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Original Article

Oncology Section

Assessment of Delay in Door-to-antibiotic Administration Time after Arrival to the Hospital among Post-chemotherapy Febrile Neutropenia Patients: A Cohort Study

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ABSTRACT

Introduction: Febrile Neutropenia (FN), a common side effect of chemotherapy, is regarded as an oncologic emergency necessitating prompt treatment. A delay in door-to-antibiotic administration time is associated with poor patient outcomes.

Aim: To assess the time lag in the administration of antibiotics after arrival at the hospital in patients with solid/haematological malignancy presenting with post-chemotherapy FN.

Materials and Methods: This was a cohort study conducted in the Department of Medical Oncology at Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India, over a period of one year from December 2019 to November 2020 among 80 patients with solid or haematological malignancy who presented with fever and Absolute Neutrophil Count (ANC) <1000/mm^3 to the Outpatient Department (OPD) or the Emergency Department and were diagnosed with FN post-chemotherapy. Upon obtaining consent, these patients were enrolled, and the timing of antibiotic administration was noted for the study participants. The participants were further followed-up for the assessment of morbidity {in terms of Intensive Care Unit (ICU) admission)}, duration of hospital stay, delay in the further chemotherapy schedule, and survival status. Data was entered into MS Excel and analysed using Statistical Packages for Social Sciences (SPSS) version 16.0. Associations were established using Chi-square tests.

Results: Out of a total of 80 study participants, the mean±SD age was 45.6±18.3 years, and the number of males was 43 (53.8%). Total 57 (71.25%) patients were on chemotherapy for solid organ malignancies. The median delay in door-to-antibiotic time was 120 minutes (ranging from 30 to 260 minutes). The median day of presentation with FN after chemotherapy was day 7. Delay in antibiotic administration was found to have a significant impact on the further chemotherapy schedule and doses (p=0.004). However, ICU admission rates (p=0.133), length of hospital stay (p=0.662), and mortality (p=0.201) were not significantly associated with the delay in antibiotic administration.

Conclusion: The adoption of standardised algorithms and protocols for the management of FN and ensuring timely health-seeking by the patients shall help reduce the delay in Time-to-antibiotic Administration (TTA).

Keywords: Delay in antibiotic administration, Fever post-chemotherapy, Time-to-antibiotic administration

INTRODUCTION

Febrile neutropenia (FN) is considered as an oncologic emergency requiring prompt treatment. It is a common adverse effect of chemotherapy in cancer patients [1], leading to a negative impact on patient morbidity and mortality, including resulting dose reductions and treatment delays [2].

Previous evidence suggests that cancer patients have a 16.8% risk of developing FN during a course of chemotherapy [3], and patients with multiple co-morbidities are reported to have a 58% higher mortality rate [4]. In cancer patients, FN might be the sole indicator of severe infection because the inflammatory symptoms are often muted by a low absolute neutrophil count (ANC) [5,6]. Despite identifying an infectious cause in almost 20-30% of FN episodes, empiric broad-spectrum antibiotics remain the standard treatment for patients with FN [7].

With more patients likely to present with FN as aggressive chemotherapy regimens are increasingly used [8,9], these patients often face delays in antibiotic administration due to various factors, including waiting times for appointments, traffic, delays in clinical evaluations, CBC reports, delays at the pharmacy, and inconsistent plans for FN treatment [10]. Prolonged durations between time of triage and antibiotic administration are associated with extended hospital stays, a delays in chemotherapy treatment, increased costs, and occasionally catastrophic outcomes from septicemia. The Surviving Sepsis Campaign and an international guideline panel of the American Society of Clinical Oncology recommend administering the first dose of empiric antibiotic therapy to FN patients as soon as possible after triage (within an hour) [11,12].

There is a lack of evidence regarding the timeliness of antibiotic delivery in the Emergency Department to febrile patients following cancer chemotherapy. In fact, the impact of delays in door-to-antibiotic administration time has not been well studied in many cancer centres [13-16], particularly in the Indian context [17]. With this background in mind, the present study was conducted to assess the time delay in antibiotic administration after hospital arrival in cancer patients presenting with FN, as well as to evaluate the impact of such delays on rates of ICU admission, hospital stay, delays in further chemotherapy, and mortality.

MATERIALS AND METHODS

The present research was a cohort study conducted in the Department of Medical Oncology at Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan, India, after obtaining approval from the Institutional Ethics Committee (vide letter number BMH/2418/2660 dated November 22, 2019). The study was carried out over a one-year period from December 2019 to November 2020.

Inclusion criteria: The study included 80 patients with biopsy-proven solid or primary haematological malignancies who were

ultimately initiated on chemotherapy and subsequently presented to the OPD or emergency department with fever post-chemotherapy. After investigation, they were diagnosed with FN.

Exclusion criteria: Patients or their legal attendants who did not provide written informed consent for participation in the study and those with other significant co-morbidities were excluded from the study.

Study Procedure

Data collection commenced only after obtaining ethical approval. All cancer patients receiving chemotherapy who presented to the OPD and emergency department with fever (temperature >38°C) were screened for inclusion in the study. The baseline assessment included a medical history, physical examination, and fever assessment. Patients were advised to undergo complete blood counts, blood culture, and any other necessary tests as determined by the treating physician to identify the primary focus of infection. In present study, episodes of FN were identified on a cycle-specific basis based on the presence of an Absolute Neutrophil Count (ANC) <1000/mm^3 with evidence of infection or fever [3]. Patients with an ANC <1000/mm^3 based-on the final Complete Blood Count (CBC) report were considered eligible for inclusion in the study. Separate informed written consent was obtained for participation in the study after explaining the investigation's goal in detail in the participants' native language. Participants were assured that their submitted information would be kept secure and anonymous. Upon receiving consent, these patients were enrolled, and the timing of antibiotic administration was recorded for each participant. Based on the calculated door-to-antibiotic time, the participants were divided into two groups: one with a door-to-antibiotic time ≤2 hours and the other with a door-to-antibiotic time >2 hours. All participants were followed up to assess morbidity (such as ICU admission), duration of hospital stay, delays in further chemotherapy schedules, and survival status.

STATISTICAL ANALYSIS

Data were collected using a predesigned, pretested structured case proforma. The data were organised and tabulated in Microsoft Excel 2016 (Microsoft Office 2016 package), and statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (IBM Corp., Illinois, Chicago). The data were categorised based on a door-to-antibiotic time of 2 hours, and the impact of delayed antibiotic administration (door-to-antibiotic time >2 hours) on morbidity, such as ICU admission, hospital stay, delays in further chemotherapy, and mortality, was assessed using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 80 patients with FN were evaluated for TTA administration. Out of them, one-fourth belonged to the age group of 51-60 years. There were six patients (7.5%) aged between 1-10 years. The mean±SD age was 45.6±18.3 years, and the median age was 51 years. The number of males was 43 (53.8%) with a male-to-female ratio of 1.16:1. Total 57 (71.25%) patients were receiving chemotherapy for solid organ malignancies [Table/Fig-1]. The most frequently occurring solid tumours for which chemotherapy was initiated were soft tissue sarcoma 13 (16.3%), breast cancer 10 (12.5%), and lung cancer 7 (8.8%). Less common organs involved included colon cancer, head and neck cancer, prostate cancer, rectosigmoid cancer, hepatobiliary cancers, cervical cancer, esophageal cancer, lung cancer, ovarian cancer, and urinary bladder cancer. Haematological malignancies included lymphoma 17 (21.3%) and leukaemia 6 (7.5%).

Baseline characteristics	Categories	Frequency n (%)
Age*	1-10 years	6 (7.5)
	11-20 years	5 (6.2)
	21-30 years	7 (8.8)
	31-40 years	7 (8.8)
	41-50 years	16 (20.0)
	51-60 years	20 (25.0)
	60-65 years	19 (23.7)
Gender	Male	43 (53.8)
	Female	37 (46.3)
Type of malignancy	Solid	57 (71.2)
	Hematological	23 (28.8)

[Table/Fig-1]: Baseline characteristics of study participants (N=80).
* Mean±SD age: 45.6±18.3 years; Median age: 51 years

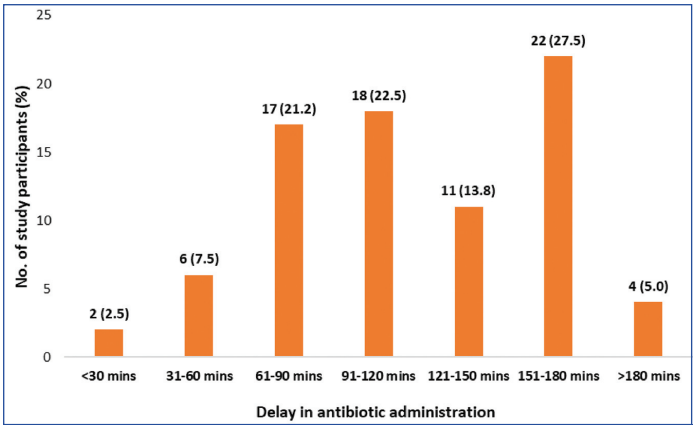
Almost two-thirds of the patients presented with fever at the Medical Oncology OPD. Nearly 59 (75%) patients presented to the hospital with such complaints between day 5 and day 10 post-chemotherapy. After conducting all necessary investigations, the most frequent primary focus of infection was identified as the lungs 29 (36.2%), oral cavity 28 (35%), and intestine 20 (25%) [Table/Fig-2]. The median ANC was 445/mm^3. The majority of patients (36.75%) presented with an ANC count between 250-500/mm^3 [Table/Fig-2].

Characteristics at hospital presentation	Categories	Frequency n (%)
Place of presentation	OPD	51 (63.8)
	ER	29 (36.2)
Post-chemotherapy day*	<5	8 (10.0)
	5-10	59 (73.7)
	11-15	10 (12.5)
	>15	3 (3.8)
Primary focus of infection	Intestine	20 (25.0)
	Lungs	29 (36.2)
	Oral cavity	28 (35.0)
	Urine	3 (3.8)
Absolute Neutrophil Counts (ANC) (/mm^3)†	≤100	4 (5.0)
	101-250	15 (18.8)
	251-500	29 (36.2)
	501-750	16 (20.0)
	751-1000	16 (20.0)

[Table/Fig-2]: Characteristics of study participants at hospital presentation (N=80).
OPD: Outpatient department, ER: Emergency; * Median post-chemotherapy day of presentation with FN- day 7; † Median Absolute Neutrophil Count (ANC)- 445/mm^3

The median delay in antibiotic administration is 120 minutes with a range of 30 to 260 minutes. 25% of patients experienced a delay of 180 minutes in antibiotic administration after arrival at the hospital [Table/Fig-3]. The median day of presentation with FN after chemotherapy is day 7 in the studied patients, with a range from day 3 to day 17. The majority of patients (22.5%) presented on post-chemotherapy day 7.

The association of delay in antibiotic administration with important factors, namely ICU admission, hospital stay, impact on further chemotherapy, and mortality has been presented in [Table/Fig-4]. Out of the 37 patients in whom a delay in antibiotic administration was noted, ICU admission was required in 16.2%, while the figure was 25.6% among those who received antibiotics within two hours. However, ICU admission rates were not significantly different between patients with delayed administration and those without delayed administration (p=0.133). Similarly, the length of hospital stay and mortality were not significantly associated with a delay in antibiotic administration.



[Table/Fig-3]: Distribution of study participants according to delay in antibiotic administration* (N=80).
* Median delay in in antibiotic administration - 120 minutes (range - 30 to 260 minutes)

Parameters	Door-to-antibiotic administration time		p-value
	>2 hours (n=37) n (%)	≤2 hours (n=43) n (%)	
ICU admission			
Yes	6 (16.2)	11 (25.6)	0.133
No	31 (83.8)	32 (74.4)	
Hospital stay			
>4 days	19 (51.4)	20 (46.5)	0.662
≤4 days	18 (48.6)	23 (53.5)	
Impact on further chemotherapy			
Yes	20 (54.1)	20 (46.5)	0.004*
No	17 (45.9)	23 (53.5)	
Mortality			
Yes	2 (5.4)	6 (14.0)	0.201
No	35 (94.6)	37 (86.0)	

[Table/Fig-4]: Impact of delay in antibiotic administration on key factors among the study participants (N=80).
*p-value was calculated using Chi-square test and value <0.05 was considered as statistically significant

Of the 37 patients who experienced a delay in antibiotic administration, further chemotherapy was affected in 54.1% of patients, while the figure was 46.5% in those who received antibiotics within two hours. Delay in antibiotic administration was found to have a significant impact on further chemotherapy (resulting in a delay in the next schedule or adjustment of doses) (p=0.004) [Table/Fig-3].

DISCUSSION

FN is a common side effect of chemotherapy. TTA administration is a crucial factor in determining favourable patient prognosis. According to various recommendations, the first dose of antibiotics should be administered within 1 hour in cases of FN [11,12]. Prolonged TTA has been shown to have an impact on mortality and morbidity, as studied in different research articles [18-21]. Therefore, the present study was conducted to determine the delay in antibiotic administration in patients with FN after their arrival at the hospital.

In the present study, the median door-to-antibiotic administration time was 120 minutes, which exceeded the standard recommendations allowing for a maximum delay of one hour [11,12]. The maximum door-to-antibiotic administration time was noted to be 260 minutes, observed in cases of OPD presentation. The TTA in cancer patients who presented to the ED with FN was evaluated in a number of studies conducted in various hospital settings outside India [18-21]. In a nationwide audit of 95 hospitals in the United Kingdom, initial empiric antibiotics within the desired one-hour "door-to-needle" time window were initiated in only 18 to 26% of patients with neutropenic fever, and there was a 9% mean fatality rate [19]. In another study by Szwajcer D et al., individuals with FN had a median latency to antibiotic treatment of five hours (range: 1.23-22.8 hours) [21]. After triage in the emergency room, only four out of 68 patients received antibiotics within two hours [21]. Perron T et al., also reported the median time to antibiotic administration as 2.5 hours [15]. Natsch S et al., noted a far longer delay in antibiotic administration in their study, with a median delay of five hours before patients received their initial dose of antibiotics, which depended on several factors [22]. Possible causes of antibiotic administration delays in the present setting include delays in patient assessment, antibiotic administration following prescription by the treating doctor, lack of knowledge on FN, lack of appropriate drug supplies, and the absence of a specific treatment protocol for FN. A study by Todurkar N et al., on post-chemotherapy FN among childhood malignancies reported delays in receiving results of blood investigations (30%), delays in preparing antibiotics (21%), and delays in allotting beds (30%) as significant reasons [23]. The use of prespecified protocols to boost antibiotic administration efficiency or implementing numerous ED initiatives to improve patient triage was shown to result in a significant reduction in TTA [24-26]. Al Sudairy R et al., designed a bundle of interventions and tested the same by executing six plan-do-study-act cycles, which reduced the mean door-to-needle time from 255 minutes to 49 minutes [27].

In the present study, more patients presented to the OPD compared to the emergency room (63.75% versus 36.25%). Perron T et al., reported that 85% of their patients presented to the ED, and the remaining 15% were hospitalised from the ambulatory clinic [15]. Keng MK et al., designed the FN Pathway (FNP) to manage neutropenic patients in the emergency department and compared them with direct admission patients. They recommended that FN patients should be admitted through the emergency department [14]. In the current hospital scenario, patients presenting in the OPD had to wait for their queue number, which led to delays in antibiotic administration. On the contrary, in emergency admissions, patients were evaluated by the duty doctor, investigations were sent, an intravenous line was secured from the emergency department itself, and antibiotics were administered there in some cases, or patients were shifted directly to the inpatient unit from the emergency department.

In the current study, the rate of ICU admission was 21.25%, and the mortality rate was 10%. A length of hospital stay of more than four days was observed in 51.4% of cases, and further chemotherapy was affected in 54.1% of the patients in whom the door-to-antibiotic time was more than two hours. Perron T et al., used the Multinational Association for Supportive Care in Cancer (MASCC) Score for risk stratification and observed a significant correlation between the diagnosis of leukaemia and bacteremia and hospital mortality and/or ICU admission [15].

A significant association was observed between the delay in antibiotic administration and the impact on further chemotherapy (p=0.004), whereas no significant association was identified with morbidity in terms of ICU admission (p=0.133), hospital stay (p=0.662), and mortality (p=0.201). These findings were supported by Szwajcer D et al., who reported no increased risk of death or increased length of hospital stay in association with delayed antibiotic administration in their study [21]. On the contrary, Keng MK et al., observed that for every 1-hour delay in TTA, adult patients with cancer experienced an 8-hour increase in Length of Stay (LOS). This was due to the fact that the majority of their patients identified with substantial antibiotic delays (top 10% of TTA) developed complications of infections and sepsis, resulting in prolonged LOS [14].

In the present cancer hospital, third-generation cephalosporins are used as empirical antibiotic treatment. In cases of unstable vitals like hypotension or low oxygen saturation, meropenem±teicoplanin were used upfront. Clinical practice guidelines from the IDSA recommend Fluoroquinolone (FQ) monotherapy, such as moxifloxacin or ciprofloxacin in combination with amoxicillin/clavulanic acid or clindamycin in place of amoxicillin/clavulanic acid in penicillin-allergic patients, in low-risk patients on an outpatient basis [2]. Among high-risk patients, inpatient admission followed by initial antibiotic monotherapy including an antipseudomonal beta-lactam (i.e., cefepime), a carbapenem (i.e., meropenem, imipenem, or cilastatin), or piperacillin-tazobactam is recommended [12]. More often, patients with FN either have an evident or occult infection. While the initial infection mostly tends to be of bacterial aetiology, the patient becomes susceptible to developing subsequent infections with an increased risk of infection with resistant strains. Therefore, the role of prompt treatment initiation with antibiotic administration remains the cornerstone of the management of FN. Thus, the present study inferred that a delay in antibiotic administration was found to have a significant impact on further chemotherapy cycles, such as a delay in further cycles, dose reduction, not receiving further chemotherapy as the patient left against medical advice, or expired during the hospital course.

Limitation(s)

The present study had some limitations. Firstly, various types of solid and haematological malignancies were included; hence, the association of a specific malignancy with FN-related mortality and morbidity could not be evaluated. Secondly, owing to different chemotherapy regimens according to the type, site, and nature of malignancy, the impact of chemotherapy on FN and related mortality and morbidity could not be assessed. Furthermore, patients reported to the hospital with a significant delay after the occurrence of fever, which could have influenced the results. Lastly, there were no objective triage criteria used or predefined protocols followed for patient assessment, decisions on the need for ICU admission, and management, which were subject to variation at the discretion of the attending and treating doctors.

CONCLUSION(S)

Based on the findings of the present study, it is inferred that delays in antibiotic administration are probably multifactorial, which include delays in patient assessment, antibiotic administration following prescription by the treating doctor, lack of knowledge on FN, lack of appropriate drug supplies, and absence of a specific treatment protocol for FN. It would be advantageous to establish a standardised protocol to guide patients experiencing an episode of FN through the emergency room. The adoption of algorithms and protocols across a range of Institutional frameworks will be imperative to reduce the door-to-antibiotic time to atleast less than two hours in the context of an event of FN attending the hospital emergency. Additionally, educating the patients regarding the urgency of fever post-chemotherapy and reaching the treatment centre without delay would also ensure quick health-seeking in such patients. Further research in larger populations and hospital set-ups across the country is warranted to corroborate the observations of the present study.

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