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Grade 3 and 4 Chemotherapy-Induced Neutropenia in Patients Followed at a Referral Hospital in Cameroon

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Abstract

Introduction: Cancer is a growing global health concern, but advances in early diagnosis and therapeutic modalities, particularly chemotherapy, have led to a decline in mortality. Despite their efficacy, cytotoxic agents are associated with hematological toxicities, most notably neutropenia. Grade 3 and 4 neutropenia carries a high risk of infectious complications, which can compromise the optimal delivery of chemotherapy protocols. To maintain effective treatment regimens, scientific societies recommend the use of granulocyte colony-stimulating factors (G-CSFs). While their benefit in managing neutropenia is well-documented, their use requires a thorough understanding of the patient, their cancer, and the specific chemotherapy regimen being administered. This study aims to describe the sociodemographic, clinical, therapeutic, and evolutionary characteristics of patients with chemotherapy-induced grade 3 and 4 neutropenia at the Yaoundé General Hospital. **Methods:** We conducted a cross-sectional, retrospective study in the oncology department of the Yaoundé General Hospital over a 10-month period, from November 1, 2022, to August 31, 2023. Our study population consisted of cancer patients aged 18 years or older who had received at least one chemotherapy cycle and experienced at least one episode of grade 3 or 4 neutropenia. Patients with incomplete medical records or those receiving concomitant neutropenia-inducing medications were excluded. We used a consecutive, non-probabilistic,

and exhaustive sampling method for retrospective data collection. The variables studied included sociodemographic and clinical characteristics, therapeutic management, and patient outcomes. **Results:** A total of 93 patients were included, representing 157 episodes of grade 3 and 4 neutropenia. The population was predominantly female (82%), with a mean age of 48.42 years ± 12.1 years. Breast cancer was the most common malignancy (53.8%), and the majority of patients (50.5%) had metastatic disease. The AC 60 protocol was the most frequent regimen associated with grade 3 and 4 neutropenia (54.7%). Most patients (80%) had a WHO performance status of 1, and 7.5% developed febrile neutropenia. All episodes of grade 3 and 4 neutropenia led to a postponement of the chemotherapy cycle, while filgrastim was administered in 24.2% of cases. At the 7-day follow-up, complete blood count (CBC), the neutropenia had resolved in 86% of the episodes. **Conclusion:** Chemotherapy-induced grade 3 and 4 neutropenia is a frequent reason for chemotherapy delays, thus hindering the optimal administration of treatment regimens. These findings highlight the importance of improving the management of this complication to enhance the efficacy of cancer treatment in this setting.

Keywords

Chemotherapy-Induced Neutropenia, Grade 3 and 4, Cancer, Granulocyte Colony-Stimulating Factor, Yaoundé

1. Introduction

Cancer remains a significant global health challenge, with its incidence rising from 10.1 million cases in 2000 to 19 million in 2020, with 5.7% of new diagnoses occurring in Africa [1]. Despite this increasing burden, cancer-related mortality has been declining, a trend attributed to improved early diagnostic methods and therapeutic advancements, particularly chemotherapy [2]. However, the use of cytotoxic agents is frequently associated with hematological toxicities, of which neutropenia is the most common and severe [3]-[5].

Chemotherapy-induced neutropenia (CIN) is defined by a decrease in circulating neutrophil count and is graded for severity by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [6]. Grades 3 (<1,000/mm^3) and 4 (<500/mm^3) are particularly critical due to the increased risk of infection, which can progress to febrile neutropenia (FN), a life-threatening complication [7] [8]. Episodes of severe CIN often necessitate treatment delays, dose reductions, or discontinuation, thereby compromising the overall efficacy of the therapeutic regimen [9] [10].

Numerous risk factors for CIN have been identified, including patient-related factors (age, comorbidities), disease-related factors (cancer type and stage), and treatment-related factors (chemotherapy protocol) [11]. To mitigate CIN, current guidelines from organizations like the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommend the prophylactic use of G-CSFs such as filgrastim or pegfilgrastim [12] [13]. These agents have

demonstrated efficacy in reducing the incidence of severe CIN and FN [14] [15].

However, the implementation of these guidelines varies significantly, particularly in resource-limited settings. A previous study in Cameroon focused on the prevalence and incidence of severe CIN but did not delve into the specific sociodemographic, clinical, and therapeutic characteristics of affected patients [16]. A deeper understanding of these factors is crucial for tailoring preventive measures and management strategies to improve patient outcomes, reduce hospitalizations, and lower associated costs.

The main objective of this study is to describe the sociodemographic, clinical, therapeutic, and evolutionary characteristics of patients with chemotherapy-induced grade 3 and 4 neutropenia at the Yaoundé General Hospital.

2. Methods

2.1. Study Design and Setting

This was a descriptive, cross-sectional, and retrospective study conducted at the Medical Oncology Department of the Yaoundé General Hospital (YGH). The YGH is a major referral hospital in Cameroon and has both a day-hospital and an inpatient unit. The study period spanned 10 months, from November 1, 2022, to August 31, 2023.

2.2. Study Population

The study population included all adult patients (≥18 years) with a histologically confirmed cancer diagnosis who received at least one cycle of chemotherapy and experienced at least one episode of grade 3 or 4 neutropenia during the study period.

2.3. Exclusion Criteria

- Incomplete medical records.
- Patients taking other neutropenia-inducing medications.
- Patients with myelodysplastic syndromes or active bacterial infections prior to chemotherapy.

We used a consecutive, non-probabilistic, and exhaustive sampling method, meaning all eligible patient episodes identified in the departmental registry during the 10-month study period were included. For the total cohort of eligible patients identified (N = 136), 43 patients were excluded for having incomplete medical records (24 files were not found, and 19 files had missing key data).

2.4. Variables Studied

Data collected covered the following domains:

- Sociodemographics: Sex, age.
- Clinical: Primary tumor location, cancer stage (based on TNM classification), comorbidities, WHO performance status, Body Mass Index (BMI), circumstances of neutropenia diagnosis, clinical signs (gastrointestinal, general, etc.), neutropenia

grade (according to CTCAE v.5.0), and presence of febrile neutropenia.

- Therapeutic: Chemotherapy protocol, number of cycles, therapeutic actions taken in response to neutropenia (cycle postponement, G-CSF administration, dose reduction, antibiotic therapy, etc.).
- Outcomes: Duration of neutropenia and resolution at follow-up CBC.

2.5. Statistical Analysis

Data were entered and analyzed using SPSS version 21. Continuous variables were described using mean and standard deviation, while categorical variables were described using percentages. Chi-squared tests and Analysis of Variance (ANOVA) were used to compare frequencies and means, with a significance level set at $p < 0.05$. Results are presented in tables and figures.

2.6. Ethical Considerations

The study protocol was approved by the Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences at the University of Yaoundé I (N°0201/UYI/FMSB/VDRC/DAASR/CSD of the 05/13/2023) and the General Management Department of Yaoundé General Hospital. The confidentiality of all patient data was ensured, and the results were used strictly for scientific purposes.

3. Results

A total of 93 patients were recruited, accounting for 157 episodes of chemotherapy-induced grade 3 and 4 neutropenia.

3.1. Sociodemographic Characteristics

The mean age of patients was 48.42 years ± 12.1 years, with a range of 21 to 72 years (Figure 1). The study population was predominantly female (82%), with a male-to-female ratio of 0.2.

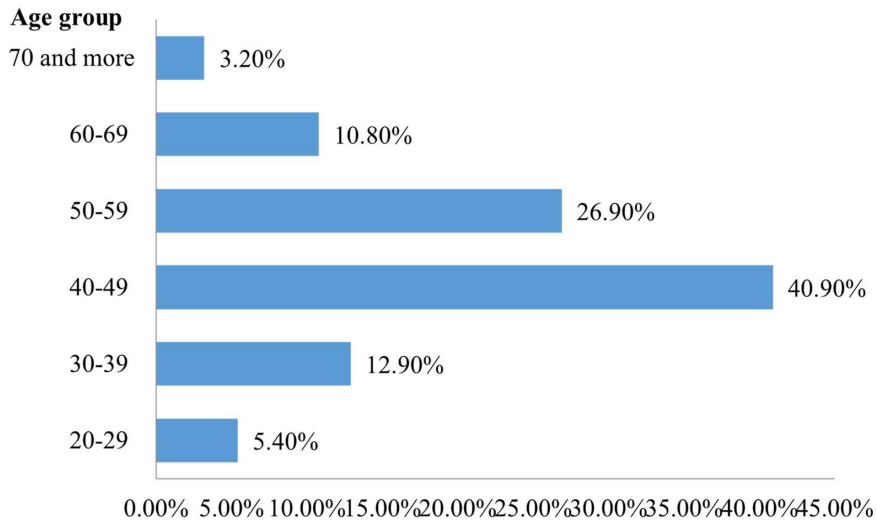

Figure 1. Distribution of patients with grade 3 or 4 neutropenia by age group.

3.2. Clinical Characteristics

Breast cancer was the most common malignancy (53.8%), followed by cancers of the hematopoietic system (9.6%) and colon/rectum (8.1%). Regarding disease stage, nearly half of the patients with solid tumors (47.6%) were at a metastatic stage. Among the 9 patients with hematopoietic cancers, 7 had stage IV lymphoma (Table 1).

Table 1. Distribution of patients according to tumor location.

Tumor Location	Location Number of Cases (N = 93)	Percentages (%)
Breast	50	53.8
Hematopoietic system	9	9.6
Colon and rectum	7	8.1
Cavum	4	4.5
Endometrium	4	4.5
Stomach	4	4.5
Cervix	3	3.5
Mouth	3	3.5
Skin	2	3.0
Others	7	8.0

The AC 60 protocol was the most frequent regimen associated with CIN in 54.7% of episodes (Figure 2). The majority of neutropenia episodes (31.9%) occurred after the first chemotherapy cycle.

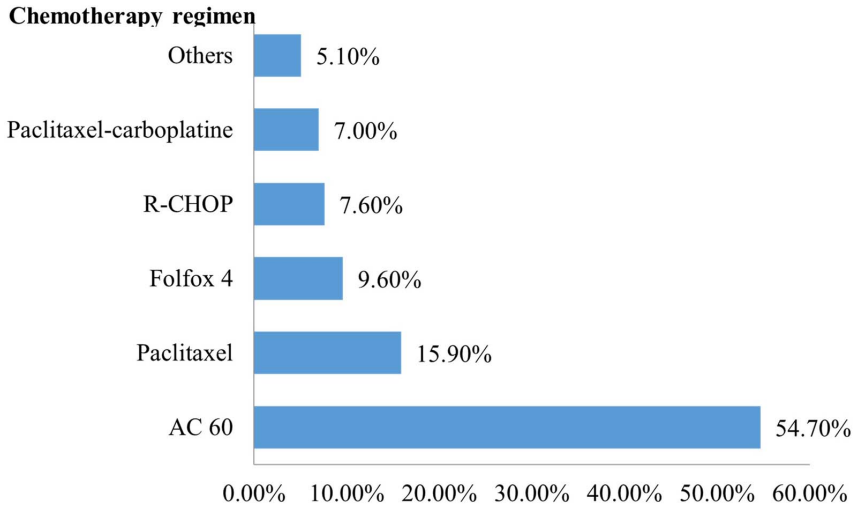

Figure 2. Distribution of patients with grade 3 and 4 chemotherapy-induced neutropenia according to the chemotherapy protocol received.

The most common comorbidities were alcohol consumption (35.5%) and hypertension (23.7%).

The neutropenia diagnosis was an incidental finding on a routine CBC before the next cycle in 59.2% of cases. When symptoms were present, gastrointestinal signs (nausea, vomiting, diarrhea) were the most frequent (43.7% of episodes).

Most patients had a good general condition, with a WHO performance status of 1 in 80% of cases. Furthermore, 51.1% of patients had a normal BMI.

The majority of neutropenia episodes were Grade 3 (76.4%), and isolated neutropenia was the most common finding on the CBC (79%). Seven patients (7.5% of the 93 included patients) developed febrile neutropenia. This represented 4.5% of the total 157 neutropenia episodes recorded.

3.3. Therapeutic Characteristics

A chemotherapy cycle postponement was implemented in 100% of cases of grade 3 and 4 neutropenia. Filgrastim was administered in 24.2% of cases. Empiric antibiotic therapy was used in 17 patients, and a chemotherapy dose reduction was performed in 2 patients (Table 2).

Table 2. Distribution of patients according to therapeutic approach.

Therapeutic Approach	Number of Patients (N = 157)	Percentages (%)
Chemotherapy deferral	157	100.0
Filgrastim administration	38	24.2
Probabilistic antibiotic therapy	17	10.8
Chemotherapy dose reduction	2	1.3
Antifungals	1	0.6
Antimalarials	6	3.8

3.4. Outcome of Neutropenia

In 86% of episodes, the neutropenia had resolved at the 7-day follow-up CBC.

4. Discussion

This study characterized the sociodemographic, clinical, therapeutic, and evolutionary profiles of patients with CIN at the Yaoundé General Hospital.

The mean age of 48.42 years is consistent with data from other studies [17], reflecting that cancer patients are often in the 35-49 age group. The strong female predominance (82%) is explained by the high prevalence of breast cancer, which accounted for 53.8% of cases in our cohort, in line with national data from Globocan 2020 [18].

The metastatic stage, found in 50.5% of patients, is also similar to findings from other sub-Saharan African studies [19] [20], reflecting a pattern of late diagnosis.

The involvement of the AC 60 protocol in the majority of CIN cases (54.7%) is consistent with prior research [21] [22]. This regimen, combining anthracyclines and alkylating agents, is known for its high myelosuppressive potential [23].

The incidental diagnosis of neutropenia (59.2%) highlights the importance of routine hematological monitoring. When present, clinical signs were primarily gastrointestinal, which differs from some studies reporting a predominance of respiratory or cutaneous signs [24] [25]. This discrepancy might be due to differences in study populations, particularly those focused on febrile neutropenia in more severely ill patients.

A WHO performance status of 1 in 80% of patients is a crucial finding, as a good initial general condition is generally considered a protective factor against severe complications [26] [27]. It is also noteworthy that the majority of patients had a normal BMI, although obesity is often cited as a risk factor [28]. However, ASCO guidelines do not establish a direct link between obesity and increased myelosuppression [29].

The systematic postponement of chemotherapy in 100% of cases of grade 3 and 4 CIN is a common practice, but can be detrimental to treatment efficacy. Delays can promote tumor resistance and negatively impact long-term outcomes [9]. This high rate of treatment deferral stands in stark contrast to the low rate of filgrastim use (24.2%), which was not observed in other countries like Ethiopia [30]. The inability to systematically administer G-CSFs for prophylaxis or treatment forces clinicians to delay treatment to allow for hematological recovery, which ultimately compromises the optimal delivery and intensity of the therapeutic regimen. This low rate could be linked to financial constraints and limited access to G-CSFs, which pose a major barrier in this context. In this resource-limited setting, G-CSFs (Filgrastim/Pegfilgrastim) are typically an out-of-pocket expense for the patient, as they are generally not covered or are only partially covered by local or national health insurance schemes, making them prohibitive for many patients.

The favorable outcome, with 86% of episodes resolving within 7 days, is encouraging. However, the lack of daily CBC monitoring made it impossible to precisely evaluate the duration of neutropenia, a limitation that reflects the logistical and financial challenges of resource-limited settings.

5. Study Limitations

The main limitation of this study is its retrospective nature, which introduced a selection bias due to incomplete medical records and difficulties in standardizing data collection. The small sample size also limits the generalizability of our findings.

6. Conclusions

Chemotherapy-induced grade 3 and 4 neutropenia remains a significant complication in cancer patients at the Yaoundé General Hospital, frequently leading to systemic chemotherapy deferral (100% of episodes) and suboptimal utilization of Granulocyte Colony-Stimulating Factors (24.2%). The high prevalence of breast cancer, the predominant use of the myelosuppressive AC 60 protocol, and the late diagnosis stage of cancer contribute to this complication burden.

These findings highlight the critical importance of improving the management of CIN to ensure the maintenance of treatment intensity and efficacy. To this end, we recommend developing and implementing local risk-assessment protocols for the systematic use of prophylactic G-CSFs in patients receiving high-risk chemotherapy regimens (like AC 60) or presenting with patient-specific risk factors and advocating for the inclusion of G-CSFs in essential oncology medication lists with

subsidies or full coverage by national health schemes to remove the primary financial barrier to access.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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