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## Impact of targeted treatment in non-Hodgkin's lymphoma with primary lymph node involvement

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### Abstract

**Background:** Non-Hodgkin's lymphomas (NHL) are malignant tumors that develop from lymphoid tissue. Primary lymph node (LN) involvement is the most common localization (52-70%). The integration of Rituximab (R) in the NHL treatment represented a turning point. The aim of this study was to evaluate the therapeutic impact of the use of R in combination with conventional polychemotherapeutic (PChT) in the treatment of nodal onset NHL.

**Material and methods:** A descriptive cohort study was performed on 80 patients diagnosed with NHL.

**Results:** In the study participated: men – 39(48.8%), women – 41(51.2%). The mean age of the patients was  $56.09 \pm 13.6$  years. The onset of NHL occurred in peripheral l/n in 85.0% of cases, in mediastinal LN – 7.5%, and abdominals in 7.5%. Stages I-II were identified in 21(26.2%) patients, stages III-IV in 59(73.8%) cases. Aggressive NHLs were diagnosed in 54(67.5%) patients, indolent NHLs in 26(32.5%) cases. In 61(76.3%) patients, first-line R+PChT treatment was applied – group 1(G1), and in 19(23.8%) cases conventional PChT was applied – group 2(G2). The overall response rate (ORR) in G1 was 86.8%, in G2 – 63.1%. Complete remissions (CR) were obtained in G1 in 63.9% of patients, in G2 – 47.3% of cases. Progression-free survival (PFS) in G1 had a median of 20 months, and in G2 the median was 12 months ( $p < 0.05$ ).

**Conclusions:** The use of Rituximab increased the ORR rate (86.8% vs 63.1%), the frequency of CR (63.9% vs 47.3%) and PFS (20 months vs 12 months ( $p < 0.05$ )).

**Key words:** Non-Hodgkin's lymphoma, lymph nodes, treatment.

### Cite this article

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### Introduction

Non-Hodgkin's lymphomas (NHL) are malignant tumors of lymphatic tissue [1, 2]. They are some of the most common malignant hematological disorders having a proportion of 3.1-4.3% of the structure of malignant tumors, being ranked as the 5th to 9th most common cancer in most countries worldwide [3-5]. NHL morbidity in the Republic of Moldova is estimated to be 4.1 cases per 100000 inhabitants [1,6]. NHL can develop at any age group, however NHL morbidity increases with age, with a maximum incidence between 45 and 65 years, thus affecting the working age population [3, 7].

These malignancies arise from the malignant transformation of mature and immature cells of immune system, affecting either B lymphocytes – representing around 86% of all NHL, and a smaller proportion of T- and natural killer (NK) cells – 14% in developing regions [5]. A series of prognostic factors are recognized for the influence of NHL evolution, among them: age, sex, clinical stage, LDH level, etc. NHL prognosis is also influenced by the location of the primary affected area [1, 8].

The onset of NHL can occur in any organ and tissue. More often primary NHL develops in lymph nodes (52-70%). Among other risk factors the progression of NHL is also influenced by the location of the primary affected area.

Rituximab represents a humanized chimeric anti-CD20 monoclonal antibody, that is a powerful tool for treating B-cell malignancies being licensed for the treatment of non-Hodgkin's lymphomas, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, etc. [9]. Direct signaling, complement-mediated cytotoxicity (CMC), and antibody-dependent cellular cytotoxicity (ADCC) all appear to play a major role in rituximab efficacy in association with chemotherapy in treatment of NHL [9, 10].

Since the approval of rituximab, anti-CD20 monoclonal antibodies have revolutionized the treatment of B cell NHL and have become a cornerstone of modern gold standard practice [11, 12].

The aim of the paper is to identify and evaluate the clinical and evolutionary features of non-Hodgkin's lymphomas with primary involvement of peripheral lymph nodes under the influence of chemoimmunotherapeutic treatment with rituximab in combination with conventional chemotherapy.

**Material and methods**

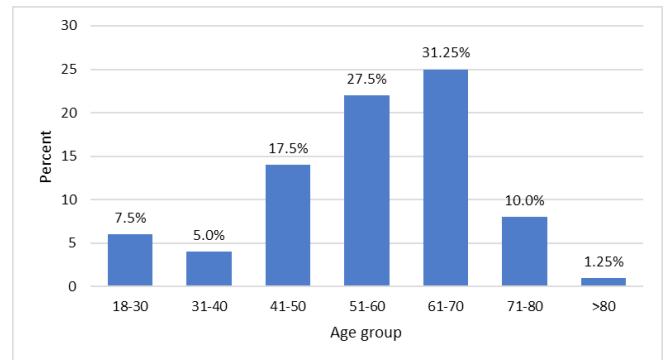
The clinical aspects and the evolution of the disease were studied in 80 patients with NHL with primary lymph node (LN) involvement, aged between 22 and 83 years. The diagnosis was morphologically confirmed by lymph node biopsy. The spreading degree of the tumor process was determined according to the International Clinical Classification adopted in the city of Ann Arbor (USA), in 1971 [13].

For the staging of the tumoral process and determination of the degree of initial expansion of NHL, were used data received from: clinical examinations, imaging and ultrasound investigations, bone marrow aspiration, bone marrow biopsy, endoscopic or radiological research of the gastrointestinal tract (if necessary), fibroepipharyngoscopy (if necessary).

For the statistical analysis of the data, the standard descriptive statistics kit was used through the data analysis of Microsoft EXCEL and on IBM SPSS Statistics 26.0. The use of the standard descriptive statistics kit facilitated the calculation of mean, median and p value. To assess patient survival, the Kaplan-Meier's life-table method of forming survival curves, was used.

**Results**

Out of the 80 patients participating in the study, 39 (48.8%) were men and 41 (51.2%) women. The mean age of the patients was 56.09±13.6 years. The age categories most often affected by NHL in the study group were: age group 61-70 years – 25 patients (31.25%), age group 51-60 years – 22 patients (27.5%) followed by age group 41-50 years – 14 cases (17.5%), (fig. 1).



**Fig. 1. Distribution of patients in the study group according to age categories**

The analysis of the statistical distribution of the study group in correspondence with the area of the LN primary involved showed that more often the NHL onset occurred in: peripheral l/n in 85.0% of cases, in mediastinal LN – 7.5%, and in abdominals LN in 7.5%, (tab.1).

**Table 1. Distribution of patients in the study group according to area of lymph nodes primary involved in the tumoral proliferation**

Area of lymph nodes primarily involved	Patients	Frequency (%)
Peripheral LN	68	85.0
Mediastinal LN	6	7.5
Intrabdominal LN	6	7.5
Total	80	100.0

**Table 2. Distribution of NHL patients with primary lymph node involvement according to the localization of the primary involved area and age category**

Age, years	Count / % within age category	Onset in the area of the lymph nodes						Total
		Cervical	Axillary	Inguinal	Mediastinal	Intra-abdominal	Supraclavicular	
18-30	Count	1	0	0	3	1	1	6
	%	16.7%	0.0%	0.0%	50.0%	16.7%	16.7%	100.0%
31-40	Count	2	1	0	0	0	1	4
	%	50.0%	25.0%	0.0%	0.0%	0.0%	25.0%	100.0%
41-50	Count	8	2	2	0	1	1	14
	%	57.1%	14.3%	14.3%	0.0%	7.1%	7.1%	100.0%
51-60	Count	7	4	3	0	2	6	22
	%	31.8%	18.2%	13.6%	0.0%	9.1%	27.3%	100.0%
61-70	Count	11	5	2	2	2	3	25
	%	44.0%	20.0%	8.0%	8.0%	8.0%	12.0%	100.0%
71-80	Count	3	2	0	1	0	2	8
	%	37.5%	25.0%	0.0%	12.5%	0.0%	25.0%	100.0%
>80	Count	1	0	0	0	0	0	1
	%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Total	Count	33	14	7	6	6	14	80
	%	41.3%	17.5%	8.8%	7.5%	7.5%	17.5%	100.0%

Among the peripheral lymph nodes, the cervical lymph nodes served, most frequently, as the area of onset of the tumor process – 33 (41.3%) cases, followed by the supraclavicular and axillary area with 14 cases each (17.5% each), whereas the onset of lymphoma occurred in the inguinal lymph nodes in 7 (8.8%) patients. The analysis of the distribution by age categories shows that the area of onset of lymphoma proliferation starting from the cervical lymph nodes was predominant in all age groups, except for the age category 18-30 years where in 50% of cases the onset of tumor proliferation began in mediastinal lymph nodes (tab. 2).

According to the International Clinical Classification, approved in Ann Arbor (USA), most patients were diagnosed in generalized stages: stage III – 17 (21.3%) cases, stage IV in 42 (52.5%) patients. Localized stages were diagnosed in 26.3% of cases, from which: stage I – 7 (8.8%) patients, stage II – 14 (17.5%) cases.

The histological examination of the tissue samples has determined aggressive types of NHL in 54 (67.5%) cases. However, it should be mentioned that indolent NHLs were also found quite frequently, in 26 (32.5%) patients. Aggressive non-Hodgkin's lymphomas were the only types of NHL (100%) that were detected in cases of primary mediastinal localization of the tumor process. Aggressive NHLs also predominated in patients with primary involvement of the inguinal, cervical, abdominal, and axillary lymph nodes (85.7%, 72.7%, 66.7%, and 57.1%, respectively). Indolent NHLs were recorded more frequently in patients with primary supraclavicular lymph node involvement (57.1%) cases (tab. 3).

**Table 3. Distribution of NHL patients with primary lymph node involvement according to evolutionary type of NHL and primary involved area**

Area of l/n primarily involved	Count / within area of l/n primarily involved	Evaluative type of NHL		Total
		Aggressive	Indolent	
Cervical	Count	24	9	33
	%	72.7%	27.3%	100.0%
Axillary	Count	8	6	14
	%	57.1%	42.9%	100.0%
Inguinal	Count	6	1	7
	%	85.7%	14.3%	100.0%
Mediastinal	Count	6	0	6
	%	100.0%	0.0%	100.0%
Intra-abdominal	Count	4	2	6
	%	66.7%	33.3%	100.0%
Supraclavicular	Count	6	8	14
	%	42.9%	57.1%	100.0%
Total	Count	54	26	80
	%	67.5%	32.5%	100.0%

Aggressive NHLs constituted the majority of NHL types in patients diagnosed in localized stages: stage I – 7 (100%) cases; stage II – 10 (71.4%) of patients. In the case

of generalized stages, the ratio between aggressive NHL vs indolent NHL looks like this: stage III – 47.1% vs 52.9%; stage IV – 69% vs 31% (tab. 4).

Symptoms of general intoxication were present in 42 patients (52.5%), mostly (73.8%) in the generalized stages of the disease. Symptoms of intoxication were present in 100% of cases in the primary involvement of the mediastinal lymph nodes, 64.3% in the primary involvement of the axillary lymph nodes, and 51.5% in the primary involvement of the cervical lymph nodes. The primary involvement of intrabdominal and supraclavicular lymph nodes in half of the cases (50%) was associated with B symptoms, in contrast, the onset of lymphoma in the inguinal lymph nodes was associated with B cell symptoms in only 14.3% of patients.

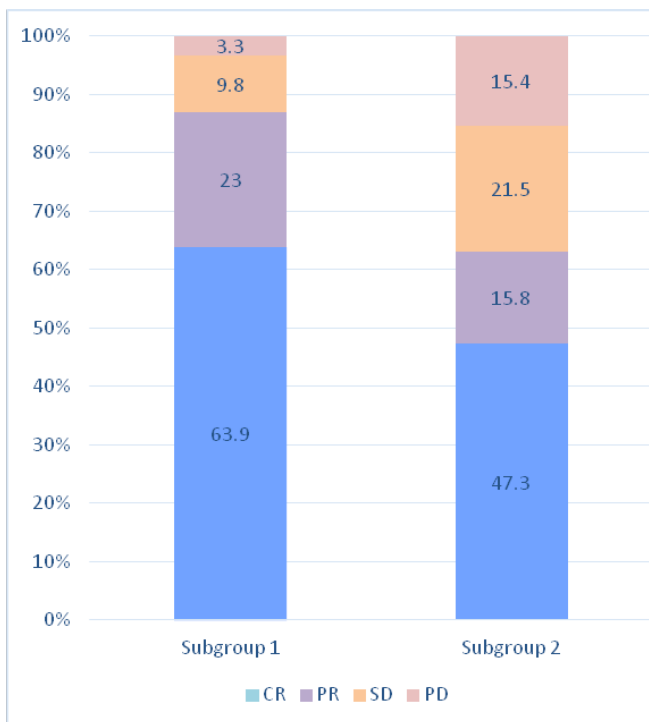
**Table 4. Distribution of NHL patients with primary lymph node involvement according to clinical stage and evaluative type of NHL**

Disease stage	Count / % within disease stage	Evolutive type of NHL		Total
		Aggressive	Indolent	
I	Count	7	0	7
	%	100.0%	0.0%	100.0%
II	Count	10	4	14
	%	71.4%	28.6%	100.0%
III	Count	8	9	17
	%	47.1%	52.9%	100.0%
IV	Count	29	13	42
	%	69.0%	31.0%	100.0%
Total	Count	54	26	80
	%	67.5%	32.5%	100.0%

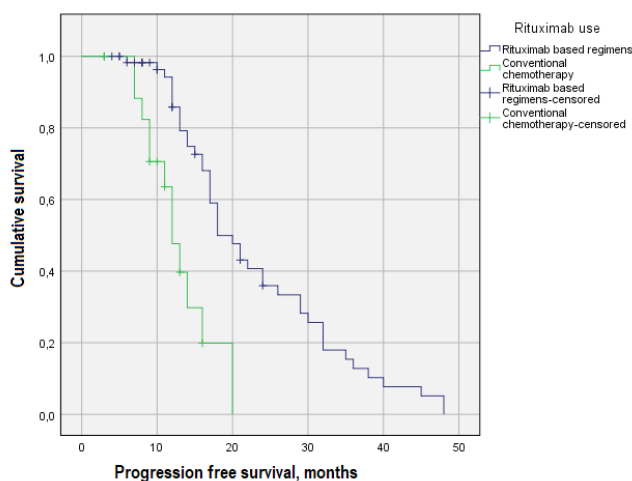
Depending on the type of treatment given to patients, the group of patients was subdivided into 2 subgroups: subgroup 1 – subgroup of patients, whose conventional polychemotherapeutic (PChT) treatment (CHOP, COP; FC, etc., in accordance with the provisions of the national clinical protocol) was associated with the administration of rituximab, and subgroup 2 – the subdivision of patients who, for various reasons (medical contraindications, personal allergic history, personal choices of the patient, etc.), followed the treatment only with the use of conventional polychemotherapy. In subgroup 1 (R + PChT) were included 61 (76.3%) patients, and the subgroup 2 (PChT alone) included 19 (23.8%) cases.

Analyzing the treatment efficacy it has been observed that the overall response rate (ORR) in subgroup 1 constituted 86.8%, compared with subgroup 2 where the ORR was equal to 63.1%. Complete remissions (CR) were obtained in subgroup 1 in 63.9% of patients, and in subgroup 2 in 47.3% of cases (fig. 2).

Progression-free survival (PFS) in subgroup 1 had a median of 20 months, and in subgroup 2 the median was 12 months (p=0.001) (fig. 3).



**Fig. 2. Effectiveness of treatment within study subgroups. CR – complete remission, PR – partial remission, SD – stable disease, PD – progressive disease**



**Fig. 3. Kaplan Meier estimates of progression free survival (PFS), within the study subgroups**

**Discussion**

As a result of this study, it was found that NHL with primary lymph node involvement more frequently developed in people aged between 61-70 years (31.25%), and 51-60 years (27.5%), which corresponds to the literature data [3, 14-16]. At the same time, this study confirmed the primary predilection for involvement of non-Hodgkin's lymphomas in the peripheral lymph nodes, with 85% of cases beginning here.

Cervical and supraclavicular lymph node area served as area of origin of tumoral expansion in 41.3% and

17.5%, respectively. Large descriptive studies that have been realized, previously have also shown that the most common sites of involvement are localized in cervical and supraclavicular area. The percentage reported by the literature data varied in the case of primary cervical lymph node involvement ranged from 31 to 37% [17, 18], and the supraclavicular area served as the area of primary involvement in the lymphoma process in 11%, more or less similar to our data [18]. Similarities between data from other scientific articles and our data were also found in case of primary involvement of the axillary lymph nodes (17.5% – our data vs 11.9% in the literature data [18]). Meanwhile, must be paid attention to a slight dissonance in the case of primary involvement of the inguinal lymph nodes. Our data determined a primary involvement of the lymph nodes in 8.8%, while studies show that the groin area is involved in approximately 16.4-18% [17-19]. The correlation of the primary location of the tumor localisation according to the age category did not show discrepancies compared to the general frequency of the primary implications of non-Hodgkin's lymphomas, the cervical area remaining predominant. The exception was the age category 18-30 years, in which 50% of the tumor's process onset served the mediastinum area. Similar data regarding the onset of non-Hodgkin's lymphoma in correlation to age can be found in several studies of the literature [20-22]. The group of patients was homogeneous, as a confirmation comes the mutual ratio between the percentages of aggressive non-Hodgkin's lymphomas vs indolent non-Hodgkin's lymphoma (67.5% vs 32.5%). Epidemiological studies showed similar values in terms of the frequency of detection of aggressive lymphomas (59-65%) vs indolent (35-41%) [16, 23-25]. The correlation between the clinical stage of non-Hodgkin's lymphomas and their evolutionary type determines another peculiarity, namely, the only or most aggressive NHLs are determined localized in stages I and II (100% and 71.4% respectively) while in generalized stages the ratio between aggressive NHL vs indolent NHL is more or less equal and constitutes: 47.1% vs 52.9% in clinical stage III and 69.0% vs 31.0% in clinical stage IV. These data can be explained by the earlier addressing of patients with aggressive NHL who have a more overt clinical picture [23].

Treatment with the monoclonal anti-CD-20 antibody, rituximab, increased the overall response rate. Thus, within subgroup 1 there was an ORR of 86.8% compared to subgroup 2 where ORR constituted 63.1%. Specialized analyses performed on various treatment groups in terms of structure and demography provided results comparable to those obtained by us, ORR ranged from 79-92% in treatment groups using rituximab, compared to 57-75% in groups where best available treatment was used [26-30].

PFS in the study subgroup using rituximab in combination with conventional chemotherapy had a median of 20 months (p=0.001) at a 36-month follow-up period. PFS in the subgroup treated with rituximab in our case is slightly shorter compared to previously published data [12, 26, 28]. A possible explanation would be the comorbid status,



which required a decrease in the total therapeutic doses of the drugs used.

### Conclusions

1. NHL with primary involvement of peripheral lymph nodes developed more often in the age category 61-70 years (31.25%).

2. The onset of NHL occurred more frequently in the peripheral lymph nodes (85.0%), in which the involvement of the cervical lymph nodes predominated (41.3%).

3. The frequency of aggressive NHL was 67.5%. Indolent NHL was diagnosed in 32.5% of cases.

4. The use of rituximab in combination with PChT increased the ORR rate (86.8% compared to 63.1%), the frequency of CR (63.9% as opposed to 47.3%) and PFS (20 months compared to 12 months).

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**Authors' contribution**

VT designed the research, reviewed statistics and interpreted the data, drafted the manuscript; MR conceptualized the project and designed the research, revised the manuscript critically; SB interpreted the data, revised the manuscript critically; VF, AG, CD, DU and MS collected the data, made statistical analysis. All the authors revised and approved the final version of the manuscript.

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**Ethics approval and consent to participate**

The research was approved by the Research Ethics Committee of *Nicolae Testemitanu* State University of Medicine and Pharmacy (protocol No 1 of July 03, 2020).

**Conflict of Interests**

There is no known conflict of interests and financial or non-financial support associated with this publication.

