Lymphoid Neoplasms in Bulgaria according to the WHO classification (2001). The Experience of the National Center of Haematology

The aim of the present study was to assess the incidence of lymphoma subtypes in the largest cohort of patients in Bulgaria, referred to the National Center of Haematology and Transfusiology between 01.01.2003 and 31.12.2004, applying the WHO classification criteria, including precursor and mature cell neoplasias, plasmacytoma and Hodgkin lymphomas. A total of 790 cases were newly diagnosed. Hodgkin lymphomas comprised 24.6% of the cases, B-cell neoplasias – 66.5% whereas T/NK-cell neoplasias – 6.9% of the total. Specimens were inadequate for subclassification in 2.2% of the cases. Detailed data on the subtypes are presented and compared to reported data from other geographic locations.

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Lymphoid neoplasms are a heterogeneous group of diseases with a steadily increasing incidence that has already been recognized worldwide.[1,2] However, there are data showing that these tendencies are more marked for particular histological categories.[1] Only a few large-scale epidemiological studies using the REAL[3] and WHO[4] classification schemes,[5] taking subtypes into account, are currently available, showing significant variations in the distribution patterns of the recognized entities in different countries thus suggesting possible differences in the etiology and pathogenesis. Differences may also be explained by different levels of ascertainment. A region specific approach would be useful to plan health care measures for lymphoid malignancies (LMs).

According to the International Agency for Research on Cancer (IARC) the incidence of Non-Hodgkin's lymphomas, Hodgkin's lymphomas (HLs) and Multiple myeloma (MM) for the Bulgarian population in 2002 is estimated to be 352; 208 and 111 newly diagnosed cases, respectively.[6] However, the exact intra-group distribution remains elusive. The aim of the present study was to

Table 1.Distribution of lymphoid malignancies diagnosed at the National Center of Haematology, Bulgaria per entity and gender.

Entity	*Total number of cases (% of all LMs)*	*Male number of cases (% within entity group)*	*Female number of cases (% within entity group)*
Hodgkin's lymphoma (HL)			
Nodular lymphocyte predominance HL	2 (0.3)	1 (50.0)	1 (50.0)
Classical HL	9 (1.1)	6 (66.7)	3 (33.3)
Nodular sclerosis HL	125 (15.8)	70 (56.0)	55 (44.0)
Lymphocyte rich classical HL	2 (0.3)	0 (0)	2 (100)
Mixed cellularity HL	45 (5.7)	28 (62.2)	17 (37.8)
Lymphocyte depleted HL	11 (1.4)	4 (36.4)	7 (63.6)
B- cell neoplasms			
Precursor B cell neoplasms			
Precursor B-lymphoblastic leukaemia	9 (1.1)	6 (66.7)	3 (33.3)
Precursor B-lymphoblastic lymphoma	10 (1.3)	7 (70.0)	3 (30.0)
Mature B cell neoplasms			
B-cell chronic lymphocytic leukaemia	82 (10.4)	47 (57.3)	35 (42.7)
B-cell small lymphocytic lymphoma	22 (2.8)	9 (40.9)	13 (59.1)
B-cell prolymphocytic leukaemia	11 (1.4)	7 (63.3)	4 (36.4)
Lymphoplasmacytic lymphoma	16 (2.0)	9 (40.9)	7 (43.8)
Splenic marginal zone lymphoma	6 (0.8)	4 (66.7)	2 (33.3)
Hairy cell leukaemia	25 (3.2)	18 (72.0)	7 (28.0)
Plasma cell myeloma	98 (12.4)	47 (48.0)	51 (52.0)
Marginal zone B-cell lymphoma of MALT-type/Nodal marginal zone B-cell lymphoma	44 (5.6)	21 (47.7)	23 (52.3)
Follicular lymphoma	37 (4.7)	10 (27.0)	27 (73.0)
Mantle cell lymphoma	22 (2.8)	15 (68.2)	7 (31.8)
Diffuse large B-cell lymphoma	127 (16.1)	60 (47.2)	67 (52.8)
Mediastinal (thymic) large B-cell lymphoma	4 (0,5)	3 (75%)	1 (25%)
Burkitt's lymphoma	9 (1.1)	4 (44.4)	5 (55.6)
Burkitt's leukaemia	2 (0.3)	0 (0)	2 (100)
T-cell and putative NK-cell neoplasms			
Precursor T-cell neoplasms			
Precursor T-lymphoblastic leukaemia	5 (0.6)	4 (80.0)	1 (20.0)
Precursor T-lymphoblastic lymphoma	3 (0.4)	2 (66.7)	1 (33.3)
Mature T-cell and NK-cell neoplasms			
Extranodal NK-/T-cell lymphoma nasal type	1 (0.1)	0 (0)	1 (100)
Primary cutaneous anaplastic large cell lymphoma	4 (0.5)	3 (75.0)	1 (25.0)
Mycosis fungoides	5 (0.6)	2 (40.0)	3 (60.0)
Angioimmunoblastic T-cell lymphoma	6 (0.8)	2 (33.3)	4 (66.7)
Peripheral T-cell lymphomas, unspecified	24 (3.0)	11 (45.8)	13 (54.2)
Anaplastic large cell lymphoma	7 (0.9)	3 (42.9)	4 (57.1)
Unspecified lymphoid malignancy	17 (2.2)	10 (58.8)	7 (41.2)
Total	790 (100)	412 (52.2)	378 (47.8)

Table 2. Primary presentation of lymphoid malignancies at diagnosis at the National Center of Haematology and Transfusiology.

	Primry presentation – number of cases (% within entity group)				
Entity	*Nodal*	*Extranodal*	*Leukaemic and/or bone marrow*	*Not specified*	*Total*
Precursor B cell neoplasms	4 (21.0)	6 (31.6)	9 (47.4)	0 (0)	19 (2.4)
B-cell chronic lymphocytic leukaemia	0 (0)	0 (0)	82 (100)	0 (0)	82 (10.4)
Plasma cell myeloma	1 (1.0)	8 (8.2)	89 (90.8)*	0 (0)	98 (12.4)
Other mature B-cell neoplasms	149 (45.8)	122 (37.6)	45 (13.8)	9 (2.8)	325 (41.1)
Precursor T cell leukaemia	1 (12.5)	2 (25.0)	5 (62.5)	0 (0)	8 (1.0)
Other mature T-cell neoplasms	30 (63.8)	16 (34.1)	0 (0)	1 (2.1)	47 (5.9)
Hodgkin lymphoma	180 (92.8)	12 (6.2)	0 (0)	2 (1.0)	194 (24.6)
Unspecified	0 (0)	2 (11.8)	12 (70.6)	3 (17.6)	17 (2.2)
Total	365 (46.2)	168 (21.3)	242 (30.6)	15 (1.9)	790 (100)

** - isolated bone marrow involvement without leukaemic presentation.*

Table 3. Distribution of major lymphoma subtypes (diagnosed on the basis of biopsy evaluation other than bone marrow) in different geographic locations, in per cent.

Major entities	*Omaha*[5]	*Capetown*[5]	*Hong Kong*[5]	*Wurzburg*[5]	*London*[5]	*Locarno*[5]	*South-East Turkey*[8]	*Greece*[7]	*Bulgaria Present study*
B-cell small lymphocytic lymphoma	7	8	3	11	8	5	6.2	6.5	6.1
Mantle cell lymphoma	7	1	3	8	7	14	7.5	3.6	6.1
Follicular lymphoma	32	33	8	18	28	11	6.1	9.7	10.3
Marginal zone B-cell lymphoma of MALT-type	6	4	10	9	3	9	4.3	10.5	12.2
Diffuse large B-cell lymphoma	28	28	36	30	27	36	41	47.3	35.3
Mediastinal (thymic) large B-cell lymphoma	0	3	3	0	2	9	1.2	1.2	1.1
Peripheral T-cell lymphomas, unspecified	3	8	10	4	8	6	4.6	5	6.7
Anaplastic large cell lymphoma	2	3	3	1	2	0	2.5	4.7	1.9
Extranodal NK-/T-cell lymphoma nasal type	0	0	8	0	0	0	0.6	0.25	0.27
Others	15	12	16	19	15	10	26	10.6	20
Total number of reported patients	200	188	197	203	119	79	250	801	360

assess the incidence of lymphoma subtypes in the largest cohort of patients in Bulgaria, referred to the National Center of Haematology and Transfusiology (NCHT) between 01.01.2003 and 31.12.2004 applying the WHO classification criteria.

A total of 790 newly diagnosed cases were reviewed at the Laboratory of Cytopathology, Histopathology and Immunology of NCHT. The mean age was 53.7 years (range 7 to 87 years) and the male/female ratio was 1.09:1. At least one paraffin block of tissue biopsy and/or bone marrow specimen representative for the neoplasia was reviewed by two experienced haematopathologists. The phenotype was determined by immunohistochemistry on tissue sections and/or flow cytometry in leukaemic cases in 409 of the patients (87% of cases other than classical HLs – mixed cellularity and nodular sclerosis, and plasma cell or lymphoplasmacytic lymphoma, where immunochemical analysis was essential). Descriptive statistical analysis was performed using SPSS 13.0 for Windows.

In 17 (2.2%) cases, we were unable to define the exact subtype of LM due to inadequate material for subsequent diagnostic procedures. Hodgkin lymphomas (HLs) comprised 24.6% of the cases, B-cell neoplasias – 66.5%, and T/NK-cell neoplasias – 6.9% of the total. Detailed distribution of cases per entity and gender is presented in Table 1. Within the group of HLs, nodular sclerosis was the most common type (64% of all cases of HL), followed by mixed cellularity (23.1%), unspecified classical HL (4.8%), lymphocyte depleted (5.9%), lymphocyte rich and lymphocyte predominant (1.1% each). The most common type of B-cell neoplasms in our series was diffuse large B-cell lymphoma, diagnosed in 24.2 % of all B-cell malignancies, followed by B-cell small lymphocytic leukaemia/ lymphoma (19.8%), whereas we found a relatively low incidence of follicular lymphoma (7.1%) and a comparatively higher incidence of hairy cell leukaemia (4.8%). Among the T/NK-cell neoplasias, which accounted for a minor portion of LMs in our study, peripheral T-cell lymphomas were the most common subtype.

Data regarding another issue of concern in the WHO classification – the primary organ involvement, are presented in Table 2. The extranodal primary presentation was more than twice less frequent than nodal (168 vs. 365 cases), accounting for 93.2%, 45.5% and 37.8% of the cases of marginal zone lymphomas, small lymphocytic lymphoma and diffuse large B-cell lymphoma, respectively. The most common extranodal presentation was the gastrointestinal tract (29.8% of all extranodal cases). Leukaemic and/or isolated bone marrow presentations, as expected by definition, were most common in acute and chronic leukaemias and plasmacytoma.

To our knowledge the present study is the first study based on the WHO classification in Bulgaria. Comprising the largest series of lymphoma patients in our country, it aims at providing data for the relative distribution of pathologic subtypes. The results concerning the most common categories most likely reflect the actual distribution in Bulgaria, because patients were referred from all parts of the country. In general, our data show a distribution of lymphoid neoplasms similar to that in most of the mainland European countries except for the generally reported frequency of follicular lymphoma in North America, Capetown and London[4,5] (Table 3). However, when interpreting our results we must have in mind that the variations in the incidence of LMs reported in different studies might be also due to methodological issues – some do not include precursor and plasma cell disorders in the group of LMs, which may alter significantly the distribution pattern in the entire group. Besides there are differences in the established practical patterns concerning biopsy rates at diagnosis of some lymphomas (e.g. small lymphocytic, lymphoplasmacytic, etc.) We therefore propose the strict implication of WHO classification when performing epidemiological studies.

Our study is one of the very few reported for the Balkan peninsula[7,8] and the data might yield a more consistent evidence-based approach in planning appropriate health care and therapies for hematological malignancies in Bulgaria, providing effective groupings for clinical trials and accurate cancer registration. Furthermore, we need retrospective and prospective studies regarding the prevalence of risk factors such as immunosuppression, viral infections, environmental and occupational factors among patients with LMs in order to establish whether there are any population specific inborn or acquired predispositions.

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