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Chemotherapy-Induced Febrile Neutropenia in Pediatric Cancer Patients

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Abstract

Background and aims. *Febrile neutropenia is one of the major acute complications in pediatric cancer patients treated with intensive chemotherapy. The present study aimed to report a cohort of pediatric cancer patients presented with febrile neutropenia at the National Cancer Institute (NCI), Misrata, Libya.* ***Patients and Methods****. This is a retrospective study that included patients under 18 years old admitted to NCI with malignancies and febrile neutropenia from January 2021 to September 2022.* ***Results****. The total cohort comprises 50 pediatric patients with malignancies and febrile neutropenia who were admitted to the NCI. There were 36 males (72%) and 14 females (28%). Febrile neutropenia was observed in all different age groups but was more frequent (42%) in the children of age group between four to six years followed by age group one to three years old. Febrile neutropenia was observed mainly in the 6th and 7th day after initiation of the chemotherapy. Majority of the patients (73%) had B-cell acute lymphoblastic leukemia. Most of the cases were treated empirically, and the most frequent prescribed-antibiotic agents were Tazocin and Amikacin (67%). If no clinical, biochemical and/or microbiological response achieved after 72 to 96 hours, these antibiotics were changed or escalated to the second line of treatment.* ***Conclusion****. We described in this study the clinical course of febrile neutropenia in pediatric cancer patients admitted to our center. Due to a weak immune response, febrile neutropenic cancer patients, are at high risk for any kind of infection including opportunistic infections. It is therefore necessary to take precautions for infection prevention and choose the best way management to obtain optimal results in these high-risk patients.*

Keywords: *Antibiotics, Chemotherapy, Febrile Neutropenia, Management, Pediatric Cancer.*

Introduction

Cancer is the uncontrolled growth of abnormal cells in the body. It develops when the body's normal control mechanism stops working. Old cells do not die and instead grow out of control, forming new, abnormal cells. These extra cells may form a mass of tissue, called a tumor. Some cancers, such as leukemia, do not form tumors. [1,2]. The most common cancers in children are leukemia, brain and spinal cord tumors, neuroblastoma, lymphoma (including both Hodgkin and non-Hodgkin), rhabdomyosarcoma, retinoblastoma, and osteosarcoma [3]. The four types of leukemias are acute myeloid (or myelogenous) leukemia (AML), chronic myeloid (or myelogenous) leukemia (CML), acute lymphocytic (or lymphoblastic) leukemia (ALL), which occurs more often in children and can be classified as B-cells ALL or T-cells ALL, and chronic lymphocytic leukemia (CLL) [4].

Febrile neutropenia remains one of the most concerning complications of cancer chemotherapy and is a major cause of morbidity and mortality; it has diminished steadily but remains significant [5]. Febrile neutropenia is a life-threatening condition that requires immediate attention, especially in patients with chemotherapy-related neutropenia. Patients with febrile neutropenia have a much greater risk of developing bacterial disease, and fever may be the only indicator of a severe infection. Adequate management of febrile neutropenia emphasizes early recognition of patients, risk stratification, and antibiotic therapy administration during the first 60 minutes of admission to the emergency room. It is common for no source of infection to be identified when patients have febrile neutropenia. It must be managed because febrile neutropenia can increase the severity of an infection at commonly infected sites. Patients with febrile neutropenia are initially investigated for infection at the sites of

previous procedures or catheters, as well as on or in the skin, alimentary tract, oropharynx, gastrointestinal tract, and lungs [5].

As part of the risk assessment, children with febrile neutropenia are classified as low- or high-risk. Some of the factors reported for risk stratification in various pediatric studies include duration of neutropenia (>10 days), severity of neutropenia (<100/mm3), type of cancer (solid tumor, lymphoma, ALL, AML), state of disease (remission, progressive disease, recurrence), bone marrow involvement, type of treatment (conventional chemotherapy, hematopoietic stem cell transplantation), and additional health problems (such as respiratory and neurologic problems, hypotension, and hypoxia) [6]. The relative risk of infection is related to both the degree and duration of neutropenia. The risk of infection is greater in patients with an Absolute Neutrophil Count (ANC) of <500 cells/microL and greatest at an ANC of <100 cells/microL (profound neutropenia) and in patients with a longer duration of neutropenia (> 7–10 days).

The initial management of pediatric febrile neutropenia includes rapid assessment of the patient, recognition of those exhibiting signs and symptoms of sepsis, rapid initiation of broad-spectrum antimicrobial agents regardless of the result of their blood culture because potentially life-threatening infections need early treatment to ensure a better clinical outcome [7], and other necessary supportive care measures, as well as subsequent admission to the hospital. Although multiple risk stratification models have been published, none has been validated across varied pediatric oncology cohorts. Therefore, the current recommendation for pediatric patients is for admission in all cases of febrile neutropenia. Antibiotic selection should be based on microbial prevalence and sensitivity patterns at individual institutions. Due to the acute risk of gram-negative sepsis, empiric coverage must include these organisms, including Pseudomonas. Multiple empiric regimens are acceptable, although in general, monotherapy has supplanted dual therapy. Empiric antibiotic therapy should have a wide spectrum (covering Gram-positive and Gram-negative bacteria, including P. aeruginosa), high bactericidal drug levels in serum, low toxicity, and be easy to administer. Treatment may begin with monotherapy (a single antibiotic). Duotherapy (addition of aminoglycosides to monotherapy) or glicopeptides should be considered for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high grade of resistant pathogens as the regimens of choice [6].

The present study aimed to report a cohort of pediatric cancer patients presented with febrile neutropenia at the National Cancer Institute, Misrata, Libya.

Patients and Methods

A retrospective descriptive, observational, cross-sectional study was conducted between January 1, 2021, and September 25, 2022, of oncologic patients aged less than 18 year who were diagnosed with febrile neutropenia at the National Cancer Institute in Misurata, Libya during the study period. A total of 50 patients were included in the study. Age, gender, the underlying diagnosis, the initial antimicrobial therapy profile, the ANC, and hospital stay were analyzed. Fever was defined as a temperature ≥38 °C and neutropenia was defined as an ANC <500 cells per cubic millimeter.

Statistical Analysis

Data of all categorical variables are summarized using frequencies and percentages.

Ethical Approval

The study was approved by ethical committee at the National Cancer Institute, Misurata.

Results

The total cohort comprises 50 pediatric patients with malignancies and febrile neutropenia, there were 36 males (72%) and 14 females (28%). As shown in Figure 1, febrile neutropenia was observed in all different age groups of the patients but was more frequent (42%) in the pediatric age group between four to six years followed by age group one to three years old (Figure 1). The mean temperature degree was 38.5 °C and the median duration of fever was 4 (3-5) days. Up to 30% of patients had a temperature reading greater than 39 °C.

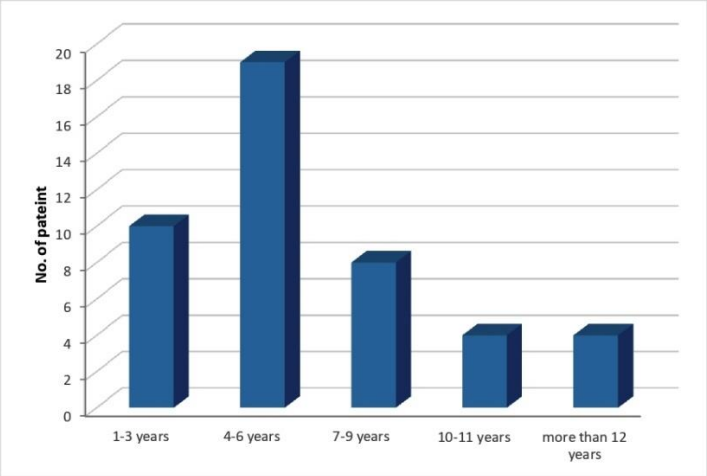

Figure 1: Distribution of febrile neutropenia patients by age

Figure 2 shows the distribution of cancer types in pediatric patients presented with febrile neutropenia at the National Cancer Institute-Misrata during the study period. Seventy-three (73%) were B cells- ALL, three (6%) were T cells- ALL, three (6%) were AML, two (4%) were pelvic Rhabdosarcoma (RMS), two (4%) were neuroblastomas, one (2%) was Hodgkin's lymphoma, one (2%) was relapsed Hodgkin's lymphoma, and one (2%) was relapsed testicular RMS.

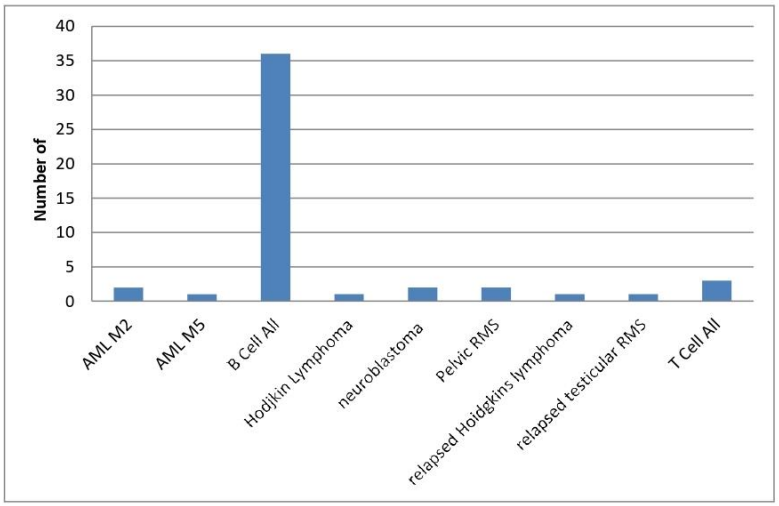

Figure 2: Distribution of cancer types in the pediatric patients with febrile neutropenia

Most patient's duration hospital stays in this study were from three to five days. some patients stayed only for one day and others stayed for more than 14 days. Those who stayed for five days or less formed 38% of patients compared with 62% for patients stayed greater than five days as shown in Figure 3.

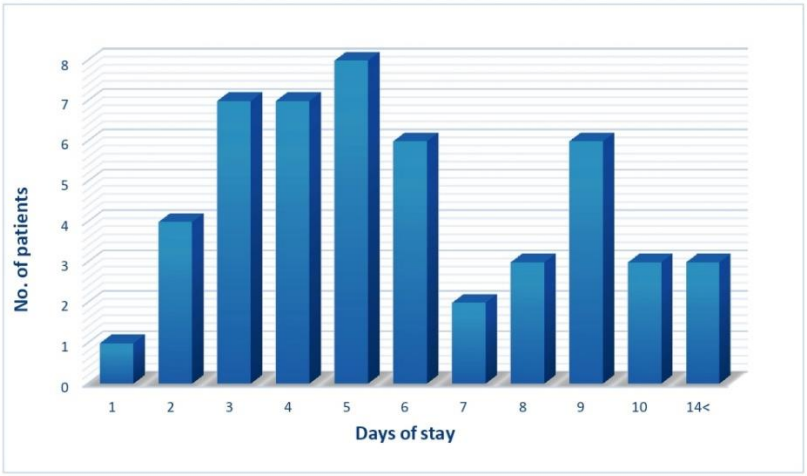

Figure 3: Distribution of patients by the number of days of hospital stay.

As shown in Figure 4, febrile neutropenia was occurred from the first day after initiation of chemotherapy, however, in majority of febrile neutropenia cases (16 cases) occurred in the sixth and seventh day after started chemotherapy (Figure 4).

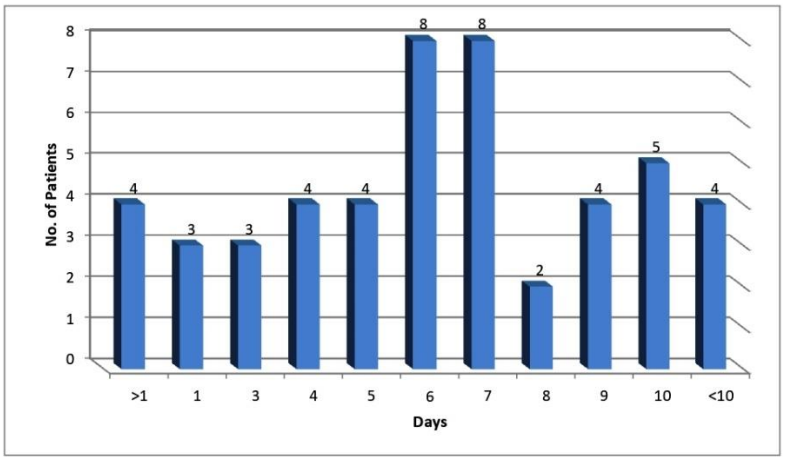

Figure 4: Time frame (days) of occurring of febrile neutropenia after initiation of chemotherapy

In patients with febrile neutropenia, the ANC is <500 cells per cubic millimeter. In this study, 38% of patients showed ANC of <100 cells per cubic millimeter, and 62% is between ≥100 and <500 cells per cubic millimeter. Most of the patients showed ANC that exceeds 500 cells per cubic millimeter after treatment initiation, as seen in Figure 5. However, some patients have been discharged from the hospital with specific precautions with an ANC of zero to protect them from any nosocomial infection.

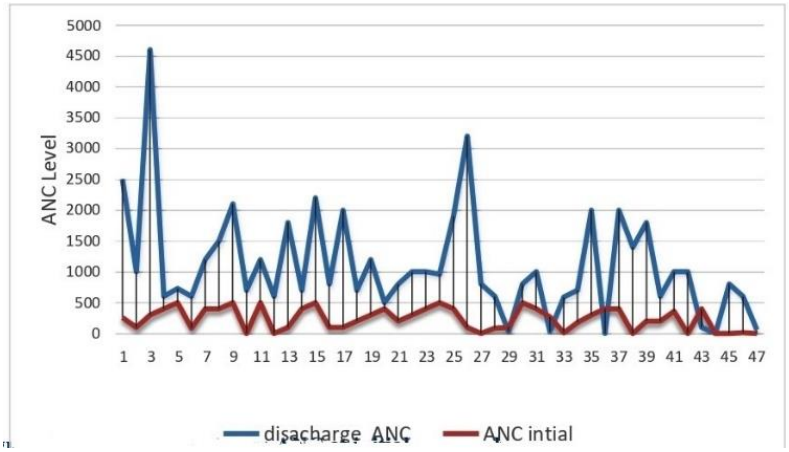

Figure 5: Distribution of Absolute Neutrophil Count at time of admission and upon discharge

The distribution of antibiotics profile that has been used in the study cohort is shown in Figure 6. Most of the cases were treated empirically, and the most frequent prescribed-antibiotic agents were Tazocin and Amikacin (67%). If no clinical, biochemical and/or microbiological response achieved after 72 to 96 hours, these antibiotics were changed or escalated to the second line of treatment (i.e., Meropenem and Vancomycin). Fungal infection was treated by Amphotericin and viral infection by Acyclovir.

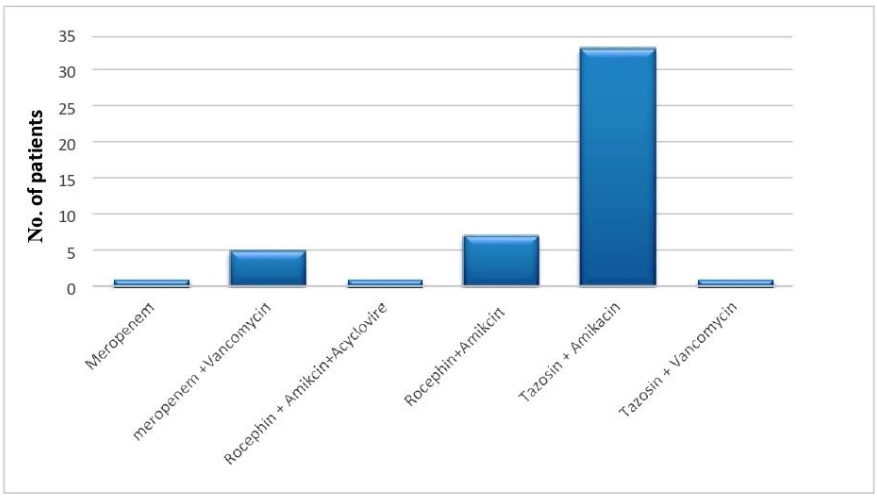

Figure 6: Distribution of used antibiotics profile

Discussion

Febrile neutropenia is common among patients receiving chemotherapy and typically results in extended hospitalization and for many patients may cause death. Children with leukemia and solid tumors are often hospitalized for empiric broad-spectrum antibiotic therapy because of fever during periods of chemotherapy-induced neutropenia. Conventional practice dictates that parenteral antibiotics be continued until the patient is afebrile and has recovered from neutropenia, i.e., until the absolute neutrophil count ANC exceeds 500 cells per cubic millimeter. Antibiotic treatment can be discontinued when clinical signs and symptoms of infection have resolved, and the patient remains afebrile. Many factors should be considered when choosing empirical antibiotic treatment in patients with febrile neutropenia; these include the risk of infection associated with the severity of neutropenia (low versus high risk), the possible focus of infection, and clinical manifestations. Empiric treatment should be modified according to culture results and clinical situation. The National Cancer Institute in Misurata used Tazosin and Amikacin as first-line therapies. However, if the patient is not responding, it can be escalated to second-line therapy, which is Meropenem and Vancomycin. After 5 days, some patients will be at high risk of developing fungal and viral infections; thus, they may need to take antifungal and/or antiviral therapy.

According to our demographic data, febrile neutropenia was observed in groups of children of all ages. The highest proportion (42%) was formed by children aged between four and six years. The reason behind occurrence of febrile neutropenia in children aged four to six years old, is unclear. In the other hand, febrile neutropenia occurred in 22% of the children aged from 1 to 3.

Angelino et al. indicated that 48% of children aged less than 12 months were female [8] and Freifeld et al. found that 35 (52%) of the patients were male and 33 (48%) were female [9]. In this study, which included 36 males (72%) and 14 females (28%), it has been noticed that the number of males was approximately two-thirds higher than that of females.

In the present study, approximately 1/3rd of patients had a temperature greater than 39 °C, this was similar to Das's et al study, in which 32% of children having a temperature above 39 °C [10]. Furthermore, Blennow and Ljungman [11] evaluated a cohort of 68 pediatric cancer patients with febrile neutropenia and reported that 73.5% (n=53) of the patients had ALL, this was similar to the finding of our study in which frequency of ALL is 73%.

Most patient's hospital stays in this study lasted from three to five days (38%) and for more than five days formed (62%) of patients. some patients stayed only for one day, and others stayed for more than 14 days. In a recent study with a large sample size of febrile neutropenia patients, Sezgin, et al. found that those patients who stayed for 5 days or less formed 54% of patients [12].

Conclusion

In the present study we described the clinical course of febrile neutropenia in pediatric cancer patients admitted to our center. Due to a weak immune response, febrile neutropenic cancer patients, are at high risk for any kind of infection including opportunistic infections. It is therefore necessary to take precautions for infection prevention and choose the best way management to obtain optimal results in these high-risk patients.

Conflict of Interest

None of the authors have any conflict of interest to declare

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