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Research article

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Management of Febrile Chemo-Induced Neutropenia: Experience of The Pediatric Hemato-Oncology Unit of The Donka National Hospital

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Summary

Introduction

Chemo-induced febrile neutropenia is a severe complication of cancer chemotherapy. Its severity is essentially linked to the depth and duration of neutropenia.

The aim of our work is to report the epidemiological, clinical, therapeutic and progressive particularities of episodes of chemo-induced febrile neutropenia from September 2021 to February 2023.

Methods

This is a cross-sectional, observational, analytical study of episodes of febrile neutropenia post-chemotherapy lasting eighteen (18) months from September 1, 2021 to February 28, 2023.

Results

There were 60 episodes of febrile neutropenia in 31 boys and 21 girls (sex ratio 1.47). The average age of the patients was 5.5 years (6 months - 17 years). The underlying neoplastic pathology was dominated by acute lymphoblastic leukemia (38.34%) and Burkitt lymphoma (23.33%). The average time to onset of febrile neutropenia was 7.72 days after chemotherapy. Fever was clinically documented in 81.67% of cases, with a predominance of digestive (55%) and respiratory (17%) foci. A pathogen was identified in 3.33% of cases.

The average time to management of febrile neutropenia during our study was 30 hours after onset with a minimum of 1 hour and a maximum of 244 hours. The median is 26 hours.

Conclusion

At the end of this work, we emphasize the need for rapid and appropriate management of febrile neutropenia with empirical antibiotic therapy adapted after clinical and bacteriological investigation. We also emphasize the need to improve the means of microbiological investigations, to develop preventive measures and to respect hygiene measures in order to reduce the incidence of infection, by informing and educating all patients undergoing chemotherapy.

Keywords: Chemotherapy, Neutropenia, Fever, Antibiotic therapy, Prevention

Abbreviation

CHU:
CRP:
g /dl:
mg/l University Hospital Center
C Reactive Protein
Gram per deciliter
Milligram per liter
LAL: Acute Lymphoblastic Leukemia
LAM: Acute Myeloblastic Leukemia
NF: Febrile Neutropenia
WHO:

ENT: World Health Organization
Oto Rhino Laryngology
PNN: Polynuclear Neutrophil

1. Introduction

Febrile Neutropenia (FN) is defined according to the WHO by a count of Polynuclear Neutrophils (PNN) less than 500/mm 3 associated with a fever (temperature greater than 38.3
°C once or greater than 38 °C on twice 1 hour apart, without taking an antipyretic) [1].

It is one of the main side effects of anticancer chemotherapy in relation to its hematological toxicity, toxicity mainly affecting the granulocytic lineage and leading to neutropenia whose severity and duration determine the potential seriousness of infections [2]. Febrile neutropenia is a therapeutic emergency due to the major risk of morbidity and mortality [3]. Its management requires careful etiological, clinical and paraclinical research without delaying treatment with probabilistic antibiotic therapy, then adapting the prescription according to the biological results or the antibiogram [4].

The frequency of occurrence of chemo-induced febrile neutropenia remains high according to the results obtained by the different series of patients treated in specialized centers, whether in developed, developing or third world countries [5]. This study aimed to investigate the management of chemo-induced febrile neutropenia at the pediatric hemato-oncology unit of Donka National Hospital.

2. Methods

This study was carried out in the pediatric hemato-oncology unit of the pediatric department of Donka University Hospital (Conakry). This was a prospective, observational study of a descriptive and analytical type covering a period of eighteen (18) months from September 1, 2021 to 28 February 2023 covering all patients followed for febrile neutropenia in the pediatric hemato-oncology unit during the study period. She included in this study all children aged 0 to 18 years, of any sex, followed in the pediatric hemato-oncology unit for chemo-induced febrile neutropenia during the study period. For each file, the parameters studied were: Age, sex, clinical characteristics of the children as well as the etiological data and the management of the chemo-induced febrile neutropenia that appeared. The evolution was assessed on the basis of the regression or not of the clinical signs. The data was collected on a pre-established survey form, entered and processed using the Epi info 7.2.2.6 software then presented in the form of results using the Word and Excel software from the 2016 office pack.

The anonymity and confidentiality of the information collected were preserved.

3. Results

During the period from September 1 , 2021 to February 28, 2023, taking into account the non- inclusion criteria; we retained 52 eligible patients who presented at least one episode of febrile neutropenia, i.e. 60 episodes in total

In our series, the age group of 0 - 5 years was the most dominant at 35% for an average age of
7.02 ± 6 years.

The male sex is the most dominant with 65% with a sex ratio of 1.86.

Annexes

Socio-demographic characteristics	Numbers (N=60)	Percentage (%)
Age range (years)		
[0 - 5]	21	35
[6 - 10]	17	28.33
[11 - 15]	13	21.67
[16 - 20]	9	15

The average age is **7.02 ± 6 years Extreme 3 months - 16 years**

Sex		
Male	39	65
Feminine	21	35
Sex ratio = 1.86		

Table 1: Distribution of cases of Chemotherapy-induced Febrile Neutropenia according to socio-demographic characteristics

In our study, the most frequent cancers were represented by Acute Leukemia (41.66%) followed by Burkitt's lymphoma (23.33%) and Retinoblastoma (21.67%).

Diagnostic	Frequency	Percentage (%)
Acute Leukemia	25	41.66
Burkitt's Lymphoma	14	23.33
Retinoblastoma	13	21.67
Osteosarcoma	4	6.67
Nephroblastoma	3	5.00
Sacrococcygeal Teratoma	1	1.67
TOTAL	60	100.00

Table 1: Distribution of cases of chemo-induced febrile neutropenia according to the type of cancer

Text 1: Distribution of cases of chemo-induced febrile neutropenia according to the origin of the fever in the pediatric hemato-oncology unit from September 1, 2021 to February 28, 2023.

At the end of clinical, radiological and microbiological explorations, fever was documented in 49 cases (81.7%), microbiologically documented in 2 cases (3.3%) and of unknown origin, i.e. neither documented nor clinically. nor microbiologically in 9 cases (15%).

Respiratory signs are found in 16.67% of cases: cough with rales on auscultation and signs of respiratory distress.

Mucocutaneous signs are found in 3.33% and are all represented by a venous catheter call point.

	Frequencies	Percentage (%)
Digestive origin	33	67.35
Pulmonary origin	10	20.41
Mucocutaneous origin	04	08.16
Origin ENT	02	04.08
Total	**49**	**100%**

Table 3: Distribution of cases of chemo-induced febrile neutropenia according to the origin of clinically documented fevers.

Among the 60 cases in our study, the majority, i.e. 93.3%, received probabilistic antibiotic therapy based on a combination of a 3rd generation cephalosporin + aminoglycoside (Ceftriaxone + Gentamycin in 71.7% of cases and Ceftazidime + Amikacin in 21.7% of cases). A small part of our population received the 3rd generation cephalosporin + 5-nitroimidazole combination.

In the present study, additional antifungals and antibacterials were added for some patients; others benefited from a change of antibiotics after 3 to 4 days of initial antibiotic therapy without apyrexia. An antifungal was initially administered when there was suspicion of candidiasis in 23.33% of cases but also when the fever persisted after 5 days of antibiotic therapy in 31% of cases. Regarding factors associated with death, there is a statistically significant relationship between PNN level < 250, hemoglobin level < 5 g/dl, platelets < 20,000, CRP > 100 and time to administration of the antibiotic with a P value < 0.05. During our series, the death rate was 11.67%.

Features	Living	Deceased	P
PNN rate:	25	6	0.04
Inf. at 250 PNN	28	1	
Between 250 and 500 PNN			
Hemoglobin level:			
⩽ 5g/dl	10	6	0.031
> 5g/dl	43	1	
Platelet rate (elements/mm ^{3})		5	0.0001
<20,000	29	2	
> 20,000	24		
CRP			
> 100 mg/l	13	4	0.0001
< 100 mg/l	40	3	

Antibiotic administration time (in days)			
< 1	34	01	0.04
> 1	19	06	

Table 4: Distribution of living and deceased patients according to paraclinical data and the time taken to administer antibiotic therapy

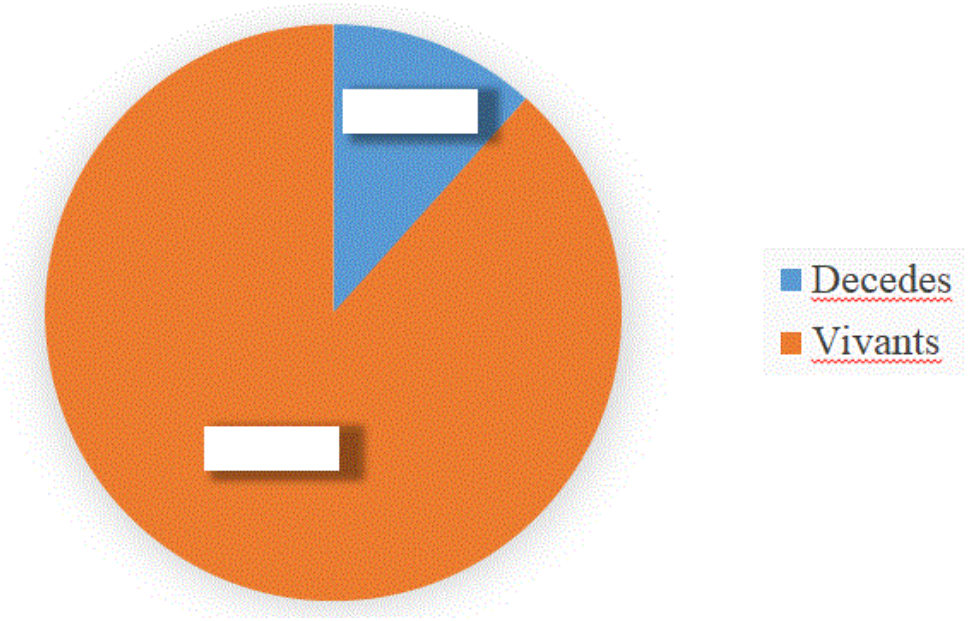

Figure 1: Distribution of Cases of Chemo-Induced Febrile Neutropenia According to Thei Evolution.

4. Discussion

In our series, the age group of 0 - 5 years was the most dominant. Mohammed et al. [6]. In a study to evaluate management practices of febrile neutropenia (FN) in pediatric cancer patients at Tikur Anbessa Specialist Hospital, Ethiopia also found a mean age of 5.5 ± 3.2 years. This could be explained by the fact that most cases of acute leukemia are encountered in this age group, which makes them vulnerable to neutropenic fever after chemotherapy [7]. In this study, the most common cancers were represented by acute leukemia. Mohammed et al. [6]. In their study in Ethiopia also showed that acute lymphocytic leukemia (ALL) was the most frequently diagnosed type of cancer (60%), followed by non-Hodgkin's lymphoma (7.4%) and solid tumors in febrile neutron patients. Similarly, a study carried out in Pakistan by Llamas R. et al. [8]. showed that ALL was the most common underlying malignancy (84.3%) and that the most frequent NF episodes (72.1%) occurred during the induction phase of treatment.

In line with the present study, a Mexican study carried out by Matloob M. et al. [9]. Reported that acute leukemia was the most common type (65.2%) of cancer diagnosis, followed by lymphoma (14.1%) and solid tumors in pediatrics. This could be explained by the fact that the type of tumor constitutes a risk factor for NF, in the case of hemopathy the risk is greater compared to solid tumors because the hematological complications are linked to the underlying tumor, the type of treatment used and the intensity of this treatment [10]. It appears from this study that microbiologically documented fever is the most represented. Malk S. et al . [11]. In their study on the experience of the Rabat pediatric oncology and hematology center regarding chemo-induced febrile neutropenia found unexplained fevers in 39.5% of cases. Infection was clinically documented in 32.9% of cases; microbiologically documented infections represented 27.6% of cases. Classically, in the literature, the distribution is 30% microbiological documentation, 10% clinically documented fever and 60% undetermined etiology [12]. The proportion of microbiological identification in our work is much lower than the data in the literature. This is explained by the high cost of blood culture, which was difficult for parents, most of whom did not have sufficient means and did not have medical coverage. On the other hand, we have eight times more clinically documented fever. This result could be explained by more frequent hospital referral for patients presenting symptoms associated with fever. Among the 81.67% of clinically documented fever, digestive manifestations were found in 55% of cases: the signs were represented by mucositis, anitis, abdominal pain and diarrhea. Respiratory signs are found: cough with rales on auscultation and signs of respiratory distress. Mucocutaneous signs are found and are all represented by a venous catheter call point. These figures are different from a study carried out in Rabat by Gharbi O. et al. [13]. Which showed that 78% of patients had a clinically documented outbreak, it was ENT in 47% of cases, digestive in 12% of cases, cutaneous in 5.7% of cases. During this study, we evaluated the time between the onset of fever and the administration of antibiotic therapy. It had an average

of 1.26 days in those alive after treatment and was 2.14 days in patients who died during treatment. From the association of the time between the onset of fever and the administration of antibiotic therapy and the occurrence of death, it emerged that there is a statistically significant relationship between these two elements (p = 0.041). The long consultation period is therefore in our study a factor influencing the occurrence of death.

This time is significantly longer than the current American Infectious Disease Association guideline recommends (< 2 hours) [14]. It should be mentioned that this delay in initiating antibiotic therapy is mainly due to parental delay in seeking medical assistance. In addition, administration of the antibiotic within 30 min reduced the mortality rate from 18.1% to 3.0% (log Rank p = 0.0002). Based on these results, many oncology centers recommend administration of antibiotic therapy within a time limit of less than 60 min [15,16]. Indeed, although patients undergoing chemotherapy receive education in terms of monitoring and warning signs (fever and symptoms), in order to present themselves at the hospital for diagnosis, this measure has not always been respected by parents. However, it remains the best way, to date, and in our context, to quickly diagnose cases of NF in order to quickly begin treatment.

In our study, all cases of febrile neutropenia were hospitalized for treatment given that social conditions and therapeutic compliance were not guaranteed. The most used antibiotic regimen was the combination of a β-lactam (mainly cephalosporins: ceftriaxone or ceftazidime) with an aminoglycoside (gentamycin or amikacin) in 93% of cases with the ceftriaxone gentamycin combination representing 71.67% of cases. Another study carried out by Santolaya et al. [17]. On the management of febrile neutropenia showed that 77.1% of patients were treated with a combination of ceftazidime and gentamycin. Similar results were reported by Llamas et al. [18]. Since 75.5% of patients received a combination of a beta-lactam with an aminoglycoside side. Empirical antibiotic therapy with agents active against viridians group streptococci and Pseudomonas aeruginosa is recommended as standard of care in high-risk NF childhood cancer patients to cover virulent organisms while minimizing exposure to unnecessary antibiotics, as indiscriminate use of broad-spectrum antibiotics can accelerate rates of antibiotic resistance [19]. In the present study, additional antifungals and antibacterials were added for some patients; others benefited from a change of antibiotics after 3 to 4 days of initial antibiotic therapy without apyrexia. An antifungal was initially administered when there was suspicion of candidiasis in 23.33% of cases but also when the fever persisted after 5 days of antibiotic therapy in 31% of cases. A Tunisian study carried out by Fedhila et al. [20]. reported that antifungals were added in 6% unresolved NF episodes. In the literature, the addition of an antifungal agent is recommended in patients with neutropenia who remain febrile for 4–7 days after broad-spectrum antibiotic therapy or relapsing fever with persistent neutropenia [21]. Regarding the mortality rate in our study, it is 19.44%. Klastersky J. et al. [22]. in their study on the management of febrile neutropenia reported a mortality of 10% of cases of febrile neutropenia. Our result is highly high than the rates reported in the literature, these varying from 7 to 10% [23,24].

5. Conclusion

Post-chemotherapy febrile neutropenia is one of the most common and potentially serious complications of cancer disease that can induce early mortality. In our study, more than half of the children receiving chemotherapy suffered from this condition. The age group of 0 to 5 years was the most affected with a male predominance. Acute leukemia and Burkitt lymphoma were the cancers most represented in the occurrence of febrile neutropenia. Treatment at the pediatric hemato-oncology unit of Donka National Hospital is based on urgent initiation of empirical antibiotic therapy as well as monitoring of temperature and signs of shock. Therapeutic escalation and the administration of an antifungal are also carried out if the fever persists. The promotion of microbiological investigation methods with a view to more targeted treatment would be a valuable contribution.

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