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– ORIGINAL PAPERS –

The Experience of Timisoara Hematology Clinic on the Management of Aggressive Non-Hodgkin Lymphoma Patients

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Abstract

Objectives. *One of the most prevalent types of malignant lymphoproliferative disorders is non-Hodgkin lymphoma (NHL), which has shown an increased frequency worldwide of roughly 168% since 1975, coinciding with a decline in the age at diagnosis. Despite a ten-year improvement in overall survival, NHL accounts for approximatively 3% of all cancer-related deaths. Delays in diagnosis and the emergence of related comorbidities are caused by the diverse symptomatology and symptoms associated with NHL. Thus, the purpose of this study was to assess patients treated at Timisoara's Clinical Emergency Municipal Hospital who had been diagnosed with aggressive HNL.*

Material and methods. *This cross-sectional study comprised 76 patients diagnosed with aggressive NHL between January 2020 and June 2023 who were admitted to Timisoara's Clinical Emergency Municipal Hospital. Biopsy along with histopathologic examination served as the basis for the diagnosis. As part of the first assessment, bone marrow biopsy and imaging studies (PET/CT) were carried out in addition to laboratory tests. The NHL was staged using the Ann Arbour classification. The present protocols were followed in the establishment of the treatment. PET/CT was used to assess the response to treatment.*

Results*. In this study cohort 72% were stage 4 of NHL at the diagnosis, 16% were stage 3, 5% were stage 2, while only 2% were stage 1. B symptoms were present in 69% of cases. In patients with 4th stage of NHL, bone marrow represents the most frequent extranodal site. 57 patients finished minimum a complete chemotherapy line, from which 90% of the patients had complete (63%) or partial (24%) remission after first-line treatment.*

Conclusion. *The importance of this study was to emphasize the heterogeneity of NHL and to evaluate the treatment response and survivance of aggressive NHL patients.*

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Introduction

Malignant lymphomas encompass a heterogenous group of neoplasms that originate from the lymphoreticular system [1]. They are mainly categorized into Hodgkin Lymphomas (HL) and non-Hodgkin Lymphomas (NHL), with clearly defined distinctions, with criteria that aid in differentiating between subtypes within this class of cancers [2,3].

HL and NHL share common origins and symptoms, but they are distinct entities based on cellular morphology, immunophenotyping, genetic features, age group at diagnosis, clinical behavior, type of treatment and survival rate [2].

Moreover, while HL consists as a clearly defined group, NHL is much more diverse. Regarding the epidemiology, NHL is one of the most common malignant lymphoproliferative disorders. It currently ranks as the 11th most commonly diagnosed cancer in the world and has seen a significant increase in prevalence in recent decades [4]. While the majority of NHL are considered an elderly disease, with a median age at diagnosis of 67 years, there has been an uptick in its occurrence among younger patients [5,6].

NHL is divided into over 30 groups and nearly over 60 subgroups characterized by various factors including etiology, cell-type proliferation, growth rate, immunophenotypic features, genetic factors as well as clinical presentation [7]. The primary classification of NHL is made based on NHL is primarily divided based on the cellularity growth rate, leading to classification as indolent or aggressive [7]. Indolent NHL are characterized by a slowly tendency of growth and spread, having few or even no symptoms and in some cases no treatment is needed in early stages. In comparison, aggressive NHL have a faster spread and growth rate, with worsen sing and symptoms, frequent extranodal involvement [8].

Aggressive B-cell lymphoma encompasses variants such as diffuse large B-cell lymphoma, Burkitt lymphoma, mantle cell lymphoma, and B-lymphocytic lymphoma. Due to the heterogeneity of symptomatology and extranodal determinations associated with NHL, patients are often diagnosed in advanced stages of the disease with a poor prognosis [9]. This situation was further complicated during the COVID-19 pandemic, which has made regular medical examinations difficult and exacerbated an already challenging situation for oncologic patients [10].

Regarding the therapy, the absence of an early proper treatment for aggressive NHL could lead to death of the patient [11]. Over the last 30 years, a chemotherapy regimen featuring cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been widely used as the primary treatment for these individuals [12]. In recent times, integrating rituximab into this approach—a monoclonal antibody designed to target the CD20 B-cell antigen—has notably enhanced patient outcomes in aggressive NHL [12]. These developments in therapy have led to an elevated rate of complete response and overall survival without a significant rise in adverse effects, particularly among older patients.

These advancements have solidified the combination therapy of rituximab and the CHOP regimen (R-CHOP) as the gold standard for first line treatment of aggressive NHL [13,14]. Additionally, the introduction of other novel therapies, such as immunomodulatory agents, bispecific antibodies or CAR-T cell therapy, have further personalized treatment options for patients with aggressive NHL [15]. However, despite the emergence of novel targeted treatments that have led to improved survival and quality of life for patients, NHL still accounts for 3% of all cancer deaths globally [16].

Therefore, the aim of this study was to evaluate the management of patients with aggressive NHL diagnosed in the past 3 years. The purpose of this study is to provide the clinical experience of Hematology Clinic in Timisoara and to foster collaboration among healthcare professionals in order to improve patient outcome and diagnosis treatment.

Material and methods

Study design and patients.

In this cross-sectional, non-interventional, population-based, consecutive-case enrollment study, 76 patients prior diagnosed during January 2020 - June 2023 with aggressive non-Hodgkin lymphoma in Timisoara Hematology Clinic from Municipal Emergency Hospital, were included. All patients enrolled had at least one complete chemotherapy cycle finished. In this study cohort, 39 (51.3%) were men and 37 (48.7%) were women, with a median age at diagnosis of 64 years (interquartile distance 21 years). B symptoms were present in 69% of cases.

Diagnosis and staging of NHL assessment

The diagnosis of NHL was established based on biopsy of affected adenopathy, or by bone marrow biopsy, followed up by histopathological and immunohistochemical examination.

For all participants of the study, anthropometrical, clinical and paraclinical data were collected from the patients' medical files. Investigation of the presence of B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, along with laboratory investigations (complete blood count, biochemical evaluation, screening for viral infection - such as B hepatitis, C hepatitis and HIV, inflammatory samples, etc.) were carried out for all patients at the initial evaluation.

All patients had been multidisciplinary evaluated (such as cardiovascular, neurological, gastroenterological and so on) prior treatment admission.

An initial imaging assessment (through CT or PET/CT) was performed. Staging of NHL was made according to Ann-Arbor classification. All patients were treated according to national and European guidelines, based on the subtype of NHL, stage at diagnosis and the presence of other associated comorbidities. Moreover, all patients received antibacterial, antiviral and antifungal prophylaxis according to present guidelines. Stage and final evaluation were made by PET/CT, along with bone marrow biopsy for selected cases. ECOG Performance Status Scale was determined for every patient at diagnosis, along with different prognostic score, such as IPI, R-IPI and HALP. [17].

Statistical analysis

Data collection and statistical analysis was made using Microsoft Excel.

Results are presented as mean ± standard deviation for continuous variables with Gaussian distribution, median and interquartile range for the variables continuous with non-parametric distribution or absolute frequency and percentage of the total group for categorical variables.

Results

The median age at diagnosis in this study group was 64 years, ranging from 21 to 84 years. The age-group distribution showed that the most affected group was in the 61-80 years range (61.8%), follow by 41-60 years category (27.6%). (Figure 1). Baseline characteristics are illustrated in Table 1.

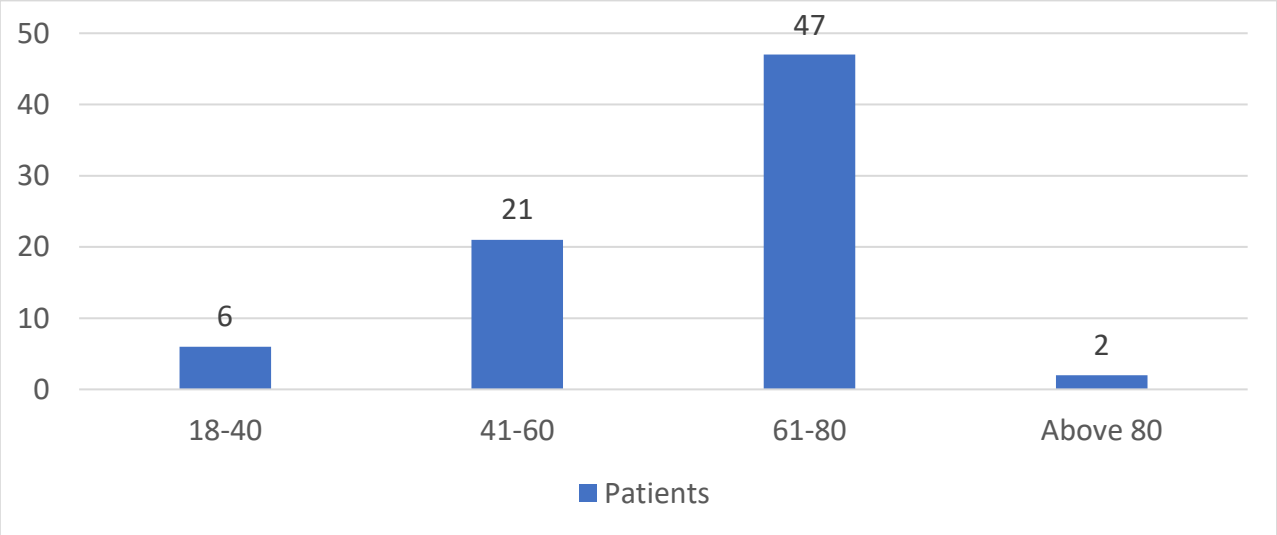

Figure 1. *Age-group distribution according to the age of the study group patients at diagnosis*

Men (%)	*38 (51.3 %)*
Median age [IQR]	*64 [21]*
B symptoms (%)	*51 (68,9 %)*

Table 1. *Baseline characteristics*

Regarding the stage at diagnosis, most of patients were classified in an advanced stage of NHL. Thus, 72% of patients were stage 4 of NHL at the diagnosis, 16% were stage 3, 5% were stage 2, while only 2% were stage 1. (Figure 2)

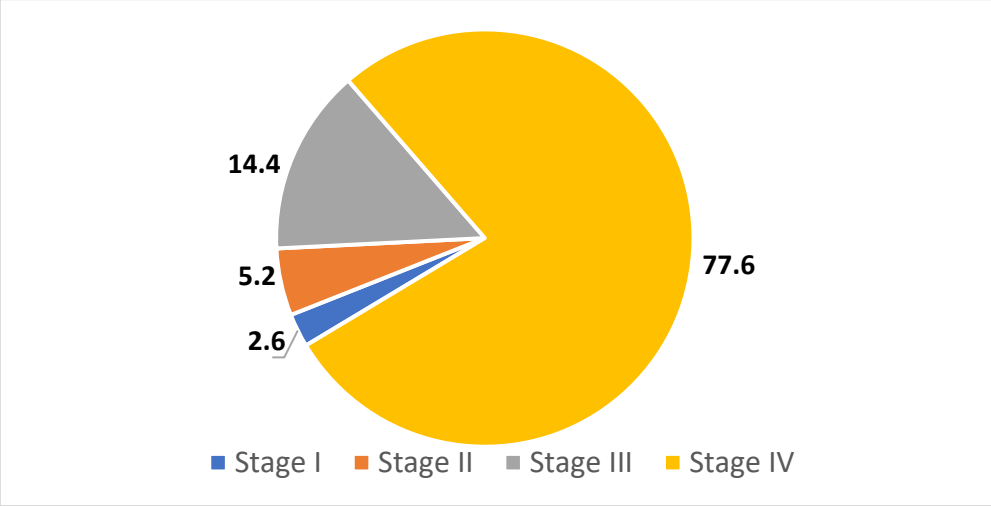

Figure 2. *Patients study-group distribution according to stage at diagnosis.*

In patients with stage 4 of NHL, the extranodal sites at diagnosis were as follows: bone marrow (24%), abdominal sites (16%), mediastinal (9%), nasopharyngeal sites (8%), tonsils (5%), cerebral (5%) and liver (4%). (Figure 3)

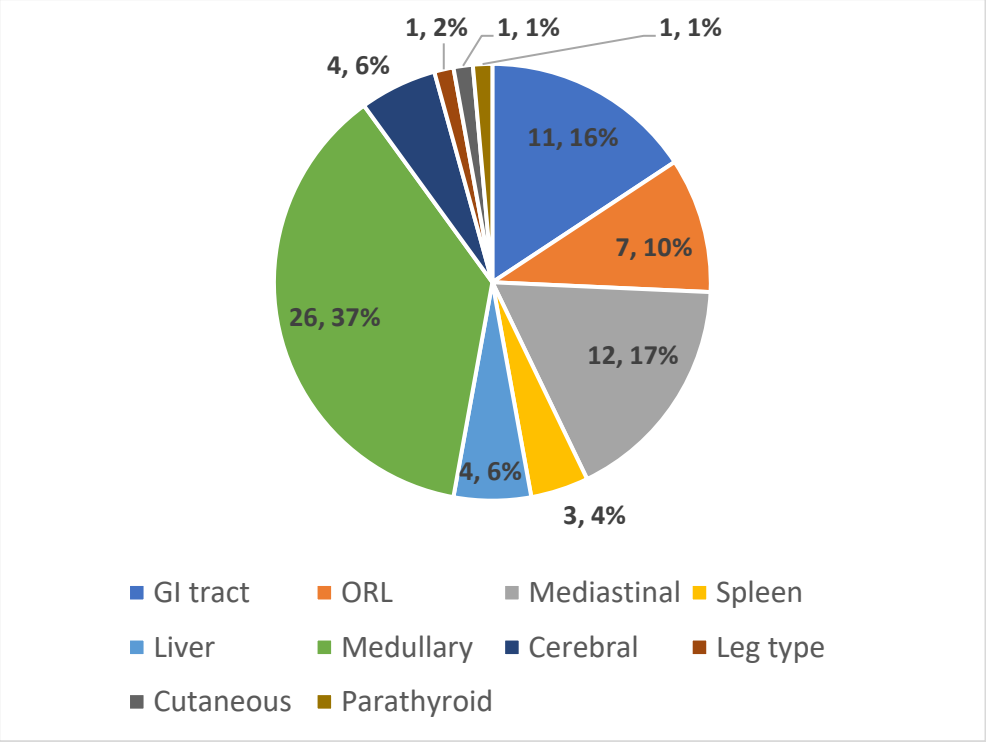

Figure 3. *Fourth stage patients distribution according to extranodal sites involvement*

According to aggressive NHL subtypes, 47 (61.8%) patients were diagnosed with Diffuse Large B cell Lymphoma (DLBCL), 23 (30.2%) with mantle cell lymphoma, 3 (3.9%) with primary mediastinal lymphoma, 2 (2.6%) with Burkitt lymphoma and 1 (1.3%) with composite B-cell/T-cell lymphoma. Data are represented in Table 2.

DLBCL	*47 (61.8%)*
Mantle Cell Lymphoma	*23 (30.2%)*
Primary Mediastinal Lymphoma	*3 (3.9%)*
Burkitt Lymphoma	*2 (2.6%)*
Composite B cell/T cell Lymphoma	*1 (1.3%)*

***Table 2**. Aggressive NHL subtypes*

Regarding the specific hematological treatment, in the first line, all patients received chemo-immunotherapeutic regimens based on the use of the anti-CD 20 monoclonal antibody, Rituximab. The most used chemotherapeutic protocol was R-CHOP (66 patients), followed by other Rituximab-based protocols. Data are illustrated in Table 3.

R-CHOP	*66 (86.8%)*
R-DA-EPOCH	*3 (3.9%)*
R-CNOP	*3 (3.9%)*
R-CVP	*2 (2.6%)*
R-CHOEP	*1 (1.3%)*
R-HYPER-CVAD	*1 (1.3%)*

***Table 3**. First-line treatment protocols used in this study-group.*

57 patients out of total, finished minimum a complete chemotherapy treatment line, from which 63% (36 patients) obtained complete remission, 24% (14 patients) partial remission and 12% (7 patients) had progressive/refractory disease.
From the 50 patients that had a complete or partial remission, 7 patients relapsed. The median relapse time-period was 12 months. 1 patient died at the end of the 1st line of chemotherapy.
In this cohort, 13 out of 14 patients followed the second line of chemotherapy. The second line treatment protocols used for the study group is illustrated in Table 4.

R-DHAP	*4 (28.5%)*
RFC	*3 (21.4%)*
Ibrutinib	*2 (14.2%)*
High-dose Methotrexate	*2 (14.2%)*
R-ICE	*1 (7.1%)*
Pola-BR	*1 (7.1%)*

***Table 4**. Second-line treatment protocols used for patients with relapsed/refractory disease.*

Discussions

This study evaluated the management of patients with aggressive NHL diagnosed and treated in the Hematology Clinic of Clinical Municipal Hospital from Timisoara from January 2021 till October 2023. The mortality in this cohort was 27.6% and could be explained by several factors: the majority of patients were diagnosed in an advanced stage of NHL, being known that their prognostic is low; moreover, these patients were diagnosed and treated during COVID-19 pandemic, which was an additional risk factor, both from the point of view of the effects of the SARS-CoV-2 virus on immunosuppressed patients, but also from the point of view of the associated risk of COVID-19 infection during Rituximab treatment.
In this study cohort, R-CHOP was the most used first line treatment. Current guidelines, such as National Comprehensive Cancer Network (NCCN) or European

Society for Medical Oncology (ESMO), are considering R-CHOP as the standard first-line treatment for most aggressive NHL including DLBCL, because of its effectiveness in inducing remissions along with improving overall survival [18]. However, it is known that anthracyclines, such as doxorubicin used in R-CHOP, has a cardio-toxic effect, especially in elderly patients [19]. Considering the age group that is affected by NHL, in certain situations it is necessary to replace doxorubicin with pharmaceutical preparations with less toxicity, such as mitoxantrone, which was reported to have less cardiological and gastrointestinal adverse effects. Despite the treatment safety, several studies showed that, when compared doxorubicin (50mg/m2) vs. mitoxantrone (10-12mg/m2), CNOP therapy (cyclophosphamide, mitoxantrone, vincristine, and prednisone) was significantly inferior compared to CHOP, in both overall survival and complete response [20–22]. However, the use of the R-CNOP regimen should be considered for selected groups of patients. In this study R-CNOP was used for 2 patients [23].

R-CVP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) is also considered as a less intensive alternative to R-CHOP for elderly patients with some aggressive NHL, such as mantle cell lymphoma, offering a balance between efficacy and tolerability in this patients group [24,25]. Even if, when compared, R-CVP does not offer the same response rates compared to R-CHOP, it is reported to be generally more tolerated for elderly/compromise patients [26]. In this study 1 patients followed R-CVP regimen.

On the other hand, distinct entities of aggressive NHL such as primary mediastinal lymphomas or double hit B-cell lymphoma appear to have improved outcomes by using alternative Rituximab based regimens. Some studies showed that use of R-DA-EPOCT (rituximab, etoposide phosphate, prednisone, vincristine, cyclophosphamide and doxorubicin) have better complete response and overall survival compared to R-CHOP [27,28]. Even so, overall response rate, progression free survival and response rate were similar in R-CHOP vs R-DA-EPOCH, with lower febrile neutropenia in R-CHOP. Moreover, addition to etoposide to R-CHOP, R-CHOEP, showed promising results for younger patients with DLBCL [29]. 3 patients undergo R-DA-EPOCH, respectively 1 patient R-CHOEP in this study group.

R-Hyper-CVAD is a regimen associated with significantly increased toxicity such as myelosuppression, febrile neutropenia, or increased risk of severe infections, but is taken into consideration for younger fit patients, with some aggressive subtypes of NHL such as Burkitt lymphoma, which are reported to have a high risk of relapse or refractory disease [30,31]. One patient from this study was a candidate for R-Hyper CVAD protocol.

Treatment-response in aggressive HNL is variable, depending on multiple factors, but in most cases is consider that most patients will obtain a complete or partial response after fist chemotherapy treatment-line [32]. However, most of these patients could relapse or could develop associated complications that can result in death of the patient [33]. In addition, COVID-19 pandemic worsens the patients outcome, especially for those received Rituximab based regimens [34].

At the end of the first line, 87.7% of the patients had complete (63%) or partial (24%) remission after treatment, of which 13 (22.8%) patients with relapsed/refractory disease received a second chemotherapy line. It is known that the primary aim of second-line treatment is to attain a complete response, but establishing the second treatment protocol could be challenging due to several factors. First, there is a lack of a standardized second-line chemotherapy regimen. Secondly, there is an increased risk of accumulated toxicity, considering the fact that patients already received an extensive treatment; therefore, the risk of associated complications is much higher compared to first-line treatment. Thirdly, patients with aggressive NHL could develop resistance to chemotherapy. Lastly, when choosing second-line chemotherapy protocol, in relapsed patients, the newly affected site of HNL should be considered [35]. Even if there are several therapeutic options for relapse/refractory disease patients, the prognostic is verry poor. However, newly developed targeted therapies seems to sown promising outcomes for these patients. Therefore, availability for clinical trials is needed.

Conclusion

Management of NHL patients is a complex and multidisciplinary endeavor that requires a tailored approach based on individual patient characteristics, disease subtype, and treatment response. Through advancements in understanding the biology of NHL, as well as the development of novel treatment modalities, significant progress has been made in improving outcomes for patients with aggressive NHL. R-CHOP, remain the cornerstone of first-line treatment for most aggressive NHL, however several NHL subtypes could be approched by alternative Rituximab-based regimens. Even if novel targeted agents, immunotherapies, and

combination treatment approaches offer promising avenues for improving outcomes and overcoming treatment resistance in aggressive NHL, the management of relapsed/refractory disease patients remain a constant challenge. Further clinical studies are needed in order to improve the outcome is this group of patients.

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Conflicts of interest

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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