BANGLADESH J CHILD HEALTH 2021; VOL 45 (2) : 83-88

Efficacy and Safety of Piperacillin-Tazobactam and Cefepime as Empirical Therapy for Febrile Neutropenic Children with Acute Lymphoblastic Leukaemia (ALL)

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Abstract:

Background: *Infection is a major clinical challenge in ALL treatment. Prompt administration of empirical antibiotic in febrile neutropenic patients has reduced the mortality. Both Cefepime or Piperacillin-Tazobactam has been used as empirical treatment.*

Objective: *To compare the efficacy and safety between Piperacillin-Tazobactam with Cefepime in febrile neutropenic children with ALL.*

Materials and methods: *This randomized study was conducted from August 2015 to August 2016 in BSMMU. Sixty one episodes of febrile neutropenia in children with ALL, aged 0 to18 years were included in this study. Patients were randomized into two groups. One group received Piperacilln/Tazobactam and another group received Cefepime and data of 60 febrile neutropenic episodes were analyzed.*

Results: *Febrile neutropenic episodes in the Piperacillin/Tazobactam group were 28 and in Cefepime group was 32 episodes and 34(57.63%) were male and 25 (42.37%) female. Median age was 5 years and 38(62.3%) neutropenic episodes were in induction phase. Majority had fever without focus 21(35%). Microorganisms isolated in 13 (21.66%) patients and majority 6 (46.15%) had blood infection. Most of the isolated organisms were Gram negative 11(84.61%). Overall treatment success without modification in the Piperacillin/Tazobactam group was 17(60.7%) and in Cefepime group 18 (56.3%) and that comparison was not statistically significant (p= 0.732). Significant difference was also not found comparing the mean duration of fever, neutropenia and hospital stay.*

Conclusion: *Both Piperacillin/Tazobactam and Cefepime were found effective and safe as an empirical therapy for febrile neutropenic children with ALL.*

Key words: *Acute lymphoblastic leukaemia (ALL), Febrile neutropenia, Empirical therapy, Efficacy and safety.*

Introduction:

Acute Lymphoblastic Leukaemia (ALL) is the most common malignancy in children. It accounts for one fourth of all childhood cancer and 72% of all cases of childhood leukaemia. The peak incidence of ALL occurs between 2 to 5 years of age.[1] Chemotherapy and Hematopoietic stem cell transplantation (HSCT) are the established therapeutic options for these patients. Typically ALL is treated by chemotherapy in different phases- induction phase, early consolidation, interim maintenance, delayed consolidation and maintenance therapy.[2] Infection due to neutropenia is more common during induction phase.[3] Fever and neutropenia in children with cancer is common, potentially fatal complication of chemotherapy. The empirical use of antibiotic therapies is widely accepted in patients with fever and neutropenia during cancer chemotherapy.[4] Management of febrile neutropenic period in patients with ALL requires prompt therapy

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Received: 8/11/2020 **Accepted:** 23/07/2021

with empiric broad-spectrum antimicrobial agents. While substantial morbidity and mortality results from Gram-negative infections, infections with Gram-positive organisms appear to be predominant.[5]

Cefepime is an extended spectrum fourth generation cephalosporin. It is active against a broad spectrum of Gram-positive and Gram negative bacteria, including methicillin-sensitive Staphylococcus aureus, alpha hemolytic streptococci and some strains of *Pseudomonas aeruginosa.* Reports showed that Cefepime is effective and safe for empiric treatment of febrile neutropenic pediatric patients.[4,6] Success rate of Cefepime monotherapy was reported 60% and no significant adverse effects were seen.[7]

Pipercillin – a synthetic broad spectrum penicillin – in combination with the potent β-lactamase inhibitor tazobactam has been available for the empirical initial therapy of febrile neutropenic patients since 1993. Piperacillin /tazobactam was chosen for the comparative single-agent arm of this study because of its broad antimicrobial spectrum – which includes *P.aeruginosa* –and its excellent efficacy against Gram-positive pathogens including Streptococci.[8] Reports showed that clinical efficacy rate of Piperacillin/ Tazobactam in paediatric patients is 75% and safety appears similar to that of other beta lactam/beta-lactamase inhibitor combinations.[9,10]

Materials and Methods:

This study was an open blinded randomized clinical trial. Primary purpose was to compare efficacy and safety of monotherapy with Cefepime and Piperacillin/ Tazobactamin febrile neutropenia. Study was conducted at Paediatric Haematology and Oncology Department, BSMMU (Bangabandhu Sheikh Mujib Medical University), Dhaka from July 2015 to August 2016. All children with febrile neutropenia who had received chemotherapy for ALL ages were ≤18 years at diagnosis were enrolled in this study according to these inclusion criteria, patients with ALL who had undergone chemotherapy with febrile neutropenia, presence of neutropenia (ANC < 500 cells/mm^3 or if count < 1000 cells/mm^3 and decreasing) within 24-48 hours preceding chemotherapy, having an axillary temperature ≥38^0 C on two occasions at least 1h apart or ≥38.3^0 C on one occasion in 24 h in the absence on any other obvious cause of fever. Patients with presumed infections was the cause of fever, not receiving any antimicrobial therapy within 1 week prior to admission, having no known allergy or other incompatibility to one of the study drugs were included. Exclusion of patients were done due to presence of fever attributable to malignancy or transfused blood products or other medications, the administration of any systematic antibiotics within one week prior to enrollment, hepatic or renal insufficiency, those patients who have indication for giving Vancomycin at the start of empiric therapy. Also those patients admitted with febrile neutropenia with co-morbidity, like diarrhoea and meningitis, septic shock were excluded. Sampling type was simple randomized method by doing lottery. Patients were randomly assigned to one of the treatment arms by lottery method. Patients were included in randomization more than once when they had completed the previous treatment cycle at least one week ago and were divided into two groups: Group 1: Piperacillin-tazobactam group (dose- 100mg/kg, 8 hourly) amd in Group 2: Cefepime (dose -1500mg/m^2, 8 hourly). On admission a detailed history was taken. All children were examined with particular attention to occult sites of infection. The following lab tests was performed: CBC, Blood Culture (before giving antibiotic), BACTEC blood culture system in a FAN bottle, chest radiography, urine R/E & C/S, stool C/S was done in case of diarrhea, culture of wound, throat or aural swab needle aspirates from abscess was done in selected patients. Safety was evaluated by analyzing adverse events, vital signs, clinical laboratory results, and physical examination.

Patients were examined daily by the investigator and the first evaluation of the therapy was performed 72 hours after the start of antibiotic therapy. The initial treatment was retained in the event of defervescence (freedom from fever for 5 days or neutrophils>1000/ cmm). If the fever not subsided and/or the clinical symptoms deteriorated, supplementary treatment with vancomycin was be given (400mg/m^2, 6 hourly). A further evaluation was carried out 48-72 hours later. If the fever persisted, the initial treatment was replaced by imipenem/meropenem. After 5 days systemic Amphotericin-B treatment (0.5-1mg/kg body weight) was considered. After receiving the antibiogram the therapy was modified accordingly in the event of microbiologicaly documented infection. Therapeutic response was considered as successful, if patient remains afebrile (<38^0 C) for 120 hours, clearance of sign-symptoms of infection, no occurrence of primary infection within 1 week after

discontinuation of treatment.[11] Failure defined as the persistence of fever and infectious signs beyond 120 hours following initiation of the antibiotic therapy, and a required change or modification in the initial antibiotic therapy, or deterioration/death due to infection.[11] Investigator and on duty resident has taken care of the patient at Paediatric Haematology and Oncology ward round the clock for 24 hour. Age and sex of the patients, phases of chemotherapy, type of infections, isolated microorganisms were observed and analyzed. Efficacy of the drugs is determined by duration of neutropenia, duration of fever, duration of hospital stay, response to treatment, additional antibiotics used, adverse effects of both the drugs also observed. For statistical analysis IBM-SPSS v 22 software used. In data analysis for age, sex distribution and haematological findings median, range was calculated. Proportion was used for empirical drugs in different phases of chemotherapy, clinical infection, results of positive culture of different specimen, microorganisms isolated. The chi-square test and compare means test used for comparison. P-value of <0.05 was considered statistically significant.

Results:

Total 61 febrile Neutropenic episodes from 59 patients were studied. Among them 28 febrile neutropenic episodes were in the Piperacillin/Tazobactam group and 33 episodes in the Cefepime group. One patient from the Cefepime group lost to follow up, so finally 60 febrile neutropenic episodes were analyzed, 28 from Piperacillin/Tazobactam group and 32 from Cefepime group. In this study, 34(57.63%) were male and 25 (42.37%) were female and median age was 5 years and 38 (62.3%) neutropenic episodes were in induction phase.

Majority of the febrile neutropenic episodes had fever with unknown foci 21(35%). Microorganisms isolated in 13(21.66%) patients and majority 6 (46.15%) had blood infection. Most of the isolated organisms were Gram negative 11(84.61%).

Overall treatment success without modification in the Piperacillin/Tazobactam group was 17(60.7%) and in Cefepime group was 18 (56.3%), P value was found 0.732 that was not significant. Regarding the other parameters the mean duration of fever, median duration of neutropenia and duration of hospital stay, there were no statistically significant difference. Both Piperacillin/Tazobactam and Cefepime were equally effective and safe as an empirical therapy for febrile neutropenic children with ALL.

Table-I

Age & gender distribution of ALL patients with febrile neutropenic episodes (n=59)

	Piperacillin/ Tazobactam	Cefepime
Total Patients	27 (45.8%)	32 (54.2%)
Age (median, range)	5 (1-16)	4 (1-15)
<1 Year (n)	2	0
1-5 years (n)	11	18
5-10 years (n)	10	10
>10yrs (n)	4	4
Gender		
Male	16 (59.3%)	18 (56.2%)
Female	11(40.7%)	14(43.8%)

Table-II

Febrile Neutropenic episodes at different phases of chemotherapy (n=61).

Phases of chemotherapy	Piperacillin-Tazobactam	Cefepime
Induction	17(60.7%)	21(63.6%)
Early Consolidation	3(10.7%)	1(3%)
Interim Maintenance	4(14.3%)	2(6.1%)
Delayed Consolidation	0	5(15.2%)
Maintenance	4(14.3%)	4(12.1%)
Total	28	33

Febrile neutropenic episodes were almost equal in both Piperacillin/Tazobactam (60.7%) and Cefepime (63.6%) group during induction phase of chemotherapy. Distribution was different in early consolidation, interim maintenance and delayed consolidation phase, but in other phases distribution were equal.

Table-III

Haematological profile in two treatment groups. (n= 60)

	Piperacillin-Tazobactam (Median, range)	Cefepime (Median, range)	P-value
WBC Count/cmm	760 (160-5870)	935 (50-7180)	0.463
Hb% (gm/dl)	8.7 (5.8-14.6)	9.2 (4.2-13.9)	0.714
Platelet/cmm	27500 (20000-120000)	37000 (75000-279000)	0.155
ANC /cmm	120 (5-700)	115 (2-930)	0.247
<100 /cmm	30 (5-80)	45 (2-90)	0.386
100-500 /cmm	200 (110-410)	150 (110-310)	0.386

Table-IV

Distribution of clinical infection between two groups. (n=60)

Site of Infection	Piperacillin-Tazobactam	Cefepime
Fever without focus	9	12
Resp. tract infection	9	7
GIT	6	7
Procedure Site	2	3
Others	2	3
Total	28	32

Table- V

Result of culture of different specimen (n= 148)

Specimen	Number of specimen	Positive n (%)
Blood	60	6(10%)
Urine	60	5(8.3%)
Stool	15	0
Pus	2	0
Aural Swab	5	2(40%)
Throats swab	3	0
Wound Swab	3	0

Among the cultures 60 were blood, 60 were urine, 15 were stool, 2 were pus, aural swab 5, throat swab andwound swab were 2. Blood culture positive in 6(10%), urine culture in 5(8.3%) and aural swab culture positive in 2 (3.3%) episodes.

Table-VI

Isolated microorganisms in both the study groups.

Microorganisms	Piperacillin-Tazobactam	Cefepime
Febrile neutropenic episodes with microbiologically documented infection, total-13	8	5
Gram negative organism, Total, 11 (84.6%)		
Klebsiellaspp (n)	1	2
Pseudomonas spp (n)	1	1
Escerichia coli (n)	1	0
Enterobactorspp (n)	1	1
Acinetobactor (n)	2	1
Others (n)	0	0
Gram positive organism, Total, 2 (15.4%)		
Staphylococcus aureus (n)	0	0
staphylococcus (n)		
Coagulase (-)tive	0	0
Enterococcus (n)	2	0

Among 60 febrile Neutropenic episodes 13 (21.66%) organisms were isolated. Majority, 11(84.6%) were Gram negative and 2 (15.38%) were Gram positive. The most common organisms were *Klebsiella* 3 (23.07%) and *Acinetobactor* 3(23.07%), the next common were *Pseudomonas spp* and *enterobactor*. two Gram positive isolates were *enterococci*.

Table-VII

Treatment response and clinical outcome of the two study group.

Duration in days (Median, range)	Piperacillin-Tazobactam	Cefepime	P-value
Fever	5 (1-11)	4 (1-15)	0.653
Neutropenia	9 (6-16)	9 (3-21)	0.48
Hospital stay	9 (1-24)	8.5 (4-24)	0.673
Success (n, %)	17 (60.7)	18 (56.3)	0.732
Fever	2.5 (1-5)	3 (1-7)	0.990
Neutropenia	9(6-11)	7(3-20)	0.941
Hospital stay	7(4-9)	7(5-10)	0.760
Failure (n, %)	11 (39.3)	14 (43.7)	0.732
Fever	7(4-11)	6(3-15)	0.781
Neutropenia	11(8-16)	10.5(8-21)	0.531
Hospital stay	15(6-24)	15(7-24)	0.832
Total Modification, (n= 25, 41.66%))	11	14	0.732

Overall treatment success without modification in the Piperacillin/Tazobactam group was 17(60.7%) and in Cefepime group is 18 (56.3%) P value was 0.732. Duration of fever, duration of neutropenia and duration of hospital stay were also not statistically significant both in success and failure patients.

Discussion:

This randomized clinical trial was carried out to determine the comparative efficacy and safety between Piperacillin-Tazobactam and Cefepime for febrile Neutropenic children with ALL. Overall treatment success without modification in the Piperacillin/ Tazobactam group was 17(60.7%) and in Cefepime group was 18 (56.3%). P value was (0.732) that was not statistically significant. This result is consistent with the study done by Sano et al., no significant differences were observed in the success rates of the Piperacillin/Tazobactam and Cefepime treatments (62.1% vs 59.1%, P= 0.650).[11] Saito et al, also reported the similar results.[12]

In this study, regarding age among 59 patients, 27(45.8%) were in Piperacillin/ Tazobactam group, median age 5 years, range (1-16) and 32 (54.2%) patients in Cefepime group, median age 4 years, range (1-15 years). Maximum patients were in age group 1.1 to 5 years (49.15%) and 5.1 to 10 years (33.89%) and 8(13.55%) patients were above 10 years and remaining 2(3.38%) patients below 1 year. Regarding the gender distribution, a total number of 59 acute lymphoblastic leukaemia with febrile neutropenia patients were included. Among them male was 34(57.63%) and female were 25(42.37%). The male and female ratio was 1.36:1. This finding indicates that ALL occurs more commonly among the male.

In this study 38(62.3%) neutropenic episodes were in induction phase of chemotherapy. That means maximum febrile neutropenic episodes occurred in the induction phase. The study by, Chong et al is consistent with our study[3]. Regarding the distribution of febrile neutropenic episodes with ALL according to clinically documented infection between two groups, fever without focus found in 21 (35%) episodes, respiratory tract infection in 16(26.6%), GIT 13 (21.6%), procedure site 5 (8.3%) and others 5(8.3%) episodes respectively. Fever without focus was found in majority of the episodes in other studies.[13]

Among the 59 patients with 61 episodes there were 3 (5%) deaths. One patient expired due to intracranial haemorrhage, remaining two patients expired due to septic shock. Death was relatively less (1.88%) in other study of Sano et al.[11] but also was 4.35% in the study of Bow et al.[14]

Regarding the other parameters, like the median duration of fever in the patients with success without modification, in Piperacillin/Tazobactam group was 2.5 days and Cefepime was 3 days, it was not statistically significant, means equally effective. Which is consistent with the study of Uygun et al.[13]

Regarding treatment modification in Piperacillin/ Tazobactam group 11 (39.3%) and Cefepime group

14 (43.8%) episodes needed treatment modifications. Uygan et al describes the treatment modifications in Piperacillin/Tazobactam and Cefepime group is (40%) and (38.7%) respectively.[13] Similar findings have been reported in another study by, Corapsioglu, Sarper & Zengin, where the total number of modifications was 36% in both groups.[15]

Microorganisms were isolated in 13(21.66%) patients in this study. Blood culture was found positive in 6(10%), means majority 6(46.15%) of organism were isolated from blood. This findings are consistant with other studies of Baskaran et al.,[16] Ahmedzadeh et al.[17] and Yeamin et al.[18] In this study out of 13 isolated microorganisms 11(84.61%) were Gram negative, Karanwal et al.[19] also stated Gram negative bacteria was the most common organisms.

Conclusion:

Both Piperacillin/Tazobactam and Cefepime were effective and safe as an empirical therapy for febrile neutropenia in children with Acute Lymphoblastic Leukaemia. Piperacillin/Tazobactam can also be used as monotherapy for febrile neutropenic children with ALL.

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