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Profile of Chemotherapy-Indused-Severe Neutropenia and Associated Risk Factors among Cancer Patients at the Yaounde General Hospital

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Abstract*— *Background: *Neutropenia is a spontaneous complication of chemotherapy. When severe, it is significantly associated with important infectious diseases that increase morbidity, mortality and the cost of management.*
Objective*: determine the prevalence, incidence, frequency of severe neutropenia in cancer patients treated with chemotherapy and associated risk factors.* ***Materials and Methods****: This was a prospective and descriptive study conducted at the Yaounde General Hospital from January 2016 to December 2017. Neutrophil levels in blood were evaluated before and during chemotherapy treatment. These values were compared to the risk of severe neutropenia in the various subgroups of patients. Statistical analyses were performed using EPI software*. ***Results****: Two hundred and seventy-six patients were recruited, 54 were excluded. There were 594 cycles of chemotherapy treatment, ranging from 1 to 4 cycles, with an average of 2.6 cycles per patient. The prevalence of neutropenia before treatment was 19.56% with 0% severe neutropenia. The incidence of neutropenia during treatment was 25% with 22.34% of severe neutropenia (G3 = 16.30%; G4 = 6.04%). The overall frequency of neutropenia was 44.5%, we observed an association between severe neutropenia and lymphocyte count < 1000/mm^3 (p value < 0.01), female sex (P = 0.04), chemotherapy (p = 0.01). Lymphopenia was the only independent risk factor (OR: 5.14, CI: 2.34 – 8.24).* ***Conclusion****: we suggest that lymphopenia < 1000/mm^3 as well as Neutropenia <1000/mm^3 should be used as a threshold value below which chemotherapy should be contraindicated.*

Key words*: Chemotherapy, severe neutropenia, incidence, prevalence, risk factor*.

I. INTRODUCTION

Cytotoxic chemotherapy is currently used for the management of multiple cancers. The non-specificity of these drugs used is responsible for the destruction of normal cells in the body. This cytotoxicity is mainly hematological and particularly affects cells of the granulocyte lineage leading to neutropenia [1,3].

Neutropenia is a decrease in the blood level of neutrophils (PNN) below 1500 cells / mm^3 of blood [4]. However, according to the WHO, neutropenia can be classified according to the neutrophil count. As a result, normal neutropenia will be grade 0 (≥ 2000 / mm^3); insignificant grade 1 neutropenia (1500 ≤ PNN < 2000 / mm^3); light grade 2 neutropenia (1000 ≤ PNN <1400 / mm^3); severe neutropenia of grade 3 (500 ≤ PNN <1000 / mm^3) and grade 4 (PNN <500

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/ mm^3). Severe neutropenia (Grade 3 and Grade 4) is common and presents significant complications for both the patient and his treatment[1,14]. One of the major consequences is the occurrence of polymicrobial infections that can be life-threatening for patients. As a result, a bacteremia is diagnosed in 20-30% of patients with a PNN of less than 1000 / mm^3. In addition to infections, these neutropenia are the main factor responsible for postponing treatment or reducing the standard dose [5,6] .Therefore, this change in treatment regimen would have a negative impact on the efficacy of chemotherapy [7] and patient survival [8].

The chemotherapy regimen used is the main determinant of neutropenia after chemotherapy [6]. Individual patient characteristics may also increase this risk. This study aimed to determine the prevalence, incidence, frequency of chemotherapy-induced-severe neutropenia and risk factors associated with patients treated for cancer at the Yaoundé General Hospital.

II. Materials and Methods

a. Patients

This study was prospective and descriptive. It took place at the Yaounde General Hospital from January 2016 to December 2017. Ethical approval was obtained from the Institutional Ethics Committee of the Catholic University of Central Africa, number: 2015/0017/CEIRSH/ESS/MIM.

Patients were recruited by a non-probabilistic technique of convenience. They had to fulfill certain inclusion criteria: to be at least 18 years old, to have histologically proven cancer, to give informed consent and to have initiated chemotherapy. Other patients were not included because they had chemotherapy whose duration of a cycle was different from twenty-one days or were under oral chemotherapy, or having a relapsed cancer. Follow-up ended for patients who received: four successive courses of chemotherapy; an injection of growth factors in primary prophylaxis or patients who received a change in the dose of anticancer drugs. Patients who died or were lost to follow-up also came out of this study. The withdrawal of informed consent was an exclusion criterion. The patient's follow-up was one cycle minimum and four maximum. The doses of drugs administered depended on the surface area the patient's body. These patients were grouped four subgroups corresponding to the four cycles of treatment followed.

Socio-demographic information was collected using a questionnaire. Clinical parameters such as cancer types, performance status, comorbidity and types of treatment were considered. Blood count for a complete blood count (CBC) was performed on the starting day of chemotherapy and day 21 post-chemotherapy to assess hemoglobin level, absolute neutrophil count (ANC), total leukocyte count, lymphocyte count. The chemotherapy regimen was assessed at study entry.

b. Clinical criteria for definition

Prevalence of neutropenia was defined as the percentage of patients who had neutropenia prio any treatment i.e. at enrollment. Incidence was defined as the percentage of patients who were neutropenic during treatment. We had four cycles of treatment and each cycle had a percentage of patients who developed toxicity. Hence, the mean of the percentages coming from the allcycles was considered as the incidence. The frequency of neutropenia was defined as the percentage of patients who had this toxicity at birth or during the study. Severe neutropenia was defined as PNN <1000 / mm^3 after three weeks of chemotherapy

c. Statistical analyzes

The risk factors for severe neutropenia were determined in univariate and multivariate analyzes. The software used was Epinfo, version 7.1.3. The relationship between the clinical and laboratory characteristics of patients and the incidence of severe neutropenia was obtained using the Fisher and Pearson test. The variables tested were: sex, age> 60, type of cancer, stage of cancer, presence of comorbidity, status> 1 performance, pre-treatment with chemotherapy and radiotherapy, PNN <1500 mm^3, hemoglobin <12 g/dl, white blood cells <2500 mm^3, lymphocytes <1000 mm^3. All these variables were evaluated taking into account the four cumulative cycles.

Significant variables in univariate analysis were subjected to logistic regression analysis to rule out any confounding factors. It allowed us to define the risk factors independent of NS. P-value less than or equal to 0.05 was considered statistically significant.

III. Results

The population consisted of 276 patients, more than half of the patients (60.36%) were females and the rest (39.64%) were males, with a female to male ratio of 1.52: 1 (Figure 2). The median age was 45 years old with a modal class between [35-50] years old. The youngest patient was 19 years old and the oldest 79 years old.

Of the types of cancer encountered, breast cancer was the most common (46.84%) followed by kaposi sarcoma (20.72%). The other category includes cancer of the cecum, oral cavity, cheek, esophagus tongue, bones, pancreas, skin, nasopharynx, uterus and eyes (Figure 3).

Seventeen associations of drugs in all were used. The first three were respectively AC, ABV and FAC. The other drug combinations were represented by: 5-FU; Navelbine, Carboplatin; Docetaxel, Docetaxel; Carboplatin, Docetaxel; 5-Fu, Doxorubicin; Docetaxel, Methotrexate; 5_Fu, Oxaplatin; Vepeside, Cypsplatinie (Table 1).

The frequency of patients was different depending on the chemotherapy cycle with a mean of 2.6 per patient out of a total of 594 cycles followed (Table 2)

The prevalence of neutropenia was 19.56% with 0% of severe neutropenia (Figure 1). At the beginning of each cycle, there is a presence of mild neutropenia (Grade 2). (Figure 4). However, twenty-one days after chemotherapy, grades 3 and 4 occur that are high grade neutropenia or severe neutropenia (Figure 5). Thus, of the 594 treatment cycles followed, an overall severe toxicity rate showed that 97 cycles (16.30% or 37 patients) were induced at grade 3 toxicity and 36 cycles (6.04% or 13 patients) at grade toxicity 4 (Figure 6). Incidence of neutropenia during treatment was 25%, with 22.34% of

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severe neutropenia (Figure 5). Frequency of neutropenia was 44.56%.

This study shows that there is no significant correlation between chemotherapy cycle and NS occurrence after chemotherapy. No cycle is more at risk than others (Table 2). However, the relationship between biological data and severe neutropenia showed that there is a significant association between blood levels of PNN (<1500 / mm^3, p <0.01) lymphocytes (<1000 / mm^3, P = 0.01). Similarly, there is a relationship between the type of protocol and the NS showed that there was an association between chemotherapy (p = 0.01). The only sociodemographic variable associated with severe neutropenia was sex (p = 0.04). These variables were taken for the 594 cycles of chemotherapy regardless of cycles (Table 3). After multianalysis we found lymphopenia as the only independent risk factor (OR: 5.14, CI: 2.34 – 8.24).

IV. Discussion

Neutropenia is a major risk factor for infections [9]. It may also be responsible for modifying the patient's regimens that may affect the effectiveness of chemotherapy [10]. As its effects are proportional and severe, NS are those that pose a risk of complications [1]. It was therefore a question for us in this study to determine the profile of NS in patients treated with cancer chemotherapy at the Yaoundé General Hospital.

We recruited 276 patients, of whom 222 were followed for one to four cycles of chemotherapy, i.e. 594 cycles in total with an average of 2.6 cycles per patient. Our results show that the frequency of NS was 44.56% for the 594 Cycles performed. We also had a prevalence of 19.56% with 0% NS. An incidence of 25% among which 22.34% severe neutropenia (16.49% for Grade 3 and 6.06% for Grade 4). This overall neutropenia was calculated taking into account the occurrence of NS at each chemotherapy cycle. Our results are similar to those of Won Choi et al., In 2003, who obtained 18% of NS in patients after a first course of chemotherapy [11]. However, they are different from those obtained in a study that was working on breast cancer patients. In fact, they obtained 65.5% and 49.3% of NS (respectively for grades 3 and 4) with the docetaxel, Doxorubicin, Cyclophosphamide and 5-Fuorouracil, Doxorubicin and Cyclophosphamide protocols [12] . These differences may be explained by the fact that the protocols used in the Martin et al. Study were high risk and intermediate risk protocols for deep neutropenia while in our study and that of Won Choi et al. this proportion has been obtained for all chemotherapy protocols whether they have high potential or not. Subsequent studies, taking into account a limited number of protocols, can be used to define the toxic potential of each entity.

Our results also show a non-significant variation in NS proportions as a function of the treatment cycle. It was 22.53% for C1; 21.96% for C2; 27.11% for C3 and 17.78% for C4. In contrast to Crawford, the proportion of grade 4 neutropenia was higher in the first cycle compared to the others [6]. This difference may be due to the fact that in crawford et al., The study population was homogeneous with only one type of cancer (small cell lung cancer) and was receiving concomitant intensive radio chemotherapy.

Taking into account the biological parameters at day 0 our results show a possible link between a level of PNN <1500 / mm^3 (P <0.001), lymphocytes <1000 / mm^3 (P = 0.01) and the risk of NHG with univariate analysis. This risk has been confirmed with multivariate analysis. Therefore, these are risk factors independent of NS after chemotherapy. Other parameters were not significant (GB, p = 0.98, hemoglobin, p = 0.18). These results are similar to those of Choi et al., 2003 who found early lymphopenia as a risk factor for chemically induced neutropenia.

Female gender that was significant in univariate analysis was not significant in multivariate analysis. Patients who had neutropenia or lymphopenia before chemotherapy had to be mostly women.

A PNN = 1500 / mm^3 is the minimum limit for allowing chemotherapy. It is ≤ a grade 2 neutropenia. Since chemotherapy can reduce the production of this cell population via the destruction of the marrow, it is logical that the patient develops a deeper neutropenia.

A lymphocyte count <1000 / mm^3 (P = 0.01) would increase the risk of NS at HGY. The implication of lymphocytes for the occurrence of neutropenia is that they may play a role in the restoration of normal hematopoiesis after cytotoxic chemotherapy. In fact, the decrease in lymphocyte levels leads to a reduction in the production of cytokines, this reduction may interfere with normal hematopoiesis after chemotherapy [11]. Similar results were found in three population groups who received chemotherapy. Lymphopenia at the 700 / mm^3 threshold was an independent risk factor for NS. Lymphopenia on days D1 and D5 was implicated. In group 1, J1 lymphopenia was associated with risk of NF (P = 0.05); J5 data were not available. In group 2, only J1 lymphopenia was associated (P = 0.004) and for group 3 only J5 (P <001) [13]. Note that the only criterion for differentiating these groups was the place of treatment. The results obtained in our study and that of Ray Indicate that lymphopenia is involved in the occurrence of chemically induced neutropenia. Moreover, the day of its realization would also be a factor to consider. Further research should be done to clarify this role and specially to determine the most favorable day for the exploitation of this biological data. The discovery of a positive result may make lymphopenia a marker of severe neutropenia in patients treated with chemotherapy for cancer.

V. Conclusion

The purpose of this study was to determine the profile of severe neutropenia at the Yaoundé General Hospital. This study was conducted for a period of 10 months during which 276 patients were enrolled, of whom 222 were included. The female sex was dominant with 60% against 40% for the men. 297 treatment sessions were performed in total. It shows that: 22, 55% (64/297) of severe neutropenia was induced by chemotherapy. However, this severe neutropenia was not dependent on a particular cycle. In addition, lymphopenia <1000 / mm^3 was determined as an independent risk factor for NS. Therefore, Lymphopenia <1000 / mm^3 as well as Neutropenia <1000 / mm^3 should be considered as a threshold

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value below which chemotherapy is contraindicated. This will help reduce the proportion of severe neutropenia in oncology.

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Conflicts of interest: There are no conflicts of interest.

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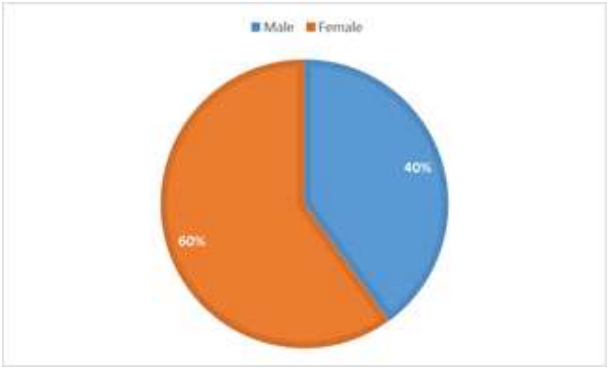


Figure 1: representation of study population according to sex

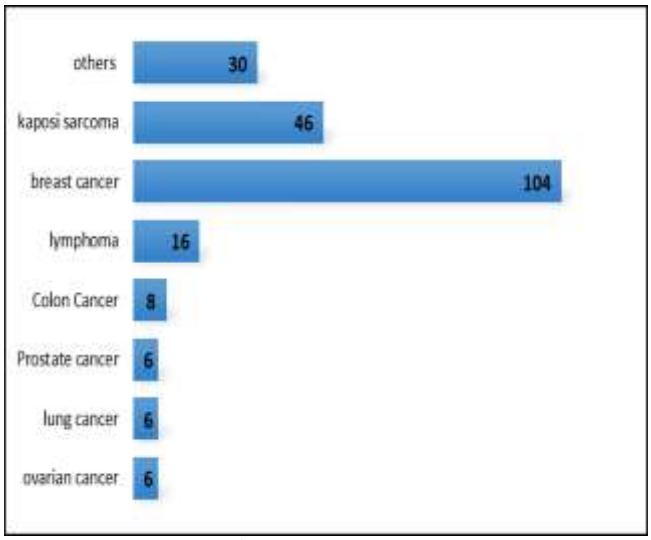
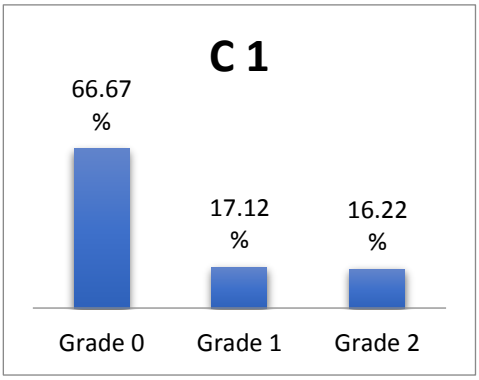
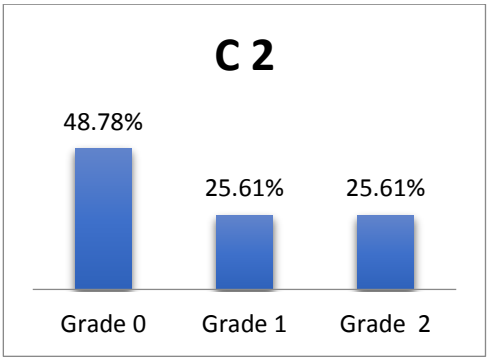
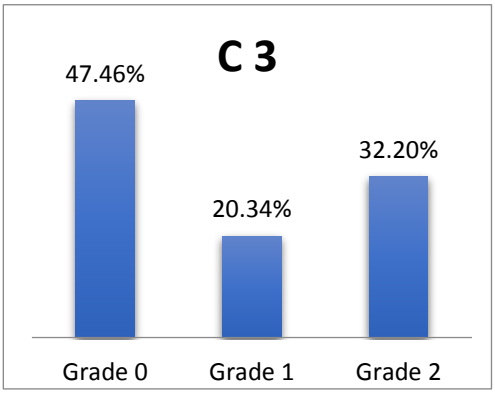


Figure 2: representation of study population according to types of cancer







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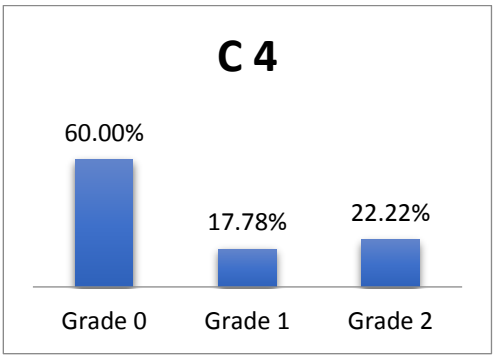


Figure 4: distribution of neutrophil level variation prior chemotherapy

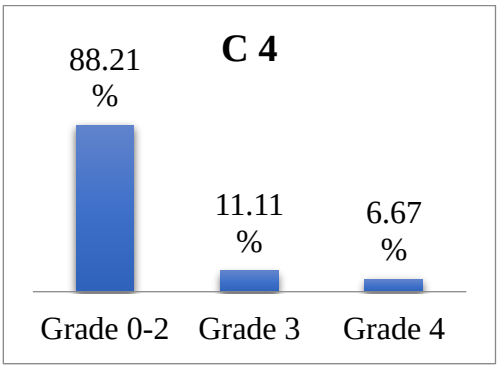
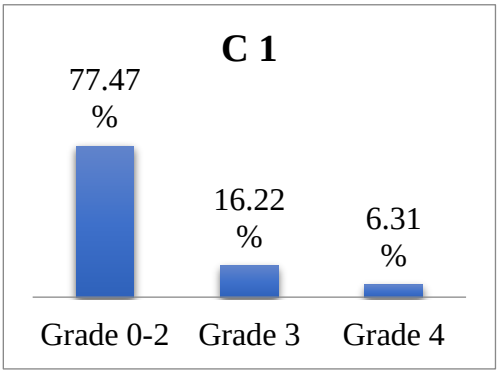
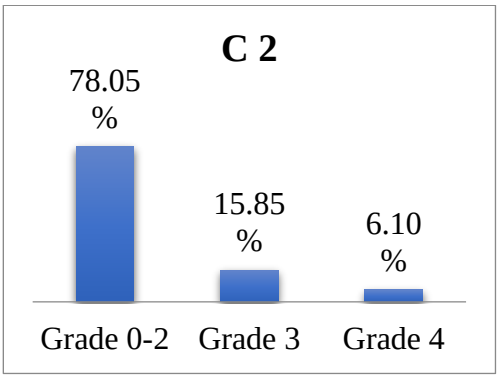
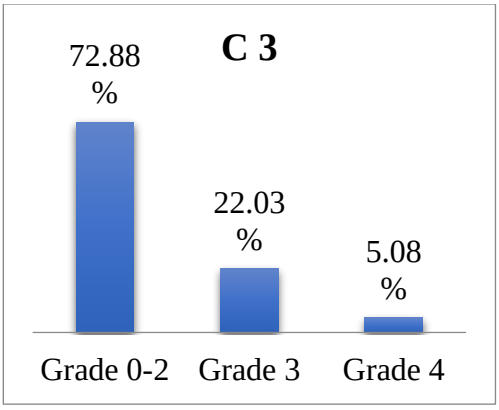


Figure 5: distribution of neutrophil level after chemotherapy

Legends : C1, C2, C3, C4 represent cycle 1, 2, 3,4 respectivement







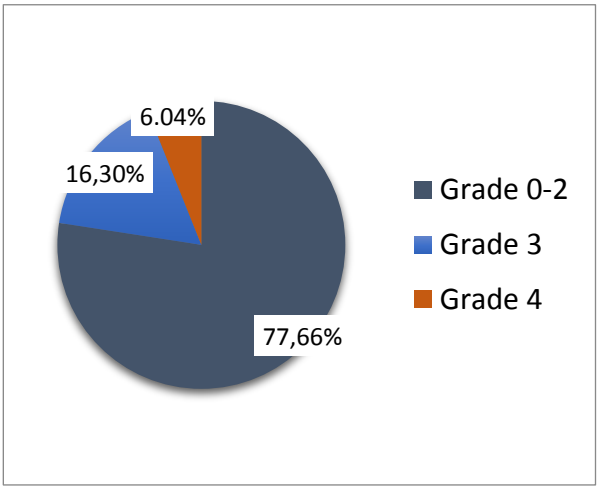


Fig 6: frequencies of cytotoxicities

Table 1 distribution of drugs association used

Drugs association	Frequency
5-FU	6(2, 70%)
5-FU,Doxorubicine, Cyclophosphamide (FAC)	34(15,32%)
Cisplatine, Doxorubicine	26(11, 71%)
Docetaxel	12(5, 41%)
Doxorubicine, Cyclophosphamide (AC)	64(28, 83%)
Doxorubicine, Cyclophosphamide, Vincristine	18(8, 11%)
Doxorubicine, Vincristine, Bléomycine (ABV)	42(18, 92%)
Others	20(9.0%)

Others: 5-FU; Navelbine, Carboplatin; Docetaxel, Docetaxel; Carboplatin, Docetaxel; 5-Fu, Doxorubicin; Docetaxel, Methotrexate; 5_Fu, Oxaplatin; Vepeside, Cypsplatinie

Table 2: relation between cycle of chemotherapy and neutropenia.

	GRADE 3 – 4		
	Oui	Non	p.value
Cycle 1			
Yes	50	172	0 .97
No	84	286	
Cycle 2			
Yes	36	128	0,87
No	98	332	
Cycle 3			
Yes	23	86	0,34
No	102	374	
Cycle 4			
Yes	16	74	0 ,40
No	118	386	

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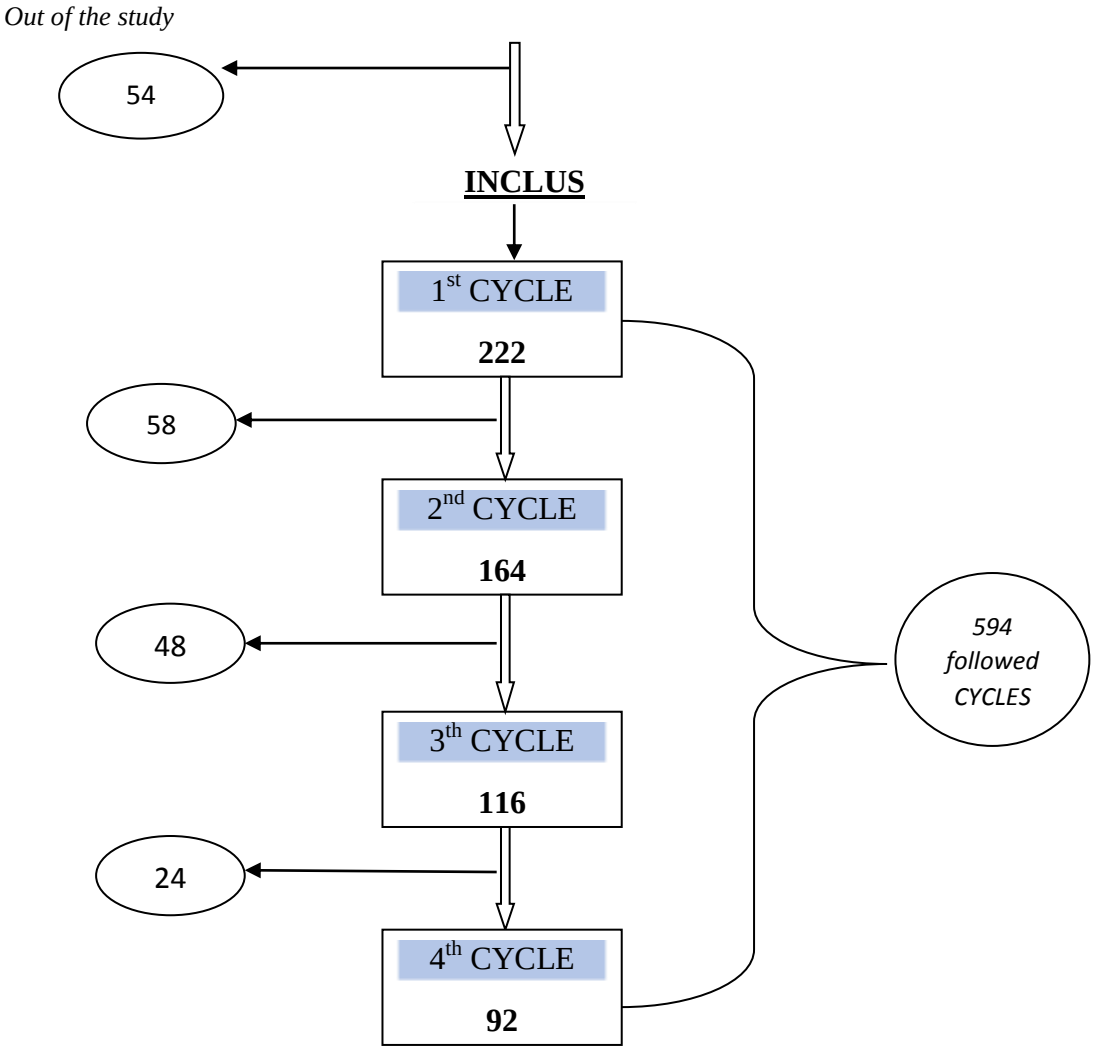

Figure 1**:** Synoptic representation of patient follow-up

Table 3: relation between study variables and severe neutropenia

Variables		Severe neutropenia		P.value
		Yes	No	
Age	> 60	42	144	0.64
	≤ 60	8	28	
Sex	Female	30	104	**0.04**
	Male	20	68	
Comorbidity	Yes	6	8	0.41
	No	44	164	
PS	>1	11	16	**0.01**
	1≤	5	190	
Chemotherapy	Yes	50	6	**0.01**
	No	0	54	
Radiotherapy	Yes	0	8	**0.2**
	No	50	164	
According to the whole number of chemotherapy's cycle				
PNN	< 1500	60	82	0,01
	≥ 1500	74	378	
Hemoglobin	< 12	90	262	0,29
	≥ 12	46	196	
Leucocytes	< 2500	4	14	0,20
	≥ 2500	130	446	
Lymphocytes	≥ 1000	20	28	**0,01**
	≥ 1000	114	432	

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