STUDY OF CLINICAL, ANATOMO-PATHOLOGICAL AND BIOLOGICAL PROGNOSTIC FACTORS IN NON- HODGKIN’S LYMPHOMAS

The continuous improvement of the specific and supportive therapeutic means makes the oldest interest accorded to prognostic stratification of non-Hodgkin’s lymphomas (NHL) a perennial favorite. Together with the classical clinical-biological and histological factors, proved by time, new markers with prognostic or predictive properties keep being discovered. Immunohistochemistry is a method that through the collected capital of experience, occupies an important place in the diagnostic of NHL, showing also important prognostic values.

The present dissertation is 334 pages long, from which 39 pages of references. The first 53 pages are dedicated to the description of the state of the art in the field, and contain present data on NHL classification as well as principles, markers and modern methods of prognostic stratification.

The author’s research is presented in the next 242 pages, and it covers two main areas of interest:

1. the evaluation of „classical“ prognostic factors
2. immunohistochemical markers with prognostic and predictive potential.

Data are presented as tables and figures, including histological images of immunohistochemistry. For statistical analysis, it were used descriptive statistics, comparison of groups, survival analysis (Kaplan-Meier estimation for survival curves, with log-rank comparison and co-varied Cox analysis). The predictive parameters were the percentage rates of remissions (Cheson criteria), the prognostic parameters were mainly the overall survival (OS) and relapse-free survival (RFS).

The study of „classical“ prognostic factors was conducted on 188 NHL cases, patients newly diagnosed, treated and followed in the I Medical Clinic –Hematology, Emergency Clinical Hospital Tîrgu Mures, between 1996-2006. The patients cohort was structured in 7 principal groups: primary nodal diffuse large B-cell lymphomas–DLBCL (62 cases), diffuse large B-cell lymphoma with primary localization at Waldeyer’s ring (8 cases), primary gastric NHL (30 cases), T-cell peripheral lymphoma, unspecified -TCL-U (27 cases), anaplastic T-cell lymphoma (40 cases), follicular NHL -FL (40 cases), splenic marginal zone lymphoma (12 cases). The „classical“ analyzed prognostic markers were grouped in categories:

- demographic factors (sex, age at diagnose),
- factors reflecting the tumor burden and its invasive potential (Ann Arbor stage, bulky tumor, serum lactate dehydrogenase, serum alkaline phosphatase, the presence and histological pattern of the marrow involvement, liver and/or spleen enlargement),
- factors reflecting the host answer to the tumor aggression (B symptoms, performance status, hemoglobin level, platelets count, serum albumin, erythrocyte sedimentation rate),
- prognostic models (the classical model -International Prognostic Index-IPI and versions of it, alternate prognostic models),
- primary localization as a prognostic variable,
- response to treatment as a prognostic variable,
- histological particularities as prognostic elements.

Their analysis was done on each group and also comparatively between groups and subgroups. There were analyzed and quantified the individual incidence, relationship with the other prognostic variables, the predictive and prognostic impact. The correspondence with data from scientific literature is evaluated and peculiar characteristics of the cases from
groups and subgroups are underlined. For classical and alternative prognostic models, the repartition of cases from the considered groups and subgroups is presented, the predictive and/or prognostic influence of the stratifications is studied, with emphasis on the practical relevance.

The immunohistochemical (IHC) markers with prognostic potential were determined using the tissue-microarray technique, on 49 cases, newly diagnosed, treated and followed in the 1st Medical Clinic –Hematology, between 2002-2006:

- 27 primary nodal DLBCL –immunohistochemically evaluated markers: CD79a, bcl2, bcl6, CD10, Ki67, p53, CD138, CD5, CD44s, CD44v3, CD44v4, CD44v5, CD44v6 on tumor cells and CD68 on non-tumor, infiltrating macrophages;
- 15 FL – evaluated markers: CD79a, bcl2, bcl6, CD10, Ki67, p53 on tumor cells and CD68 on non-tumor, infiltrating macrophages;

On DLBCL cases, the individual incidence of the immunohistochemical expression for studied markers is evaluated, together with its correlation with the „classical“ clinico-biological factors and also with the other studied IHC markers. The predictive and prognostic impact is presented and quantified on the considered group. It is analyzed whether the cases belong to the subgroup with germinal-center, activated B-cell or unspecified phenotype of the proliferating tumor cells (using the IHC surrogate models proposed by Tzankov, Murrini and Zinzani), with the associated predictive and prognostic influences.

The reduced number of FL evaluated did not allow for a study of the influence of IHC markers on the predictive and prognostic parameters. Observation on their qualitative and quantitative expression were made, underlining the correlations with histological grade. All 7 TCL-U cases expressed CD4, with CD8 co-expression in 4 cases and an weak expression of granzyme B in 2 cases. The expression of p53 positively correlate with Ki67 expression and a high number of CD68+ infiltrating macrophages appears as a positive predictive element.

The so called „classical“ clinical-biological and anatomo-pathological factors have an old career in the field but they keep over the years both their utility and actuality. The aspects revealed from the present analysis of prognostic markers in NHL cases from personal casuistry, during 11 years, with proper statistical methodology, can represent a piece in the vast and controversial study field witch is the prognostic and predictive evaluation of NHL. Aside from the classical model IPI and its constitutive elements, a series of other factors, reflecting clinical, para-clinical and morphological aspects, reveal important prognostic and/or predictive values. Their utility is obvious mostly on smaller groups of patients, or in the individual prognostic study of a specific case, the final evaluation considering the whole specter of factors.

The immunohistochemical markers brings, for NHL prognostic stratification, useful information that, together with other classical factors, can configure better the risk profile for certain groups of patients, with important impact on the therapeutic decision.

By embodying, in a larger block, tissue samples originated from more cases, the IHC tissue-microarray technique allows good concordance with the standard IHC method, with an important time and reagents economy. This technique, used on an increasingly larger scale abroad, especially for retrospective studies, is at the present moment applied only in a few medical centers from Romania; at Tîrgu Mureș, the present study is the first one using this histological method.