benefit from more aggressive approaches while treatment reduction might be useful in low-risk patients.

Approaches to identify reliable immunohistochemical prognostic factors have so far failed, so we are left with clinical prognostic factors, most of which are included in the IPI: age, stage, extranodal involvement, LDH and performance status. An important prognostic factor not included in the IPI is bulky disease.

Studies have shown that more than 90% of patients with stage I disease and no adverse prognostic factors are cured with 3 CHOP21 cycles and involved-field radiotherapy. The prognosis of those with stage I and risk factors or stage II and no risk factors is only slightly worse if treated with 6 cycles of R-CHOP21, 2 additional doses of rituximab with and (in cases of bulk) radiotherapy.

For intermediate risk patients (aaIPI=1), it seems that shortening the period between R-CHOP cycles to 2 weeks does not improve outcome but less cycles need to be given, so 8 cycles of R-CHOP21 or 6 cycles of R-CHOP14 can be regarded as optimal, resulting in cure rates of 60-70%. This is also the treatment of choice for patients over 60 years who do not tolerate more aggressive approaches. In younger high-risk patients (aaIPI >1) the situation is less favorable and less clear. Less than 50% are cured with R-CHOP21. Studies suggest that their outcome can probably be improved with R-ACVBP or R-CHOEP14 regimens.

Finally, patients with cardiac systolic dysfunction cannot tolerate CHOP. For them, infusional R-EPOCH or R-CEOP, a regimen in which doxorubicin is replaced by etoposide, offer a realistic possibility for cure.

WORKSHOP ON PLASMA CELL DISORDERS, SECRETORY LARGE CELL LYMPHOMAS AND PITFALLS AND DIFFICULT CASES

L-11

Histological and immunohistochemichemical study of malignant lymphomas in Macedonia-Study of 222 cases

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The recognition of several new types of non-Hodgkin's lymphoma (NHL) in the beginning of 1990-ties has led to proposals for changing lymphoma classifications to the new WHO classification of NHL-s by the International Lymphoma Study Group (ILSG).(1) The proposed classification defined NHL subtypes using contemporary morphologic, immunologic and mollecular techniques, but did not include original data on patients characteristics and outcome, nor the distribution of the various NHL subtypes.

In 1995, a group of leading hematopathologists, clinicians and statisticians conducted a retrospective clinical evaluation of the ILSG classification of NHL. In this study, besides the main clinical characteristics and treatment outcomes for the common NHL subtypes, the distribution of the major subtypes of NHL-s across geographic regions, was also presented. This study provided evidence that the distribution of NHL subtypes differed by geographic region. Since then, many regional epidemiological studies were done by the ILSG together with the local leaders. The clinical significance of the new entities and the practical application of the new WHO Classification of malignant lymphomas in Macedonia has been done by the help of the leaders of the ILSG.

In this presentation we present the main results from this study: the distribution of the major subtypes of NHL with their main histological and immunophenotypic features; main epidemiological features of the diagnosed NHL-s; pitfalls in the differential diagnosis of NHL-s. The results from the clinical data will be presented elsewhere.

Material and methods: According to the design of the study, we have collected 222 consecutive cases of previously untreated NHL that were representative of the geographic region, in the period between January 1, 2009 and July 31, 2010. The study included cases diagnosed mainly at the Institute of Pathology and University Clinic of Radiotherapy and Oncology at the Medical Faculty in Skopje (two main referent centers in the country).

In all cases, tissue biopsy samples that were adequate for diagnosis and classification before initial therapy were included; positive bone marrow specimens were included in the pathology review, as well. Clinical data, treatment data, and some follow-up information were also collected for all cases from the medical records by a clinician at the University Clinic of Hematology. All the data were recorded on a standardized form for direct computerized data entry given from the ILSG – Nebraska University.

These data included coded patient, patient sex, ethnic origin, and date of birth; the date and site of the diagnostic biopsy; a tabulation of nodal and extranodal sites of involvement; Ann Arbor stage at the time of diagnosis.

Available laboratory data, performance status and maximum diameter of the largest tumor mass were recorded, as well as the initial therapy and therapeutic response, details of remission, progression and follow –up were tabulated in each case.

The pathology slides and reports were collected at the Institute of Pathology in Skopje, including the cases from the Laboratory for Histopathology and Cytology at the University Clinic of of Radiotherapy and Oncology. All the slides were stained by H&E, Giemsa, PAS and Reticulin and immunostained with LSAB technique at the Institute of Pathology.(2,4) All the cases were restained at the Institute of Pathology, University of Wuerzburg .

The original stained slides and restained slides were organized for review from five expert hematopathologist, and additional sections, immunostains, as well as mollecular analyses, were performed if deemed necessary by the expert pathologists. These results were recorded on a standardized form for direct computerized data entry. These additional analyses were done at the Institute of Pathology in Wuerzburg by courtesy of Prof. Konrad Muller-Hermelink and Prof. A. Rosenwald. Diagnostic slides were previously diagnosed from a domestic pathologist (Petrushevska G., Zografski G., Ivkovski Lj.). Afterwards, they were reviewed and classified independently by each expert hematopathologist (Muller-Hermelink H. K., Weisenburger D., Diebold J., Natwani B., Maclennan K.). In addition to independent diagnoses rendered by each of the expert pathologists, a consensus diagnosis was reached in each case on multi-headed microscope by discussion of the five expert pathologists at the end of each day. If there was no agreement, additional immunostains, mollecular analyses and additional information were required, (mainly done from the Prof. Hermelink laboratory in Wurzburg). Few additional clinical informations were available for this purpose. Finally,

all the data were sent to Prof. Weisenburger, who made final consensus diagnoses of the Macedonian cases with NHL. Mollecular analyses done from the Prof. Hermelink laboratory in Wurzburg were as follows: Case#6, #14; #85; #141: EBER (-) ; Case# 45; #112; #217: PCR-IgH: FR3A (oligoclonal), FR2A (monoclonal) ; Case#53; #72: FISH c myc BAP; Case #106; #112: Bcl2-BAP FISH; Case # 125: PCR-TCRg.

Results: Fourteen from the 222 cases (6.8%) were diagnosed as other than NHL and, thus, were excluded from further analysis. Approximately 32.7% of the cases were forms of diffuse large B-cell lymphoma . Approximately 11.21% of the cases were types of marginal zone lymphoma (extranodal, nodal and splenic marginal zone NHL) . SLL/CLL was observed in 9.21% of the cases and follicular lymphoma was observed 7.31 of the cases. Mantle cell lymphoma comprised 4.39% of the cases. There were solitary plasmacytic lesions (bone and extraosseal lesions) in 6.34% of the cases. All types of T cell proliferations made up only 5.85% from the cases and anaplastic large T/null-cell lymphoma was present in 1.46% of the cases.

Percent of disagreement was lower for low grade NHL-s, probably due to insufficient immunophenotyping in the domestic laboratories. However, for these low grade lymphomas, information on the immunophenotype did not increase significantly the diagnostic accuracy even in the expert hematopathologists group. From this point of view, further mollecular analyses were significantly helpful, as well as clinical data. Immunostains for other NHL-s were significantly accurate and resulted in greater agreement in the diagnoses. For some cases, clinical data were very important for final decision for making a diagnosis. Opposite to this, precise histologic diagnosis of a specific type of lymphoma provides both clinically and prognostically important information. Immunophenotyping added significantly to the accuracy of diagnosis of many of the lymphoma types, including MCL, DLBCL and PTCL. This was not the case with the other low grade NHL-s, such as FL, SLL and MZL, where major pitfalls were observed. Also, it is very important to have tissue available for immunostaining and other special analyses to facilitate proper patient care.

That implies the need for more intensive communication among the surgeon, hematologist and pathologist. One of the final conclusions of this study was that besides the importance of the clinical presentation for the precise diagnosis of the NHL, it is also important to have other clinical parameters such are prognostic factors as defined by the International Prognostic index. They must be combined with the histologic classification for appropriate clinical decisions (3,5).

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