Original Article

Impact of Door to Needle Time of Antibiotics Administration on Outcome in Cancer Patients with Febrile Neutropenia

Hafsah Iqbal[1]*, Fattahullah Khan Hassanzai[1], Faizan Shaukat[1], Abdul Qadir[1], Amer Rehman Farooqi[1,2]

[1] Department of Obstetrics Medicine, Shaukat Khanum Memorial Cancer Hospital, Peshawar - Pakistan
[2] Department of Gastroenterology, Shaukat Khanum Memorial Cancer Hospital, Peshawar - Pakistan

Article Info

Corresponding Author
Hafsah Iqbal
Department of Obstetrics Medicine, Shaukat Khanum Memorial Cancer Hospital, Peshawar, Pakistan
Email: khafsah.iqbal@skm.org.pk

Abstract

Objective: To determine the outcome of the door-to-needle time of antibiotics in cancer patients with febrile neutropenia.

Methodology: It was a prospective cross-sectional study conducted at the emergency department of Shaukat Khanum Memorial Hospital Peshawar from April 2023 to December 2023. All the patients presenting to the emergency room with fever and a history of diagnosed malignancy, who received chemotherapy in the past 14 days and confirmed febrile neutropenia (fever ≥100˚ F and absolute neutrophil count of <500 cells/microliter) were included. Patients younger than 18 years of age were excluded. Data was analyzed through SPSS 24.0. A P value less than 0.05 was considered significant.

Results: A total of 79 patients fulfilled the eligibility criteria. Most were males, i.e., 52 (65.8%). The mean age of patients was 51.71 ±9.8 years. The most common malignancy was lymphoma (25.3%), followed by sarcoma (12.6%) and breast cancer (11.3%). The mean duration of stay was 4.2±3.2 days. The mean MASCC score was 17.6 ±1.76. Sixty-two (78.5%) patients received antibiotics within one hour of arrival at the emergency room. Only two patients died during a hospital stay. A significantly increased number of admissions to the intensive care unit, length of hospital stay, and escalating antibiotic use were observed in patients who did not receive antibiotics within one hour of arrival compared to the other group. No statistically significant difference was noted in-hospital deaths among both groups.

Conclusion: Timely antibiotics significantly lowered intensive care admissions and length of hospital stay. However, our study did not find its impact on in-hospital deaths.

Keywords: Cancer, Antibiotics, Febrile neutropenia, Door to needle time, Chemotherapy

Check for updates

Introduction

Febrile neutropenia, a critical complication of cancer treatment, particularly chemotherapy, presents a significant challenge in the management of cancer patients. Neutropenia is characterized by an abnormally low concentration of neutrophils (less than 500 cells/mm3). The condition is associated with various symptoms, but when it is associated with fever (≥ 38.3°C), it is referred to as febrile neutropenia (FN).[1] As the main targets of chemotherapeutic agents are rapidly dividing cells, including both cancerous and healthy ones, the ability of bone marrow to produce sufficient neutrophils is compromised. This leads to heightened vulnerability to infections with potentially adverse outcomes. Neutropenia is, therefore, considered an oncologic emergency.[1] The prevalence of FN in patients taking chemotherapy varies with hematologic malignancies more at risk of developing chemotherapy-induced FN (>80%) than those having solid tumors (10-50%).[2] It has been reported that 50% of deaths in patients receiving chemotherapy for solid tumors and 50-75% of deaths in those receiving chemotherapy for acute leukemia are attributable to FN.[1]

An infectious source is identified in approximately 20 to 30% of episodes of FN. Empiric broad-spectrum antibiotics are the universal therapy for these patients. It involves initiating antimicrobial treatment in patients with neutropenia at the onset of fever without establishing a definitive diagnosis of microbial infection.[3] Administration of intravenous fluids and antibiotics has proven beneficial in managing neutropenic sepsis. Besides providing proper supportive treatment and empirical therapy, the time between the patient's arrival and administration of antimicrobial agents is a very important variable and correlates with better outcomes such as morbidity and mortality. This variable, known as 'door-to-needle time' (DNT), is defined as the time between arrival at the emergency department (ED) and administration of intravenous antibiotics.[4] In one study, the rapid administration of antibiotics has been found to reduce mortality by up to 10%.[1] The benefit of reducing the time of antibiotic initiation in the emergency department (ED) for these patients is, however, still controversial.[5] Further studies are needed to gain a better understanding of this aspect. This study will help determine the impact of antibiotics administration time in cancer patients with FN and whether early intervention improves clinical outcomes.

Methodology

It was a prospective cross-sectional study conducted at the Department of Internal Medicine Shaukat Khanum Memorial Cancer Hospital & Research Centre Peshawar from April 2023 to December 2023. Ethical approval was taken from the Institutional Review Board. All patients were enrolled through consecutive sampling after obtaining verbal consent. Informed verbal consent was taken from all the patients. The sample size was calculated using Epitools sample size calculator through the reported frequency of FN of 13.1% in cancer patients at a 95% confidence interval.6 All the patients age 18 or above presenting to the emergency department with a history of diagnosed malignancy, confirmed febrile neutropenia (fever ≥100°F and absolute neutrophil count of <500 cells/microliter), and who have received chemotherapy within the last 14 days were included in the study. Afebrile neutropenic patients, chemotherapy duration of more than 14 days, and younger than 18 years were excluded. Data was extracted from the hospital management and information system using the patient's hospital number and uploaded on Microsoft Excel sheets. The demographics, clinical characteristics, duration of hospital stay, need for antibiotics and administration, and supportive investigations were extracted and recorded accordingly. Duration of antibiotic administration after receiving patients in an emergency was categorized into two groups (group I and II) with a cut-off of sixty minutes, i.e., ≤1hr and >1hr, respectively. Duration of hospital stay, the need for escalation of initially administered antibiotics, the need for intensive care admission, and in-hospital deaths were the primary outcomes of this study. Statistical Package for the Social Science (SPSS) version 25.0 was used to analyze the data. Continuous variables were described as mean± standard deviation. The Chi-square test was applied to check the correlation between the time of antibiotics received and study outcomes. A p-value less than 0.05 was considered significant.

Results

A total of 79 patients fulfilled the eligibility criteria. Most were male, i.e., 52 (65.8%). The mean age of all the patients was 51.71± 9.81 years. The mean Multinational Association for Supportive Care in Cancer (MASCC) score was 17.66± 1.76. Twenty-seven (34%) patients presented with respiratory symptoms at arrival, and 32 (40.5%) patients had emergency chest X-rays ordered by the consulting physician, table I. The most common cause of malignancy in all patients was lymphoma (27, 34%), followed by breast carcinoma (11, 14%) and sarcoma (10, 12.6%), figure I. Sixty-two (78.5%) patients received antibiotics within one hour of arrival to the emergency department, while 17 patients did not receive antibiotics within one hour of presentation. The mean time of antibiotics administration in both groups was 41.35± 11.62 and 95.35± 24.29 minutes, respectively. Only two patients expired during their hospital stay, one from each group (p= 0.32).Twelve (19.3%) patients from group I needed escalation of antibiotics during treatment compared to 7 (70%) from group 2 (p= 0.06). Significant statistical difference was observed in both groups regarding the need for escalation to the intensive care unit during an admission, i.e., 4.8% vs.

23.5% in groups I and II, respectively (p= 0.016). Hospital stay was significantly lowered in group I compared to group II, with the mean length of stay of 3.61± 2.45 and 6.35± 4.83 days, respectively, (p= 0.04), table II.

Discussion

Gathering data from the emergency department, we evaluated the outcomes of febrile neutropenia in already diagnosed cancer patients presented to this department. All of them were admitted for in-patient care and initially started on empirical antibiotics according to the regional antimicrobial resistance pattern. This study was the first of its kind on this population from this hospital, and it highlights the importance of early administration of antibiotics in the emergency department. The average MASCC score in our patients was lower than 21 in both the groups referring to high-risk patients, with an overall mortality of 2.5% in all patients. This is slightly lower compared to the results reported by Nicholas et al., where 5% mortality was observed in high-risk patients with febrile neutropenia.[2] In addition, no significant relation of in-hospital mortality was observed with delay in antibiotics administration in our study, which validates the findings of other researchers.[2,3] Lymphoma is the principal primary diagnosis in

Table 1. Dedemographic and clinical characteristics of patients

Parameter	Value Mean± SD
Age (years)	51.71± 9.81
MASCC	17.66± 1.76
Length of stay (days)	4.2± 3.29
Antibiotics administered time (mins)	52.97± 26.9
	n (%)
Gender	52 (65.8) 27 (34.1)
Respiratory Symptoms	27 (34)
CXR pperformed n (%)	32 (40.5)
Escalation of antibiotics	19 (24.01)
Escalation to intensive care unit	7 (8.86)
Group I Group II	62 (78.5) 17 (21.5)

Table 2. Comparison of different parameters in both groups

| Variable		Group I	Group II	P value
Age (years)		51.95± 10.01	50.82± 9.26	
Antibiotics administration time		41.35± 11.62	95.35± 24.29	
MASCC		17.73± 1.56	17.41± 2.40	0.11
Length of stay (days)		3.61± 2.45	6.35± 4.83	0.04
Respiratory Symptoms	Yes No	22(35.5) 40 (64.5)	5 (29.4) 12 (70.6)	0.64
CXR performed	Yes No	25 (40.3) 37 (59.7)	7 (41.2) 10 (58.8)	0.95
In-hospital deaths	Yes No	1 (1.6) 61 (98.4)	1 (5.6) 16 (94.1)	0.32
Escalation of antibiotics	Yes No	12 (19.3) 50 (80.1)	7 (41.2) 10 (58.8)	0.06
Escalation to ICU	Yes No	3 (4.8) 59 (95.2)	4 (23.5) 13 (76.4)	0.01
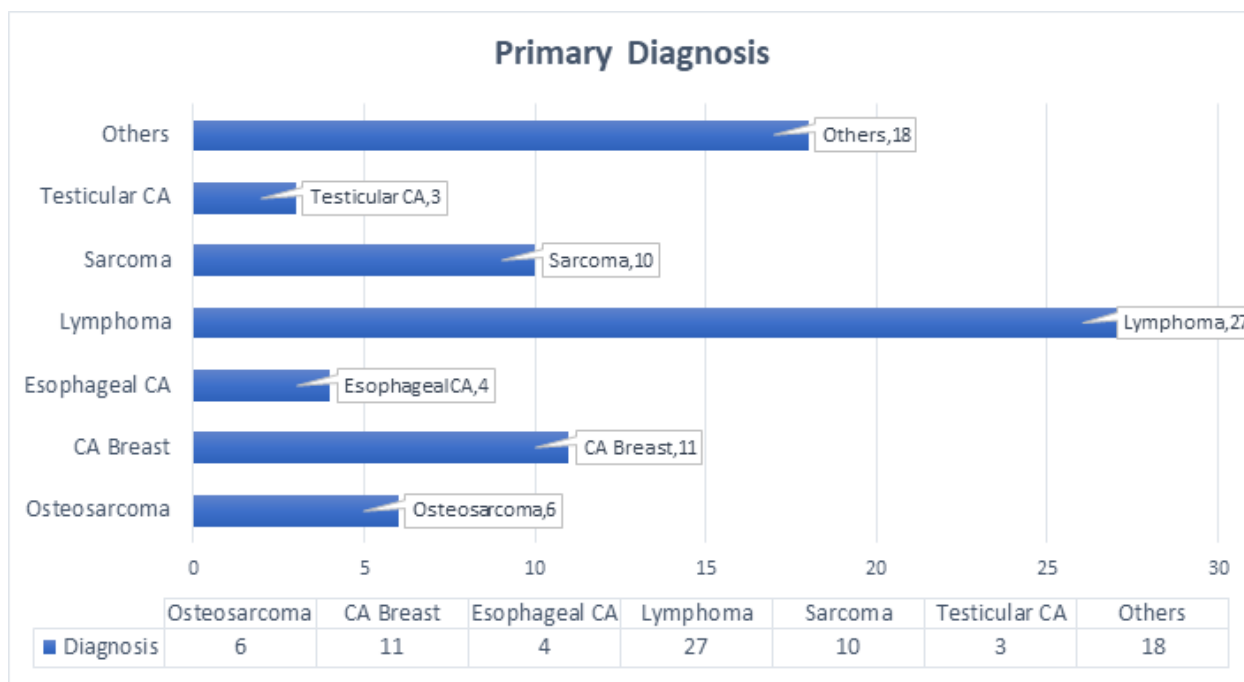
Figure 1: Primary diagnoses of patients in both groups

these patients, and middle age could be the possible reason for low mortality as the former has a better prognosis if treated accordingly. Our strict hospital patient selection criteria for cancer treatments could also be the other reason for metastatic diseases with poor prognoses. Due to the majority of patients from high-risk groups in our patients, we could not compare our outcomes with low-risk patients in the same setting. Time to antibiotics administration was significantly associated with increased hospital stay in our study. This was in a similar comparison to the results reported by Thomas and coauthors.[3] The Need for intensive care treatment was also significantly lowered in patients who received early antibiotics on arrival. This reflects the findings reported by Theis et al., where increased intensive care admissions were reported in cancer patients with febrile neutropenia.[7] Similarly, 4.7% of patients required ICU care in the subjects studied by Thomas et al. compared to 4.8% in group I of our study participants.3 However, the median time of administration in their study was 2.5 hours, with only 9% receiving antibiotics within one hour of arrival. Meanwhile, ICU admissions in group II participants were 28%, reflecting the significant increase in hospital care burden due to delays in antibiotic administration. Lastly, the escalation of antibiotics was higher in group II participants. Inadequate initial regimens in the emergency room without aminoglycosides or vancomycin due to multiple organ injury limiting their use may be one reason for this significant difference. Extensive studies with more detailed parameters are needed to identify the possible factors causing this change. Likewise, a significant reduction in the length of hospital stay was noted with timely administered antibiotics in group I patients. A systematic review by Christa et al. highlighted the[8] hours of extra hospital stay with a significant Pearson correlation in patients with delayed antibiotics administration.[8] Matthew and his colleagues conducted a similar study on the pediatric population. They found that a delay in antibiotic administration of more than sixty minutes was associated with adverse outcomes when adjusted for relevant covariates.[9]

This study's limitations include a lack of follow-up of culture growth and a history of antibiotics used before presentation.

Conclusion

Timely antibiotics significantly lowered intensive care admissions and length of hospital stay. However, our study did not find its impact on in-hospital deaths.

References

1. Rasmy A, Amal A, Fotih S, Selwi,W. Febrile neutropenia in cancer patient: epidemiology, microbiology, pathophysiology and management. J Cancer Prev Curr Res 2016;5(3):273-8.

2. Pettit N, Boadu D, Bischof JJ. Emergency department management of chemotherapy-related febrile neutropenia: An opportunity to improve care. Am J Emerg Med 2021;50:5-9.

3. Perron T, Emara M, Ahmed S. Time to antibiotics and outcomes in cancer patients with febrile neutropenia. BMC Health Serv Res 2014;14:162

4. Ali N, Baqir M, Hamid A, Khurshid M. Febrile neutropenia: median door-to-needle time - results of an initial audit. Hematology 2015;20(1):26-30.

5. Peyrony O, Gerlier C, Barla I, Ellouze S, Legay L, Azoulay E, et al. Antibiotic prescribing and outcomes in cancer patients with febrile neutropenia in the emergency department. Plos one 2020;15(2).

6. Weycker D, Li X, Edelsberg J, Barron R, Kartashov A, Xu H, et al. Risk and consequences of chemotherapy-Induced febrile neutropenia in patients with metastatic solid tumors. J Oncol Pract 2015;11(1):47-54.

7. Aagaard T, Reekie J, Jørgensen M, A Roen, G Daugaard, L Specht, et al. Mortality and admission to intensive care units after febrile neutropenia in patients with cancer. Cancer Med 2020;9(9):3033-42.

8. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review. Support Care Cancer 2020;28(3):1369-83.

9. Fletcher M, Hodgkiss H, Zhang S, Browning R, Hadden C, Hoffman T, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer 2013;60(8):1299-306.

Authors' Contribution Statement

HI contributed to the conception, design, acquisition, analysis, data interpretation, manuscript drafting, and final approval of the version to be published. FK contributed to the conception, design, acquisition, and interpretation of data and reviewed the manuscript. FS contributed to drafting the manuscript, and review. AQ contributed to drafting and critically reviewing the manuscript for important intellectual content. AR contributed to the conception, design, and acquisition of data. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Confilct of Interest

Authors declared no conflict on interest

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.