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MALIGNAT LYMPHOMA -DIAGNOSIS, THERAPY AND PROGNOSIS HODGKIN'S LYMPHOMAS -HODGKIN'S DISEASE, DIFFUSE LAGRGE CELL B LYMPHOMA - DLCBL

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Abstract

Hodgkin's lymphoma (HL) is a malignant disease of clonal origin from B lymphocytes from the germinal center of the lymph nodes.

Many etiologies that are not fully explained, there are risk factors that cause HL disease, the most common of which is the family predisposition, various infections, etc. Hodgkin's lymphomas are categorized into two main groups according to their specificity and the presence of Reed-Stenberg (RS) cells, neoplastic cells with varying degrees of fibrosis.

The diagnosis of LH is confirmed by lymph node biopsy, haemogram, CT of the chest, abdomen, and pelvis, bone marrow biopsy MR, scan, and PET scan.The treatment of HL is done according to protocols using cytostatic to achieve successful therapeutic goals.

Diffuse large cell B lymphoma - DGKBL is the most common type of non-Hodgkin lymphoma, occurring in the age group, in the white race in the United States, and equally in both sexes.Characteristically, non-Hodgkin lymphomas are fast-growing tumors with mature B lymphocytes. Diagnostic procedures include blood count, Coombs test, Sedimentation, protein status, electrolyte status, degradation products, LDH, transaminases and liver tests, Flow cytometry. Computerized, PET scan Biopsy and bone marrow aspiration.

***Keywords**:* Hodgkin's lymphoma, lymph nodes, disease, non-Hodgkin cells, lymph nodes, growing tumors, diagnostic procedures, lymphomas

Hodgkin's Lymphomas (Hodgkin's Disease)

Introduction

Hodgkin's disease was first described by Thomas Hodgkin in 1833. The linear origin of the Hodgkin's cell has been the subject of debate for almost 160 years. Using sensitive PCR methods, it was shown that the malignant cell in HL was clonal in origin from B lymphocytes from the germinal centers of the lymph nodes.

Epidemiology

The annual incidence of HL in Europe and North America is about 3 cases per 100,000 inhabitants. The incidence is higher in men compared to women. In terms of age, HL has a bimodal age distribution with two peaks present, one between 20-29 years and a second peak around 60 years. The most common histological type in the younger population is nodular sclerosis (NS). As much as 75% of HL in people <40 years of age is nodular sclerosis.

Etiology

The etiology of HL, as well as other clonal, malignant diseases, is not fully understood. Risk factors associated with the occurrence of HL are:

- Familial predisposition: 99 times higher risk of developing HL in identical twins; 7-fold increased risk of HL in young siblings; increased risk of HL in close relatives.

- The incidence of Hodgkin's Lymphoma (HL) is more common in children and young people with higher socioeconomic status and of white European descent in the United States.
- EBV infections; increased risk of HL in individuals who have had Infectious Mononucleosis.

Classification

The classification of HL according to the World Health Organization (WHO) based on REAL (Revised European American Lymphoma) changes is generally accepted, shown in Table 1.

There are two major groups of HLs:

1. **Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL**): 3-8% of HL; contains large atypical B lymphocytes and histiocytes; CD30-, CD15-, CD20 +, CD45 +, CD75 +, cd79A +.
2. **Classical Hodgkin's lymphoma:** contains mononuclear Hodgkin's cells or dual-nucleus / multinucleated Reed-Stenberg (RS) cells that make up 1-2% of the cells in the affected lymph node. These cells are CD30 +, CD15 +, CD20-, CD45-, CD75-, CD79a-. Predominant cells are lymphocytes, plasma cells, eosinophils, and histiocytes that contain neoplastic Hodgkin cells and varying degrees of fibrosis. The classic type of HL has 4 histological subtypes:

- **Nodular sclerosis (NSHL):** ~ 80% of HL; multitude of fibrous filaments and nodular growth present, lacunar Hodgkin cells present, and varying numbers of RS cells.
- **Mixed cellularity (MCHL):** ~ 17% of HL; mixed infiltrate of lymphocytes, eosinophils, and histiocytes present with varying numbers of classic RS cells.
- **Lymphocyte depletion (LDHL):** a rare subtype; diffuse hypocellular infiltrate with necrosis, fibrosis, and RS cells present.
- **Lymphocyte dominance (LRCHL):** a rare subtype; diffuse lymphocytic infiltrate with rare typical RS cells.

Table 1. Classification of lymphomas according to the World Health Organization

Number	**WHO classification of lymphoid neoplasms**
1	**B-cell neoplasms**
1.1	**Precursor B-cell neoplasms**
	• Precursor B-lymphoblastic lymphoma / leukemia (precursor B-cell acute lymphoblastic leukemia)
1.2	**Mature (peripheral B-cell) neoplasms**
	• Chronic lymphatic leukemia / B-cell small lymphoma
	• B-cell proliferative leukemia
	• Lymphoplasmacytic lymphoma
	• Splenic B-cell marginal lymphoma (splenic lymphocyte lymphocyte lymphoma)
	• Hairy cell leukemia
	• Plasma cell myeloma / plasmacytoma
	• Extra nodal B-cell marginal lymphoma (MALT lymphoma)
	• Nodal B-cell lymphoma from the marginal zone
	• Follicular lymphoma
	• Mantle cell lymphoma
	• Diffuse large cell B lymphoma
	• Burkitt lymphoma / leukemia
2	**T-cell neoplasms**
2.1	**Precursor T-cell neoplasms**

	• Precursor T-lymphoblastic lymphoma / leukemia (precursor T-cell acute lymphoblastic leukemia) • Blastoid NK-natural killer lymphocytes
2.2	**Mature (peripheral B-cell) neoplasms**
	• T-cell proliferative leukemia
	• T-cell large granular lymphocytic leukemia
	• Aggressive NK-cell leukemia
	• Adult T-cell leukemia / lymphoma
	• Extra nodal NK / T-cell lymphoma (nasal type)
	• Enteropathy type T-cell lymphoma
	• Hepatosplenic T-cell lymphoma
	• Subcutaneous panniculitis-like T-cell lymphoma
	• Mycosis fungoides / Cesarean section syndrome
	• Primary cutaneous anaplastic large cell lymphoma
	• Peripheral T-cell lymphoma (not specified)
	• Angioimmunoblastic lymphoma
	• Primary systemic anaplastic large cell lymphoma
2.3	**Hodgkin's lymphoma**
	• Nodular lymphocytic predominant Hodgkin's lymphoma
	• Classical Hodgkin's lymphoma
	✓ Nodular sclerosis Hodgkin lymphoma
	✓ Lymphocyte-rich classical Hodgkin lymphoma
	✓ Mixed cellularity (Hodgkin lymphoma)
	✓ Lymphocyte depleted Hodgkin lymphoma

Clinical presentation

- It usually begins with painless enlargement of the lymph nodes, usually in the cervical region, and spreads along regional lymph pathways.
- The capture of Waldeyer's ring is rare and more in favor of the NHL
- Enlarged lymph nodes may recede and enlarge again at the onset of the disease
- Splenomegaly is less common (~ 30%), palpable splenomegaly occurs in 10% of cases, and hepatomegaly in only 5%
- Extranodal spread of the disease (through blood vessels) is less common
- One third of patients have more than 1 constitutional symptom such as night sweats, weight loss, fever and night sweats. Specific signs of HL include alcohol-induced lymph node pain and nocturnal pruritus
- Cellular immunity is often reduced and there is an increased risk of infections such as tuberculosis, HIV, fungal and viral infections.

Diagnostic and staging procedures

- Recording of B symptoms in the anamnesis
- Detailed history and physical examination to determine peripheral lymphadenopathy and / or organomegaly
- Histological diagnosis by an experienced histopathologist is mandatory to make a diagnosis and determine the type of HL. It is performed after a previous surgical biopsy of the enlarged lymph nodes or a fine-needle biopsy of the mediastinal or abdominal lymph nodes; sometimes an open thoracotomy or laparotomy is required to provide tissue for histological analysis.

- Hemogram, peripheral smear, and sedimentation (may indicate the presence of normocytic, normochromic anemia, reactive leucocytosis, eosinophilia, or thrombocytosis)
- Determination of levels of urea, creatinine, uric acid, hepatic enzymes, LDH and β2-microglobulin
- CT of the chest, abdomen, and pelvis to detect nodal and extranodal tumor mass
- Bone marrow biopsy to see if there is involvement (stage IV)
- If necessary lumbar puncture and CT of the head and spine in patients with CNS symptoms or highly aggressive lymphomas with testicular or paranasal localization
- If necessary MRI, gallium scan
- PET scan
- Cryopreservation of sperm in young men before starting chemotherapy.
- Determining the stage is important for the further treatment of the patient and for defining the prognosis. Ann Arbor's staging system is a generally accepted system for defining the stage of the disease in HL as well. [1]

Therapy for Hodgkin's Lymphoma

Hodgkin's disease is a highly curable disease. Therefore, the goal of treatment is to provide the highest possible cure ra в te for each patient, but with a minimum percentage of early and / or late complications.

Treatment of the early stages of HL

Prognostic factors: patients in stage I and II of the disease are divided into two subgroups: **favorable and unfavorable prognostic group** based on certain risk factors, which are:

- Age> 40 years
- Sedimentation> 50mm / h or> 30mm / h in the presence of B symptoms
- Occlusion of 4 or more nodal regions or mediastinal mass> 0.35
- Other risk factors such as sex, histology, disease localized in the upper cervical nodes, anemia, and low serum albumin.

Treatment of the early stages of HL with a favorable prognosis

Purpose: cure with minimal side effects.

Therapy of choice is a combination of 4 cycles of chemotherapy according to ABVD protocol (Adiamycin, Bleomicyn, Vinblastine, Decarbasine) and local radiotherapy (36-40Gy). The percentage of remissions is around 90%, while the 5-year survival is over 95%. Initial treatment of NLPHL patients with localized disease in one region can only be based on localized radiotherapy in order to minimize the long-term side effects of chemotherapy.

Treatment of the early stages of HL with an unfavorable prognosis

Purpose: cure as small but acceptable side effects as possible.

Therapy of choice is a combination of 6 cycles of chemotherapy according to ABVD protocol and local radiotherapy (36-40Gy). The expected remission rate is> 85%, while the 5-year survival is around 90%. [2]

Treatment of advanced stage HL

Prognostic factors: Negative prognostic risk factors according to IPI for patients with advanced HL include:

- Hb <10.5g / L
- male gender

- Stage IV
- Age> 45 years
- Le> 16x109 / L
- Lymphocytes <0.6x109 / L or <8%
- Albumin <40g / L

Treatment of patients with advanced HL is based on combination chemotherapy with 6 cycles of ABVD or more aggressive chemotherapy protocols such as escalated BEACOPP, Stanford V in combination with radiotherapy in case of residual disease or large tumor mass. Overall survival does not differ with the use of different chemotherapy protocols.

Patients without adverse prognostic factors have a 5-year survival without disease progression of 84%. Each of these unfavorable prognostic factors reduces the period without progression by 7%, so that patients with 4-7 unfavorable risk factors have a 5-year survival without disease progression of about 40%.

Treatment of refractory or relapsing Hodgkin's disease

In case of primary refractory disease or early relapse of HL after first-line therapy, high-dose chemotherapy (ICE, DHAP, ESHAP, mini-BEAM) is planned with subsequent autologous transplantation, if the patient's age and performance score allow. In the case of elderly patients with poorer performance status, less aggressive chemotherapy protocol or palliative chemotherapy (Gemcytabine, Cisplatil, MOPP) is used. [2], [3]

Late complications from HL therapy

- Infertility is one of the most common complications, significant for young patients in the reproductive period. Infertility has been more common in the use of the MOPP protocol in the past. Today it is much rarer due to the use of the ABVD protocol.
- Premature menopause in older women and irregular menstrual cycles during chemotherapy
- Increased risk of secondary malignancies (relative risk of 6.4)
- Solid tumors (most often breast, lung, melanoma, sarcomas, thyroid cancers); the risk increases with the time spent after therapy (13% after 15 years, 22% after 25 years). The risk of developing solid tumors is higher in radiation sick people
- Acute myeloblastic leukemia is more common after application of the MOPP protocol and the risk is about 3%, 10 years after treatment
- NHL - the risk for this type of malignancy is 7% and is highest 10-15 years after the end of therapy
- Cardiotoxic effect with increased risk of infarction, post-traditional pericarditis and dilated cardiomyopathy. The cardiotoxic effect is usually due to mediastinal radiotherapy and the use of Doxorubicin
- Pulmonary toxicity is usually mild, associated with radiotherapy and the use of Bleomicyn
- Thyroid toxicity is manifested by hypothyroidism, thyroid carcinomas, Hashimoto's thyroiditis most often after radiotherapy to the cervical region.
- Patients treated with highly learned chemotherapy and autologous transplantation have an increased risk of myelodysplastic syndrome and secondary AML [4]

Diffuse large cell B lymphoma - DLCBL (diffuse large cell B lymphoma – DLCBL)

Diffuse large cell B lymphoma - DLCBL is the most common type of non-Hodgkin's lymphoma with an age-related incidence ranging from 2 cases per 100,000 population aged 20-24 years to 112 cases in the 80-84 age group. The incidence of non-Hodgkin's lymphomas has been steadily rising since all the malignancies of the 1970s. The total incidence increased by 73% in the period 1971-1991. The current U.S. rate of non-Hodgkin's lymphoma is 15 cases per 100,000 people of all ages and genders.

The estimated rate of DLCBL in the United States is about one-third of all lymphomas, or 4.7 cases per 100,000 population per year. There is a significant difference in incidence with respect to race. The incidence is over 50% higher in the white population than in the black population in the United States, 54% higher in the US population of Japanese descent, and 27% in the Chinese population. The same incidence persists in both sexes.

Non-Hodgkin's lymphomas are known to be somewhat more common (1.3 / 1) in the male population, but it is interesting to note that diffuse large cell B lymphoma is more common in the female population.

DLCBL is a disease of middle and advanced age. The average age in large series ranges between 60 and 65 years.

Classification of hematological malignancies by the WHO Classification of Hematological malignancies in the group of DGKBL includes numerous variants of this disease, special clinical entities listed in Table 2, but for all it is characteristic that they are fast-growing tumors of mature B lympho of large or relatively large cell type. [5]

Table 2. Clinical classification and frequency of different NHL

Number	**Clinical classification and frequency of certain types of NHL**	**Percent %**
1	**Indolent lymphomas (low risk)**	
	Follicular lymphomas	22%
	B-cell extra nodal marginal lymphomas (MALT)	8%
	Chronic lymphatic leukemia / Small lymph node lymphoma	7%
	Nodal B-cell lymphoma from the marginal zone	2%
	Lymphoplasmacytic lymphoma	1%
2	**Aggressive lymphomas (intermediate risk)**	
	Diffuse large B-cell lymphoma	31%
	Mature (peripheral) T-cell lymphoma	8%
	Mantle cell lymphoma	7%
	Anaplastic large cell lymphoma	2%
3	**Very aggressive lymphomas (high risk)**	
	Burkitt lymphoma	2%
	Precursor T-lymphoblastic lymphoma	2%
4	**Other lymphomas**	7%

Immunophenotyping of malignant tissue, lymph nodes, or extranodal tumors obtained by surgical biopsy is the basic diagnostic procedure for identifying and defining a diffuse large cell type of lymphoma. Standard recommended immunophenotypic panel includes CD 20, CD 45, CD3, CD 5, CD 10, bcl-2, bcl-6 and MUM-1, Ki-67 (MI). A typical finding corresponds to CD 20+, CD45 + and CD3-.

DLCBL is further subclassified to germinal center type cells which is CD10 + or CD10 -, bcl-6 + and MUM-1 -, and to non-germinal center type (CD 10 -). , bcl-6 - or CD10-, bcl-6 + MUM1 +. Germ cell tumors are generally associated with a better clinical prognosis, but the

therapeutic approach remains the same and according to accepted criteria the origin of the malignant cell should not be an indicator of treatment choice. The significance of this subclassification is less clinically relevant in the era of monoclonal antibody application that invalidates this prognostic parameter.

Bcl-2 positivity corresponding to translocation (14,18) is observed in 15-20% of cases of DLCBL. These patients are associated with an aggressive clinical course and a worse overall prognosis even with a change in Rituximab — combined immunochemotherapy or intensive chemotherapy with autologous stem cell transplantation.

The percentage of cells that are Ki-67 positive determines the degree of mitotic index and indirectly the degree of malignancy of the tumor [6]

Etiology

B cell restriction markers-antigens (CD19, CD20, CD22) are present consistently in DLCBL. Activation antigens are excreted variably, most commonly HLA-DR and CD23 in less than 25% of cases. The presence of CD5 and CD10 indicates that at least one-third of these lymphomas occur by transformation or progression from nodular-follicular lymphoma or CLL lymphoma, small lymphocytic lymphoma.

Most cases of DLCBL present rearrangement of immunoglobulin genes by DNA hybridization that confirms their B cell line. Numerous cytogenetic abnormalities such as translocation (14:18), t (8:14), trisomy 12, and deletion of chromosome 6 have also been confirmed.

These lymphomas are often associated with other immune disorders, drugs, and chemical agents:

- ✓ Hereditary immunodeficiency conditions such as ataxia-telangiectasia syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, Wiskott Aldrich syndrome, Duncan Syndrome, Chediak-Higashi syndrome.
- ✓ Infection with HIV (AIDS), Epstein Barr virus (EBV), Helicobacter pylori, hepatitis C virus, Humat T-cell leukemia virus (HTCLV), human herpes viruses (HHVs).
- ✓ Rheumatoid arthritis, Sjogren syndrome, lupus systemicus erythematodes.
- ✓ Use, especially long-term immunosuppressive therapy (after kidney and other organ transplantation) and chemotherapy for other malignancies,
- ✓ Exposure to toxic substances, herbicides, vinyl chloride, and organic solvents
- ✓ Occupational risk factors - unproven and as yet unconfirmed.

Clinical presentation

The clinical manifestations of diffuse large cell lymphoma are different and are related to the primary localization and site of lymphoma involvement. This type of lymphoma has a rapid and progressive growth and leads to tumor masses causing infiltration of organs and tissues and sometimes organ obstruction. Pain in a particular organ or in the region of enlarged and growing lymph nodes occurs with a sharp increase in lymphoma masses. As with other types of lymphomas, DLCBL can manifest with the so-called B symptomatology, with fever, subfebrile to febrile, without a clear infectious cause and which do not respond adequately to antibiotic therapy, fever, especially evening, profuse, profuse night sweats and progressive weight loss. Generalized pruritus, itching may be present without visible skin changes, but is usually not as characteristic as in Hodgkin's disease.

Other symptoms may be caused by, for example, mediastinal lymphadenopathy, including chest discomfort, heaviness and chest pain, shortness of breath, dry cough, superior vena cava syndrome with swelling of the neck and face, and swelling of the cervical venous system; swelling of the feet and legs entirely caused by extensive pelvic lymphadenopathy, even compression-induced deep vein thrombosis of the lower extremities; abdominal pain, nausea,

indigestion, upper abdominal distension in case of primary gastric lymphoma localization (clinical picture almost identical to gastric cancer); non-specific symptoms such as anorexia, fatigue, and adynamic despite seemingly normal hematological parameters.

During the detailed clinical examination, it should not be forgotten that diffuse large cell lymphoma most often occurs in the lymphoreticular tissues and organs, ie. in the lymph nodes, spleen, liver, and bone marrow.

However, any other extra nodal localization may be involved, either primary or secondary, including the central nervous system, lungs, gastrointestinal tract, bones, thyroid, genitourinary tract, and others. Unlike primary CNS and primary testicular diffuse large cell lymphoma, which are rare, secondary involvement of these protected zones (with the haematoencephalic and hematotesticular barrier) is much more common in Burkitt lymphoma, lymphocytic acid-associated ASH leukemia-lymphoma. Common findings on physical examination include lymphadenopathy, cervical, axillary and inguinal, much less commonly cubital and popliteal. It is painless, firmly elastic, without skin changes, with a tendency to form bundles and tumor masses.

It is always desirable to document it in detail according to the localization and numerical size in cm. Splenomegaly, palpable is present in different percentages from mild to enormous. The examination of the oral cavity, especially the tonsils with special reference to asymmetric hypertrophy of the same is of special attention. Swelling of the lower extremities is present in inguinal and pelvic adenopathy. On palpation, a slight rise in temperature and heat of the skin can be noticed.

Diagnostic before therapeutic procedure

In patients with suspected DKBL, a complete blood count with a differential formula is routinely examined. Bone marrow involvement can result in anemia, leukopenia, and thrombocytopenia. It must not be forgotten that all three haematological disorders can be autoimmune due to the presence of autoantibodies to their own erythrocytes (positive Coombs test, direct and / or indirect) as well as antibodies to platelets and neutrophils. Anemia is usually normochromic with normal serum iron and normal or reduced transferrin, except in cases of gastrointestinal blood loss when secondary iron deficiency occurs.

Sedimentation as an initial laboratory result is not of great importance, except in cases of major disturbances of the protein (albumin-globulin ratio) ratio in cases of hyper or immunoglobulin hypoproduction.

Serum electrolyte levels are routinely checked, as their disturbances may be part of early renal disease.

Abnormal renal function may be the result of obstructive urinary tract changes or renal infection and is important for planned dosing of chemotherapy based on creatinine, urea, and potassium levels. Elevated uric acid counts indicate a tumor lysis syndrome or may be indicative of a large tumor lymphoma mass.

The level of LDH (lactate dehydrogenase**)** before therapy is important as a non-specific indicator of tumor size, an important prognostic factor (within the IPI index) and an important parameter for measuring the effectiveness of treatment.

Routine tests include determination of transaminase levels (GOT, GPT), alkaline phosphatase, and bilirubin, as well as virologic status for hepatitis B and C, particularly due to the possibility of reactivation of viral hepatitis as part of chemotherapy and immunosuppressive therapy (a) Rituximab).

Detailed protein status includes determination of serum albumin and total globulins, immunoglobulin levels (IgG, A and M), possible presence of paraprotein by modulation of kappa and lambda monoclonal light chains in serum and urine.

Flow cytometry of peripheral blood and / or bone marrow determines the existence of a clonal cell population and determines their immunophenotype.

FISH (fluorescent in situ hybridization) examination in a sophisticated and modern diagnostic laboratory allows the definition of common chromosomal abnormalities, as follows:

- ✓ t (3q27) bcl-6 = present in cca 35% of patients with DLCBL
- ✓ t (14; 18) bcl-2 = present in 15-20% of patients
- ✓ t (8; 14) = present in less than 5% of patients

Pre-therapeutic stagnation procedure includes routine examination of the chest and lungs with classical X-ray and computed tomography, as well as detailed examination of the abdominal organs with ultrasound and computed tomography of the abdomen, with special attention to the localization (mesenteric), mesenteric, mesenteric nodules, size, and possible infiltrative changes in the spleen and liver.

PET scan in the pre-therapy procedure is not yet accepted as standard and is dependent on the availability of the technique.

Bone marrow biopsy and aspiration (preferably bilateral from posterior crista iliaca) is part of a routine diagnostic procedure to confirm or rule out the presence of lymphoma dissemination and correlate with the histological features of the lymphoma from the primary site. Given that bone marrow infiltration increases the overall risk, lumbar puncture for cytological and biochemical examination of cerebrospinal fluid is often indicated in patients with a positive finding. Patients with present CNS symptoms require detailed examination with contrast-enhanced computed tomography and magnetic resonance imaging in correlation with the cerebrospinal fluid finding.

In patients with gastrointestinal symptoms, endoscopic examination of the upper parts with multiple biopsies of suspected changes is indicated. Routine examination is not recommended in asymptomatic patients.

Patients with severe bone pain and possibly elevated alkaline phosphatase and serum calcium are suspected of having osteolytic lymphoma changes in the bone and are examined for additional bone X-ray.

Based on previous recordings and laboratory analyzes, the Ann-Arbor staging system is still generally accepted, which systematizes lymphomas in the following 4 clinical stages:

Stage I - involvement of a single lymph node region or a single extranodal region or organ (I-E),

Stage II - involvement of two or more lymph regions on the same side of the diaphragm or localized involvement of an extranodal region or organ (II-E) and involvement of one or more lymph regions on the same side of the diaphragm,

Stage III - involvement of lymph regions on both sides of the diaphragm which may be accompanied by localized involvement of the extranodal localization or organ (III-E), spleen (III-S) or both (III-ES), and

Stage IV - diffuse or disseminated involvement of extranodal organs with or without associated nodal involvement. [11]

Prognostic factors in DLCBL

Based on the International Prognostic Index (IPI), patients with diffuse large cell lymphoma are grouped into prognostic categories. IPI uses 5 pretreatment prognostic features to identify different risk groups:

- ✓ age under vs over 60 years
- ✓ number of extranodal sites of involvement (<1 vs> 1)
- ✓ disease stage I-II (localized) vs III-IV (advanced)
- ✓ performance status 0 or I vs 2 and> 2
- ✓ serum LDH level (normal vs elevated)

Based on the above characteristics, patients are divided into 4 categories:

- ✓ category 0 or 1 = **low risk** (0 or 1 unfavorable factor)
- ✓ category 2 = **low intermediate risk** (2 unfavorable factors)
- ✓ category 3 = **high intermediate risk** (3 unfavorable factors)

- ✓ category 4 or 5 = **high risk** (4 or 5 unfavorable factors)

IPI data date back to the pre-Rituximab era, and since immunochemotherapy was used as first-line treatment, IPI has been shown to be less discriminatory and significant.

Some authors suggest reducing the number of risk factors, adapting based on age and reducing the number of risk groups to 3, very good, good and weak. In the application of the comorbidity index which increases the risk of the underlying disease and partially or completely limits the use of adequate chemotherapy, shown in Table .3 [7]

Table 3. Chars Lon Comorbidity Index

Condition	**Adverse factors**
Myocardial infarction, congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, dementia, Chronic lung disease, mild liver damage, Diabetes without organic damage	1
Hemoplegia Moderate or severe renal disease Organic Impairment Diabetes, Another malignancy	2
Moderate or severe liver damage	3
Metastatic disease (non-lymphoma)	6

Therapy

Modern treatment of DLCBL is defined by 4 major advances in the last seventy years. First, in 1940, high-voltage radiotherapy was introduced, which resulted in a cure in a small number of patients, probably only in severely localized disease, so that radiotherapy still played a significant role in localized lymphomas.

Radiation monotherapy, in stage I-A patients without tumor burden of lymphoma, provides about 50% cure with the highest number of relapses occurring outside the radiation field. Radiotherapy as the only approach is still justified in elderly patients with localized disease, with multiple comorbidities when it is assumed that chemotherapy would not be tolerated. The standard approach for stage I-A lymphoma is the use of a combined modality of therapy with reduced duration of chemotherapy (typically 3-4 cycles of CHOP), accompanied by consolidation involved-field radiotherapy. The standard dose of radiotherapy is usually 36-42 Gy but today it is considered that even smaller radiation doses are equally effective. In some centers this type of strategy is applied in stage II-A and DLCBL without risk factors, but the results are less satisfactory. Recent studies, however, report encouraging results with the addition of Rituximab to CHOP + radiotherapy in localized disease.

It has not yet been definitively confirmed whether in localized disease the addition of a biopsy and bone marrow aspiration is better without adjuvant radiation, ie. whether he can avoid and compensate the benefit.

Radiotherapy has a significant role as a consolidation treatment in initial bulky disease (tumor mass over 9 cm), as well as in partial remission in localized but persistent disease. Today's approach is very much in line with the findings of the CT and PET scan. This is especially present in primary mediastinal B lymphoma (PML), when the disease is initially often bulky and post-therapeutic residue is common. Whether to conduct consolidation radiation therapy in PET-negative patients with residual mass remains a controversial question.

The next big step and breakthrough was the establishment of CHOP, a combined chemotherapy protocol in 1976 (McKelvey et al.), which resulted in long-term survival in about

30% of patients with histologically aggressive lymphomas in stage III and IV (advanced disease). Further improvement in the final outcome was gradual over the next 20 years, without much substantial breakthrough in therapy, primarily thanks to advances in supportive care and therapy. It was primarily about more effective antibiotic therapy, better management of neutropenic sepsis, but it was probably equally important to increase the confidence of physicians in the application of more and more cycles of chemotherapy at full recommended doses without delay.

The use of granulocyte stimulation factor (GCSF) columns has certainly led to increased self-confidence in the application of aggressive chemotherapy. In any case, by twenty years of using the CHOP protocol alone until the late 1990s, overall long-term survival has improved by about 50% in aggressive lymphomas or more by 15% of initial results. The last major breakthrough in the treatment of diffuse large cell B lymphoma is the addition of a monoclonal anti-CD 20 antibody (Rituximab) to chemotherapy, the standard R-CHOP protocol: [8]

- ✓ Rituximab 375 mg / m2 (d.1)
- ✓ Vincristine 1.4 mg / m2 i.v. (d.1)
- ✓ Cyclophosphamide 750 mg / m2 i.v. (d.1)
- ✓ Doxorubicin 50 mg / m2 i.v (d.1)
- ✓ Prednisolone per os 60 mg / m2 (d. 1-5)

The application is performed in an outpatient setting and is repeated on day 21, usually 8 cycles.

In the already historically randomized study by Coiffier et al., 2002 (GELA LNH 98-5 study), Rituximab (375 mg / m2) was added (or not) to the classic CHOP in elderly patients with DGKBL for a total of 8 cycles. Significant improvement in the final outcome associated with antibody use has been confirmed. PFS-progression free survival over a 5-year period was 54% in the R-CHOP group compared with 30% in those treated with CHOP alone ($p = 0.00001$). Accordingly, 5-year overall survival (OS-overall survival) was 58% compared with 45% in the two randomized groups ($p = 0.0073$).

The benefit of adding anti-CD 20 antibody has been confirmed in both low and high risk groups of patients according to IPI. These results have been confirmed by the USA Intergroup Trial (Habermann, 2006), as well as in young patients with a good prognosis in the Mint study (Pfreundschuh, 2008). application of chemotherapy at 14-day intervals. [9]

Current summary results from the long-term use of a standard R-CHOP with more than 10 years of follow-up show an average survival of 8.4 years, a 10-year survival of over 40%, and a progression-free survival of 4.8 years (GELA).

Attempts to improve these results are numerous, mainly with the addition of an adjunct chemotherapist and time concentration of therapy. The French lymphoma group in a randomized study with ACVBP protocol (addition of Bleomycin, 50% dose support with pegylated GCSF) only improved PFS in young patients with high-risk DGCL, but with increased therapy-associated mortality.

There is still no confirmation from randomized studies that maintenance with Rituximab after completion of prescribed immunochemotherapy and achieving haematological remission has significant value and benefit in preventing relapses, as is the case with follicular lymphoma. Interestingly, maintenance with Rituximab showed significant improvement in patients receiving induction-only CHOP treatment.

Central nervous system prophylaxis

The incidence of CNS lymphoma progression or CNS relapse is relatively low and is below 5% in most studies. The introduction of initial treatment with monoclonal antibodies has led to some reduction in the percentage of CNS relapses (Boehme et al., 2009; Villa et al., 2010). It is accepted that the incidence of CNS relapses is low enough that prophylaxis is not warranted in all patients. Much attention is paid to defining risk factors for secondary CNS disease.

It is recommended that lumbar puncture be performed routinely in all patients with bone marrow involvement, elevated LDH, and more than one extranodal localization. Liquid examination involves cytology, cell count (cytospin), biochemistry (glucose, protein), and preferably PCR analysis.

In case of a positive finding, treatment for CNS lymphoma should be applied. In case of a negative finding in the cerebrospinal fluid, CNS prophylaxis is performed in high-risk IPI groups or in cases with elevated LDH values and more than one extranodal localization, with the testicles, paranasal sinuses, epidural space, and breasts being considered at particular risk.

Recommended therapy for CNS prophylaxis includes at least 5 intrathecal applications of Methotrexate 10 mg / m2 with each cycle of chemotherapy. After completion of immunochemotherapy, the recommendation is the application of 2 sessions of high doses of Methotrexate i.v. at 14 days (3g / m2). The assumption is that intravenous administration of MTX is the key to significantly reducing CNS relapses (Tilly et al., 2003) from 5.8% to 2.2%.

Therapy of relapse or refractory disease

Patients with primary refractory disease who do not respond to initial treatment with immunochemotherapy, patients with progressive disease during therapy, as well as patients with partial remission and patients with early relapses (especially shorter than 6 months) are candidates with highly learned salvage chemotherapy with autologous haematopoietic stem cell transplantation.

Saklvage protocols are standardized and apply ICE + Rituximab or DHAP + Rituximab. It is standard practice to add Rituximab to second-line protocols, but given that the patient has not previously responded or had an early relapse with antibody application, use is still debatable. In relapses occurring 6 months after defining haematological remission, re-histological evaluation of the lymphoma is recommended.

In patients with relapsing-resistant hemorrhagic disease and in cases of progressive disease or primary failure of therapy, allogeneic transplantation from an identical donor should always be considered. Patients up to a large tumor mass after transplantation should also receive adjuvant radiotherapy. [10]

Problem of cardiotoxicity

It is clearly defined that the total cumulative dose of doxorubicin is the major risk factor for cytostatically associated congestive heart failure. The upper cumulative toxic dose is 450 mg / m2 and is usually met with the initial treatment. Unfortunately, even at lower doses in some patients, cardiac function is compromised. The risk increases with age, coronary artery disease, valvular heart disease, diabetes, smoking, weight gain, and hypertension.

It is very important to maintain blood pressure before and during anthracycline therapy. Numerous attempts have been made to develop new anthracyclines or their derivatives to improve the therapeutic window. Epi (doxo) rubicin can be used in almost double the dose, without increased cardiotoxicity, but the dilemma remains for its equivalent efficacy in these doses as well. The second possible replacement is Idarubicin 10 mg / m2 (CIOP) but the results are inferior to the standard CHOP. The equivalent dose should be at least 14 mg / m2, at least in terms of myelosuppression achieved.

An alternative strategy is to use liposomal doxorubicin with the same oncological activity and reduced incidence of heart failure, but the approach has not yet been standardized and accepted.

Growth factors

In patients with DLCBL chemotherapy with standard R-CHOP protocol to varying degrees leads to secondary myelosuppression. Neutropenia complicated by a febrile condition with this therapy develops in 20 to 22% of patients. In the development of febrile neutropenia, the

use of column stimulating factors (GCSF) with regular monitoring of leukocyte count and absolute granulocyte count and timely and appropriate treatment of any infection is recommended during each subsequent cycle of chemotherapy. Preventive administration of antibiotics is not generally accepted or recommended.

For patients with anemia as part of the underlying disease and as a consequence of myelosuppression, supportive treatment with erythropoietin (EPO) subcutaneously once a week for 30-50,000 units (or 10,000 times three times a week) is recommended. The hemoglobin level should be maintained at least above 90 g / l, both because of the general condition of the patient and because of the efficacy of the cytostatics in a normally oxygenated cell.

Diet and activities

No special diet is recommended for patients with DLCBL except reasonable salt reduction during chemo and steroid therapy due to fluid retention and maintenance of normal blood pressure values.

Special replacement of vitamins and minerals is not recommended.

There is no reason to limit physical activity, except in cases of severe thrombocytopenia to reduce the risk of traumatic bleeding or haematomas. Fatigue is usually associated with lymphoma and as a consequence of therapy.

Patient education and counseling

Patients with DLCBL should receive appropriate tailored information on:

- ✓ therapeutically induced nausea and vomiting,
- ✓ therapeutically induced alopecia,
- ✓ febrile neutropenia,
- ✓ therapeutically associated thrombocytopenia and the possibility of bleeding,
- ✓ therapeutically induced menstrual disorders and the possibility of sexual dysfunction,
- ✓ avoiding pregnancy during and after therapy,
- ✓ possibility of permanent sterility in men and recommendation for sperm conservation,
- ✓ possibility of late sequelae of chemotherapy (anaphylactic reactions, secondary myelodysplastic syndrome, acute leukemias, fatal infecti

References:

1. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International P rognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998; 339:1506-1514.
2. Canellos GP et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD or MOPP alternating with ABVD. N Engl J Med 1992; 327:1478-1484.
3. Sureda A et al. Reduced Intensity conditioning compared with conventional allogenic stem cell transplantation in relapsed and refractory Hodgkin's Lymphoma: An analysis from Lymphoma Working Party of the European Group for Blood and Marrow transplantation. J Clin Oncol 2008;26:45-462.
4. Heutte N et al. Quality of life after successful treatment of early stage Hodgkin's Lymphoma: 10 years follow up of the EORTCGELA H8 randomised controlled trial. Lancet Oncol 2009; 10:1160-70.
5. Jaffe ES et al. (2001). In Kleihues P, Sobin L eds. WHO Clasifications of Tumours. Lyon; ARC Press.
6. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Clasification Project. Blood, 1997;89:3909-3918.
7. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Prognostic Factors Project. N Engl J Med, 1993;329:987-994.

8. McLaughlin P et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolend lymphoma:half of patients respond to a four-dose treatment program. J Clin Oncol, 1998;16:2825-2833.
9. Coiffier B et al. CHOP chemotherapy plus rituximab compared with CHOP alone in eldery patients with diffuse large B-cell lymphoma. N Engl J Med, 2002;346:235-242.
10. Philip T et al. Autologous bone marrow transplantation as comperaed with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med, 1995;333:1540-1545.
11. Cheson BD et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014;32:3059-3068.
12. WHO. https://www.who.int/en/