Open Access Maced J Med Sci **electronic publication ahead of print,**
published on August 18, 2018 as https://doi.org/10.3889/oamjms.2018.310

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2018.310
eISSN: 1857-9655
Clinical Science

Effect of Combination Therapy of Ceftazidime/Amikacin and Monotherapy with Imipenem on the Treatment of Fever and Neutropenia in Patients with Cancers

Ali Arash Anoshirvani[1], Nader Zarinfar[2*], Mohammad Rafiee[3], Zahra Zamani[4]

[1]Department of Hematology and Medical Oncology, Arak University of Medical Sciences, Arak, Iran; [2]Department of Infectious Disease, Arak University of Medical Sciences, Arak, Iran; [3]Department of Statistics and Epidemiology, Arak University of Medical Sciences, Arak, Iran; [4]Department of Internal Medicine, Arak University of Medical Sciences, Arak, Iran

Citation: Anoshirvani AA, Zarinfar N, Rafiee M, Zamani Z. Effect of Combination Therapy of Ceftazidime/Amikacin and Monotherapy with Imipenem on the Treatment of Fever and Neutropenia in Patients with Cancers. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2018.310

Keywords: Imipenem; Ceftazidime; Amikacin; Fever; Neutropenia

***Correspondence:** Nader Zarinfar. Department of Hematology and Medical Oncology, Arak University of Medical Sciences, Arak, Iran. E-mail: Zahravahab_md@yahoo.com

Received: 25-Jun-2018; **Revised:** 23-Jul-2018; **Accepted:** 26-Jul-2018; **Online first:** 18-Aug-2018

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: This study aimed to compare the effect of Imipenem monotherapy and combination therapy with Ceftazidime/Amikacin in febrile episodes in neutropenic cancer patients.

MATERIALS AND METHODS: In this double-blind randomised trial, 122 adult patients with cancer, neutropenia and fever who were treated by chemotherapy were gathered by simple sampling method and were divided randomly to two equal Imipenem (IP) and Ceftazidime/Amikacin (CA) groups. 500 mg of Imipenem was administered every 6 hours IP group and 2 g of Ceftazidimeplus 15 mg/kg/day in 2 equally divided doses of Amikacin was administered in the CA group. The treatment was continued for 72 hours in both groups. Data were analysed with SPSS19.

RESULTS: There was a significant difference between the mean temperatures of three days in each group ($P < 0.001$). There was no significant difference between the two groups regarding microbial response to antibiotics. There was no significant difference between 19 patients of IP and 13 patients of CA groups regarding bacteriologically documented infection ($P = 0.3$).

CONCLUSION: Unmodified therapy by Imipenem is as effective as combinational therapy by Ceftazidime/Amikacin in clinically and bacteriologically documented infection.

Introduction

Cancer is the second leading cause of death after heart disease [1] [2]. Cancer patients are susceptible to neutropenia following chemotherapy. One of the complications of chemotherapy is a fever in neutropenic patients. Neutropenia is a medical emergency [3] [4] [5]. Fever occurs in 10-50% of patients with solid tumours and more than 80% of patients with haematological malignancies during chemotherapy-induced neutropenia [6] [7]. Bacteremia can occur in 10-25% of all patients, especially at neutrophil levels below 100 cells/µl. Gram-negative bacteria resistant to the drug increase the risk of infection in patients with febrile neutropenia [9]. In the initial assessment of fever, blood collection of all catheter lumens (if present) is important as a culture of the peritoneal vein in the patient with neutropenic cancer [11]. Choosing the right antibiotic in patients with neutropenic fever can effectively improve survival and quality of life and reduce the cost of treatment in health centres. No specific drug or drug combination cannot be recommended to all patients for the treatment of neutropenic fever.

There is no consensus to manage fever and neutropenia in cancers, which can be due to several factors including the emergence of new risk factors in hosts with reduced immunity, changes in the epidemiology of infections, increased bacterial

resistance, and treatment costs [12] [13]. The combination of amikacin and ceftazidime is considered as a standard treatment. Ceftazidime is widely used in this field, and the effect of its combination with aminoglycosides has been applied in the treatment of neutropenic fever [11]. Imipenem can be used as a single drug and has been very effective in controlling infection in neutropenic patients due to its wide-ranging bactericidal properties. Imipenem is an intravenous β-lactam antibiotic that has a nephrotoxic potential. Today, imipenem is widely used as a broad-spectrum antibiotic in the first line of treating fever and neutropenia in patients with cancer [14].

Previous studies have reported that the efficacy of ceftazidime in the treatment of fever and neutropenic was 44% and 41% respectively [15], while in other studies, the efficacy of ceftazidime and amikacin were determined to be similar [16] [17] [18] [19] [20] [21] [22]. However, it has been demonstrated that the use of imipenem is superior to ceftazidime in the treatment of chemotherapy-induced febrile neutropenia [15]. It has been revealed that the efficacy of meropenem in comparison with the combination of ceftazidime and amikacin did not have any significant difference [20] [23]. While a similar study depicted that, the use of meropenem in the treatment of fever and neutropenia was more effective than combination therapy of ceftazidime and amikacin [21] [22] [23]. Since our country is different regarding climate, economic, antibiotic availability and possibly the type of microbial flora with other countries, revision of the studies undertaken by other countries is necessary because the selection of these regimes in each region and even in each hospital is unique. Few studies have been done on the therapeutic effect of imipenem, ceftazidime/amikacin. Imipenem also has a high price compared to ceftazidime/amikacin. Reducing the monetary burden on patients and the state is important in treating the disease. Furthermore, the continued use of a high-value, broad-spectrum antibiotic by the most physician is a factor in the development of drug resistance in organisms that give the drug a good response.

This study aimed to determine predominant germs in patients with febrile neutropenia and to determine the antibiotic resistance in febrile neutropenic cancer patients. Also, patients' responses to these two drug regimens were investigated to help clinicians decide on appropriate treatment for this condition [23].

Material and Methods

In this interventional study, 122 patients with neutropenic fever who referred to Khansari Hospital in Arak were enrolled in the study. Inclusion criteria include a person less than or equal to 18 years old with cancer (a hematologic or a solid tumour), Patients undergoing chemotherapy, Oral temperature >38.3°C or > 38°C for one hour, neutrophil count below 1500 µL, satisfaction to participate in the study. Exclusion criteria include pregnancy, lactation, and antibiotic intake at least three days before the study, history of pneumonia or anaphylaxis with antibiotics studied, patients with history of seizure, localized leukemia and central nervous system infection, cystic fibrosis, liver and kidney failure, aplastic crisis, coma, septic shock, bone marrow transplantation, acquired immunodeficiency virus, fever with a specific origin.

To validate the hypotheses and analysis of the symptoms, if patients were diagnosed with another episode of fever and neutropenia, patients have not re-entered the study. Patients were randomly divided into two groups. The first group received 500 milligrams of imipenem (built in Iran) intravenously every 6 hours (at 100 ccs normal saline diluted) in 30 minutes. For the second group, 2 g of ceftazidime (made in Iran) every 8 hours (in 100 ml of normal saline) was intravenously used over 30 minutes and immediately followed by amikacin therapy (15 mg) twice a day.

Before administration of antibiotics, all eligible patients underwent an initial assessment including history, physical examination, and culture from any potential site of infection (e.g., blood culture, oral and urinary tract). Laboratory tests included complete blood count (CBC), Na, K, blood urea nitrogen *(*BUN*),* Cr, Ca, aspartate aminotransferase (*AST*), Alanine aminotransferase (*ALT*), alkaline phosphatase (Alk-p), Bilirubin. Patients were checked daily for the presence of fever, and the patient's body temperature was recorded accurately by using a mercury thermometer. All patients in both groups were evaluated for response to treatment after 72 hours of antibiotic therapy. Clinical confirmation of infection is defined as Clinical evidence of infection with or without microbiological confirmation. Bacteria are defined as fever and at least one positive blood culture. Clinical response to treatment included fever in the patient.

If the symptoms of the infection were resolved without modification in the diet, it was considered an improvement. Moreover, the condition was classified as a treatment failure, if the symptoms were not changed or worsened, or even the signs of infection improved by changing the antibiotic regimen or the occurrence of death following infection.

On the third day, blood and urine culture was performed from patients to assess the bacteriological response to treatment. The bacteriological response for all infections was measured by comparing the cultures before treatment with post-treatment cultures. The positive bacteriological response is defined as 1: Eradicating which pathogens are eliminated on the treatment lines. 2: Eradicating with potentially strong, where appropriate principles for cultivation are not

available, but the patient has a satisfactory clinical response. The failure of the bacteriological response is defined as 1 - Continuity means the removal of some or all of the pathogens before treatment. 2 - Failure with a high probability where positive culture is unavailable, but the clinical signs of infection in the patient persist or worsen. In patients who responded to treatment, we continued treatment for up to 7 days or 4 days after the fever. If after 72 hours, the fever did not stop, another drug was added for treatment, and the patient was excluded from the study.

Death in the first three days of treatment was considered as treatment failure for clinical and bacteriological responses. Patients were regularly evaluated for adverse drug-related side effects. Before starting an antibiotic, three blood samples, urine culture, stool culture, and catheter tip were obtained from each patient. Mac Conkey agar and blood agar were used in this study, followed by urine culture (Chocolate agar), blood cultures (Mac Conkey agar and xld agar), stool culture (Thioglycolate), and catheter tip (elemental environment) all of which were made by CONDA.

An antibiogram test was performed, where antibiotic disks containing imipenem (with 10 µg per disk) and ceftazidime (30 µg per disk) and amikacin (30 µg per disk) (antibody medicine, Iran) were placed on the medium, followed by incubation in 37°C for 24 hours.

After 24 hours, the diameter of the inhibition zone was measured. The susceptibility and resistance of isolated microbes from culture media were determined based on the diameter of the inhibition zone (mm).

Data were analysed by SPSS 19 software. The Independent Samples t-Test was applied to compare the means of two independent groups for data with normal distribution, and the Mann-Whitney test was used in the absence of normal distribution.

Results

In this study, 122 patients with neutropenic fever were studied in cancer patients. Of these, 68 (55.7%) were male, and 54 (44.3%) were female. The mean age of the imipenem group was 49.9 (SD: 11.73), and the mean age of the Ceftazidime / Amikacin group was 43.36 (SD: 11.65), with a significant difference between the two groups (P = 0.002). The underlying disorders of the patients were as follows; leukaemia: 50 subjects (41%), lymphoma: 24 (19.7%), solid tumour: 38 subjects (31.1%), myelodysplastic syndrome: 7 subjects (5.7%). There was no significant difference between the two groups regarding the distribution of underlying disease (P = 0.93). All patients entering the study had a temperature of more than 38.3°C on the first day. The average body temperature on the first day in the imipenem group was 39.08 (SD: 0.22), while it was determined to be 39.2 in the ceftazidime/amikacin group (SD: 0.25), which depicted a significant difference between the two groups in terms of mean fever on the second and third days (P = 0.004). Of all patients entering the study, 17 (13.9%) were febrile on the third day, 7 (11.5%) were in the imipenem group and 10 (16.4%) in the ceftazidime/amikacin group. There was no significant difference between the two groups regarding the number of discontinuation of fever in the two groups (P-value = 0.60). In this study, the neutrophil count was mild in 19 patients (15.6%), followed by medium neutrophilia in 80 subjects (65.6%), severe neutrophilia in 23 patients (18.9%). There was no significant difference between the levels of neutrophil in the first day (P = 0.20) and the third day (P = 0.13) between the two groups. On the third day, 13 patients (10.7%) had neutrophil levels below 500 cells/µl. Twelve patients (52.2%) with severe neutropenia remained febrile on the third day, of which 5 subjects (38.5%) belonged to the imipenem group, and 7 subjects (70%) were assigned into ceftazidime/amikacin group. There was no significant difference in fever on the third day in both groups (P = 0.21). Furthermore, 21 patients (17.2%) had positive blood culture on the first day. No significant difference was found between the two groups regarding positive blood culture (P-value = 0.63).

Seventy patients (33.3%) had positive blood culture on the third day, where 3 (25%) patients belonged to the imipenem group, while 4 subjects (44.4%) belonged to ceftazidime/amikacin group. No significant difference was found between the two groups regarding positive blood culture on day 3 (p=0.39). Moreover, sixteen patients (13.1%) had a positive urine culture on the first day. There was no significant difference between the two groups regarding positive urine culture in the first day (p=0.78), while 100% of patients had a negative urine culture on day 3. No patient showed any positive stool culture. One patient (1.6%) had a positive catheter tip culture, where it was observed in the imipenem group. There was no significant difference between the two groups regarding the catheter tip culture at day 1 (P = 1.00). The catheter culture of this patient remained positive on the third day.

Out of 21 patients who had positive blood culture on the first day, 5 patients (23.8%) showed Staphylococcus epidermidis, Followed by the presence of Staphylococcus aureus (9.5%; 2 patients), Escherichia coli (57.1%; 12 patients) and Pseudomonas aeruginosa (9.5%; 2 patients). There was no significant difference between the two groups regarding bacterial isolation from the blood on the first day (P = 0.77). Blood culture in the third day of patients with gram-negative organisms (E. coli and Pseudomonas spp.) was negative. Blood cultures of all patients with Gram-positive organisms (*S. aureus*

and *S. epidermis*) remained positive on day 3. No significant difference was observed between the two groups regarding the type of bacteria isolated from blood culture on day 3 (P = 0.90).

It is worth noting that the only bacterial species isolated from urine culture was *Escherichia coli*. We did not observe a significant difference between the two groups regarding bacterial isolation from the urine (P-value = 0.78). The only bacteria isolated from the catheter tip culture were *S. aureus*. In 16 patients, we had to modify the type of antibiotic. Vancomycin was added to the regimen of 14 patients (87.5%), of which 5 patients (83.3%) belonged to the imipenem group and 9 subjects (90%) was observed in the ceftazidime/amikacin group. Two patients (12.5%) also received amphotericin, of which 1 patient (16.7%) was determined to belong to the Imipenem group, and 1 patient (10%) was observed in the group of ceftazidime/amikacin. Therefore, no significant difference was found between the two groups regarding the need for drug modification (P = 1.00). Bacteriologic infection was confirmed in 32 patients (26.2%) during episodes of fever, of which 19 patients (31.1%) were in the imipenem group and 13 patients (21.3%) in the ceftazidime/amikacin group. There was no significant difference in bacteriological infection between the two groups (P = 0.30).

The clinical response of patients to antibiotics was divided into three groups: 1) fever reduction occurred in 105 patients (86.1%), of which 54 patients (88.5%) in the imipenem group and 51 patients (83.6%) in the ceftazidime/Amikacin; 2) improvement with antibiotic adjustment occurred in 16 patients (13.1%), of which 6 subjects (9.8%) were in the Imipenem group, and 10 patients (16.4%) were observed in the group of ceftazidime/amikacin; and 3) death occurred in one patient (1.6%) in the imipenem group.

There was no significant difference between the two groups regarding clinical response to antibiotics (P-value = 0.35).

Of the 38 patients with positive microbial culture, 29 (80.6%) had a positive microbial response to antibiotics.

The results were negative on the third day, of which 18 patients (85.7%) were in the Imipenem group, and 11 patients (73.3%) were in the ceftazidime/amikacin group. There was no significant difference between the two groups regarding microbial culture response to an antibiotic (P = 0.41). Imipenem was more effective than ceftazidime/amikacin reducing fever and improving clinical symptoms of patients with and without bacteriological confirmation. However, there was no significant difference between the two groups. Both drugs were more effective in patients with bacteriological confirmation than non-bacteriologic confirmation.

Nevertheless, there was no significant difference between the two groups. No side effects were seen in any of the patients. Because the fever values were measured in three consecutive periods in two groups, advanced analysis of the repeated measurements analysis has been used. Using this analysis, there was a statistically significant difference between the mean fever in three periods (P < 0.001), but there is no significant difference between the mean fever in the three consecutive periods in the two groups.

Imipenem was depicted to be more effective than ceftazidime/amikacin in clinical improvement and fever reduction. However, no significant difference was observed in the two groups. Also, ampicillin was more effective than ceftazidime/amikacin in clinical improvement and fever reduction in patients with severe neutropenia, but no significant difference was found between the two groups.

Table 1: Demographic and statistical information in two intervention groups (The table should be corrected)

Group / variable		Imipenem	Ceftazidime and amikacin	P-value
Body temperature of the first day		39.08)(0.22	39.20(0.25)	0.004
The body temperature of the second day		37.63)0.93(	37.641.01)(	0.14
The body temperature of the third day		37.19)0.72(	37.40)0.96(	0.09
	1000-1500	6)%9.8(	13)%21.3(	0.20
Neutrophil counts on the first day	500-1000	42)%68.9(	38)%62.3(	
	<500	13)%21.3(	10)%16.4(	
	1000-1500	8)%13.1(	51)%24.6(	0.13
Neutrophil counts on the third day	500-1000	48)%78.7(	38)%62.3(	
	<500	5)%8.2(	8)%13.1(	
Body temperature on day 3 in patients with neutrophil counts below 500	38.3<	5)%38.5(	7)%70(	0.21
	37.2>	8)%61.5(	3)%30(	
Blood culture on the first day	Positive	12)%19.7(	9)%80.3(	0.63
	Negative	49)%14.8(	52)%85.2(	
Blood culture on the third day	Positive	3)%25(	4)%44.4(	0.39
	Negative	9)%75(	5)%55.6	
Urinary culture on the first day	Positive	9)%14.8(	7)%11.5(	0.78
	Negative	52)%85.2(	54)%88.5(	
Urinary culture on the third day	Negative	(%100)9	(%100)7	_
First-day stool culture	Negative	(%100)61	(%100)61	_
The first day of the catheter tip culture	Positive	1)%1.6(	0)%0.0(	1.00
	Negative	60)%98.4(	61)%100(	
The third day of the catheter tip culture	Positive	1)%100(	_	_
Tabs episode classification	With bacteriological confirmation	22)%36.06(	16)%26.22(	0.30
	No bacteriological confirmation	39)%63.93(	45)%73.77(	
Clinical response to antibiotics	Stop the fever	54)%88.5(	51)%83.6(	0.35
	Improve with antibiotic change	6)%9.8(	10)%16.4(	
	Death	1)%1.6(	0)%0.0(	
Microbial culture response to antibiotics	Positive	18)%85.7(	11)%73.3(	0.41
	Negative	3)%14.3(	4)%26.7(	
Body temperature on day 3 in patients without bacteriological confirmation	38.3<	(%11.42)4	(%15.38)6	
	37.2>	(%88.57)31	(%84.61)33	0.77

None of the Gram-positive bacteria was susceptible to three antibiotics. One hundred per cent of the gram-negative bacteria were sensitive to imipenem and ceftazidime, and 86.6% were sensitive to amikacin. Both *P. aeruginosa* and two *E. coli* blood cultures were resistant to amikacin.

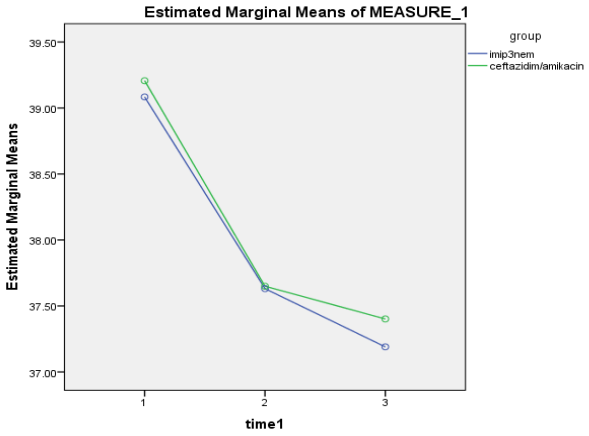

Figure 1: The effect of imipenem and ceftazidime/amikacin on discontinuation of fever for 3 consecutive days

Discussion

The present study compared the effect of imipenem with the standard drug combination of ceftazidime/amikacin as an experimental therapy in controlling fever and improving clinical and microbiological outcomes for confirmed infections and unspecified fever in neutropenic cancer patients. There was no significant difference between the two groups in the rate of discontinuation of fever, unmodulated treatment time, or the response of patients to bacteremia. After 72 hours from the beginning of experimental therapy and body temperature measurement and experimental results analysis, we found that the clinical and therapeutic effect of monotherapy with imipenem as an experimental therapy in febrile episodes in patients with neutropenic cancers, which was similar to combination therapy with ceftazidime/amikacin. It is worth noting that imipenem was more effective than ceftazidime/amikacin to reduce fever and to improve clinical efficacy in cancers with severe fever and neutropenia (approximately two times), but there was no significant difference between groups due to the small number of these patients.

The death of one patient (1.6%) occurred on imipenem group on the third day. The patient had a background of large diffuse b-cell lymphoma. There was no positive culture in this patient. It should be noted that the patient had severe neutropenia at admission. On the third day, the patient suffered from abdominal pain and tenderness. During the diagnostic evaluations, the patient had an intestinal rupture. Furthermore, the patient suffered from a severe fall in cardiac blood pressure during surgery, following underlying ischemic heart disease and then died. The patient's death did not correlate with the drugs used in the present study.

In the present study, after 3 days and checking the patient, it was determined that the clinical effect of imipenem in the experimental treatment of febrile episodes in patients with neutropenic cancer is similar to that of ceftazidime/amikacin. The level of improvement at the end of treatment was similar in both groups. Similarly, there was no difference between the two groups in the rate of discontinuation of the fever. Finally, unlike the available studies, which noted that the gram-positive bacteria are the common cause of fever in patients with neutropenic cancer, gram-negative organisms were more common in the current study.

Our positive bacterial cultures in 78.9% of cases included gram-negative bacteria and in 21% of them were gram-positive bacteria. The dominant organism was gram negative. *E. coli* was the most commonly isolated organism. All isolated gram-positive bacteria were resistant to our antibiotics. All Gram-negative bacteria were sensitive to imipenem and ceftazidime, while 28.5% of gram-negative bacteria isolated from the blood were resistant to amikacin. Both *P. aeruginosa* and two *E. coli* blood cultures were resistant to amikacin. No urine culture showed resistance to amikacin. Imipenem was more effective than ceftazidime/amikacin in reducing fever and improving clinical symptoms of patients with and without bacteriological confirmation. However, there was no significant difference between the two groups. Both drugs were more effective in patients with bacteriological confirmation than patients without bacteriological confirmation. However, there was no significant difference between the two groups.

There was no difference in drug tolerance in the two groups, and no drug complications were seen in the two groups. It is very important that in the present study, none of the patients died due to gram-negative sepsis, which indicated the strength of both drug regimens including imipenem monotherapy and ceftazidime/amikacin combination therapy against gram-negative bacteria. All gram-negative bacteremia responded to our drugs without adding additional antibacterial agents. However, the bacteremia induced by gram-positive pathogens showed a very poor response to treatment in both groups.

There was no significant difference in drug tolerance in the two groups, and no side effects were seen in the two groups. On the other hand, the poor clinical effect of imipenem and ceftazidime/amikacin on gram-positive bacteremia in recent studies suggests that there is no reason to delay the addition of glycopeptides such as vancomycin to imipenem and ceftazidime/amikacin following a lack of clinical response after 72 hours of treatment.

Medication modification has occurred in 9.8% of the imipenem group and 16.3% of the ceftazidime/amikacin group. The higher response to imipenem compared to ceftazidime/amikacin may be due to a wider range of coverage against uncommon

pathogens or resistant pathogens; however, more studies are needed for this. Various studies have been conducted since 1992, with conflicting results from the effects of these drugs. A study has shown that the use of imipenem in the treatment of fever and neutropenia has been more effective than combination therapy of ceftazidime/amikacin [23].

Ronald and colleagues have shown that the rate of successful clinical response at the end of unmodified treatment was higher in the imipenem group (43%) than ceftazidime group (32%). Meropenem was significantly more effective in neutropenia below 100 cells/µl than ceftazidime [27]. It has been indicated that meropenem monotherapy has been well tolerated and produced response rates similar to those obtained with ceftazidime/amikacin. The least success rate in both methods was consistent with other recent studies and was probably associated with a combination of several factors, including the adoption of strict evaluation criteria [20]. Concerning the efficacy of meropenem in comparison with combination therapy with ceftazidime and amikacin, there has been no statistically significant difference between the two groups in the efficacy of these drugs [23].

It has been shown that single-agent therapy with ceftazidime or imipenem can be effectively suitable for the experimental treatment of febrile episodes in patients with neutropenia and solid tumours. Early addition of amikacin or vancomycin could provide an opportunity for treatment in the first step [25].

Another study has reported that monotherapy with meropenem, can lead to suitable treatment of fever in patients with granulocytopenia cancer, as effective as ceftazidime plus amikacin, where both regimens have been indicated to be tolerated in the mentioned study [28]. Another study found that Imipenem/cilastatin and ceftazidime/amikacin combination have been shown to be effective in treating episodes in neutropenic patients [26]. It has been depicted that the patient's response to an antibiotic with fever in patients receiving imipenem (77%) is significantly better than those receiving ceftazidime (56%), especially in patients with confirmed microbial infection [24]. A study also revealed that there had been no significant difference between ceftazidime and Imipenem regimens in febrile and neutropenic episodes in patients with cancer. It has been suggested that ceftazidime can be used as an experimental treatment for fever and neutropenia in cancer patients, due to lower prices and availability [23]. In one study, it was concluded that Gram-negative organisms were more common in cancer patients with neutropenic fever undergoing chemotherapy, unlike most of the available sources that indicated the most commonly reported Gram-positive agents are causes of fever in these patients [29] [30].

About the above, the combination regimen of ceftazidime/amikacin in the treatment of febrile episodes of neutropenic patients can have the same effect as imipenem monotherapy. Given the lower cost of this therapeutic regimen, it can be a cost-effective alternative to imipenem. Considering the two-fold effect of imipenem on the reduction of fever and the improvement of clinical symptoms in patients with severe fever and neutropenia compared to the combination of ceftazidime/amikacin and no significant difference between the two groups, it seems that the low number of these patients were associated with current results. It is recommended that a study is conducted with a larger sample size or a study in which only patients with severe neutropenia be studied. The current was performed for 3 days, and the patients were followed up for 4 days after the discontinuation of the fever or 7 days. Patients were not followed up after the study period, and no information was available on the return of the fever, the incidence of fatalities, the improvement of severe neutropenia, and the death rate of the patients after the Study period. It is therefore recommended that a similar study is conducted with a longer follow-up of the patients. We recommend that the standardisation of laboratory and microbiological tools be considered for better results. Considering the limited studies in this area and different microbial flora in each region, it can be recommended that similar studies be carried out in each region, followed by determination of the predominant microbial flora in neutropenic febrile patients and measurement of the sensitivity and resistance of the organism to this antibiotic. Because of the contradiction in the definition of "response" in various studies, comparing the results of this study with other studies in the evaluation of experimental antibiotic therapy in febrile neutropenia is difficult. However, the results of neutropenic studies are affected by the definition of "response", especially when the response rate of two or more antibiotic regimens is compared. The final choice of experimental antibiotic regimen for use in the treatment centre should be based on the antimicrobial resistance patterns of each region.

In conclusion, the results of our study showed that imipenem and ceftazidime/amikacin are both effective in the initial experimental treatment of febrile neutropenic patients, and both are well tolerated. Results should be interpreted with caution in the absence of confirmatory studies in a specific subgroup of patients.

Acknowledgements

This study has been obtained from doctoral dissertations (code of ethics: 6_133 _91, Arak University of Medical Sciences) with a clinical practice

code (IRCT2012121511756N1). Finally, we thank all the people who participated in this study and the deputy director of research and technology in Arak University of Medical Sciences.

References

1. Braunwald E, Fauci J, Kasper B, Hauser J,Longo G and Jameson C.Harrison principles of internal medicine, 15th Ed.Newyork: MacGraw-Hill, 2008:552-553. PMid:18721511

2. Mandell G, Douglos M, Bennett J. Textbook ofprinciple and practice ofinfectious diseases, 5th Ed. HoustonChurchill Livingstone, 2004:3090-3113.

3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of anti - microbial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases society of America. Clin Infect Dis. 2011; 52:e56. https://doi.org/10.1093/cid/cir073 PMid:21258094

4. Hughes WT, Armstrong D, Bodey GP, et al. guidelines for the use of antimicrobial agents in neutropenic patients with cancer. ClinInfect Dis. 2002; 34:730-51. https://doi.org/10.1086/339215 PMid:11850858

5. Klastersky J. Management of fever in neutropenic patients with differentrisks of complications. Clin Infect Dis. 2004; 39(Suppl 1):S32–7. https://doi.org/10.1086/383050 PMid:15250018

6. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenicpatients andthe susceptibilities of the currently isolatedpathogens. Clin Infect Dis. 2004; 39(Suppl 1):S25–31. https://doi.org/10.1086/383048 PMid:15250017

7. Zuckermann J, Moreira LB, Stoll P, Moreira LM, Kuchenbecker RS, Polanczyk CA. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. Annals of hematology. 2008; 87(2):139-45. https://doi.org/10.1007/s00277-007-0390-7 PMid:17938926

8. Oliveira AL, De Souza M, Carvalho-Dias VM, Ruiz MA, Silla L, Tanaka PY, Simoes BP, Trabasso P, Seber A, Lotfi CJ, Zanichelli MA. Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. Bone marrow transplantation. 2007; 39(12):775. https://doi.org/10.1038/sj.bmt.1705677 PMid:17438585

9. Chen CY, Tang JL, Hsueh PR, et al. Trends and antimicrobialresistance of pathogens causing bloodstream infections among febrileneutropenic adults with hematologicalmalignancy. J Formos Med Assoc. 2004; 103:526–32. PMid:15318274

10. Freifeld A, Marchigiani D, Walsh T, Chanock S, Lewis L, Hiemenz J, Hiemenz S, Hicks JE, Gill V, Steinberg SM, Pizzo PA. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. New England Journal of Medicine. 1999; 341(5):305-11. https://doi.org/10.1056/NEJM199907293410501 PMid:10423464

11. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical Practice Guideline for the Use ofAntimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the InfectiousDiseases Society of America. Clinical Infectious Diseases. 2011; 52(4):e56–e93. https://doi.org/10.1093/cid/cir073 PMid:21258094

12. Casali A, Ameglio F, Gionfra T, Tonachella R, Paoletti G, Gallo CC. Amikacin plus ceftazidime versus amikacin plus piperacillin versus amikacin plus aztreonam in infections in neoplastic patients with granulocytopenia. Chemioterapia: international journal of the Mediterranean Society of Chemotherapy. 1987; 6(6):440-4.

13. De Jongh CA, Wade JC, Schimpff SC, Newman KA, Finley RS, Salvatore PC. Empiric antibiotic therapy for suspected infection in granulocytopenic cancerpatients:a comparison between the combination of moxalactam plus amikacin and ticarcillin plus amikacin. Am J Med. 1982; 73:89- 96. https://doi.org/10.1016/0002-9343(82)90935-4

14. Bodey GP, Alvarez ME, Jones PG. Rolston KVI, Steelhammer L, Fainstein V. Imipenem-cilastatin as initial therapy for febrile cancer patients. Antimicrob. Agents Chemother. 1986; 30:211-214. https://doi.org/10.1128/AAC.30.2.211

15. Feld R, Depauw B, Berman S, Keating A, and Ho W.Meropenem versus ceftazidime in the treatment of cancer patientswith febrile neutropenia: a randomized, double-blind trial. J Clin Oncol. 2000; 1:3690-3698. https://doi.org/10.1200/JCO.2000.18.21.3690 PMid:11054442

16. Meropenem Study Group of Leuven, London and Nijmegen. Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. Journal of Antimicrobial Chemotherapy. 1995; 36(1):185-200. https://doi.org/10.1093/jac/36.1.185

17. Rolston KV, Berkey P, Bodey GP, Anaissie EJ, KhadrdoriNM, Joshi JH, and et al. A comparison of imipenem to ceftazidimewith or without amikacin as empiric therapy in febrile neutropenicpatients. Arch Intern med. 1992; 152:283-291. https://doi.org/10.1001/archinte.1992.00400140037010 PMid:1739355

18. Freifeld AG, Walsh T, Marshall D, Gress J, Steinberg SM, Hathorn J, Rubin M, Jarosinski P, Gill V, Young RC. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. Journal of Clinical Oncology. 1995; 13(1):165-76. https://doi.org/10.1200/JCO.1995.13.1.165 PMid:7799016

19. Malik I, Shaharyar. Comparison of meropenem withceftazidime as monotherapyof cancer patients with chemotherapyinduced febrile neutropenia. J Pak Med Assoc. 2002; 52: 15-18. PMid:11963577

20. De la Camara R, Figuera A, Sureda A, Hermida G, Verge G, Olalla I, et al. Meropenem versus ceftazidime plus Amikacin in the treatment of febrile episodes in neutropenicpatients: A randomized study. Haematologica. 1997; 82: 668-675. PMid:9580087

21. Hung KC, Chiu HH, Tseng YC, Wang JH, Lin HC, Tsai FJ, Peng CT. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for neutropenic fever in children with malignancy. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2003; 36(4):254-9.

22. Corapcioglu F, Sarper N, Zengin E. Monotherapywith piperacillin/tazobactam versus cefepime as empirical therapyfor febrile neutropenia in pediatric cancer patients: A randomizedcomparison. Pediatr Hematol Oncol. 2006; 23: 177-186. https://doi.org/10.1080/08880010500506370 PMid:16517534

23. Ferdosian F, Ghiliyan R, Hashemi A, Akhondzadeh B, Gholampoor E.Comparing the efficacy of ceftazidime and meropenem in treatment of febrile neutropenia in pediatric patients with cancer. Iran J Ped Hematol Oncol. 2013; 3(3):103-7. PMid:24575280 PMCid:PMC3921881

24. Liang RA, Yung R, Chiu E, Chau PY, Chan TK, Lam WK, Todd D. Ceftazidime versus imipenem-cilastatin as initial monotherapy for febrile neutropenic patients. Antimicrobial agents and chemotherapy. 1990; 34(7):1336-41. https://doi.org/10.1128/AAC.34.7.1336 PMid:2201252 PMCid:PMC175977

25. Aparicio J, Oltra A, Llorca C, Montalar J, Herranz C, Gomez-Codina J, Pastor M, Munarriz B. Randomised comparison of ceftazidime and imipenem as initial monotherapy for febrile episodes in neutropenic cancer patients. European Journal of Cancer. 1996; 32(10):1739-43. https://doi.org/10.1016/0959-8049(96)00188-8

26. Pérez C, Sirham M, Labarca J, et al. Imipenem/cilastatin versus ceftazidime-amikacinin the treatment of febrile neutropenic patients. Rev Med Chil. 1995; 123(3):312. PMid:8525170

27. Feld R, DePauw B, Berman S, Keating A, Ho W. Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. Journal of clinical oncology. 2000; 18(21):3690-8. https://doi.org/10.1200/JCO.2000.18.21.3690 PMid:11054442

28. Cometta A, Calandra T, Gaya H,et al. Monotherapy with meropenem versus combination therapy with 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 ofCancer and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto Infection program. Antimicrob Agents Chemother. 1996; 40(5):1108-15. PMid:8723449 PMCid:PMC163274

29. Miedema KG, Tissing WJ, Abbink FC, Ball LM, Michiels EM, van Vliet MJ.Risk-adapted approach for fever and neutropenia in paediatric cancer patients-a national multicentre study. Eur J Cancer. 2016; 53:16-24 32.

30. El-Mahallawy H, Sidhom I, El-Din NH, et al. Clinical and microbiologic determinants of serious bloodstream infections in Egyptian pediatric cancer patients: a one-year study. Int J Infect Dis. 2005; 9:43-51. https://doi.org/10.1016/j.ijid.2003.11.010 PMid:15603994

31. Maschmeyer G, Link H, Hiddemann W. Pulmonary infiltrations in febrile patients with neutropenia. Risk factors and outcome under empirical antimicrobial therapy in a randomized multicenter study. Cancer. 1994; 73:2296–2304. https://doi.org/10.1002/1097-0142(19940501)73:9<2296::AID-CNCR2820730910>3.0.CO;2-7

32. Raad II, Bodey GP. Infectious complications of indwelling vascular catheters. Clin Infect Dis. 1992; 15:197–208. https://doi.org/10.1093/clinids/15.2.197

33. Bodey GP. Empirical antibiotic therapy for fever in neutropenic patients. Clin infect Dis. 1993; 17:378–384. https://doi.org/10.1093/clinids/17.Supplement_2.S378