinical outcomes of treatment with cefepime monotherapy vs. amikacin-ceftriaxone combination in children with chemotherapy-induced fever and neutropenia

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Abstract

***Background & Aims*:** Fever and neutropenia are major causes of mortality in cancer patients. This study compares the effectiveness of cefepime monotherapy with a ceftriaxone–amikacin combination in treating these complications.

***Materials & Methods*:** In a randomized clinical trial, 60 febrile neutropenic children with cancer at Shahid Motahari Hospital, Urmia, were assigned to receive either cefepime monotherapy or ceftriaxone–amikacin combination therapy. The hospital length of stay, time to defervescence, and frequency of therapy escalation were compared between the two groups.

***Results*:** The cefepime group had a shorter hospital stay, fewer febrile episodes, reduced antipyretic use, and less frequent antimicrobial escalation compared to the combination group. No significant differences were observed in laboratory results between admission and discharge in either group.

***Conclusion*:** Cefepime monotherapy was significantly more effective than ceftriaxone–amikacin combination therapy in managing fever and neutropenia in pediatric cancer patients.

***Keywords*:** Amikacin**,** Cefepime, Ceftriaxone, Amikacin, Fever, Neutropenia, Pediatric

Received 16 September 2023; accepted for publication 09 April 2025

Introduction

Chemotherapy drugs have a cytotoxic effect on cancer cells. However, since their action is not selective, they can also be lethal to normal body cells in addition to affecting cancer cells. Many side effects have been reported for these medications. An important and serious side effect of cytotoxic chemotherapy is fever and neutropenia, which can be the first and only sign of infection in affected patients (1).

Infectious Diseases Society of America, the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN)

define fever and neutropenia as an oral temperature greater than or equal to 101 degrees Fahrenheit (38.3 °C), or greater or equal to 100.4 F (38 °C) for at least one hour, with an absolute neutrophil count (ANC) of less than 1500 cells per microliter. In severe neutropenia, the ANC falls below 500 cells per microliter and to less than 100 cells per microliter in profound neutropenia. The risk of bacteremia increases with neutropenia (2–4).

The child's age, duration of neutropenia, ANC, type of cancer, and microorganisms identified in the patient's culture sample are other important factors that play a role in the occurrence of fever and neutropenia in children with cancer (5).

A wide variety of microorganisms can be involved in fever and neutropenia, and bacteria, either gram-positive or gram-negative, viruses, and fungi should be considered as infectious causes in this patient population. Gram-negative bacilli, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, were among the important causes of bacteremia in fever and neutropenia patients during the 1960s and 1970s. However, with the increase of gram-negative bacteria resistance to fluoroquinolones due to the use of fluoroquinolones as prophylaxis, the prevalence of Enterobacteriaceae producing broad-spectrum beta-lactamase enzymes, the multidrug resistance of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* bacteria, and gram-negative bacteremia are increasing (6, 7).

Antibiotics are the main treatment for fever and neutropenia, which affects the clinical outcome of the infection. The selection of empiric antibiotic therapy should be based on the patient's infectious risk, the possible site of infection, the main causative pathogens, and the sensitivity of those organisms to antibiotics, which is different in each center (8).

According to ASCO's guidelines, for high-risk febrile neutropenia (FN), initial treatment should include monotherapy with an antipseudomonal β-lactam, like piperacillin-tazobactam, cefepime, or a carbapenem. The addition of a second gram-negative agent or a glycopeptide is recommended only for clinically unstable patients, when a resistant infection is suspected, or in institutions with a high prevalence of resistant pathogens. If the fever persists after 96 hours, antifungal coverage should be discontinued (9).

Due to episodic shortages of broad-spectrum antibiotics in the country, and in an attempt to limit the development of antimicrobial drug resistance, the protocol for treating pediatric fever and neutropenia at Shahid Motahari Hospital in Urmia calls for combination therapy with amikacin and ceftriaxone.

Based on the available literature, no significant difference has been observed between combination and monotherapy with antibiotics for initiating fever and neutropenia treatment, and monotherapy is considered the standard treatment (10,11). Reducing chemotherapy-induced neutropenia-associated infectious complications is critical. Considering the long-term use of the mentioned protocol in Motahari Hospital, to evaluate the effectiveness of this protocol, we compared the effectiveness of ASCO versus the hospital's protocols in controlling and improving the symptoms of fever and neutropenia in hospitalized children.

Materials & Methods

This study was conducted as a randomized clinical trial on febrile and neutropenic children with cancer admitted to The Hemato-oncology Department of Shahid Motahari Hospital in Urmia.

Study Setting and Population

This randomized controlled study was done between November 2021 and April 2023 and involved children suffering from cancer, admitted to the hematology/oncology departments of Shahid Motahari Hospital in Urmia.

Patients aged between 3 months and 18 years, with active cancer, diagnosis of fever and neutropenia (oral temperature ≥ 38.3 in one measurement or temperature ≥ 38 that remains for one hour, along with ANC < 500), informed consent of the parent or legal guardian to participate in the study protocol, absence of

contraindications to receiving amikacin, ceftriaxone, and cefepime were included in the study.

Patients with a history of type 1 allergy to one of the above antibiotics, patients who had a positive culture with a specific microorganism on admission, and patients in whom extensive antibiotic coverage was needed from the beginning of hospitalization due to their clinical condition were excluded from the study.

Sample Size, Randomization, and Blinding

According to the previous studies and the wide range of standard deviation, using the values reported in the study of Lal et al., a sample size of 30 episodes of fever and neutropenia in each group was calculated (12). The primary outcome measure was hospital length of stay. The secondary outcome measure was the frequency of the need to escalate antimicrobial treatment and the mean time to defervescence.

All patients who met the inclusion criteria were included in the study. Patients were randomly assigned to one of the two study groups (cefepime monotherapy or ceftriaxone/amikacin combination) using block randomization, with a block size of four. This random list was created by sealedenvelope.com by specifying the sample size and block size and using a random seed (13).

The study was single-blinded, and the person in charge of the final statistical analysis was unaware of the treatment allocation of each patient.

Study Protocol

Patients assigned to the combination group (C) received a combination of ceftriaxone 50-100 mg/kg/daily in one or two doses (maximum: 1000 mg/dose) and amikacin 15-22.5 mg/kg/daily in three divided doses, and monotherapy group (M) patients received cefepime 50 mg/kg/dose every 8 hours (maximum: 2000mg/dose).

Blood, urine, and respiratory cultures (if applicable) were obtained before starting antibiotics. Appropriate laboratory tests were done on admission and then routinely. The patients' vital signs were regularly charted, and the frequency of fever episodes and the need to receive acetaminophen were recorded. In patients whose cultures came back positive during the study, the antibiotic regimen was adjusted according to the culture result. In case of no clinical improvement after 48 hours, the patient's antibiotics were escalated, and if the process of non-improvement continued after 96 hours, antifungal agents were added to the treatment regimen.

Statistical Analysis

Categorical variables are described as proportions and continuous variables are described as mean (± standard deviation) or median (interquartile range) as appropriate. Differences between two proportions were tested using the chi-square test or Fisher's exact test as appropriate using IBM® SPSS® software version 26. Parameters with excessive missing data, whose absence would introduce significant bias into the analysis, were excluded from the final analysis.

Results

During the study period, 60 patient episodes with neutropenia were enrolled in the trial. The consort diagram of the study can be found in Figure 1.

The mean patient age was 7.45 ± 2.81 years and 6.48 ± 2.44 years for the M and C group, respectively (P = 0.378). (Table 1). Hematological malignancies were the most commonly observed and their incidence didn't differ significantly between the two groups (48.57% in the M group and 51.42% in the C group, P = 0.377).

Clinical outcomes and laboratory data of the two groups after receiving therapy are shown in Table 2. As can be seen, the duration of fever in the M and C groups was 3.60 ± 2.90 days and 5.22 ± 4.08 days, respectively, without a significant difference (P = 0.087). Seven point one percent of patients in the M group and 18.8% in the C group had positive blood cultures (P = 0.187).

The duration of neutropenia-related hospital stay, which was the primary outcome measure of the study, was 3 (2-5) days in the M group and 5 (3-7) days in the C group (P = 0.021). Also, the frequency of the need to escalate antibiotic coverage in the two groups is shown in Table 2.

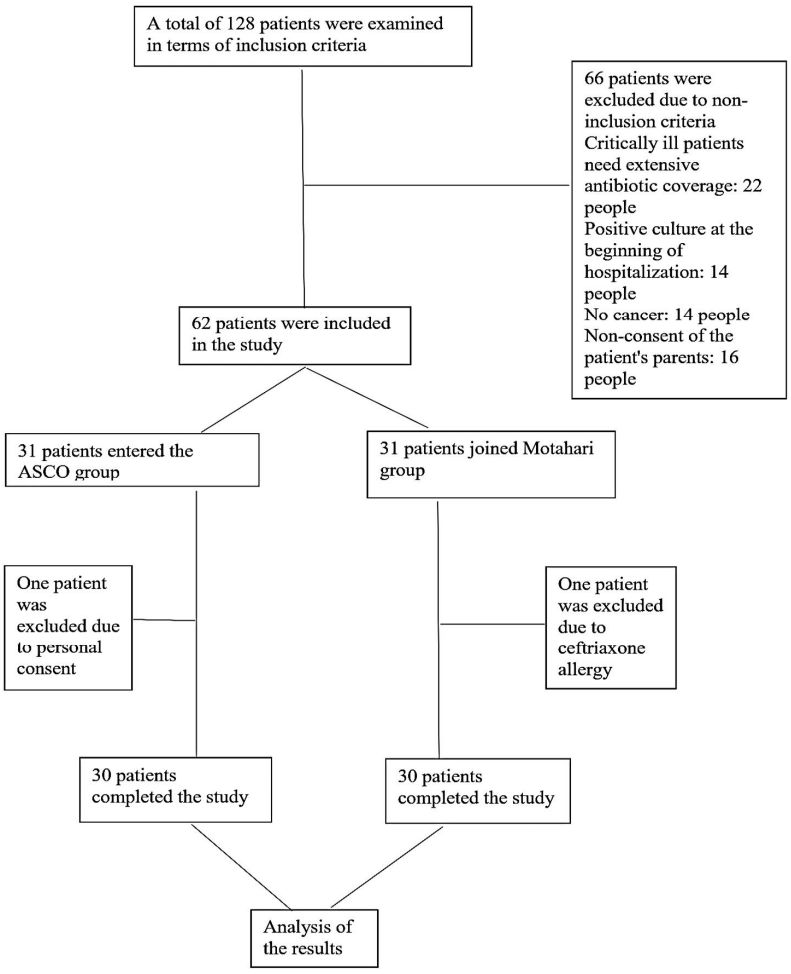

Fig. 1. Consort diagram of the study

Table 1. Demographic characteristics in the combination and monotherapy groups

		Combination group	**Monotherapy group**	***P-value***
(Mean ± SD) Age		2.44 ± 6.84	2.81 ± 7.45	0.378
(Mean ± SD) Weight		14.25 ± 24.98	11.91 ± 24.00	0.774
median (Q1-Q3) Height		112 (101-134.7)	124 (108-135.7)	0.202
Sex (female): number (%)		12 (37.5%)	11 (39.3%)	0.887
Cancer Type n (%)	ALL	14 (43.8%)	7 (25.0%)	0.377
	AML	4 (12.5%)	10 (35.7%)	
	NHL	2 (6.3%)	2 (7.1%)	
	Abdominal sarcoma	2 (6.3%)	2 (7.1%)	

	Combination group	Monotherapy group	*P-value*
Ewing sarcoma	4 (12.5%)	4 (14.3%)	
Brain tumor	2 (6.3%)	2 (7.1%)	
Rhabdomyosarcoma	0 (0.0%)	1 (3.6%)	
PNET	2 (6.3%)	0 (0.0%)	
HL	1 (3.1%)	0 (0.0%)	
Osteosarcoma	1 (3.1%)	0 (0.0%)	

ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; NHL: non-Hodgkin's lymphoma; PNET: primitive neuroectodermal tumor; HL: Hodgkin's lymphoma

Table 2. Clinical results in the combination and monotherapy groups

	Combination group	Monotherapy group	*P-value*
Duration of neutropenia hospital stay (days) Median (Q1-Q3)	5 (3-7)	3 (2-5)	0.021
Duration of fever (Mean ± SD)	5.22 ± 4.08	3.60 ± 2.90	0.087
Antibiotic escalate: n (%)	19 (59.37%)	9 (32.14%)	0.035
Vancomycin: n (%)	18 (58.06%)	9 (32.14%)	0.046
Meropenem: n (%)	16 (50%)	7 (25%)	0.047
Positive blood culture: n (%)	6 (18.8%)	2 (7.1%)	0.187
Types of microorganisms	25% *E. Coli*, 25% *Staph. intermedius*, 50% *Acinetobacter baumannii*		
Positive urine culture: n (%)	1 (3.1%)	1 (3.6%)	0.047
Types of microorganisms	100% *E. Coli*		

Discussion

Age, duration of neutropenia, the nature of the specific cancer, the pathogen involved, and the availability of new effective drugs all have a profound effect on the treatment success (14).

The optimal management and effective treatment of these patients is still controversial, especially whether it is better to use a beta-lactam alone or in combination with an aminoglycoside (14). In a study conducted by Davis and Wilson, monotherapy with a broad-spectrum antibiotic reduced mortality and had fewer side effects than combination treatment (15).

Fourth-generation cephalosporins have good activity against *streptococci*, including the *viridans* group, methicillin-sensitive *staphylococci*, and beta-lactamase-producing *Pseudomonas aeruginosa*, which are all pathogens that are mostly isolated in patients with fever and neutropenia with bacteremia. Also, C-3' quaternary ammonium, cefpirome, and cefepime have increased activity and lower affinity for chromosomal beta-lactamases compared to other cephalosporins which pose an advantage against resistant mutants of some gram-negative species (14).

Thus, in this study, we decided to compare the effectiveness of Shahid Motahari Hospital's empiric antibiotic treatment protocol (ceftriaxone plus amikacin) for fever and neutropenia with the ASCO protocol (cefepime monotherapy) in children with cancer.

We observed a shorter hospital stay with cefepime monotherapy ($P = 0.021$). In a similar study conducted by Mohammed et al., which compared the efficacy of ceftriaxone monotherapy with ceftriaxone plus gentamicin for the treatment of fever and neutropenia,

the average length of hospitalization was nine days ($P = 0.052$) in both study groups (16). In another study conducted by Çorapçioğlu and Sarper, cefepime monotherapy was compared with ceftazidime plus amikacin. The cefepime group had a shorter length of stay ($P = 0.021$) (15).

In our study, a significantly lower percentage of patients in the M group needed their antimicrobial regimen escalated (M: 32.14% vs C: 59.37%, $P = 0.035$). It should be noted that among the patients who needed to receive second-line antibiotics in M and C groups, 32.14% and 58.06% ($P = 0.046$) received vancomycin, respectively, and 25% and 50% received meropenem ($P = 0.047$).

In a study conducted by Mustafa et al., cefepime was compared with ceftazidime in children with neutropenic fever. A similar result was observed for the need to add vancomycin (35% cefepime vs. 44% ceftazidime, $P = 0.063$) (17).

Neither the fever duration nor the frequency of fever detection differed significantly between the groups, although the observed values were lower for the M group for both parameters. This may be explained by the sample size, which may not provide enough study power to detect a significant difference, as Çorapçioğlu and Sarper were able to detect a significant difference in favor of the cefepime group ($P = 0.038$) (15).

Although using a narrow-spectrum antibiotic is generally more appropriate, this does not seem to be the case in the neutropenic fever population. Furthermore, despite Pseudomonas coverage provided by aminoglycosides, their use does not seem to provide as much efficacy as cefepime monotherapy does. This may be related to the limited penetration of aminoglycosides in selected tissues, which outweighs their synergistic antimicrobial effect.

Study Limitations and Future Research Directions

As mentioned before, the sample size calculation was done with the length of hospital stay as the primary outcome measure. Therefore, in cases where the difference is not significant, insufficient sample size can be one of the possible reasons, and a larger sample size may provide different results. Also, antimicrobial resistance patterns can affect the results. Although the data on adverse effects was collected, this data was only used to adjust the treatment plan for each patient and was not analyzed.

Considering the results of this study, exploring the cost-effectiveness of cefepime monotherapy compared to combination therapy or investigating specific patient populations that might benefit more from one treatment option over the other can be of value.

Conclusion

Despite the frequent and successful use of ceftriaxone plus aminoglycoside combination for a variety, our results suggest that cefepime monotherapy provides a better result in the treatment of pediatric fever and neutropenia.

Acknowledgments

The authors would like to thank the patients and their families for participating in this study.

Ethical statement

The study protocol was reviewed by the ethics committee for human research at Urmia University of Medical Sciences with the Code of Ethics IR.UMSU.REC.1400.245. This study is registered at the Iranian Clinical Trial Registration Center with the registration number IRCT20151205025372N3. The study is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data availability

No specific plan for data availability has been set.

Conflict of interest

All the authors have declared no competing interests.

Funding/support

This study was funded by Urmia University of Medical Sciences.

Author contributions

Sarah Mohsenzadeh contributed to data gathering and manuscript draft preparation. Zahra Ghelichkhan contributed to manuscript draft preparation and revision. Mehran Noroozi and Farid Ghazizadeh provided expertise and revised key sections of the study.

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