ORIGINAL ARTICLE

PIPERACILLIN-TAZOBACTAM AS A COST EFFECTIVE MONOTHERAPY IN FEBRILE NEUTROPENIA

Samir Fasih, Neelam Siddiqui, Narjis Muza, Abdul Hannan, Sohail Sarwar, Azhar Shafi, Sohail Athar

Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital (SKMCH), Lahore, Pakistan

Background: Fever in neutropenic patient is a medical emergency. Timely intervention with antibiotics has been demonstrated to be effective. We assessed Piperacillin-Tazobactem as a cost effective mono-therapy in solid malignancy patients in our institution in relation to dual antibiotic therapy and other monotherapies. **Methods:** This study was conducted to determine the efficacy, and cost effectiveness of Piperacillin-Tazobactem as monotherapy in febrile neutropenia. Total 150 patients with chemotherapy induced febrile neutropenia were selected. Piperacillin-Tazobactem was given intravenously 4500 mg every 6 hour. Outcome was assessed as success and failure. Success was defined as afebrile for four consecutive days, clearance of signs of infection, no new cultures, and no recurrence of primary infection after completion of therapy. Failure was defined as modification or addition of antibiotic due to clinical deterioration, cultured organism resistant to Piperacillin-Tazobactem and Death. **Results:** The mean age was 43 years, 31% males and 69% were females. Out of total 150 patients, 73 patients were of breast carcinoma. There were 143 patients with negative blood cultures, and 7 patients with positive blood cultures, out of which 3 patients were resistant to Piperacillin-Tazobactem. Success was achieved in 83.3% of total patients. Daily cost of Piperacillin-Tazobactem was much less in relation to other monotherapies and dual antibiotic therapy including Gentamicin. None of the patient had adverse effects of Piperacillin-Tazobactem. **Conclusion:** We concluded that Piperacillin-Tazobactem is a safe, well tolerated as well as cost effective monotherapy in patient with febrile neutropenia with solid cancers. Only two percent organisms were resistant to Pipercillin-Tazobactam.

Keywords: Febrile Neutropenia, Pipercacillin-Tazobactem, Monotherapy

J Ayub Med Coll Abbottabad 2013;25(3-4):19–22

INTRODUCTION

Febrile neutropenia should be considered a medical emergency. Early studies documented up to 70% mortality if initiation of appropriate antibiotics was delayed.[1] Neutrophils constitute the majority of the blood leucocytes.[2] In response to chemotactic stimuli, neutrophils marginate and migrate from the blood into the tissues and to the sites of infection. They engulf micro-organisms within vacuoles termed phagosomes, which fuse with lysosomes to form phagolysosomes that destroy the ingested organisms.

Neutropenia is defined as decreased circulating neutrophils in the peripheral blood less than 1500 cells/mm^3.[3] Febrile neutropenia is defined as fever of 38.3 ºC or greater with a neutrophil count of less than 1000 cells/mm^3.[4] When the neutrophil count decreases to <1000 cells/mm^3, increased susceptibility to infection can be expected with the frequency and severity inversely proportional to the neutrophil count. The absence of granulocyte; the disruption of mucosal barriers; and the inherent microbial flora shifts that accompany severe illness and predispose the neutropenic patients to infection. Other sign and symptoms of infection are often absent or muted in absence of neutrophils but fever remains an early sign.[5,6]

In the past when empirical antibiotics were not given to patients, infections accounted for 75% of mortality.[7] Initially antibiotics were given to leukaemia or lymphoma patients. Now patients with all types of malignancies having fever and neutropenia are given empirical antibiotics. This is because now it has become evident that neutropenic cancer patients are not a homogeneous group and they have a variable risk of complications.[8] Administration of empirical antibiotic therapy is now standard practice in the management of febrile neutropenia, but there has been considerable debate about the selection of an efficacious empirical antimicrobial regimen over the past two decade.[8]

A variety of approaches including both mono-therapeutic and multidrug regimens have been demonstrated to be effective, although no one regimen proved to be superior to another.[8] Pizzo *et al*. introduced the concept of mono-therapy for febrile neutropenia.[9] As new antibiotics are emerging, therapeutic options are also broadening, becoming more varied with the advent of new third generation cephalosporins and carbapenems.[10] Several studies show no striking differences between mono-therapy and multidrug combinations for empirical treatment of uncomplicated episodes of fever in neutropenic patients.[11–13] Patients with solid tumours often have a period of febrile

neutropenia without having any microbiological or clinical documentation of infection and their response to empirical antimicrobial therapy is excellent. Studies done at different centres of the world show that Piperacillin-Tazobactem, Meropenem and Imipenem have demonstrated significant superiority over Ceftazidime and cefipime.[14–16] So they can be used as single agent therapy with ease to administer. The only issue is cost comparison of these antibiotics in developing countries. Meropenem and Imipenem are considerably more expensive when compared to other agents. In our institution Piperacillin- Tazobactem is the first antibiotic of choice in febrile neutropenia being used as a cost effective single agent. The infectious disease society of America (IDSA) guideline for management of febrile neutropenia (updated 2010) recommends mono-therapy with anti-pseudomonal-lactam agents, including Piperacillin-Tazobactem.[17] In our population there is no trial available to date which can suggest that Piperacillin-Tazobactem be used as mono-therapy even in low risk patients. In our institution monthly anti-biogram is maintained on the basis of which Piperacillin is routinely used as mono-therapy. However no analysis has ever been done to find the exact clinical benefit.

MATERIAL AND METHODS

We reviewed the medical charts of 150 patients with solid malignancies admitted in Shaukat Khanum Cancer Hospital medical oncology ward with diagnoses of febrile neutropenia. Patients with fever of at least 38.0 °C on at least two occasions within 24 hours or a single oral temperature of at least 38.3 °C with presence of absolute neutrophil count less than 1000 cells/microL were included in the study. All patients were admitted, given Piperacillin-Tazobactem 4500 mg intravenously every 6 hours along with other supportive care measures for at least 7 days. All sensitivities of blood and urine cultures sent from emergency and prior administration of antibiotic were noted. Complete blood count, serum creatinine, liver function tests, fever, blood pressure at the time of admission, 72 hours and 7 days after admission were noted. Outcome was assessed as success and failure. Success was defined as afebrile for four consecutive days, clearance of signs of infection, no new cultures, and no recurrence of primary infection after completion of therapy. Failure was defined as modification or addition of antibiotic due to clinical deterioration, cultured organism resistant to Piperacillin-Tazobactem and death. Daily cost of antibiotic including carbapenems, Meropenem 1000mg three times a day and Imipenem 500 mg four times a day, and Piperacillin-Tazobactem 4500 mg four times a day was calculated in Pakistani rupees (Rs.).

RESULTS

Age range was 19–86 years; mean age was 43 years with 31% males and 70% female. Out of 150 patients, 73 (48.7%) patients were of breast carcinoma, ovarian carcinoma and mixed germ cell tumour patient were 13 (8.7%) and 11 (7.3%) respectively. Success was achieved in 125 (83.3%). Categorizing it further, 143 (95.3%) patient had no growth in cultures, only 4 patients grew organisms sensitive to Piperacillin-Tazobactem which includes growth of *Streptococcus viridans, Staphylococcus aureus* (coagulase negative) and *Pseudomonas aeruginosa*. No patient showed recurrence of infection (same organism detected in cultures) after the completion of therapy. Patients who had failure: 15 (10%) remained febrile while on Piperacillin-Tazobactem, 7 (4.7%) developed septic shock defined as systolic BP <90 mmHg with decreased urine output; 3 patients (2%) grew ESBL +ve *E coli* resistant to Piperacillin-Tazobactem. No death occurred during the hospital stay. Thirty-five patients were given granulocyte colony stimulating factor (GCSF) in view of repeated febrile neutropenic admissions.

Daily cost of Piperacillin-Tazobactem was Rs.3280, compared to Meropenem Rs. 6000 and Imipenem Rs.4280; hence it was much less in relation to carbapenems mono-therapy. None of the patients had adverse effects related to Piperacillin-Tazobactem.

Table-1: Malignancy Distribution (n=150)

Type of Cancer	Number	Percentage
Breast Carcinoma	73	48.67
Ovarian Carcinoma	13	8.67
Ewing's Sarcoma	8	5.33
Osteosarcoma	6	4.0
Others	50	33.33

Table-2: Distribution of Success (n=125)

Outcome	Percentage
Afebrile for 4 consecutive days	100
No growth in cultures	95.3
Cultures growth sensitive	2.7
Recurrence of infection	0

Table-3: Distribution of Failure (n=150)

Reason For Failure	Number of Failure
Fever	15 (10%)
Septic shock	7 (4.7%)
Culture resistant	3 (2%)
Death	0

Table-4: Cost Effectiveness of Piperacillin-Tazobactem

Agents	Price in Rs.
Meropenem	6000
Piptaz	4200
Imipenem	5000

DISCUSSION

Infectious complications are an important cause of morbidity and mortality in cancer patients, especially those receiving chemotherapy. Furthermore,

neutropenia, fever and infection limit the dose-intensity of anti-neoplastic chemotherapy in cancer patients.

When we see the pattern of febrile neutropenia, our patients had female predominance 69.3% with only 4.7% cultures positive. We do not have any study to compare the pattern in Pakistani population. However a similar study done in Saudi Arabia by MS Al-Ahwal *et al* reviewed the pattern of febrile neutropenia in solid tumour patients. In this study female and male patients were 67.2% and 38.2% respectively, duration of neutropenia was less than 7 days in 92.5% patients, positive blood cultures were only found in 16.4% patients.[18] In another study culture positivity was only 14% in solid tumour patients.[19] First thing to note is that pattern was very similar to our population; secondly duration of neutropenia was less than 7 days in almost all patients, which further reinforce the concept that 7 days duration of treatment is safe enough in neutropenic patients, as in our study.

The concept of empirical antibiotic therapy was developed more than 30 years ago. In 1962, Curtin and Marshall realized that in some patients therapy must be instituted before the bacteriological data are available.[20] Several combined treatments for the greater part broad-spectrum b-lactames plus aminoglycoside have been tested in the last 20 years. Before the last decade standard treatment option was dual antibiotic therapy. In 1993 Pizzo *et al* published the first large-scale randomized study involving single-agent therapy.[9] Since then broad-spectrum b-lactames have been approved as single agent treatment regimen.[17]

In 2006 Mical Paul *et al*, published a meta-analysis on empirical antibiotic mono-therapy for febrile neutropenia. Thirty-three trials were reviewed; b-Lactams were assessed in more than one trial which were Ceftazidime, Cefepime, Imipenem, Meropenem, Piperacillin/Tazobactam and Cefoperazone/Sulbactam. Cefepime was associated with a higher all-cause mortality rate; Carbapenems were associated with an advantage with regard to treatment failure when compared with Ceftazidime. Piperacillin- Tazobactem comparison with Cefepime and Carbapenems showed no significant differences with regard to clinical and microbiological success. They concluded that Ceftazidime, Piperacillin/ Tazobactam, Imipenem/Cilastatin and Meropenem appear as suitable agents for mono-therapy.[16]

Again in 2006, C. Viscoli *et al* used Piperacillin-Tazobactem as mono-therapy in high risk febrile neutropenic patients. Their study concluded that Piperacillin-Tazobactem is a safe and efficacious mono-therapy even in high risk patient. When compared to our study they added Vancomycin on third day if patient remains febrile on Piperacillin-Tazobactem. They had 18% mortality which was not present in our study likely attributed to lower risk patients. The success rate was only 50–60% again related to higher risk patients.[8]

In a similar study done in 2008 Fanci *et al* used Piperacillin-Tazobactem in leukemic patients. They reported 75% overall success, but only 34% patients in total received Piperacillin- Tazobactem till discharge without addiction of second antibiotic. Overall mortality was 10%.[12] Again showing that, more than half of high risk patients need addition of second antibiotic. To date multiple studies have been done, and show that monotherapy with Piperacillin-Tazobactem is safe and efficacious, even when compared to carbapenems and fourth generation cephalosporins.[14,21–23]

Limitations of our study is that we conducted it in only solid tumour patients who are considered low risk due to duration of neutropenia less than 7 days.[4] Reason for very low culture rate is likely related to low risk patients. There is need to conduct a further studies in patients with haematological malignancies who are intermediate to high risk.[4]

CONCLUSION

Piperacillin-Tazobactam is a safe, well tolerated, as well as cost effective mono-therapy in cancer patients with febrile neutropenia receiving chemotherapy.

Authors and Co-authors do not have any conflict of interest and this study is SRC and IRB approved.

REFERENCES

1. Schimpff SC, Satterlee W, Young. VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971;284:1061–5.
2. Jandl. JH. Blood, editor. Textbook of Hematology. 2nd ed. Boston: Little Brown & Company; 1996.p. 1,11,615–9, 624–34.
3. Watts RG. Neutropenia. In: Lee GR, Foerster J, Lukens J, *et al*, eds. Wintrobe's Clinical Hematology. 10th ed. Baltimore, Md: Lippincott, Williams & Wilkins; 1999.p.1862–88.
4. Freifeld AG, Segal B, H., Robert. L, Brown. A.E, Casper .C, deShazo. M, *et al*. Prevention and Treatment of Cancer-Related Infections. NCCN Clinical Practice Guidelines in Oncology 2012. Available at: http://www.nccn.org.
5. Sornsuvit C, Komindr S, Chuncharunee S, Wanikiat P, Archrarti N, Santanirand P. Pilot study: Effects of parenteral glutamine dipeptide supplementation on neutrophil functions and prevention of chemotherapy-induced side-effects in acute myeloid leukaemia patients. J Int Med Res 2008;36:1383–91.
6. Lockhart B, Sonis T. Relationship of oral complications to peripheral blood leukocyte and platelet counts in patients receiving cancer chemotherapy. Oral Surg Oral Med Oral Pathol 1979;48(1):21–8.
7. Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care, 3rd ed. New York: McGraw Hill; 2005.
8. Pizzo PA. Management if fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993;328:1323–32.
9. Pizzo PA, Hathorn JW, Hiemenz J, Browne M, Commers J, Cotton D. A randomized trial comparing ceftazidime alone

with combination antibiotic therapy in cancer patients with fever and neutropenia. N Engl J Med 1986;315:552–8.
10. Glasmacher A, von Lilienfeld-Toal M. An evidence based review of the available antibiotic treatment options for neutropaenic patients and a recommendation for treatment guidelines. Int J Infect Dis 2006;10:9–16.
11. Viscoli C, Cometta A, Kern WV, R De Bock, M. Paesmans, F. Crokaert, *et al*. Piperaciilin-tazobactam monotherapy in high risk febrile neutropenic cancer patients. Clin Microbiol Infect 2006;12:212–6.
12. Fanci R, Bartolozzi B, Longo G, Bosi A. A prospective, open label noncomparative study with piperaciilin-tazobactam monotherapy as management of fever in patients with acute leukemia. J Chemother 2008;20:492–6.
13. Shah P, Heller A, Fuhr G, Walther F, Halir S, Schaumann R *et al*, Empirical monotherapy with meropenem versus imipenem/cilastatin for febrile episodes in neutropenic patients. Infection 1996;24:480–4.
14. Oztoprak N, Piskin N, Aydemir H, Celebi G, Akduman D, Keskin AS, *et al*. Piperacillin–tazobactam Versus Carbapenem Therapy With and Without Amikacin as Empirical Treatment of Febrile Neutropenia in Cancer Patients: Results of an Open Randomized Trial at a University Hospital. Jpn J Clin Oncol 2010:40:761–7.
15. Bow EJ, Rotstein C, Noskin GA, Laverdiere M, Schwarer AP, Segal BH, *et al*. A randomized open label multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematological malignancies. Clin Infect Dis 2006;43:447–59.
16. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2006;57:176–89.
17. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, *et al* 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 2011;52:e56–93.
18. Alahwal MS. Pattern of febrile Neutropenia in solid tumors - a hospital based study Pak J Med Sci 2005;21(3):249–52.
19. Rasool Hassan BA, Yusoff ZB, Otman SB. Fever/clinical signs and association with neutropenia in solid cancer patients--bacterial infection as the main cause. Asian Pac J Cancer Prev 2010;11:1273–7.
20. Curtin JA, Marshall BD Jr. Use of Antibiotics in cancer and leukemia. J Chronic Dis 1962;15:713–8.
21. Harter C, Schulze B, Goldschmidt B, Benner A, Geiss K, Hoppe-Tichy T. Piperacillin/tazobactamvsceftazidime in the treatment of neutropenic fever in patients with acute leukemia or following autologous peripheral blood stem cell transplantation: a prospective randomized trial. Bone Marrow Transplant 2006;37:373–9.
22. Saito T, Ichinohe T, Kanda J, Nagao M, Takakura S, Ito Y, *et al* Historical Cohort Study of the Efficacy and Safety of Piperacillin/Tazobactam versus Fourth-Generation Cephalosporins for Empirical Treatment of Febrile Neutropenia in Patients with Hematological Malignancies. Int J Clin Med 2011;2:18–22.
23. Miyazaki K, Kamata H, Kimura H, Okina S, Ishii R, Osaka M, *et al.* The efficacy and safety of piperacillin-tazobactam for febrile neutropenic patients in Japan. Rinsho Ketsueki 2012l;53:686–90. [Article in Japanese]

Address for Correspondence:

Dr. Samir Fasih, Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Lahore.
Email: samirf@skm.org.pk