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DOCTORAL THESIS

**SURVIVAL PREDICTIVE FACTORS IN EARLY AND
ADVANCED STAGES OF HODGKIN LYMPHOMAS**

A B S T R A C T

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ABSTRACT

In the last decades, the prognosis of Hodgkin's lymphoma (LH) has been significantly improved by introducing new chemotherapy regimens administered according to the risk class in which the patient falls. The identification of risk factors is essential for the orientation of the treatment during the disease. Both clinical and biological factors have been implicated in LH prognosis and are often used in prognostic scores to discriminate at risk groups. To prevent under- or over-treatment, patients are usually assigned to one of the three risk groups for first-line treatment, based on clinical risk factors (1).

Treatment of Hodgkin's lymphoma (LH) has progressed greatly in recent years. Healing rates are found in 80-90% of patients, and LH is among the neoplastic diseases that have the best long-term outcome after chemotherapy treatment. However, 15-20% of patients will develop resistance to therapy or relapse after treatment, usually within the first two years (1).

A multitude of prognostic factors are available in LH. Traditional clinical and laboratory prognostic factors are often a surrogate marker for biological characteristics that are often not included in the standard assessment. There is no current consensus on how to integrate these biological markers as accepted clinical prognostic risk factors in prognostic scores or how to use this information to tailor treatment. It remains a challenge to identify the best parameters to play in predicting the prognosis in a single patient and to identify the significant group of patients for whom standard treatment is not sufficient.

Both the National Cancer Network [4] and the guidelines of the European Society of Oncological Medicine (ESMO) [5] provide recommendations for both personalized treatment and long-term follow-up of patients in complete remission with Hodgkin's lymphoma. (4, 5) Most relapses occur within the first 3 years after therapy, and Hodgkin's lymphoma is the leading cause of mortality in the first 10-15 years of follow-up. (109) Follow-up visits are recommended every 2-4 months for the first 1-2 years and every 3-6 months for the next 3-5 years.

The examination includes the following [109]:

- History and physical examination
- Completion of blood cell counts and changes in lactate dehydrogenase (LDH), hematoma sedimentation rate (ESR), glucose and lipid levels
- Levels of thyroid stimulating hormone (TSH) (at least once a year if the patient has had radiation therapy to the neck)
- Chest x-ray or chest CT scan every 6-12 months in the first 2-5 years
- Abdominal and pelvic CT scan may be added every 6-12 months in the first 2-3 years, especially if the disease has started sub-diaphragmatically

After 5 years, NCCN recommends the following surveillance program [4]:

- Annual history and physical examination

- Annual blood pressure
- Aggressive management of cardiovascular risk factors
- Pneumococcal, meningococcal and Haemophilus influenzae revaccination after 5-7 years if the patient received splenic irradiation or splenectomy
- The annual influenza vaccine
- stress test / echocardiogram at intervals of 10 years after treatment completion
- carotid ultrasound at 10-year intervals if the patient has had a throat irradiation
- Annual hematological and biochemical profile
- TSH at least once a year if the patient has had a throat irradiation
- The biannual lipid levels
- Blood glucose
- In patients at increased risk of developing lung cancer, CT scans at low doses may be considered.
- Patients who have received chest irradiation should be examined annually with mammography, starting at age 40 or 5-8 years after radiotherapy;

However, the American Cancer Society also recommends breast magnetic resonance imaging (MRI) for patients who have received mediastinal radiotherapy between the ages of 10 and 30 (110).

The use of PET scans for surveillance in patients with complete remission is not particularly encouraged by NCCN, due to the possibility of false positive results.

Pulmonary involvement may result from irradiation in the mantle or post ABVD chemotherapy. Initial tests and further evaluation with lung function tests are recommended. The best parameter to track is the diffusion capacity of carbon monoxide.

Objectives visible in the pursuit of Hodgkin's lymphoma survivors include the following (111):

- Timely identification of secondary cancers
- Sepsis should be considered as a possible cause of fever in a splenectomized patient
- Diagnosis and treatment of predictable complications of treatment with Hodgkin's lymphoma, such as coronary arteries, ulcerative or thyroid disease

The paper consists of a general part that performs a synthesis of current knowledge regarding Hodgkin's lymphoma. Aspects of pathogenesis, treatment diagnosis and the response of these patients to the treatment as well as the evolution of these patients over time are addressed.

The purpose of this thesis is to identify the prognostic factors based on which we can predict and monitor the evolution of the patient diagnosed with Hodgkin's lymphoma and the optimal treatment modalities.

Over the years, many prognostic factors have been identified, some of them losing their usefulness over time, but new ones have emerged with the development of medical technology.

Prognostic factors provide useful information so that the patient can benefit from targeted therapy.

In the special part after the description of the objectives of the paper and of the approached methodology, the results obtained on the study lot are presented. The work ends with the chapters of discussions and conclusions.

A number of prognostic factors are available in LH. Evaluation of them from the beginning of the disease is important to classify patients in different risk categories and to adapt their treatment in order to obtain a most favorable response. In our study we evaluated as risk factors with negative prognosis: anthropometric parameters such as age and sex, hematological and biochemical parameters, disease extension,, extra-ganglionic affect, presence of tumor masses, stage of the disease, presence of type B symptoms.

A very important factor is age. It has an impact on prognosis in at least two ways: on the one hand, it is associated with LH biology and, on the other hand, older age is often associated with co-morbidities and reduced tolerability of the chemotherapy regimens used in younger patients. . LH epidemiology is characterized by a bimodal age distribution. Following the peak at the age of 20 of young adults, there is a second increase in the incidence, especially in men, after the age of 50-55 years. Compared to other neoplastic hematologic diseases, which usually establish the cut-off to define the elderly patients at 60, the cut-off in the case of LH is shifted to a younger age. In the International Prognostic Score for patients with advanced stage disease, the age is lowered to 45 years, EORTC considers age at more than 50 years as a risk factor for patients with limited stage disease. Older age is associated with a higher frequency of mixed cell histotype and EBV presence in neoplastic cells compared to younger patients. (18) EBV association seems to be a negative prognostic factor in older patients (19-21). It is assumed that loss of immunological control of EBV-infected cells could contribute to the development of EBV associated with LV in the elderly. The aging of the immune system (immunosenescence) is characterized by the reduced function of the adaptive immune response, which includes the function of T and B cells. It has not yet been established that immunosenescence is a mechanism in the pathogenesis of LH in the elderly and whether it contributes to the negative effect on the prognosis.

Disease spread and tumor burden is the most important feature of the disease, which is used to stratify treatment strategies. (11) In the limited stage disease, the presence of a large mass detected on the mediastinal radiograph or CT at staging is considered a negative predictor of the treatment response. (12) In contrast, in the advanced stage of the disease, the presence of a large tumor is not a risk factor in the International Prognostic Score (IPS) for LH. (13) Because volume measurement is limited to the largest single mass, it could underestimates total tumor burden in patients with diffuse disease. Newer methods of measuring tumor burden may give a more accurate estimate of tumor volume. (14-15) The complexity of evaluating all lesions in any scan section with decreasing normal structures present in the tumor tissue and approximating the involvement of the bone marrow has limited a wider application of this type of evaluation.

The spread of LH beyond its lymph node microenvironment to the extralymphatic organs is associated with a lower outcome. In the limited stage, damage to an extranodal site is defined as a risk factor by the GSHG scoring system. In patients with advanced stage

disease, diffuse organ damage in stage IV is an independent risk factor in IPS (16-17). In our study, the extra-angular involvement and the presence of large tumor masses are correlated with an unfavorable response to treatment, even if there is no statistical significance except in the case of the response to the third line of treatment.

LH therapy in the elderly is often complicated by the toxic side effects of chemotherapy. Standard treatment with ABVD is often not recommended for patients over 70 years of age. Bleomycin causes an increased frequency of pulmonary toxicity. In a recent report, the incidence of pulmonary toxicity with bleomycin was 32%, with a mortality of 25%. (22) Neither high-dose BEACOPP regimen is recommended for patients with LH in advanced age over 60 years. (23) An increase in mortality of up to 13.3% was found in these situations. (24) Therapy of elderly patients with LH remains a challenge and an effective regimen with acceptable toxicity profiles is still lacking. The availability of monoclonal antibodies such as Brentuximab may be a major step. In our study there was no statistically significant correlation between age and response to treatment, probably due to the fact that the average age of patients in our study is below 42 years.

This study is a prospective-retrospective study that included patients diagnosed with Hodgkin's lymphoma between January 2014 - December 2017 based on clinical, biological, immunohistochemical and therapeutic response parameters, with proven prognostic value.

The main objectives pursued in this paper were:

1. Identification of prognostic factors
2. Follow-up of clinical evolution and response to treatment in Hodgkin's lymphoma, correlated with prognostic, clinical and biological factors.
3. Comparing the evolution of patients according to the treatment applied

In order to achieve the proposed objectives we analyzed the following factors:

- a) clinical parameters (sex, age, presence of B signs of disease, stage of disease, number of lymph node / extraganglionic determinations)
- b) hematological parameters: (hemoglobin value, leukocyte count, platelet count, leukocyte formula)
- c) biological parameters (VSH, LDH, C-reactive protein, beta 2 microglobulin, fibrinogen level, albumin, total proteins, immunoglobulins)

Based on the results obtained, we evaluated the survival of patients with Hodgkin's lymphoma and the appropriate therapeutic means. The different evolution of patients with Hodgkin's lymphoma at the same clinical stage is mainly due to the characteristics of the host organism, the time of diagnosis and the period from the onset of the disease to the time of diagnosis.

The most realistic assessment of the prognosis of a patient at the time of diagnosis is the premise of an optimal therapeutic approach.

The study included 71 patients diagnosed with Hodgkin's lymphoma between January 2014 - December 2017, in the Clinic of Hematology of the Municipal Clinical Hospital Timișoara. The study being a prospective-retrospective study, included patients diagnosed prior to the start of the study and who presented for control, as well as patients who first appeared in the Clinic of Hematology of the Municipal Emergency Clinical Hospital in Timisoara during the study. All the patients included in the study expressed their agreement in this regard.

In order to carry out the study, the observation sheets of the patients admitted to the Clinic of Hematology of the Municipal Clinical Hospital were analyzed, thus constituting the group of patients included in the study. All data were recorded electronically in a table in the Excel program in Microsoft Office 2010. Then the data was transferred to the SPSS20.0 program for statistical processing.

Clinical, biochemical, hematological, immunohistochemical and imaging parameters were followed for each patient as follows:

- clinical evaluation (performance status, presence of lymph node / extraganglion determination, hepatosplenomegaly)
- biochemical evaluation (VSH, LDH, C-reactive protein, beta 2 microglobulin level)
- hematological evaluation (hemoglobin level, leukocyte count, lymphocyte percentage, platelet count)
- immunohistochemical evaluation (proliferating cell phenotype)
- image evaluation

The diagnosis of Hodgkin's lymphoma was established after several stages:

1. Clinical examination
2. Paraclinical diagnosis including histopathological, immunohistochemical and immunophenotypic examination
3. Imaging diagnosis
4. Highlighting the complications

❖ Clinical examination: it was performed at the patient's presentation in the Hematology clinic and subsequently at all the hospitalizations. It consisted of examining all the ganglionic areas (occipital, retro- and pre-auricular, submentonary, submandibular, laterocervical, supraclavicular, axillary, epitrochlear, inguinal and popliteal) and description of the characters of the adenopathies. The presence of organomegaly (the dimensions of the liver and spleen) was also appreciated. Direct examination of oropharyngeal lymphoid tissue (Waldeyer ring) and / or indirect laryngoscopy. Highlighting clinical signs that suggest the presence of large tumor masses (mediastinal; abdominal), as well as the presence of extraganglionic determinations (salivary, cutaneous, digestive, orbit, thyroid, etc.). During the clinical examination, the status of the

clinical performance was evaluated, important in establishing the prognosis and the choice of the therapeutic behavior and illustrating the host-tumor relationship.

- ❖ Paraclinical diagnosis including histopathological, immunohistochemical and immunophenotypic examination

The data were collected from the observation sheets for each patient, following the anthropometric parameters, the stage of the disease, the adverse events that occurred, the type of treatment performed and the response to the treatment. Statistical processing of the data was performed with the program SPSS20.0. For descriptive statistics the results were expressed in percentages and absolute values. In order to identify the prognostic factors within the group, linear regression analyzes were performed. For the analysis of the survival curve in the 2 groups, the Kaplan Meyer analysis was used.

In conclusion, treatment in Hodgkin's Lymphoma is guided by traditional clinical and laboratory prognostic factors that are often a surrogate marker for biological features that are often not included in the standard evaluation. There is no current consensus on how to integrate these biological markers as accepted clinical prognostic risk factors in prognostic scores or how to use this information to tailor treatment.

Although a number of factors that may influence the response to treatment and survival of these patients are still being studied, it remains a challenge to identify the best parameters to play in predicting the prognosis in a single patient and to identify the significant group of patients for whom the treatment standard is not enough.