Original Article

FOUR-YEAR SINGLE-CENTER EXPERIENCE IN TREATING PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN ALBANIA

Bledi Kreka[1], Enkeleida Çuedari[1], Flutura Proko[1], Anila Pema[1], Albana Shahini[2], Alma Idrizi[2], Manika Kreka[2], Arvin Dibra[2]

[1]University Hospital Center "Mother Teresa", Tirana, Albania
[2]University of Medicine, Tirana, Albania

Correspondent E-mail: manika.kreka@umed.edu.al

ABSTRACT

Introduction: Non-Hodgkin Diffuse Lymphomas are known for their high responsiveness and effectiveness to chemotherapy compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. Today, with modern therapies, significant progress has been made in treating more than 50% of cases. Treatment with the anti-CD20 monoclonal antibody rituximab has dramatically improved the prognosis for patients with aggressive NHL.

Aim: Evaluation of FPS (Progression Free Survival), CR (Complete Response), and PR (Partial Response) for patients diagnosed with Diffuse Large B-cell Lymphoma (DLBCL) in our patient group.

Materials and Methods: We followed up 57 patients all treated at the Oncology Service. These patients diagnosed with DLBCL have been treated from January 2019 to January 2022. We have analyzed patients' data for whom the minimal time from the end of treatment has been at least 24 months. We have measured the time since the beginning of treatment until relapse of disease or the patient's death. We have used the Cheson 1999 criteria to evaluate the response of treatment.

Results:57 patients were enrolled and followed up in this study. Among our patients, the majority were CD 20 +**.** Many patients have been diagnosed in stage 2. Most relapses happened within the first 24 months; only two relapses happened after 24 months. Relapse-free disease interval is seen in at least 32 patients, more than 24 months and over 40 months in 12 patients at the time of evaluation.

Conclusion: In general, progression-free survival (PFS) seems to be 50 % and 28 % respectively, for R-CHOP and CHOP. Overall survival is over 5 years in patients treated with rituximab. We've been using rituximab IV or sc for more than 12 years in our hospital. This study was conducted in order to establish a registry in the framework of a NASRI project as well.

Keywords. complete response, partial response, progression disease, progression-free survival, non-Hodgkin Lymphoma, Diffuse Large B-cell Lymphoma

PËRVOJA KATËRVJEÇARE E NJË QENDRE TË VETME NË TRAJTIMIN E PACIENTËVE ME LIMFOMË DIFUZE TË QELIZAVE TË MËDHA B (DLBCL), NË SHQIPËRI

ABSTRAKT

Hyrje. Limfomat difuze non-Hodgkin karakterizohen nga efikasiteti i lartë i trajtimit me kemioterapi, krahasuar kjo me limfomat e tjera indolente. Kombinimi i Doxorubicinës, Vincristinës, Cyclofosfamidit dhe Prednisonit ka qenë trajtimi standard për shumë vite. Në ditët e sotme, në epokën e trajtimeve moderne është arritur një progres i rëndësishëm në trajtimin e tyre në më shumë se 50% të rasteve klinike. Trajtimi me antikorpe monoklonale anti-CD20, si rituximabi, ka ndryshuar në mënyrë dramatike prognozën e pacientëve që vuajne nga NHL (Non-Hodgkin Lymphoma) agresive gjatë dy dekadave të fundit.

Qëllimi. Vlerësimi i FPS (Mbijetesa pa Progres e Sëmundjes), CR (Përgjigja e plotë) dhe PR (Përgjigje e Pjesshme) për pacientët e diagnostikuar me Limfomë Difuze me Qeliza B (DLBCL) në grupin e pacientëve tanë.

Materiali dhe Metodat. Ne ndoqëm 57 pacientë, të gjithë të trajtuar në Shërbimin e Onkologjisë. Këta pacientë të diagnostikuar me DLBCL janë trajtuar nga janari 2019 deri në janar 2022. Terapia anti CD 20 + (Rituximab) është perdorur ne vetem 28 pacientë. Ne kemi analizuar të dhënat e pacientëve për të cilët koha nga fundi i trajtimit ka qenë të paktën 24 muaj. Ne kemi matur kohën që nga fillimi i trajtimit deri në rikthimin e sëmundjes ose vdekjen e pacientit. Për vlerësimin e përgjigjes janë përdorur kriteret e Cheson 1999.

Rezultatet. 57 pacientë u regjistruan dhe u ndoqën në këtë studim. Në mesin e pacientëve tanë pjesa më e madhe, karakterizohej CD20.+. Shumica e pacientëve janë diagnostikuar në stadin II. Shumica e recidivave ndodhën brenda 24 muajve të parë, vetëm dy rikthime ndodhën pas 24 muajsh. Intervali i sëmundjes pa rikthim vërehet në të paktën 32 pacientë më shumë se 24 muaj dhe mbi 40 muaj në 12 pacientë në kohën e vlerësimit.

Përfundimi. Mbijetesa pa Progres e Sëmundjes është 50% dhe 28% për R-CHOP dhe CHOP. Në vendin tonë prej më shumë se 12 vitesh pacientët trajtohen me rituximab me adminsitrim intravenoz ose subkutan. Ky studim u realizua edhe në kuadrin e një projekti të NASRI-t për krijimin e një regjistri kombëtar.

Fjalë kyçe. përgjigje e plotë, përgjigje e pjesshme, sëmundje progresive, mbijetesë pa progress, NHL: Limfoma Non-Hodgkin, DLBCL: Limfoma Difuze me qeliza të mëdha B

INTRODUCTION

Non-Hodgkin lymphomas account for 2–3% of all malignancies in developed countries. They cover a range of neoplasms from slow-growing to aggressive tumors, the latter having a rapidly fatal course. The age-specific incidence increases throughout life. Their cause remains unknown, but environmental factors, virus infections, and genetic abnormalities are

all considered important. The clinical presentation of non-Hodgkin lymphoma varies widely. Many patients seek medical attention because of a tumor mass, which may be nodal or extranodal. General symptoms such as weight loss, fever, infections, and lethargy are common and may be the first signs. Often, patients have widespread disease with bone marrow involvement at diagnosis.

Non-Hodgkin Diffuse Lymphomas are characterized by high efficacy of chemotherapy treatment compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. Nowadays, in the era of modern treatments, there has been great progress in treating more than 50% of clinical cases. Treatment with the monoclonal antibody anti-CD20 (rituximab) was first approved for indolent lymphomas in progress since 1997, and it has dramatically improved patient outcomes, significantly changing the prognosis for patients suffering from aggressive NHL in the last two decades.

Non-Hodgkin lymphoma (NHL) is classified into more than 30 types based on the type of lymphocyte involved: B lymphocytes (B cells) or T lymphocytes (T cells). Non-Hodgkin lymphoma is also categorized by other factors, including whether it is aggressive (fast-growing) or indolent (slow-growing). Nearly 90 percent of non-Hodgkin lymphoma cases originate in B cells.

The most Common forms of B-cell non-Hodgkin lymphoma include: Diffuse large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle cell lymphoma (MCL), Marginal zone lymphoma, Mucosa-associated lymphoid tissue (MALT) lymphoma, Splenic marginal zone B-cell lymphoma. Less common forms of B-cell lymphoma include: Burkitt lymphoma, Lymphoplasmacytic lymphoma

Our topic of interest is **Diffuse large B-cell lymphoma (DLBCL), which seems to be** the most common type of non-Hodgkin lymphoma in the United States, Europe, and all over the world.

DLBCL accounts for about 30 percent of all cases. It is most often diagnosed in older adults. DLBCL is aggressive and may spread quickly. It may be found not only in the lymph system, but as a primary disease elsewhere in the body, including the gastrointestinal tract, testes, breasts and brain.

Subtypes of DLBCL include: Primary mediastinal B-cell lymphoma is often found in the mediastinum, the area of the chest cavity between the lungs. This type of lymphoma, which is more common in young women, may produce fast-growing tumors that may encompass the mediastinum cavity and press on the airways and blood vessels.

Primary central nervous system (CNS) lymphoma originates in the brain or spinal cord and may be found in patients with acquired immunodeficiency syndrome (AIDS) or those whose immune systems may be compromised, including organ transplant patients. When primary CNS lymphoma originates in the eye, it is called ocular lymphoma.

Symptoms of DLBCL may include swelling caused by enlarged lymph nodes in the neck, underarms, or groin. The swelling may or may not be painless. Other symptoms may include coughing or difficulty swallowing, night sweats, fever, swollen face, weight loss, and fatigue.

Treatments for DLBCL may include chemotherapy, targeted therapy, and sometimes radiation therapy. Surgery may be required in some cases to remove obstructive tumors (1) Non-Hodgkin Diffuse Lymphomas are characterized by high efficacy of chemotherapy treatment, compared to other indolent lymphomas. The combination of Doxorubicin, Vincristine, Cyclophosphamide, and Prednisone has been the standard treatment for many years. The addition of Rituximab to this regimen in the early 2000s to treat DLBCL produced better outcomes for patients (2,3). Six cycles of CHOP in combination with eight cycles every 21 days remains the standard despite the various attempts to test more dense treatment (4, 5), maintenance rituximab, and more cycles. Today, there is at least a 50% curability rate with modern treatment (6). Rituximab, a chimeric anti-CD20 antibody, was initially approved in 1997 for relapsed low-grade NHL. Rituximab binds to a surface protein, called CD20, located on mature B cells. Once bound, the antibody activates the body's immune system, which then attacks the cancer cells (7). Our study aims to evaluate FPS, CR, and PR for patients diagnosed with DLBCL in our patient group.

METHODOLOGY

This is a retrospective study involving 57 patients diagnosed and treated at our Service from January 2019 to January 2022. We included patients whose follow-up period since the end of treatment was at least 24 months. We measured the time from the start of treatment until disease relapse or patient death. The response to treatment was evaluated using the Cheson 1999 criteria. The results were assessed in July 2024.

We have excluded from our study:

- Patients with Lymphoblastic Lymphomas and Burkitt Lymphomas
- Patients who have not tolerated at least 2 first cycles of treatment (side effects or treatment interruptions for other reasons)
- Patients who have not had a minimal IHC panel documented

The diagnosis is confirmed after the lymph node biopsy result or bone marrow biopsy when necessary. The minimal IHC panel included CD20, Ki-67, CD19, and CD21. Only one patient was CD20 negative (-). Staging was performed using total body CT, measuring LDH levels, CBC (Complete Blood Count), and LFT. Extra nodal metastases were documented. Lesions larger than 7 cm were considered bulky. Treatments included chemotherapy, CHOP, R-CHOP 21, and CVP. Due to shortages, Rituximab was used in the treatment of 28 patients. CVP was administered to an elderly patient with multiple comorbidities. Radiotherapy was used palliatively in 22 patients, 10 of whom had bulky nodal lesions.

RESULTS

57 patients, 16 - 77 years old, have been diagnosed with DLCBL during the time of this study in our Service. The mean age was 55,1. In this group, 52,6 % were females and 47,4% males.

Table 1. Distribution of patients according to the stage of the disease

Classification	Stage	
IA	1	1.8%
IE	8	14.0%
II	7	12.3%
IIA	5	8.8%
IIB	1	1.8%
IIE	13	22.8%
III	4	7.0%
IIIA	2	3.5%
IIIB	1	1.8%
IIIE	2	3.5%
IV	6	10.5%
IVE	7	12.3%
Total	57	100.0%

In Table 1 is seen that many patients have been diagnosed in stage 2.

Table 2. The frequency of extra nodal manifestations

Classification	Extra nodal manifestations	
Breast	1	1.8%
Parotid glandule	1	1.8%
Liver	2	3.5%
Ileum	2	3.5%
Jejunum	2	3.5%
Bones	1	1.8%
Skin	1	1.8%
Pectoral muscles	1	1.8%
Naso pharynx	1	1.8%
Negative	28	49.1%
Pericardium& Pleural	1	1.8%
Pericardium	1	1.8%
Pulmonary and hepatic	1	1.8%
Pulmonary	1	1.8%

Pulmonary and bones	1	1.8%
Kidney and maxillary site	1	1.8%
Gastric	8	14.0%
Gastric and pancreatic	1	1.8%
Gastric and pulmonary	1	1.8%
Testicular	1	1.8%
Total	**57**	**100.0%**

In Table 2 is shown that 49,1% of patients present with no extra nodal manifestations ($p< 0.0001$)

Table 3. PS frequency (Performance Status Frequency)

Classification	**PS**	
0	6	10.5%
1	28	49.1%
2	22	38.6%
3	1	1.8%
Total	57	100.0%

Table 4. Chemotherapy regimen treatment in our patients

1 CHOP	2	3.5%
3 CHOP	2	3.5%
4 CHOP	7	12.4%
4 CVP	1	1.7%
4 RCHOP	4	7.0%
5 CHOP	4	7.0%
5 RCHOP	1	1.7%
6 CHOP	7	12.4%
6 RCHOP	19	33,.3%
8 CHOP	6	10.5%
8 RCHOP	4	7.0%
Total	**57**	**100.0%**

Table 5. Frequency of Relapse

Classification	RELAPSE

No relapse	**32**	**56.1%**
Death	3	5.2%
Multifocal	13	22.8%
CNS relapse	3	5,3%
Breast	1	1.8%
Bone	2	3,5%
Spinal cord	1	1.8%
Secondary cancer	2	3,5%
Total	57	100.0%

Table 6. Frequency of Response

Classification	RESPONSE

CR (COMPLETE RESPONSE)	36	63.2%
PD (PROGRESSIVE DISEASE)	3	5.3%
PR (PARTIAL RESPONSE)	11	19.2%
RD (REFRACTORY DISEASE)	3	5.3%
SD (STABLE DISEASE)	4	7 %
Total	57	100.0%

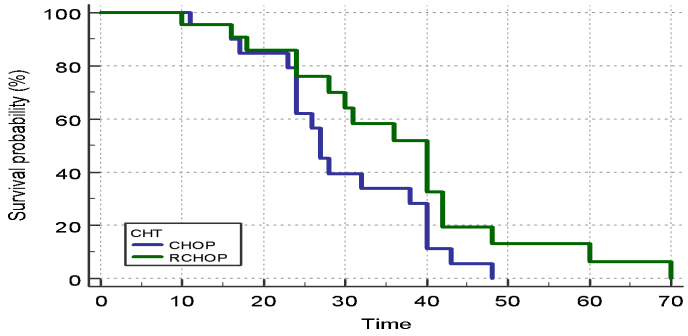
Table 6 shows that PET (Positron Emission Tomography) was performed in only 4 patients, and Complete Molecular Response was measured in 2 patients.

Table 7. Frequency of Second-Line Therapy

Classification X	SECOND LINE TREATMENT

No data	2	3.5%
No second-line treatment	**41**	**71.9%**
Second-line treatment	11	19.3%
Second-line treatment and alive	2	3,5 %
Second-line treatment (CHOP)	1	1.8%
Total	57	100.0%

Graph 1: Progression Free Survival according to Chemotherapy regimen



In Graph 1, it is shown that there is a light significance (p =0,005)
RCHOP is more effective than CHOP treatment

Graph 2: Patients' relapse-free survival.

In Graph 2, it is seen that 56% of patients were relapse-free at least after 24 months, and a considerable percentage more than 24 months.

57 patients were enrolled and followed in this study. Most of our patients were CD20+. Many were diagnosed at stage 2(see Table 1). Two patients developed secondary cancers, respectively, in the 30th and 40th months of follow-up. Most relapses occurred within the first 24 months; only two relapses happened after 24 months (see Graph 2). The relapse-free interval was observed in at least 32 patients for more than 24 months, and in 12 patients for over 40 months at the time of evaluation. Response evaluation using PET was possible in 4 patients (abroad), and in two of them, complete metabolic response was observed (see Table 6). A total of 25 patients experienced relapse, accounting for 43,8% of the cohort (see Table 5). Relapse was seen in 2 patients with stage II, 4 with stage IIE, 3 with stage III, 5 with stage IV, and 5 with stage IVE. Complete response to treatment was observed in 36 patients, representing 63,2% (see Table 6). Primary resistance to treatment was identified in 3 patients (5,3%). RCOP proved to be more effective than CHOP treatment (see Graph 1).

DISCUSSION

Treatment with CHOP in DLBCL has been used in patients since 1980 and beyond. It has been the standard treatment for aggressive Non-Hodgkin Lymphoma. This protocol achieved 5-year survival rates of 30-40% in our patients. In 30% of patients, there was no treatment response, or the disease progressed rapidly soon after treatment. The FDA approved the combination of anti-CD20 with the CHOP scheme (R-CHOP) in 2006 for the treatment of malignant lymphomas with diffuse large B-cell lymphoma (DLBCL), based on recent studies GELA/ LNH 98.5, MinTde E4494/SWOG, which demonstrated efficacy for patients both under and over 60 years of age.

One of our study's limitations is the method used to evaluate treatment response, due to the absence of PEC-CT examination in our service, which is a standard imaging technique for NHL. This exam was only performed privately on 4 patients. The slight statistical significance favoring the RCHOP combination over CHOP is because rituximab was used in only 28 patients.

CONCLUSION

Progression-free survival (PFS) was 50% for R-CHOP and 28% for CHOP. In our country, we have been using rituximab via intravenous or subcutaneous administration for over 10 years, with satisfactory results for our DLBCL patients.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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