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COMPARATIVE EVALUATION OF COMBINATION THERAPY OF IMIPENAM- CILASTATIN VERSUS CEFTAZIDIME-AMIKACIN IN PATIENTS WITH FEBRILE NEUTROPENIA

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ABSTRACT

Background: Febrile neutropenia (FN) continues to represent a major cause of morbidity, mortality, and cost in patients receiving cancer chemotherapy. The prompt initiation of empirical antibiotics in febrile neutropenia has been the most important advance in the management of the immuno-compromised host. There is limited data on efficacy of different broad spectrum antibiotics in Indian population. Present study was undertaken to compare the efficacy of two broad spectrum antibiotics in febrile neutropenia patients.

Methods: This study was conducted on patients of hematological malignancies who presented to hematology and medicine department of PGIMS, Rohtak and developed fever with neutropenia. Patients were divided in 2 groups- group A and group B. Group A patients were given imipenem-cilastatin and group B patients were given ceftazidime. Both groups were evaluated for cause of fever. Two groups were compared based on type of leukemia, clinical features at presentation, neutrophil count, duration of neutropenia, time of defervescence, clinical response to treatment and number of deaths.

Results: Baseline characters were comparable in both groups. Gram negative bacterial infections were more common than gram positive. Mean time of defervescence i e disappearance of fever was 8.7±3.23 days in group A and 8.15±2.97 days in group B. The difference was not significant. (p value >.05). total of 19 patients responded to treatment. They had disappearance of all clinical signs of infection on day 7. Ten patients (66.6%) in group A and 9 patients (60%) in group B responded to treatment. The difference in response was not clinically significant. (p value > 0.05).

Conclusion: The present study demonstrated response rate of 66.6% in patients of febrile neutropenia treated with imipenem-cilastatin and 60% in patients treated with ceftazidime plus amikacin. The difference however was not statistically significant. Since this study involved only 30 patients, other studies with large number of patients are needed to unravel the efficacy of these drugs in febrile neutropenia.

KEYWORDS

INTRODUCTION

Cancer patients are at high risk of developing infectious complications as a result of myelo-suppression due to malignancy itself and use of intensive chemotherapy. This significantly contributes to high mortality rate in these patients if empirical antibiotic treatment is not instituted at the first sign of infection.[1] The risk of developing infectious complications depends upon the duration and level of neutropenia. The risk of infections is sharply increased as the neutrophil count falls below 1000. With the onset of fever, bacteraemia is most frequently due to aerobic gram-positive cocci (in particular, coagulase negative Staphylococci, Streptococci viridens or S. aureus) or aerobic gram-negative bacilli (especially E. coli, K. pneumonia or P. aeruginosa). Fungi are common causes of secondary infections among neutropenic patients who have received courses of broad spectrum antibiotics but on occasion these organisms can be the cause of primary infection[2].

The consensus guidelines from the Immunocompromised Host Society state that a single oral temperature of 38.5°C or more, or the occurrence of three or more readings of 38°C or more within a 24-hour period, taken at least 4 h apart, is defined as fever in a neutropenic patient. Neutropenia is defined as an absolute neutrophil count (polymorphonuclear cells plus band forms) of 500/cumm or less. From a practical standpoint, patients with ANC between 500 and 1000 cells per cumm and rapidly falling because of recent chemotherapy are also considered neutropenic[3].

According to IDSA 2010 guidelines, where a causative organism is unknown or not suspected on clinical grounds, empirical broad-spectrum antibiotic therapy is recommended. For intermediate or high risk neutropenic patients with fever of unknown origin, current guidelines recommend either broad spectrum monotherapy or combination therapy where an aminoglycoside is added. Monotherapy can be given with either a carbapenem or an extended spectrum antipseudomonal cephalosporin such as ceftazidime or cefepime[4]. The goal of initial empirical antibiotic therapy is to prevent serious morbidity and mortality due to bacterial pathogens, until the results of blood cultures are available to guide more precise antibiotic choices[5].

Antibiotics have to be modified if the codition of the patient deteriorates. Modification is done based on the cause of fever. Empirical antifungal therapy may be required in case of high risk patients[4]. There is limited data on efficacy of different broad spectrum antibiotics in Indian population. Present study was undertaken to compare the efficacy of two broad spectrum antibiotics in febrile neutropenia patients.

MATERIALS AND METHODS

This study was conducted on patients of hematological malignancies who presented to hematology and medicine department of PGIMS, Rohtak and developed fever with neutropenia. Study included 30 patients who were randomly divided into 2 groups. In group A, 15 patients received imipenam plus cilastatin. In group B, 15 patients received ceftazidime plus amikacin. The aim of the study was to compare the response of these 2 combinations in febrile neutropenia. Febrile episode was defined as at least 3 oral temperature readings above 38`C at least 4 h apart within a 24 hr period OR a single oral temperature above 38.5`C . Neutropenia was defined as an absolute neutrophil count of less than 500 cells/cum. Patients were excluded from the study if they had any history of anaphylactic reaction to any β-lactam antibiotics including imipenam-cilastin, severe hepatic and renal impairment.(Serum transaminase level>3 times the upper limit of normal or Glomerular Filteration Rate <60 ml/min) or history of receiving any antibiotics except the prophylactic antibiotics within the preceding 72 hrs.

Patients who fulfilled the above mentioned criteria were included as case for the study and were evaluated with detailed clinical history, complete clinical examination, complete blood counts, urinalysis, blood biochemistry including RFT, LFT, Chest X-ray, Blood culture sensitivity, Urine culture sensitivity. Informed consent was obtained from all patients. After the initial evaluation, patients were randomized to receive either ceftazidime plus amikacin OR imipenam plus cilastatin. Group A patients were given Imipenam-Cilastatin 500 mg as intravenous infusion in normal saline over 30 min every 8 hourly. Group B patients were given Ceftazidime 2 gm 8 hourly as intravenous infusion in normal saline over 30 minutes along with amikacin 5mg/kg body weight 8 hourly.

Patients were assessed daily for changes in signs and symptoms. These included fever and any focal symptoms and signs depending on the site of infection. Complete blood count and blood biochemistry was assessed at least every other day. The organisms isolated from culture were identified by routine microbiological methods along with susceptibility to antimicrobial agents. All patients were reassessed at 72 h for their response to therapy. For patients with good response, either drug was continued for at least a total of 7 days or for 4 days after the patient became afebrile whichever was longer, unless an adverse reaction, clinical deterioration or death occured. For those who did not respond or who had clinical deterioration, further management such as empirical antifungal drug was considered .Vancomycin was added if gram-positive infection was suspected.

Fever of unknown origin was diagnosed when no clinical, radiological or bacteriological evidence of infection was found. Patients were considered to have clinically suspected infection if they had fever and other clinical evidence of an infection, even though the infective organisms were not isolated. Response was defined as complete disappearance of all clinical and laboratory evidence of infection including fever.

Two groups were compared based on type of leukemia, clinical features at presentation, neutrophil count, duration of neutropenia, time of defervescence, clinical response to treatment and number of deaths.

Statistical analysis-

The results were analysed by appropriate standard statistical methods. The data collected during the study was entered in the Microsoft excel format and was analysed using SPSS.20.0 version. For descriptive statistics frequencies, percentages, means and standard deviations of different variables were calculated. To examine difference between categorical variables, chi square test was used. Independent sample T-test was used to compare the means of two separate sets of independent samples. The p values were two tailed and probability level of significant difference was set at <0.05.

RESULTS

Out of the total 30 patients, 19 were male and 11 were female. Most of the patients had Acute Myeloid Leukemia as the underlying disorder. Most of the patients (12 in each group) were anaemic. Lymphadenopathy was present in 8 patient in group A and 6 patients in group B. Oral thrush was present in 2 patients in each group. Hepatomegaly was present in eight patients in group A and six patients in group B. Splenomegaly was present in seven patients in group A and nine patients in group B.

Table 1 Baseline characters

	GROUP A	GROUP B
Total patients	15	15
Male/Female (no.)	10/5	9/6
Mean age (years)	49.8±17.8	44.07±12.54
Underlying malignancy		
• **AML**	7	8
• **ALL**	2	2
• **CML**	2	3
• **CLL**	1	0
• **Lymphoma**	3	2
Fever (degree fahrenheit)	102.2±1.2	102.4±1.4
Duration of neutropenia before treatment (in days)	5.3±1.1	5.2±1.0
Neutrophil count at start of study (per cumm)	348±116.008	362±95.8

Total 5 patients in group A and 4 patients in group B had microbiologically documented infection. Three patients in each group had UTI. Two patients in group A and one patient in group B had bacteremia. Gram negative infections accounted for three cases in each group. Gram positive infections were seen in two patients in group A and one patient in group B.

Total 10 patients (33.3%) had no documented cause of infection. This group included 6 patients in group A and 4 patients in group B. Total 11 patients had a clinically suspected source of infection. However no organisn could be isolated. This group included 4 patients in group A and 7 patients in group B.

Mean time of defervescence i e disappearance of fever was 8.7±3.23 days in group A and 8.15±2.97 days in group B. The difference was not significant. (p value >.05). total of 19 patients responded to treatment. They had disappearance of all clinical signs of infection on day 7. Ten patients (66.6%) in group A and 9 patients (60%) in group B responded to treatment. The difference in response was not clinically significant. (p value > 0.05). In patients with fever of unknown origin, 50% patints in each group responded to treatment. In patients with clinically suspected infection, 50% patients in group A and 57% patients in group B responded to treatment. In patients with microbiologically documented infections, 100% patients in group A and 75% in group B responded to treatment. None of these differences were statistically significant. (P value >0.05). One patient in group A and two patients in group B died. Overall mortality was 10%.

Table 15 Overall Response to treatment

	Group A		Group B		P value
	Number of patients	Percent	Number of patients	Percent	
Response	10	66.6	9	60	0.705
No response	5	33.3	6	40	

DISCUSSION

In the present study, no cause of fever could be documented in ten patients(33%) Results were similar in other studies with Kenneth et al[6] showing 47% patients with unknown cause of fever and 36.5% in study by C. Cattaneo et al[7]. In study by Perez C et al[8], 46% patients had fever of unknown origin. Ronald feld et al[9] documented 249 (61%) patients with fever of unknown origin.

In remaining twenty patients (66.6%), some source of infection could be documented either clinically(36.6%) or microbiologically (30%). In the study by Kenneth et al[6], clinically suspected infection was seen in 30% patients and 30% patients had microbiologically proven infection. In the study by Perez C et al[8], 25.5% had clinically suspected infection and 28.5% had microbiologically documented infections. In a study by Ronald feld et al[9],out of total 409 episodes of febrile neutropenia, 86 (21%) had clinically defined infection and 74 (18%) were classified as microbiologically defined infections and.

Overall gram negative organisms were isolated from 6 patients, (66.6% of total microbiologically documented infections) and gram positive infections from 3 patients (33.3%). This was in contrast to study by Kenneth et al[6], where 60% of infections were caused by gram positive infections and 40% by gram negative organisms. In the study by Cattaneo C et al[7], out of all microbiologically documented infections, 40% were gram positive and 49% were gram negative. In study by Codonnier et al[10] gram positive infections constituted 63% of infections. Similar to our study, Ronald et al[9] showed 44% of gram positive infections. This variability could be due to difference in local prevalence of different bacteria in our region.

Response to treatment

In group A, Patients were given imipenem plus cilastatin. Overall response rate was 66.6%, which was comparable to response seen with this drug in other studies; Kenneth V et al[6] found a response rate of 72%, Perez C et al[8] found a response rate of 53% and in a study by R. liang et al[11], response was seen in 64.2% patients.

In group B, patients were given ceftazidime plus amikacin and over all response was seen in 9 patients (60%). Response rate was variable in other studies- it was 71% in a study by Kenneth V et al[6] and 37% in a study by Perez C et al[8]. This variability in response can be explained by difference in type of micro organisms causing infections which could not be documented in most of the cases. In spite of the variable response, no study demonstrated significant difference in response in two groups.

The difference between the two groups was not statistically significant (p value=0.705). similar observation was made by Kenneth et al[6] with insignificant difference between two groups (p value=0.14). perez C et al[8] also demonstrated p vaue >0.05.

Therefore this study demonstrated that monotherapy with imipenem-cilastatin is equally effective as combination therapy with ceftazidime plus amikacin. Findings are in accordance with other studies. A recent meta-analysis found a significant advantage of β-lactam monotherapy

over b-lactam plus aminoglycoside combinations, in that the former was associated with fewer adverse events and less morbidity, but with similar rates of survival[12] . Many centers have found that ceftazidime is no longer a reliable agent for empirical monotherapy of fever and neutropenia because of its decreasing potency against gram-negative organisms and its poor activity against many gram-positive pathogens, such as streptococci. Aminoglycoside monotherapy should not be used for either empirical coverage or for bacteremia during neutropenia because of the rapid emergence of microbial resistance to this class of agents. Therefore a combination of ceftazidime and amikacin is used as empirical therapy of febrile neutropenia[13].

Additional antibiotics, antifungals and antivirals were used in patients not responding to treatment. Total four patients in group A and five patients in group B were given additional antibiotics or antifungal or antiviral drugs.

The study concluded that both imipenem-cilastatin and ceftazidime plus amikacin are equally effective for treatment of febrile neutropenia if started at adequate time and adequate modifications are made when necessary. Main limitation of the study was small sample size and therefore results may not be representative of large population.

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