Distributions of major sub-types of lymphoid malignancies among adults in Mashhad, Iran

Z. Mozaheb [a,*], A. Aledavood [b], F. Farzad [c]

[a] Hematology-Oncology Department, Mashhad University of Medical Science, Mashhad, Iran
[b] Radiotherapy Oncology Department, Omid Hospital a Cancer Center of Mashhad University of Medical Science, Iran
[c] Islamic Azad University of Mashhad, Iran

ARTICLE INFO

ABSTRACT

Background: Global variations in the frequency of the major sub-types of lymphoma have been reported. However, studies on different sub-types of adult malignant lymphoma had never been conducted in Mashhad, Iran. In this paper, we aimed to identify the major sub-types of malignant lymphoma in our area and compare the distribution with other published studies. Methods: During a retrospective study we evaluate 391 adult patients with lymphoid malignancy from "Omid Hospital" – a cancer research center and an outpatient hematologic clinic in Mashhad – were evaluated from 2000 to 2009. Patients were reclassified using the World Health Organization (WHO) classification. Results: The frequency of non-Hodgkin lymphomas (NHL) was 92% (n = 359) and Hodgkin lymphoma (HL) was 8% (n = 32). The most frequent NHL sub-type using WHO classification was diffuse large B cell lymphoma (DLBCL) and the second most common NHL was chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The most common sub-type of HL was mixed cellularity. In this study the frequency of primary extranodal NHL in our study was 11.5%, which slightly less common than other eastern countries. Conclusion: Our findings add to the body of knowledge concerning geographic variations in the descriptive epidemiology of the major lymphoma sub-types. Such observations are extremely important since they potentially point to underling etiological variations.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Lymphoid malignancies represent a heterogeneous group of neoplasms which have been reported to show different histological sub-types according to the geography. Lymphoid neoplasms including Hodgkin's lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia as well as multiple myeloma arise from the malignant transformation of normal lymphoid cells at various stages of differentiation. In comparison to western countries, some regions of Asia including Hong Kong, Japan, China, Korea and Thailand have been reported to have higher rates of aggressive lymphoma and lower rates of follicular lymphoma and Hodgkin's disease [1]. The aim of this study is to investigate the distribution of major sub-types of malignant lymphoma in adult patients in Mashhad, Iran and compare the feature of our series with those of others.

2. Patients and methods

A total of 391 cases of lymphoid neoplasm, diagnosed at "Omid Hospital" – a cancer research center in Mashhad University of Medical Science and an outpatient hematologic clinic – were enrolled in this study from 2000 to 2009. "Omid Hospital" is the biggest referral cancer center in the east of Iran (covering more than four provinces). Most patients suffering from different kinds of malignancies are referred to this center; all kind of adult lymphoma are captured. Initially, all cases were classified using the working formulation and REAL classification. Then, they were translated into the proposed nested classification using data from the inter lymph group [2]. Due to the close relationship between the disease definitions in the REAL and WHO classification, the patients were grouped together. Most cases classified by the working formulation as follicular lymphoma, diffuse large cell lymphoma and lymphoblastic lymphoma, can be reliably translated into major NHL subtypes, even without the incorporation of immunophenotype data, and small noncleaved cell lymphoma can be translated into Burkitt lymphoma based on the inter lymph group study [2]. There are some limitation in translation from the

* Corresponding author. Tel.: +98 5117636286; fax: +98 5118444497.
E-mail address: mozahebz@mums.ac.ir (Z. Mozaheb).

Table 1
Absolute number and frequency of lymphoid neoplasms sub-types in adults classified by WHO.

Lymphoma sub-type	No. cases	% of total	% of NHL	Median age	M/F
Lymphoma neoplasm, total	391				
Hodgkin lymphoma	**32**	**8**		**29.5**	**1**
NHL	**359**	**92**		**55**	**1.7**
NHL, B-cell	344	87	95.8		
Mature NHL, B-cell					
CLL/SLL/PLL	86	21.9	23.9	64	1.5
Mantle cell lymphoma	8	2	2.2	55	8
LPL/Waldenstrom	2	0.5	0.55		
Diffuse large B-cell lymphoma	136	34.7	37.8	50	1.9
Burkitt lymphoma	2	0.5	0.55		
MALT lymphoma	8	2	2.2	51	0.5
Follicular lymphoma	5	1.2	1.4	61	0.6
Hairy cell leukemia	11	2.8	3	54.6	11
Plasma cell neoplasm	43	10.9	12	62	1.4
NHL, T-cell	15	3.8	4.2		
Mycosis fungoides	3	0.7	0.8	58	2
Peripheral T cell lymphoma	7	1.7	1.9	53	1.3
Adult T cell lymphoma/leukemia	5	1.2	1.4	45	1.5
Others	43			55	2.1

Abbreviations: M = male; F = female; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; CLL/SLL/PLL = chronic lymphocytic lymphoma/small lymphocytic lymphoma/pro-lymphocytic lymphoma; LPL = lymphoplasmacytic lymphoma; MALT = mucosal associated lymphoid tissue.
Bold numbers are amounts of major subtype of malignant neoplasm.

Table 2
Absolute number and frequency of Hodgkin's lymphoma sub-types in adults classified by WHO.

Sub-type	No cases	% of total	%of HL	Median age	M/F
Hodgkin lymphoma	**32**	**8**		**29.5**	**1**
Classic Hodgkin lymphoma	30	7.6	93.7		
Nodular sclerosis	10	2.5	31.2	23	0.8
Mixed cellularity	16	4	50	33.5	0.8
Lymphoctye-rich	3	0.7	9.3		
Lymphocyte-depleted	1	0.2	3.1		
Nodular lymphocytic predominant Hodgkin lymphoma	2	0.5	6.3		

M = male; F = female; HL = Hodgkin's lymphoma.
Bold numbers are total amounts of HL.

working formulation into the WHO classification, such as malignant lymphoma and mixed small and large cell, therefore, we placed them in the NHL "others" category. Histological and clinical data relating to age and gender were obtained from the medical records.

3. Results

In our study the frequency of non-Hodgkin's lymphoma was 92% (n = 359) and Hodgkin's lymphoma was 8% (n = 32). Based on WHO classification, diffuse large B cell lymphoma was the most common NHL representing 37.8%, SLL/CLL was the second most common, representing 23.9% of NHL. Follicular lymphoma was 1.4% of NHL. NHL was most frequently present in among middle-aged individuals and the elderly, with a median age 55 years and

Table 3
Distribution (%) of sites of primary lesion of extranodal NHL in Mashhad, Iran.

Primary site NHL[a]	No. = 248	
	No.	(%)
Nodal	216	88.5
Extranodal	32	11.5
Gasterointestinal tract	10	31.2
Waldeyer's rings	7	25
Skin	7	18.7
Bone	3	9.3
Thyroid	1	3.1
Genitourinary tract	1	3.1
Others	2	6.2

[a] Non-Hodgkin's lymphoma.

male predominance (M/F = 1.7) (Table 1). The most common sub-type of HL was mixed cellularity included 50% (n = 16) of HL, it was followed by nodular sclerosis, 31.2% (n = 10) of HL (Table 2). The median age for HL was 29.5; 50% of patients were aged between 15 and 30 years old and 34% were aged between 45 and 60 years. The median age of patients with mixed cellular HL was 10 years more than nodular sclerosing. The frequency of primary extranodal NHL in our study was 11.5%, which is less common than other countries. The most common original site was gastrointestinal (GI) tract. The second most common sites were Waldeyer ring and the skin equal to each other (Table 3). Based on the working formula classification, 88.8% of malignant lymphoma was NHL, and 11.5% was HL. 98% of non-Hodgkin's lymphoma was diffuse, and only 2% was follicular.

4. Discussion

The relative frequency of some histological subtypes of lymphoma are different between western and eastern countries [2,3], however, diffuse large B cell lymphoma is the most common NHL representing approximately one third of all non-Hodgkin's lymphomas worldwide [4,5]. DLBCL is one type of non-Hodgkin's lymphoma in which the relative incidence does not seem to vary geographically [6]. In almost all parts of the world this is the most frequent occurring non-Hodgkin's lymphoma. In some studies like this, there was a higher rate of aggressive NHL, especially diffuse large B cell lymphoma which occurs more frequently than others. It may relate to the etiology of diffuse large B cell lymphoma such as immune deficient conditions and their treatments which may cause aggressive non-Hodgkin's lymphoma [7]. As well as, genetic

factors may play an important role in this difference, because it has been reported that DLBCL was 10-fold increased among relatives of DLBCL patients, and follicular lymphoma was 4-fold increased among relatives of FL patients [7]. Previous findings provide evidence for a familial association of NHL, with little difference in the magnitude of risks for various histopathologic sub-types. The pattern of risks among parents and siblings support the hypothesis of an autosomal-dominant component for diffuse large B cell lymphoma and a recessive one for the follicular lymphoma [8]. Sometimes we could not find preexisting triggering factors for diffuse large B cell lymphoma such as CLL/SLL and mantle cell lymphoma before the transformation to diffuse large B cell lymphoma; therefore, it induces differences in frequency of some sub-types. Although NHL has increased in both genders, lymphoid malignancies are more frequent among males in comparison with females throughout all age groups [9,17], in this study, as well, DLBCL occurs about twice more among men. This pattern suggests that the underlying genetic factors and probably environmental and behavioral factors may be important and more common among men; nonetheless, this requires further investigation.

Like other studies, patients with indolent NHL, SLL/CLL had the highest frequency (23.5%), nevertheless; a low incidence has been reported in some Asian populations [3]. The oldest patients in this study suffered from CLL/SLL, with the median age of 64 years at diagnosis; this is around 6 years younger than the median reported in western countries. Some authors have reported that familial cases of CLL/SLL usually are younger than sporadic cases [10]. Some underlying risk factors such as germ-line genes might play a role in pathogenesis of familial CLL/SLL [7], as well as, may be important among our patients.

Follicular lymphoma was found more frequently in North American and Europe compared to other geographic sites [11,12]. The lowest rates of follicular lymphoma have been reported among Asian population [13,3]. In addition, the risk was lower for the first-generation of migrants from China and Japan into US in comparison with the subsequent migrant generations. The percentage of follicular lymphoma in our study in Mashhad, IRAN, was the lowest observed at any site. Although the exact reason for this difference is unknown, results of several studies suggest differences in genes and environmental factors such as diet habits, infections and smoking which play an important role in follicular lymphoma. Some cytogenetic changes such as a lower incidence of bcl-2 translocations are seen within follicular lymphoma among individuals in the west [14]. In addition, we should consider that a comparative excess of DLBCL resulting in a deficit of FL.

Despite the relative prominence of extranodal presentations, the literature of their incidence for most of specific types and sites is scant and often contradictory [15]. Extranodal presentation of lymphoma account for between 24% and 48% of new lymphoma cases in different studies [16], however, in this study the frequency of primary extranodal NHL is lower, compared with western and some eastern countries, which is about 11.5% [10] of total NHL. The most common site of origin was gastrointestinal (GI) tract and the second most common sites were Waldeyer's ring and the skin equal to each other, these feature are similar to those of Taiwan [1].

The median age of NHL in our patients was 55 (14–86) years old which is significantly lower, compared to the population-based registration in western countries. The Haematological Malignancy Research Network reported that the median age of their patients was 68 years old [17]. Our result is like the study in Korea. The median age of their patients was 52 years [18]. The reason may relate to the underlying age structure in both countries, nonetheless, it needs more population-based studies.

Based on working formula classification, Hodgkin lymphoma in this study shows a frequency like that of Korea, but it is less frequent in comparison with the US [18]. A higher incidence occurs in westernized populations including those who emigrate from low-incidence sites to the United States. Efforts to find an infectious etiologic agent have been largely unsuccessful, though a role for Epstein–Barr virus has been implicated in some cases [19]. For our patients, like others, there are a bimodal age distribution for Hodgkin's lymphoma, with one peak occurring in the third decade of life and the second peak occurring in the fifth and the sixth decades. Among 32 cases of Hodgkin's lymphoma, mixed cellularity was the most common; in comparison with other studies it is different from western countries where the most common sub-type is nodular sclerosing [2]. The median age of our patients with mixed cellular HL was higher than other sub-types (Table 2). One study also showed that elderly patients had mixed cellularity subtype, "B" symptoms, elevated erythrocyte sedimentation rate, and poorer performance status more often, however, nodular sclerosis subtype, large mediastinal mass, and bulky disease were less frequently observed [20]. In addition another study showed that the incidence of EBV positivity in reed sternberg cells from tissue sample obtained from patients with mixed cellular HL is much higher, therefore, it has been postulated that malignancy is more likely to occur when exposure to some agents are more, especially in eastern countries. These data have been interpreted as supporting the hypothesis that HL is caused by an infectious agent [21], however, it needs more study before confirmation.

In summary, the overall lymphoid malignancy incidence in eastern Asian countries is relatively low. Asians frequently display intermediate-grade, high-grade diffuse aggressive NHL. Geographic variation in lymphoma rate suggests the importance of environmental effects [22]. Risks for developing NHL include immunosuppression a causal link between infectious agents and lymphomagenesis, have also been determined, particularly for human T-cell leukemia/lymphoma virus type 1 (HTLV-1), Epstein–Barr virus (EBV), *Helicobacter pylori* infections and Hepatitis C Viruses (HCV) infection [7], which relatively frequent in our area. In addition the incidence of non-Hodgkin's lymphoma and its histological sub-types in Asian migrants to the United States which is lower in first-generation migrants confirmed this suggestion [23]. Other exogenous factors which have been implicated in lymphomagenesis are chemicals and agricultural exposures, hair dyes, and blood transfusions [24] that are used more without any protection in developing countries. They may play an important role in these differences.

5. Future

Initially, republication of the findings and the establishment of a population based registry would be beneficial. In addition, future studies are needed to identify some environmental factors such as diet habits, infectious disease and genetics in pathogenesis of lymphoid malignancies. Moreover, the role of immune related conditions and their treatment need to be identified in pathogenesis of NHL, especially aggressive lymphoma. Besides, analytic investigations should evaluate NHL risks according to the sub-type. Finally, we need further studies in the field due to the low median age of our patients.

Conflict of interest

There is no conflict of interest to be declared.

References

[1] Shih LY, Liang DC. Non-Hodgkin's lymphomas in Asia. Hematol Oncol Clin North Am 1991;5:983–1001.

[2] Anderson JR, Armitage JO. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Ann Oncol 1998;9:717–20.

[3] Gross SA, Zhu X, Bao L, Ryder J, Le A, Chen Y, et al. A prospective study of 728 cases of non-Hodgkin lymphoma from a single laboratory in Shanghai, China. Int J Hematol 2008;88(2):165–73.

[4] Lindsay M, Morton, Jennifer J. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (Inter Lymph). Blood 2007;110(2):695–708.

[5] Luminari S, Cesaretti M, Rashid I, Mammi C, Montanini A, Barbolini E. Incidence, clinical characteristics and survival of malignant lymphomas: a population-based study from a cancer registry in northern Italy. Hematol Oncol 2007;25:189–97.

[6] Mauch PM, Armitage J. Diffuse large B cell lymphoma. In: Mauch PM, Armitage JO, Coiffier B, Dalla-favera R, Harris NL, eds. Non Hodgkin's lymphomas. Lippincott Williams & Wilkins; 2005: 424–53.

[7] Kristinsson SY, Goldin LR, Bjorkholm M, Koshiol J, Turesson I, landgren O. Genetic and immune-related factors in the pathogenesis of lymphoproliferative and plasma cell malignancies. Hematologica 2009;94(11):1581–9.

[8] Altieri A, Lorenzo Bermejo J, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. Blood 2005;106(2):668–72.

[9] Müller AMS, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol 2005;84(1):1–12.

[10] Gribben JG, Hariss NL, Dalla Favera R. Small B cell lymphocytic lymphoma/chronic lymphocytic leukemia and prolymphocytic leukemia. In: Mauch PM, Armitage JO, Coiffier B, Dalla-favera R, Harris NL, eds. Non Hodgkin's lymphomas. Lippincott Williams & Wilkins; 2005: 241–3.

[11] Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histological subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92(15):1240–51.

[12] Mortom LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood 2006;107(1):265–76.

[13] Intragumtornchai T, Wannakrairoj P, Chaimongkol B, Bhoopat L, Lekhakula A, Thamprasit. Non-Hodgkin's lymphomas in Thailand: a retrospective pathologic and clinical analysis of 1391 cases. Cancer 1996;78(8):1813–9.

[14] Macon WR, Mccurley T, Kurtin PJ, Dogan A. Lymphoproliferative disorder. In: Greer JP, Foerster J, Rodgers GM, Parasxevas F, Glader B, Arber DA, Means Jr RT, eds. Wintrobe's clinical hematology. Lippincott Williams & Wilkins; 2009 : 2075–7.

[15] Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part IT. Gastrointestinal, cutaneous and genitourinarylymphomas. Ann Oncol 1997;8:727–37.

[16] Newton R, Ferlay J, Beral V, Devesa SS. The epidemiology of non-Hodgkin's lymphoma: comparison of nodal and extra-nodal sites. Int J Cancer 1997;72(6):923–30.

[17] Smith A, Roman E, Howell D, Jones R, Patmore R, Jack A, et al. The Haematological Malignancy Research Network (HMRN): a new information strategy for population based epidemiology and health service research. Br J Haematol 2010;148(5):739–53.

[18] Ko Y-H, Kim C-W, Young, Park C-S, Jang H-K, Lee S-S, et al. REAL classification of malignant lymphomas in the republic of Korea. Cancer 1998;83(4):806–12.

[19] Longo DL. Hodgkin's lymphoma: an overview. Cancer J 2009;15(2):114–6.

[20] Engert A, Ballova V, Haverkamp H, Pfistner B, Josting A, Dühmke E, et al. Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the German Hodgkin's Study Group. J Clin Oncol 2005;23(22):5052–60.

[21] Punnett A, Tsang RW, Hodgson DC. Hodgkin lymphoma across the age spectrum: epidemiology, therapy, and late effects. Semin Radiat Oncol 2010;20(1): 30–44.

[22] Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's lymphoma classification project. Ann Oncol 1998;9: 717–20.

[23] Herrinton LJ, Goldoft M, Schwartz SM, Weiss NS. The incidence of non-Hodgkin's lymphoma and its histological subtypes in Asian migrants to the United States and their descendants. Cancer Causes Control 1996;7:224–30.

[24] Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's Lymphoma. Oncogene 2004;23(38):6524–34.