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Original Article

Distribution of lymphomas in Poland according to World Health Organization classification: analysis of 11718 cases from National Histopathological Lymphoma Register project - the Polish Lymphoma Research Group study

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Abstract: Most national lymphoma registers rely on broad classifications which include Hodgkin and non-Hodgkin lymphomas (NHL), multiple myeloma and leukaemia. In Poland the National Histopathological Lymphoma Register project (NHLR) was implemented by hematopathologists in accordance with the 2008 WHO classification into haematopoietic and lymphoid tissues. We present the NHLR data and compare lymphoma distribution in Poland, Europe, as well as in North Central and South America. Records of 11718 patients diagnosed in 24 pathology departments from all over the country were retrieved and reclassified into indolent and aggressive lymphomas according to the 2008 revised WHO classification system. DLBCL (32.9%; 2587), CLL/SLL (31.84%; 2504) and MCL (9.04%; 711) were the three most frequent NHL. The ratio of indolent to aggressive NHL was 1.72; 63.25% (4809) to 36.25% (2794) of cases respectively. Multiple myeloma was less frequent as compared to the data from population-based national cancer register (13.32% vs. 28.94%). Major differences between NHLR and European and American data on NHL subtypes concered: higher incidence of aggressive B-cell lymphomas including DLBCL, lower FL and MALT incidence rate. The percentage of unclassified lymphomas in the study was minimal due to participation of hematopathologists.

Keywords: Lymphoma, register, histopathology, epidemiology, hematopathology

Introduction

Lymphomas are a heterogenous group of malignancies with different incidence rate, etiology and prognosis. Population-based studies of most cancer registers apply a broad classification into two categories: Hodgkin (HL) and non-Hodgkin lymphomas (NHL); multiple myeloma and leukemia subgroups are usually separated [1]. Some registers optionally adhere to the third revision of International Classification of Diseases-Oncology (ICD-O-3) but there is no overriding regulation of its implementation. On the other hand fundamentals for pathologists and clinicians are derived on the World Health Organization (WHO) classification of tumors [2]. Lymphoma grouping is based on the degree of cell maturation; lymphoma originates from precursor cells in primary lymph organs (bone marrow and thymus) or from mature cells, which are physiologically located in the peripheral lymphoid organs (lymph nodes, spleen, Peyer's patches). The 4th edition of WHO classification of hematopoietic and lymphoid tissues published in 2008 comprises the following 6 main groups of lymphoid neoplasms: precursor B-cell

Table 1. Distribution of lymphoid neoplasms in the The National Histopathological Lymphoma Register project

Lymphoid neoplasms	No	%
Mature B-cell neoplasms	9424	80.42
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)	2587	22.08
Chronic lymphocytic leukemia/small lymphocytic lymphoma	2504	21.37
Plasma cell myeloma	1561	13.32
Mantle cell lymphoma	711	6.07
Follicular lymphoma, all grades	573	4.89
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)	387	3.30
Hairy cell leukemia	185	1.58
Lymphoplasmacytic lymphoma	173	1.48
B-cell lymphoma, subtype cannot be determined	149	1.27
Nodal marginal cell lymphoma	127	1.08
Splenic marginal zone lymphoma	112	0,96
Burkitt lymphoma	109	0.93
Primary mediastinal diffuse large B-cell lymphoma	86	0.73
Primary cutaneous follicle centre lymphoma	31	0.26
Extraosseous plasmocytoma	26	0.22
Primary cutaneous diffuse large B-cell lymphoma, leg type	19	0.16
Primary cutaneous marginal zone B-cell lymphoma	17	0.15
Solitary plasmocytoma of bone	14	0.12
B-cell lymphoma unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma	12	0.10
T-cell/histiocyte rich large B-cell lymphoma	11	0.09
Lymphomatoid granulomatosis	9	0.08
B-cell prolymphocytic leukemia	7	0.06
B-cell lymphoma unclassifiable, with features intermediate between DLBCL and Hodgkin lymphoma	7	0.06
Intravascular large B-cell lymphoma	4	0.03
Primary effusion lymphoma	2	0.02
EBV positive DLBCL of the elderly	1	0.01
Mature T- and NK-cell neoplasms	664	5.67
Peripheral T-cell lymphoma, NOS	232	1.98
Anaplastic large-cell lymphoma	141	1.2
Mycosis fungoides	101	0.86
Angioimmunoblastic T-cell lymphoma	51	0.44
T-cell large granular lymphocytic leukemia	30	0.26
Extranodal NK/T-cell lymphoma, nasal type	21	0.18
Primary cutaneous anaplastic large cell lymphoma	17	0.15
Enteropathy associated T-cell lymphoma	15	0.13
Blastic plasmacytoid dendritic cell neoplasm	11	0.09
Lymphomatoid papulosis	11	0.09
Primary cutaneous peripheral T-cell lymphoma, unspecified	9	0.08
Sezary syndrome	9	0.08
Primary cutaneous small-medium CD4+ T-cell lymphoma	6	0.05
Subcutaneous panniculitis-like T-cell lymphoma	5	0.04
Adult T-cell leukemia/lymphoma	3	0.03
Hepatosplenic T-cell lymphoma	1	0.01
Primary cutaneous gamma-delta T-cell lymphoma	1	0.01
Hodgkin lymphoma (HL)	1567	13.37

Nodular sclerosis classical HL	823	7.02
Classical Hodgkin lymphoma, NOS	408	3.48
Mixed cellularity classical HL	177	1.51
Nodular lymphocyte predominant Hodgkin lymphoma	89	0.76
Lymphocyte-rich classical HL	56	0.48
Lymphocyte depleted classical HL	14	0.12
Histiocytic and dendritic cell neoplasms	16	0.14
Langerhans cell histiocytosis	10	0.09
Histiocytic and dendritic cell neoplasms	6	0.05
Lymphoma, NOS	47	0.40

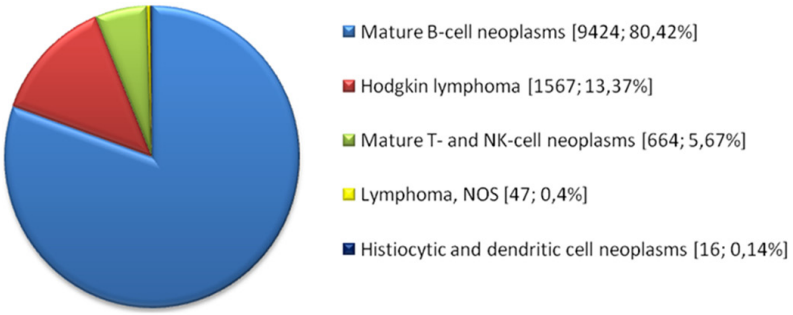

Figure 1. Distribution of lymphoid neoplasm from The National Histopathological Lymphoma Register project according to the WHO 2008 classification.

and NK/T-cell lymphoid neoplasms, mature B-cell neoplasms; mature NK/T-cell neoplasms, post-transplant lymphoproliferative disorders, Hodgkin's lymphoma and histiocytic and dendritic cell neoplasms; the first 3 groups were previously classified as NHL. According to definition lymphoma should have specific clinical, morphologic, immunophenotypic as well as the genetic features. The need for classification with implication for clinical practice and translational research is also emphasized; major changes include specification of in "situ lesions", differences in age-related diseases, evaluation of the disease site-specific impact on its definition, incorporation of some provisional entities for borderline categories, stratification and sub-classification of diffuse large B-cell lymphoma and follicular lymphoma.

The Polish National Histopathological Lymphoma Register project (NHLR) was launched in 2006 with the support of the National Cancer Control Program and in collaboration with the Polish Lymphoma Research Group and Hematopathological Section of the Polish Society of Pathologists. The data were collected by pathologists specialized in hematological malignancies.

The aim of the study is to present data from NHLR project and to compare the lymphoma distribution in Poland, Europe as well as North Central and South America. The most accurate source for data analysis were: HAEMACARE project [3], GLOBOCAN 2008 Project, International Agency for Research on Cancer [4] and Laurini JA et al. [5] publication for NHL classification in Central and South America. Additionally, the incidence of indolent and aggressive mature B-cell NHL was revised.

Material and methods

2007-2012 records of all patients with lymphoid neoplasm were retrieved from The National Histopathological Lymphoma Register. The initial study (2006 data analysis) [6] was based on report forms prepared by Hematopathology Section of the Polish Society of Pathologists and the Polish Lymphoma Research Group. The data included: personal information, basic clinical findings and histopathological results with diagnosis based on WHO 2001 system, type of the evaluated material and additional testing (immunohistochemistry, flow cytometry, molecular studies). The project involved 24 pathology departments from all over Poland divided into 4 categories according to number of application: ≥500, 300-500, 100-299, <100 cases diagnosed. All histopathological diagnoses were reclassified and assigned to 5 major groups according to the 2008 revised WHO classification system. These 5 major groups of lymphoid neoplasms were as follows: mature B-cell neoplasms, mature T-cell

Table 2. Incidence of mature B-cell non-Hodgkin lymphomas - The National Histopathological Lymphoma Register project (Poland), HAEMACARE project (Europe), Central and South America and North America data review

Lymphoid neoplasms	NHLR (Poland) % (n)	HAEMACARE % (n)	CSA % (n)	NA % (n)
B-cell NHL*	92.21 (7863)	92.08 (29399)	87.3 (809)	90.4 (359)
Indolent	63.25 (4809)	68.27 (19423)	47.1 (366)	62.5 (223)
Aggressive	36.25 (2794)	31.73 (9026)	52.9 (411)	37.5 (134)
3 most frequent B-cell NHL	DLBCL 32.9 (2587)	CLL/SLL 37.49 (11019)	DLBCL 40.0 (371)	FL 33.8 (134)
	CLL/SLL 31.84 (2504)	DLBCL 29.04 (8538)	FL 20.41 (189)	DLBCL 29.2 (116)
	MCL 9.04 (711)	FL 16.6 (4881)	MALT 6.9 (64)	MCL 6.8 (27)
Plasma cell myeloma**	16.56 (1561)	31.4 (13456)	-	-
Unknown lymphoid neoplasms+	0.46 (47)	21.66 (12547)+	1.73 (14)#	2.78 (10)#

*the percentage of all lymphomas, without plasma cell myeloma. **the percentage in B-cell NHL group. +unknown lymphoid neoplasms from all studied cases. #the unclassifiable low- and high-grade lymphomas in B-cell NHL group.

neoplasms, Hodgkin lymphoma, histiocytic and dendritic cell neoplasms, and lymphoma NOS. Duplicated data and precursor lymphoid neoplasms were excluded.

Non-Hodgkin to Hodgkin lymphoma ratio was compared to that of Polish National Cancer Register 2010 and GLOBOCAN 2012 Project, International Agency for Research on Cancer. Moreover, the mature B-cell NHL category was divided into two subgroups: indolent and aggressive lymphomas. Indolent lymphoma subgroup included: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma (LPL), mantle cell lymphoma (MCL), follicular lymphoma (FL, all grades), marginal zone lymphoma (MZL) and cases of unclassifiable low-grade B-cell lymphoma. Aggressive lymphoma subgroup included: cases of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), Burkitt lymphoma (BL), B-cell lymphoma unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (DLBCL/BL) and cases of unclassifiable aggressive B-cell lymphoma. The results were compared to the European incidence (HAEMACARE project) as well as data from the Central South and North America registries.

Results

The overall number of cases submitted to NHLR was 14792. We excluded cases of precursor B-cell and NK/T-cell lymphoid neoplasms, items of incomplete registration or duplicated forms, indefinite histopathological diagnoses and reassessed terminology inaccuracies. The final number of malignancies retrieved for analysis was 11718. The project involved 24 pathology departments grouped according to the number of applications sent: ≥500 (8), 300-500 (8), 100-299 (4), <100 (4), The highest incidence was in the 6th, 7th and 8th decade of life: 22.4%, 23.6% and 23.6% of all diagnosed patients respectively. The female to male overall ratio was 0.85. The distribution of lymphoid malignancies is presented in **Table 1**; the percentage of neoplasms in 5 major subgroups including lymphoma NOS is depicted in **Figure 1**.

According to NHLR the three most frequent types of NHL in Poland were DLBCL (32.9%; 2587), CLL/SLL (31.84%; 2504) and MCL (9.04%; 711). The major difference in the distribution between Europe and Poland versus both America was observed for FL and CLL/SLL. The indolent to aggressive NHL ratio was 1.72; 63.25% (4809) to 36.25% (2794) of cases respectively and the result was similar to that for European and North American populations. Significant differences between NHLR and HEMACARE data were observed for the percentage of unknown lymphoid neoplasm (0.46% vs. 21.66%). Geographical distributions in HNL incidence are presented in **Table 2**.

GLOBOCAN project data including NHL, HL and multiple myeloma incidence rate compared to results of NHLR analysis demonstrated the following statistical differences: multiple myeloma was less frequent (13.32% vs. 28.94%, 25.43% and 21.98% from GLOBOCAN project for Poland, Europe and North America respectively), NHL was the predominant group (73.31%) (**Figure 2**).

Disscusion

The analysis of 11718 cases of lymphoma diagnosis based on WHO classification is the first

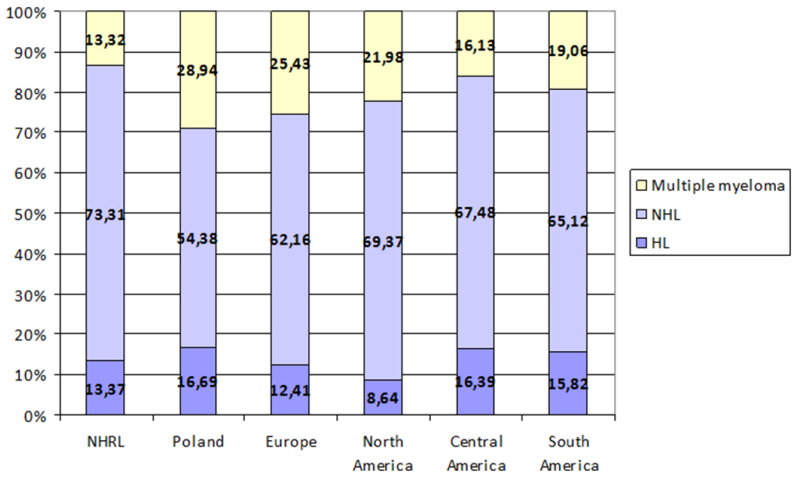

Figure 2. Comparison of the Hodgkin lymphoma, non-Hodgkin lymphoma and multiple myeloma incidence rate according to The National Histopathological Lymphoma Register project and GLOBOCAN 2012 Project, International Agency for Research on Cancer.

major study based on the National Histopathological Lymphoma Register in Poland. Up-to date the only source of lymphoma incidence data were regional cancer registries; a few of them applied both the codification system including ICD-O-3 and the general classification into HL, NHL, leukemia and multiple myeloma [7]. The differences between NHLR and GLOBOCAN 2008 [4] data for the Polish population may arise from the fact that some HNL require no pathological examination of lymph node or trephine biopsy; for diagnosis of CLL/SLL or multiple myeloma clinical and laboratory testing is essential but hematopathological evaluation is usually performed for staging purposes. According to NHLR the multiple myeloma incidence is 13.32% but in epidemiological analysis for Poland it is 2-fold higher (28.94%). The incidence rate for multiple myeloma in European and North America studies is similar (25.43% and 21.98% respectively) [5].

There were also marked discrepancies for NHL incidence: the percentage was the highest (73.31%) in the NHLR group as compared to GLOBOCAN data (for Poland 54.38%, for Europe 62.16%). The differences disappeared when analysis included data from registries based on ICD-O-3 or WHO classification (**Table 2**). The B-cell NHL incidences were comparable (NHLR 92.21% vs. HAEMACARE 92.08% vs. Central and South America 87.3% and North America 90.4%). The difference in distribution of indolent and aggressive lymphomas and NHL subtypes was the biggest between Central/South America and North America/Europe. For that population the predominant B-cell NHL was DLBLC (40%), the most common aggressive type of lymphoma. According to NHLR DLBCL (32.9%) is also the most frequent lymphoma type in Poland followed by CLL/SLL (31.84%) and MCL (9.04%). The reasons for the differences are most likely multifactorial. Incidence rates for indolent and aggressive lymphomas may be affected by social and economic factors including different patterns of medical practice in developing countries (Central and South America as well as Poland).

In NHLR the FL was not as frequent as in North America group (4.89%, 573 cases vs. 33.8%, 134 cases). Similar tendency was observed in several studies; FL is still more common in North America and Western Europe, and lower rates are reported for Asia and developing countries [2, 8]. The etiology and pathogenesis is not entirely understood but there are some environmental risk factors which might have powerful impact on FL incidence. According to population-based case-control studies the pesticide exposure (insecticides, herbicides and fumigants) were significantly associated with t(14;18) chromosomal translocation; this genetic change is being identified in approximately 70% to 90% of FL and 20% to 30% of DLBCL cases [9]. Moreover, it is thought that the risk of t(14;18)-positive NHL increases with extended pesticide use [10]. Other risk factors for NHL include intake of red meat and saturated animal fat but here the results are incoherent; notably high red meat intake may be associated with increased risk of DLBCL and high consumption of total animal fat with FL [11-13]. Etiology of MZL of MALT has been thoroughly studied and is shown to be related to chronic inflammatory disorders such as Helicobacter pylori (HP) gastritis and autoimmune response [14]. HP infection is associated

with lower socioeconomic status and is more frequently observed in developing countries [15, 16]. MALT is the third most-common subtype of NHL in Central and South America representing 6.9%; in North America the overall MALT frequency is similar (6.3%). MALT was not so commonly diagnosed in Poland (3.3% according to NHLR). Comparison of the data with HAEMACARE project is not easy as MALT was categorized in the same group as splenic marginal zone B-cell lymphoma and immunoproliferative small intestinal disease (Mediterranean lymphoma).

Moreover, NHLR demonstrated a very low incidence rate for lymphoma NOS (0.46% vs. 21.66% in HAEMACARE) most likely because WHO classification was applied and registration was made by pathologists.

The study presents NHL distribution in Poland according to National Histopathological Lymphoma Register. The strongest features of the study are the number of collected cases and the involvement of pathologists who specialize in hemathopathology. The major differencies between NHLR and European and American studies regarding NHL subtypes concered: higher incidence rate for aggressive B-cell lymphomas including DLBCL, lower FL and MALT incidence rate and a minimal percentage of unclassified lymphomas. Some of these findings are related to etiological factors but equally important for distribution of geographic differences in lymphoma incidence are the discrepanciesin diagnostic and registration criteria.

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Disclosure of conflict of interest

None.

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