Indian J Hematol Blood Transfus (July-Sept 2011) 27(3):131–135
DOI 10.1007/s12288-011-0076-0

ORIGINAL ARTICLE

Piperacillin–Tazobactum Plus Amikacin Versus Ceftazidime Plus Amikacin as Empirical Therapy for Fever in Neutropenic Patients with Hematological Malignancies

P. S. Ghalaut · Uma Chaudhary · Veena S. Ghalaut · Atul Dhingra · Gaurav Dixit · Sameer Aggarwal

Received: 1 July 2009 / Accepted: 4 May 2011 / Published online: 16 June 2011

Abstract Infections are one of the main cause of death in cancer patients particularly when granulocytopenia is present. A number of drugs have been used for the treatment of neutropenic patients with fever. Most published literature has shown piperacillin–tazobactum in combination with amikacin to be significantly more effective than ceftazidime plus amikacin in empirical treatment of febrile episodes in patients with neutropenia. In view of the reported literature we have tried this combination in our febrile neutropenic patients with haematological malignancies at PGIMS Rohtak. It was an open randomized trial. Patients were divided into two groups of 20 each. In the first group (group A) piperacillin–tazobactum (4 + 0.5 g 6 hourly) with single daily dose of amikacin 20 mg/kg was given. In the second group (group B) ceftazidime 40 mg/kg every 8 hourly with single daily dose of amikacin 20 mg/kg was given. The most common site of infection was blood followed by urinary tract, respiratory tract and oral cavity. 13 (65%) patients in group A and 12 (60%) patient in group B showed clinical success. In our study however in our patients a better response was seen in patients with piperacillin–tazobactum + amikacin (65% vs. 60%). So it is recommended that piperacillin–tazobactum + amikacin should be given in febrile neutropenic patients with haematological malignancies.

P. S. Ghalaut (✉) · U. Chaudhary · V. S. Ghalaut · A. Dhingra · G. Dixit · S. Aggarwal
Department of Medicine, Microbiology and Biochemistry, PGIMS, 2/6J PGIMS Campus, Rohtak 124001, Haryana, India
e-mail: med.pgims@hry.nic.in

Introduction

Infections are one of the main cause of death in cancer patients particularly when granulocytopenia is present [1]. Recent studies have cited a figure of 48.3 infections per 100 neutropenic patients (<1,000 granulocytes per microlitre) with haematological malignancies and solid tumors or 46.3 infections per 1,000 days at risk [2].

With the onset of fever, bacteremia is most frequently due to aerobic gram-positive cocci (in particular, coagulase-negative staphylococci, *Streptococci viridans*, or *S. aureus*) or aerobic gram-negative bacilli (especially *Escherichia coli*, *Klebsiella pneumoniae*, or *Pseudomonas 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 [3].

A number of drugs have been used for the treatment of neutropenic patients with fever. These include combination of an antipseudomonal carboxypenicillin or ureidopenicillin (ticarcillin–clavulanic acid or piperacillin–tazobactum) with amikacin [4] or an aminoglycoside with an antipseudomonal cephalosporin, such as cefepime or ceftazidime; and an aminoglycoside plus a carbapenem. Monotherapy can be given with either a carbepenam or an extended spectrum antipseudomonal cephalosporin such as ceftazidime or cefepime [5]. Piperacillin–tazobactum has also been found to be effective as monotherapy [6]. Piperacillin–tazobactum is a β lactum/β lactamase inhibitor combination with a broad spectrum of anti bacterial activity encompassing most gram positive and gram negative aerobic and anaerobic bacteria including many pathogens producing β lactamase. Advantages of combination therapy are potential synergistic effects against some gram-negative bacilli, activity against anaerobes

especially when β lactam/β lactamase combination are used and minimal emergence of drug-resistant strains during treatment [7]. The major disadvantages are the lack of activity of these combinations, and the nephrotoxicity, ototoxicity, and hypokalemia associated with aminoglycoside compounds and carboxypenicillins. Piperacillin–tazobactum in combination with amikacin is significantly more effective than ceftazidime plus amikacin in empirical treatment of febrile episodes in patients with neutropenia [8]. In view of the reported literature we have tried this combination in our febrile neutropenic patients with haematological malignancies at PGIMS Rohtak.

Materials and Methods

The study was conducted in Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak on 40 patients of hematological malignancy with fever with neutrophil count of less than 1,000 cells/mm^3. Patients over 14 years of age who received chemotherapy for haematological malignancy [leukaemia, myelodysplastic syndrome (MDS), lymphoma, multiple myeloma] etc. with febrile neutropenia [Fever in neutropenic patients is defined as a single oral temperature of $\geq$38.3°C (101°F) or a temperature of $\geq$ 38.0°C (100.4°F) for $\geq$1 h with a neutrophil count of <500 cells/mm^3, or a count of <1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3] were included in the study [9].

Patients were excluded from the trial if they had received any intravenous antibiotic during the granulocytopenic period or during the preceding 96 h; had a known allergy to any of the protocol antibiotics; had been previously randomized to this protocol during the same episode of granulocytopenia; had renal failure requiring hemo- or peritoneal dialysis, a serum creatinine level greater than 3.5 mg/dl, or an estimated creatinine clearance below 20 ml/min; were pregnant; or had known human immunodeficiency virus infection.

It was an open randomized trial. Patients were divided into two groups of 20 each. In the first group (group A) piperacillin–tazobactum (4 + 0.5 g 6 hourly) with single daily dose of amikacin 20 mg/kg was given. In the second group (group B) ceftazidime 40 mg/kg every 8 hourly with single daily dose of amikacin 20 mg/kg was given.

The patients were observed for

(1) Type of leukemia
(2) Sex and age
(3) Microbiologically documented infections
(4) Mean neutrophil count
(5) Mean duration of neutropenia
(6) Mean time of defervescence
(7) Response to treatment
(8) Additional antibiotics used

The observations were recorded in special performa designed for this study. The results were analysed by using Student's t test (paired t test, unpaired t test) and χ^2 test. Parameters analysed included age, sex, duration of neutropenia, duration of fever and duration of hospital stay.

Results

Out of the 40 patients who had chemotherapy induced febrile neutropenia 23 (11 in group A and 12 in group B) were of AML, 15 (8 in group A and 7 in group B) of ALL, and 2 (1 in each group) of CML in blast crisis. There were 13 males and 7 females in group A and 16 males and 4 females in group B. The mean age of presentation was 37.75 $\pm$ 16.28 in group A and 36.5 $\pm$ 18.56 in group B. The mean temperature at the start of treatment in group A was 102.38 and in group B was 102.57 degree Fahrenheit. Microbiologically documented infections (Table 1) were seen in 10 (25%) patients out of total 40 patients. Bacteremia was seen in 6 (15%) patients. *S. aureus* and *Pseudomonas* were seen in 2 patients each where as coagulase negative staphylococci, and *Enterobacter* were seen in one patient each. 2 patients showed positive cultures on sputum culture. *E. coli* was seen in one patient in group B and *Kliebsella* in one patient in group A. Another 2 patients showed positive culture on urine culture. On culture of urine 1 patient showed growth of *P. aeruginosa* in group A where as 1 patient showed growth of *Enterobacter* in group B. The mean neutrophil count at the onset of fever was 482.5 $\pm$ 218.16 in group A and 469.8 $\pm$ 271.30 in group B with $P > 0.05$. The mean duration of neutropenia was 4.7 $\pm$ 1.38 in group A and 5.05 $\pm$ 1.27 in group B. The most common site of infection as evident from Table 2 was

Table 1 Microbiologically documented infections

	Group A	Group B
Blood culture		
S. aureus	0	2
Coagulase negative staphylococci	0	1
Pseudomonas spp.	1	1
Enterobacter spp.	1	0
Sputum culture		
E. coli	0	1
Kliebsella spp.	1	0
Urine culture		
Pseudomonas spp.	1	0
Enterobacter spp.	0	1

Table 2 Site of infection

Sr. no.	Site of infection	Group A (n = 20)	Group B (n = 20)
1	Blood (bacteremia)	2	4
2	UTI	3	2
3	Lung	2	2
4	Oral cavity	2	2
5	Catheter site erythema	2	2
6	GIT		
	Liver abscess	0	1
	Typhilitis	0	1
7	Skin (Herpes zoster)	1	1
8	Anal	1	1
9	CNS (meningitis)	1	0

blood followed by urinary tract, respiratory tract and oral cavity. In oral cavity candidiasis was prevalent in 4 of the selected patients, 2 in group A and 2 in group B. Mean time of defervescence was 5.5 ± 2.61 in group A and 6.05 ± 2.79 in group B. The median time of defervescence in two groups was 5 days. The range was 3–12 days in group A and 3–11 days in group B. At day 3, 8 patients in group A and 6 patients in group B showed excellent response. No response was seen in 11 patients, 5 in group A and 6 in group B. Excellent response at day 7 was seen in 7 patients in group A and 5 patients in group B. No response was seen in 11 patients, 5 in group A and 6 in group B. 2 patients showed reoccurrence in both groups. 7 patients in group A and 9 patients in group B received additional antibiotics. Vancomycin was the most common additional antibiotic used, it was used in 5 patients in group A and 3 patients in group B. Amphoterecin B was used in 3 patients in group B and in 1 patient in group A. Acyclovir was used in 1 patient in each group. Linezolid and metrogyl was used in 1 patient each in group B. Additional antibiotics used were according to the culture sensitivity reports. 13 (65%) patients in group A and 12 (60%) patient in group B showed clinical success i.e. total of 25 responded to these antibiotics and another 15 needed additional antibiotics. 4 (2 in each group) patients out of 40 patients in study group died. Overall survival in study was 90%.

Discussion

The present study was undertaken to compare the effectiveness of piperacillin–tazobactum plus amikacin with that of ceftazidime plus amikacin in patients of febrile neutropenia with hematological malignancies. In our study, febrile neutropenia patients with haematological malignancies, were randomized (1:1) to be treated with either piperacillin–tazobactum (4 + 0.5 g 6 hourly) with single daily dose of amikacin 20 mg/kg or ceftazidime 40 mg/kg every 8 hourly with single daily dose of amikacin 20 mg/kg. This was similar to study done by Cometta et al. [10] in 1995. In the study by Feliu et al. [11] in 1992 patients were given piperacillin and ceftazidime in similar doses but amikacin was given in dose of 7 mg/kg 8 hourly. However the total dose of amikacin was similar in all the studies. The median neutrophil count at the onset of fever in our study was 482 cells/mm^3 in piperacillin–tazobactum + amikacin group and 408 cells/mm^3 in ceftazidime + amikacin group. In the study by Cometta et al. [10] the median neutrophil count was 0 cell/mm^3 in group A and 20 cell/mm^3 in group B. In the study by Feliu et al. [11] 40% patients in group A and 46% patients in group B had neutrophil count <100 cells/mm^3. In all the studies including our study the neutrophil count at the entry was <1,000 cells/mm^3. It was observed that the neutrophil count at which patient developed fever was higher in our study as compared to previous studies. The difference is probably due to different demographic profile and different environmental conditions at which patients were given chemotherapy. The median duration of neutropenia in our study was 4.5 days in group A and 5 days in group B. The median duration of neutropenia in the study by Cometta et al. [10] was 4 days in each group and in the study by Feliu et al. [11] was 10 and 11 days. The median duration of neutropenia was comparable to other studies which varied from 4 to 7 days.

A total of 10 (25%) patients were having microbiologically documented infections. Out of these 10, 6 (15%) had bacteremia, 2 (5%) had positive sputum culture and other 2 (5%) positive urine culture. In the study by Cometta et al. [10] 29% patients had microbiologically documented infections of which 25.6% were bacteremias. On blood culture gram positive and gram negative infections were seen with equal frequency (3 each) in our study. Staphylococci were the most common (3 out of 40) in our study followed by Pseudomonas (2 out of 40) and Enterobacter (1 out of 40). In the study conducted by Cometta et al. [10] 67% patients had gram positive bacteremia and 33% had gram negative bacteremia. In the study by Feliu et al. [11] 37% patients had gram positive bacteremia and 63% had gram negative bacteremia. The difference in type of organism causing infection may be due to local epidemiological factors.

The most common site of infection in our study was blood followed by urinary tract infection and respiratory tract infection. Fifteen percent of patients had positive culture. UTI was commonly observed in 12.5% of our patients. In the study by Feliu et al. [11] bacteremia (26%) was most common followed by respiratory tract (5%) and skin and soft tissue infections (9.4%) and infections of the

oral cavity 7.6%. skin and soft tissue infections were seen in 10% and oral cavity infections in another 10% of patients.

The time of defervescence in our study was 5–6 days. In recent analysis of 488 episodes of fever in neutropenic patients by Freifeld et al. [5], the median time of clinical response was 5–7 days. In the study conducted by Feliu et al. [11] the mean time of defervescence was 4.5 days for patients in piperacillin–tazobactum + amikacin group and 4.9 days for patients on ceftazidime plus amikacin. The mean time of defervescence in our study was 5.5 days for group A and 6.05 days for group B.

Overall clinical success (excellent and good response) was seen in 65% of patients in group A and 60% of patients in group B with $P > 0.05$. The results of our study were comparable to previous studies. Cometta et al. [10] showed response of 61% versus 54% in their study, while Feliu et al. [11] showed 68% versus 65%. Fenu et al. [12] also showed piperacillin plus amikacin to be as efficacious ceftazidime plus amikacin. Thus piperacillin–tazobactum plus amikacin appears to be as effective ceftazidime plus amikacin in initial treatment of febrile episodes in adult patients with chemotherapy induced neutropenia of modest duration.

In our study 2 patients each died in both the groups. Overall survival of the study was 90%. Overall mortality in both groups in our study was 10% compared to 8% mortality in both groups in the study by Cometta et al. [10].

In our study vancomycin was most commonly added drug in both groups followed by amphoterecin B. Vancomycin was given in 5 (25%) of the total 20 patients in group A and 3 (15%) in group B. Amphoterecin B was given to 1 (5%) in group A and 3 (15%) patients in group B. Similarly in the studies conducted by Cometta et al. [10] and Feliu et al. [11] vancomycin was the most common additional drug used. In our study, acyclovir was given to 1 patient in both the groups. In the ceftazidime amikacin group 1 patient was given linezolid and another patient was given metrogyl in standard doses.

Summary and Conclusions

A randomized comparative study was conducted to evaluate the efficacy of piperacillin–tazobactum plus amikacin and ceftazidime plus amikacin in the empirical therapy of febrile neutropenic patients with haematological malignancies admitted in PGIMS Rohtak. Mean neutrophil count at the onset of fever was 482.5 ± 218.6 in group A and 469.8 ± 271.30 in group B. Median duration of neutropenia was 4.5 days in group A and 5 days in group B (range 3–8 days). The most common site of infection was blood followed by urinary tract and respiratory tract. The most common bacteria isolated from blood culture was Staphylococci (7.5%) followed by Pseudomonas (5%) and Enterococci (2.5%). The overall clinical response was 65% in group A and 60% in group B. Excellent response was seen in 35% of patients in group A and 25% of patients in group B. Good response was seen in 30% of patients in group A and 35% of patients in group B. The combination of piperacillin–tazobactum + amikacin is as efficacious as Ceftazidime + amikacin. In our study however in our patients a better response was seen in patients with piperacillin–tazobactum + amikacin (65% vs. 60%). So it is recommended that piperacillin–tazobactum + amikacin should be given in febrile neutropenic patients with haematological malignancies. However the difference was not statistically significant. It is suggested that a larger trial with large no. of patients is needed to unravel the efficacy of these drugs in patients with neutropenic fever.

References

1. Chang HY, Rodriguez V, Narboni G, Bodey GP, Luna MA, Freireich EJ (1976) Causes of death in adults with acute leukemia. Medicine (Baltim) 55(3):259–268
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64(2):328–340
3. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 52(4):e56–e93
4. Cordonniek C, Roloston K, Elington GL (1999) Susceptibility surveillance among gram negative bacilli at a cancer center. Chemotherapy 45:325–334
5. Freifeld AG, Walsh T, Marshall P (1995) Monotherapy for fever and neutropenia in cancer patients; randomized comparison of ceftazidime versus imipenem. J Clin Oncol 13:165–176
6. Del F, Menichetif F, Martino P (2001) A multicenter, double blind placebo controlled trial comparing piperacillin–tazobactum with and without amikacin as empirical therapy for febrile neutropenia. Clin Infect Dis 33:1295–1301
7. Okereke C, Dudley MN (1998) Beta-lactam/beta-lactamase inhibitor combinations: pharmacodynamic considerations and possible role in the management of bacterial infections in the neutropenic host. J Antimicrob Chemother 41:43–49
8. Perry CM, Markham A (1999) Piperacillin tazobactum an updated review of its use in the bacterial infections. Drugs 57: 805–843
9. Huges WT, Armstrong D, Bodey GP, Feld R, Mandell GL, Meyers JD et al (1990) Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever: a statement by the Infectious Diseases Society of America. J Infect Dis 16:381
10. Cometta A, Zinner S, De Bock R, Lalandra T, Gaya H, Klastersky J et al (1995) Piperacillin tazobactum plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 39(2):445–452

11. Feliu J, Artal A, Gonzalez BM, Berrocal A, Chacon I, Garcia de Paredes ML et al (1992) Comparison of two antibiotic regimens (piperacillin plus amikacin versus ceftazidime plus amikacin) as empiric therapy for febrile neutropenic patients with cancer. Antimicrob Agents Chemother 36(12):2816–2820

12. Fenu S, Raccah R, Santilli S, Micozzi A, Girmena C, Martino P et al (1988) Treatment of febrile episodes in neutropenic leukemic patients with the antibiotic combinations piperacillin or ceftazidime plus amikacin: results of a randomize study. Chemioterapia 7(5):323–326