Original Article

# Chemotherapy-induced Neutropenia after Initial and Subsequent Chemotherapy Cycle of Non-Hodgkin Lymphoma

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## Abstract

**Background:** Cytotoxic drugs often suppress the bone marrow's ability to produce white blood cells which lead to the induction of neutropenia and the risk of febrile neutropenia. Chemotherapy-induced neutropenia (CIN) is major dose-limiting toxicity of systemic chemotherapy and it is associated with significant morbidity and mortality. **Objective:** Evaluating frequency and severity of CIN after initial and subsequent chemotherapy cycles among non-Hodgkin lymphoma (NHL) children undergoing similar chemotherapy regimens. **Patients and Methods:** A prospective study performed in the Oncology Department of Child Central Teaching Hospital/Baghdad, between August 1, 2012, and January 31, 2014, which included (59) patients <15 years, with newly diagnosed NHL who received similar chemotherapy regimens of NHL. All patients were evaluated for the incidence of neutropenia after the initial or subsequent course of chemotherapy to compare between CIN after first and subsequent chemotherapy cycles of similar regimens, that is,: COPADM1 versus COPADM2 and COPADM3, "COPADM" regimen includes the following drugs (C: Cyclophosphamide, O: Oncovine, P: Prednisone, AD: Adriamycine, and M: Methotrexate), each chemotherapy cycle was received every 21-day interval. **Results:** Of a total 59 patients with NHL,55.9% of them were male and 44.1% were female, who received initial (COPADM1) and subsequent (COPADM 2 and COPADM 3) chemotherapy cycles of NHL, there is a significant increment in the risk of CIN after initial cycle "COPADM1" in comparison to other subsequent cycles of COPADM2 and COPADM3, "$P = 0.01$." The patient characteristics (age group and gender) had no significant effect on the risk of CIN, there is a higher percent of severe neutropenia and hospitalization with parenteral antibiotic use after the first COPADM cycle in comparison with subsequent cycles but statistically not significant ($P = 0.6$ and 0.1, respectively). **Conclusion:** Frequency of CIN after the first chemotherapy cycle had significantly higher than subsequent cycles, with lesser extent to neutropenic severity and neutropenia-related hospitalization.

**Keywords:** Chemotherapy cycle, chemotherapy-induced neutropenia, childhood cancer, non-Hodgkin lymphoma

## Introduction

In the United States, an arbitrarily adopted standard of the ages used for cancer in children are 0–14 years. However, childhood cancer sometimes includes young adults between the age of 15 and 19 years.[1] Leukemia considers as the most common cancer in children and adolescents and accounts about 34%;[2] the brain and central nervous system tumors are the second most common cancer in children after acute lymphoblastic leukemia, followed by neuroblastoma and non-Hodgkin lymphoma (NHL).[3-5] NHL results from malignant proliferation of lymphocytic cells lineage. In children between the age of 5 and 19 years, the NHL accounts for 8%–10% of all malignancies.[6,7] Neutropenia is a significant reduction in the absolute number of neutrophils in the circulation. Severe neutropenia or total absence of circulating neutrophils refers to "agranulocytosis."[8] An absolute neutrophil count (ANC) is calculated from the multiply the total WBCs count by (percent of neutrophils plus percent of bands cells), more than two standard deviations below the normal mean.[9-11] Chemotherapy-induced neutropenia (CIN) is the most serious toxicity of systemic chemotherapy and may be associated with life-threatening complications of chemotherapy.[12]

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### Aim of the study

The aim was to evaluate the frequency and severity of CIN after the initial and subsequent chemotherapy cycles among NHL children who received the same chemotherapy regimens.

## Patients and Methods

A prospective study performed in the Oncology Department of Child Central Teaching Hospital/Baghdad, between August 1, 2012, and January 31, 2014, that included patients <15 years of age, with newly diagnosed NHL who were received chemotherapy regimens for NHL (United Kingdom Children Cancer Study Group Lymphoma Malign B (UKCCSG LMB) NHL protocols which are guidelines for the treatment of B-cell NHL based on the results of the FABLMB 96 study).[13] Patients were not eligible for the study included (NHL patients with bone marrow (BM) involvement and patients who were clinically deteriorated during or immediately after the course of chemotherapy due to a recent infection, bleeding, tumor lysis syndrome, or other causes). Of a total of 60 patients with NHL, one patient died before starting chemotherapy due to tumor lysis syndrome, the remaining 59 patients were included in the study and underwent analysis of the study. All 59 NHL patients received 100% of conventional-dose chemotherapy of the same chemotherapy regimen for NHL (UKCCSG LMB, NHL protocol) that included the chemotherapy courses, COPADM1, COPADM2, Cytosar and Methotrexate [CYM1]), CYM2, and COPADM3. Each chemotherapy cycle was received every 21 days, the time from the start of chemotherapy until the day before the start of the next cycle refers to one chemotherapy cycle; neutropenia is defined as ANC <1000/mm$^3$, (moderate neutropenia if 1000 < ANC>=500, severe neutropenia if ANC <500).[10] All patients after received initial or subsequent course of chemotherapy were sent for complete blood count to detect ANC during a period between the last and next chemotherapy cycle, The data were collected from the patients, included name, age, gender, body weight, and surface area, result of BM examination, prechemotherapy ANC, type of chemotherapy regimen, sequence of cycle (initial or subsequent), postchemotherapy ANC (normal ANC, neutropenia, and febrile neutropenia), degree of neutropenia (moderate and severe), hospitalization requirement, and parenteral antibiotic use. In this study, we compared between CIN after first and subsequent chemotherapy cycles of similar regimens, that is,: COPADM1 versus COPADM2 and COPADM3, but we did not compare with other subsequent chemotherapy cycles of different regimens for NHL like "CYM" regimen. NOTE: All participate patients did not receive prophylaxis of granulocyte-colony stimulating factor (G-CSF) for the prevention of CIN.

### Statistical analysis

Statistical analysis estimation was based on a *P* value that is estimated by using (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) program, included A word processing, Database and statistics program for public health to estimated P value for each comparison groups. A significance level of *p*-value if it's less than 0.05).

## Results

Of a total 59 patients with NHL, 33 (55.9%) of them were male and 26 (44.1%) female, all were received initial chemotherapy cycle of COPADM 1, one of them died after the complete course of COPADM 1, the remaining (58) continued in the analysis of the study and received subsequent chemotherapy cycles, Table 1 shows demographic criteria of the patients.

There is a significant increment in the risk of CIN after the initial cycle of COPADM "COPADM1" in comparison to other subsequent cycles (COPADM2 and COPADM3), $P = 0.01$, [Table 2].

The age and gender had no significant effect on the frequency of CIN after chemotherapy regimens of NHL [Tables 3 and 4].

In general, the frequency of severe neutropenia is more than moderate neutropenia after both first and subsequent cycles with still lower mean severity of neutropenia and higher percent of severe neutropenia after the first COPADM cycle than subsequent cycles, but statistically no significant difference ($P = 0.06$) [Table 5].

The frequency of hospitalization and parenteral antibiotic use of NHL patients due to CIN was higher after COPADM1 than COPADM2 and COPADM3, but statistically no significant ($P = 0.1$) [Table 6].

## Discussion

Many myelosuppressive chemotherapy regimens are a risk for febrile neutropenia. In this study, we assessed the effectiveness of therapy phases (early and subsequent chemotherapy cycles) on the frequency of CIN, severity, hospitalization, and anti-infective requirement.

The present study confirms that generally, the frequency of CIN among patients who received different chemotherapy cycles

**Table 1: Demographic distribution of patients with non-Hodgkin lymphoma included in the study**

| Chemotherapy cycles | Total number | Age (years) (range) | Age (years), mean±SD | Gender (male/female), *n* (%) |
|---|---|---|---|---|
| COPADM1 | 59 | 1.5-10 | 5.25±1.9 | 33 (55.9)/26 (44.1) |
| COPADM2 | 58 | 2.58-10 | 5.5±1.8 | 32 (55.2)/26 (44.8) |
| COPADM3 | 58 | 2.58-10 | 5.5±1.8 | 32 (55.2)/26 (44.8) |

SD: Standard deviation

was high, with significant increment in the risk of neutropenia after "COPADM1" (first cycle) in comparison with subsequent cycle ($P = 0.01$). This reduction in risk of CIN after subsequent cycles could be related to more supportive care and patient's tolerance in subsequent chemotherapy phases, in addition to that all patents with NHL usually receive ( Cyclophosphamide Oncovine Prednisone [COP] reduction) chemotherapy cycle before COPADM1, which may be another cause of increase percent of CIN after COPADM1.

**Table 2: Frequency of neutropenia after initial and subsequent chemotherapy cycles of non-Hodgkin lymphoma patients**

| Chemotherapy cycles | *n* | Number of neutropenic patients, *n* (%) | *P* |
|---|---|---|---|
| COPADM1 | 59 | 42 (71.2) | 0.01 |
| COPADM2 | 58 | 31 (53.5) | |
| COPADM3 | 58 | 28 (48.3) | |

**Table 3: Frequency of chemotherapy-induced neutropenia in relation to age groups**

| Chemotherapy cycles | Variables | Number of neutropenic patients, *n* (%) | *P* |
|---|---|---|---|
| COPADM1 | Age groups (years) | | |
| | ≤5 | 20/27 (74) | 0.65 |
| | >5 | 22/32 (68.75) | |
| COPADM2 | Age groups (years) | | |
| | ≤5 | 14/26 (53.8) | 1 |
| | >5 | 17/32 (53) | |
| COPADM3 | Age groups (years) | | |
| | ≤5 | 13/26 (50) | 0.80 |
| | >5 | 15/32 (46.9) | |

**Table 4: Frequency of chemotherapy-induced neutropenia in relation to gender**

| Chemotherapy cycles | Variables | Number of neutropenic patients, *n* (%) | *P* |
|---|---|---|---|
| COPADM1 | Gender | | |
| | Male | 23/33 (69.7) | 0.77 |
| | Female | 19/26 (73) | |
| COPADM2 | Gender | | |
| | Male | 18/32 (56.3) | 0.63 |
| | Female | 13/26 (50) | |
| COPADM3 | Gender | | |
| | Male | 16/32 (50) | 0.77 |
| | Female | 12/26 (46) | |

A retrospective analysis by Lyman *et al*.[14] of data on 577 patients with non-Hodgkin's lymphoma found that 62% of the initial occurrences of febrile neutropenia were in the first cycle. Another study for Lyman *et al*.[15] who reviewed CIN in patients with NHL and other malignancies and showed that the risk of febrile neutropenia was more after the first cycle than subsequent cycles. The studies by Chan *et al*.[16] and Martín *et al*.[17] were consistent with the current study and reported that the initial chemotherapy cycle associated with more risk of febrile neutropenia. Furthermore, Vogel *et al*.[18] found that the frequency of febrile neutropenia more after initial chemotherapy cycle compared with subsequent cycles (11% for cycles 1 while 2%, 2%, and 1% for cycles 2, 3, and 4, respectively), and (67%) of all febrile neutropenic events occurred in the first chemotherapy cycle.

In the current study, there is no significant association between patient characteristics (age group and gender) and risk of CIN after different phases of chemotherapy cycles; Badr *et al*.[19] reported that no significant correlation between ANC and any of the patient-specific characteristics, such as age ($P = 0.16$) and genders (male vs. female, $216.3 \pm 140.3$ vs. $234.5 \pm 114.8$, respectively; $P = 0.47$).

This study found the lower mean severity of neutropenia and a higher percent of severe neutropenia was after the first chemotherapy cycle "COPADM1" than subsequent cycles.

Bastion *et al*.[20] assessed the incidence of severe neutropenia after chemotherapy in NHL patients and reported that 43%–68% of all with severe neutropenia were in the first cycle. Crawford *et al*.[21] found that the incidence of severe neutropenia (ANC < 500/mm$^3$) in cycle 1 was 96% versus 77% for overall cycles.

The present study found that (64.3%) of neutropenic patients required hospitalization after the first cycle which was higher percent than subsequent cycles.

The higher percent of CIN and its severity after the first chemotherapy cycles "COPADM1" could be the reason for increased percent of neutropenia-related hospitalization and

**Table 5: The severity of neutropenia after initial and subsequent chemotherapy cycles of non-Hodgkin lymphoma patients**

| Chemotherapy cycles | Number of neutropenic patient | ANC of neutropenic patients, mean±SD | Severity of neutropenia (moderate 500-<1000; severe <500) | *n* (%) |
|---|---|---|---|---|
| COPADM1 | 42 | 262.8±170.1 | 500-<1000 | 9/42 (21.4) |
| | | | <500 | 33/42 (78.6) |
| COPADM2 | 31 | 302.3±183.6 | 500-<1000 | 12/31 (38.7) |
| | | | <500 | 19/31 (61.3) |
| COPADM3 | 28 | 345±127.1 | 500-<1000 | 11/28 (39.3) |
| | | | <500 | 17/28 (60.7) |

*P*=0.06. SD: Standard deviation, ANC: Absolute neutrophil count

**Table 6: Frequency of neutropenia-related hospitalization and antibiotic use after initial and subsequent chemotherapy cycles of non-Hodgkin lymphoma patients**

| Chemotherapy cycles | Number of neutropenic patients | Number of hospitalized patients and antibiotic use, *n* (%) | *P* |
|---|---|---|---|
| COPADM1 | 42 | 27 (64.3) | 0.1 |
| COPADM2 | 31 | 17 (54.8) | |
| COPADM3 | 28 | 13 (46.5) | |

intravenous antibiotic use after this first chemotherapy cycle COPADM1 compared with subsequent chemotherapy cycles.

Vogel *et al*.[18] found that 9% of febrile neutropenic patients after the initial cycle required hospitalization versus to subsequent cycles, the hospitalization requirements were 2%, 3%, and 1% for cycles 2, 3, and 4, respectively, also they are reported that the frequency of the use intravenous anti-infective was less in subsequent compared with the initial cycle (6% for cycle 1 vs. 2%, 2%, and 1% for cycles 2, 3, and 4, respectively).

## Conclusion

Frequency of CIN after the initial chemotherapy cycle is significantly higher than subsequent cycles, with lesser extent to neutropenic severity and neutropenia-related hospitalization.

### Recommendation

Encourage the use of supportive care measures including the routine use of G-CSF, especially after the initial chemotherapy cycle can reduce the frequency of neutropenia and its complications.

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### Conflicts of interest

There are no conflicts of interest.

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