ADULT LYMPHOMA IN THE PROVINCE OF SULAIMANI: DEMOGRAPHY, HISTOLOGY AND TREATMENT PLANS

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ABSTRACT

Background

Lymphomas are the third commonest adult malignancies in Iraqi Kurdistan. Geographic variation in the distribution of different histologic types of lymphoma is well known. Management has been a contest between radiation and medical oncologists.

Objectives

The aim of the study is to give an account about demographic and histologic distribution of adult lymphomas and to find out the proportion of the lymphoma treated with radiation in Kurdistan compared to the western world.

Patients and Methods

Data were collected for all patients with adult lymphomas from the two main cancer centers in the city of Sulaimani from 2013 to 2017. Six hundred forty five patients could be retrieved. Data included were age, sex, histology, and management plans. Descriptive analysis using frequencies was used to describe the study variables.

Results

A total of 645 adult lymphomas were enrolled. One third of patients had Hodgkin lymphoma, whose 138 cases were male (63%). Nodular Sclerosis histology comprised 70% of all Hodgkin lymphoma cases. Treatment plan for Hodgkin lymphoma was either chemotherapy (83%) or combined modality treatment. The commonest histologic type of Non-Hodgkin lymphoma (NHL) was diffuse large B-Cell lymphoma and it accounted for 62% of cases. Follicular lymphoma was extremely rare and encountered for only 2% of all cases. Unlike Hodgkin Lymphoma, only 8% of Non-Hodgkin Lymphoma patients were treated by combined modality approach.

Conclusion

Age distribution and histologic pattern of lymphomas are different in our region compared with other regional and western countries. Unlike the developed western world follicular lymphoma is not a common type of NHL. Although combined modality approach was a standard therapy for quite a while now most of the lymphoma cases are treated by chemotherapy alone.

Keywords: *Demography, Histology, Sulaimani, Treatment, Adult lymphoma.*

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INTRODUCTION

Significant progress had been made in recent years in the understanding of the molecular basis of lymphoma genesis, and in the diagnosis, staging, and treatment of patients with lymphoid malignancies. The current pathological classification incorporates molecular characteristics, in addition to morphological and clinical features in identifying a distinctive subtype of disease entites [1].

In the United States, lymphoma accounts for 7% of new cancer cases and 3.6% of cancer deaths annually. In Kurdistan Region of Iraq, lymphoma is the third most common type of cancer, comprising 10.9% of all cancers [2]. Hodgkin ymphoma (HL) was first described by the British physician Thomas Hodgkin in 1832 [3]. The diagnosis of HL is based on identification of Reed-Sternberg cells [4]. Histologically, it is divided into two distinct entities: nodular lymphocyte predominant HL and classical HL. The latter is subdivided to four forms [Lymphocyte Rich (LR), Nodular Sclerosis (NS), Mixed cellularity (MC) and Lymphocyte Depleted (LD)] [5]. The etiology of HL is an unresolved issue but is likely complex and may vary depending on the different subtypes [6]. HL usually presents with non-tender lymphadenopathy, mostly in cervical nodal chains. Patient evaluation needs adequate surgical biopsy for pathological assessment [7]. Currently, the optimal treatment for early-stage HL is in evolution. At this time, combined modality treatment in the form of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) followed by radiotherapy considered to be optimal [8]. In advanced stage HL (Stage III & IV), chemotherapy is the mainstay of treatment. Radiation therapy preserved for initial bulky or residual diseases [9]. Having said all that, recently the whole management plan has become dictated by the results of PET-CT scan [10].

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of malignancies of the lymphoid system characterized by an abnormal clonal proliferation of B cells, T cells, or both [11]. Both incidence and mortality of NHL are increasing worldwide [7]. Scientific knowledge regarding NHL has increased dramatically in the past two decades, resulting in specific advances in the spheres of molecular biology and immunobiology and leading to new histopathologic classifications and therapies [10]. NHL may present in any part of the body, therefore, the presenting signs and symptoms of NHL are highly variable [12] . The most common presentation is with an asymptomatic lymph node enlargement [13]. WHO classification system divides NHL into B-cell and T-cell neoplasms. Over 40 different lymphomas are delineated, with diffuse large B-cell lymphoma been commonest type in almost all the world [13]. The primary treatment modalities include chemotherapy and radiation therapy (RT) [15], although surgery is used to diagnose and manage selected cases [16]. Knowledge of histology, extent, and pattern of disease is essential to select the appropriate therapeutic strategy. For localized disease, the curative approach involves combined modality with chemotherapy and RT, chemotherapy alone, or local treatment with definitive RT [7].

Frequently used chemotherapy regimens for NHL include single agents used for indolent lymphoma [17] and anthracycline-containing regimens potentially curative for DLCBL (e.g., CHOP-rituximab) or T-cell lymphomas, and regimens used for patients with recurrent disease [18]. For high-grade lymphoblastic and Burkitt lymphomas, dose-intensive protocols are used with concurrent intrathecal chemotherapy for CNS prophylaxis [19].

Our main goal in this study, to give an account about demographic and histologic distribution of adult lymphomas in our region and to compare it to the results of the other studies in regional and worldwide countries. Also, to find out the proportion of the lymphoma patients treated with radiation therapy in Kurdistan-Iraq. As there is clear controversy about the ideal treatment of this curative disease.

PATIENTS AND METHODS

In this descriptive study; we collected data for all patients aged more than eighteen years with lymphoma (adult Lymphoma) from the data registry of two main cancer centers of the Province of Sulaimani (Hiwa Hospital & Zhianawa Cancer Center) from 2013-2017.

Patients' records were searched for; age, sex, history details, examination findings especially nodal involvement, diagnostic evaluation including biopsy of clinically involved nodes or extranodal sites. Also, we reviewed treatment modality of all patients with special consideration to see whether they were treated by chemotherapy alone, radiation therapy alone or combined modality.

The enrolled patients were fulfilling the following inclusion criteria: age more than 18 years; lymphoma diagnosis established by histopathological examination

and whether all courses of treatment had been received at Hiwa Hospital and Zhianawa Cancer Center. Patient-related variables were: age, gender, and histology of the disease. Exclusion criteria were age less than 18 years, lack of compliance with correct number of treatment courses at the above named hospitals and incomplete data about histology and treatment pattern.

RESULTS

In this study 645 patients have been included, their age ranged from 18-90 years; the median age was 50 years, while mean age was 49 years. Age-related incidence and gender have been separated for HL and NHL, as these two discrete types have different age and gender distribution.

Two hundred eighteen cases of HL have been reported in this study. Age distribution started from 18 to 90 years. We observed male preponderance among the patients, 138 males and 80 females. Most cases (44%) were between age 31-55 years Table 1. For patients with NHL, the median incidence age was 55 years. NHL incidence increased with age. Similar to HL, male predominance was evident among NHL patients (229) male and (198) female. Data are shown in Table 2.

Among the 218 (33%) patients of HL, Classical type-Nodular Sclerosis was the most frequent subtype (70%), followed by nodular lymphocyte predominant 17%. Table 3 for NHL, diffuse large B cell lymphoma was the most frequent subtype and it encountered 62% of cases. We noticed that follicular lymphoma is not very common in our population like other neighboring and western countries and it constituted only 2% of cases Table 4.

Of the 645 patients with Lymphoma enrolled in the study, only 67 (10.4%) patients were treated by combined modality approach (chemo+radiotherapy). The remaining, treated by chemotherapy alone or received RT just for palliation (17 patients).

Among HL cases, 38 patients received Radiation as a part of their treatment. RT was given for Curative purposes in 37 patients and all cases had stage I & II diseases, the other one received RT for symptomatic relief of superior vena cava obstruction syndrome Table 5.

In a total number of 427 patients of NHL, forty-six patients (10.7%) received RT with or without chemotherapy as a part of their treatment. Unlike HL, sixteen patients received RT for palliation, the remaining 30 (7.5%) patients received curative combined modality treatment; two patients treated by radiation to their extra nodal diseases Table 6.

Table 1. Age and Gender Distribution of HL by year of diagnosis

	Gender		Age Distribution		
Year	**Male**	**Female**	**18-30 years**	**31-55 years**	**>55 years**
2013	31 (73.8%)	11 (26.2%)	11	21	10
2014	36 (65.4%)	19 (34.5%)	16	26	13
2015	20 (64.5%)	11 (35.5%)	9	15	7
2016	26 (56.5%)	20 (43.5%)	21	12	13
2017	25 (56.8%)	19 (43.2%)	14	22	8
Total & percentage	138 (63.6%)	80 (36.4%)	71 (32.5%)	96 (44%)	51 (23.4%)

Table 2. Age and Gender Distribution of NHL

	Gender		Age Distribution					
Year	**Male**	**Female**	**<30 years**	**30-39 years**	**40-49 years**	**50-59 years**	**60-69 years**	**70 & >70 years**
2013	55	35	11	8	20	14	15	22
2014	33	33	10	7	14	7	16	12
2015	37	27	8	4	11	10	20	11
2016	56	50	10	16	16	21	22	21
2017	48	53	10	6	20	16	24	25
Total & percentage	229 (54%)	198 (46%)	49 (11.5%)	41 (9.6%)	81 (18.9%)	68 (15.9%)	97 (22.7%)	91 (21.3)

Table 3. Annual Incidence of HL According to WHO Classification

	Classical HL				Nodular Lymphocyte predominant
Years	**Nodular Sclerosis**	**Mixed Cellularity**	**Lymphocyte Depleted**	**Lymphocyte rich**	
2013	39(93.2%)	1(2.5%)	0(0%)	0(0%)	2(4.3%)
2014	39(71%)	0 (0%)	0(0%)	0(0%)	16(29%)
2015	22(71%)	1(3.2%)	0(0%)	0(0%)	8(25.8%)
2016	24(52.1%)	8(17.4%)	2(4.3%)	6(13.1%)	6(13.1%)
2017	28(63.6%)	4(9.1%)	1(2.2%)	5(11.4%)	6(13.6%)
Total & percentage	153 (69.8%)	14 (6.4%)	3 (1.4)	11 (5%)	38 (17.4%)

Table 4. Annual Incidence of NHL According to WHO Classification

Years	**DLBCL**	**LPL**	**Mantle cell**	**Marginal zone**	**PTCL**	**ATL**	**Hairy cell**	**FL**	**Burkitt**	**B-PLL**	**SLL**	**Other**
2013	56	18	1	2	1	0	5	1	1	0	1	4
2014	42	9	2	6	0	0	1	1	2	1	1	1
2015	41	4	2	5	0	1	1	2	2	3	1	4
2016	62	1	3	7	3	3	0	2	2	7	10	6
2017	63	3	5	5	1	2	0	3	2	0	10	5
Total & %	264 (62%)	35 (8%)	13 (3%)	25 (5%)	5 (1%)	6 (1%)	7 (1%)	9 (2%)	9 (2%)	11 (2%)	23 (5%)	21 (5%)

DLBCL: diffuse large B-cell Lymphoma, LPL: lymphocytic plasmacytic lymphoma, PTCL: peripheral T-cell Lymphoma, ATL: adult T-Cell Lymphoma, FL: follicular Lymphoma, B-PLL: B-Cell prolymphocytic Lymphoma, SLL: small lymphocytic Lymphoma

Table 5. Treatment Pattern of HL Patients (2013-2017)

Years	Total number of HL Patients per each year	HL Patients treated with RT	Percentage of patients received RT
2013	43	5	11.6%
2014	54	5	9.2%
2015	31	16	51.6%
2016	46	5	10.8%
2017	44	7	16%
Total	218	38	17.4%

Table 6. Treatment Pattern of NHL Patients (2013-2017)

Years	Total number of NHL patients per each year	Patients treated with RT	Percentage of patients received RT
2013	90	3	3.3%
2014	66	11	16.6%
2015	61	10	16.4%
2016	104	10	9.6%
2017	99	12	12.1%
Total	427	46	10.8%

DISCUSSION

Among our study population, HL comprised 33% of all the lymphomas. As far as age is concerned, 44% of cases were between 31-50 years. Male to female ratio was 1.7:1 for HL; in the US the ratio was 1.3:1, and in Jordan the ratio was 1.5:1. We notice that the male predominance of HL in our country is more evident than the other regional and western countries [21].

In NHL peak age was 65 years and age-specific incidence rate was raising with increasing age. In the US the age peak incidence of NHL was 80 years during the same period of time. This difference in age peak incidence may be due to a more ageing population in the US [22].

We found a slight male predominance of the incidence of NHL in our region. Male to female ratio was 1.3:1. This result is closely comparable to the result of the other regional and worldwide studies. According to the result Surveillance, Epidemiology, and End Results Program (SEER) data; male to female incidence ratio for NHL is 1.4:1 in the US, which is a nearly same result of this study [22].

NHL was predominant type of lymphoma, representing about 66% of patients compared with 33% of HL. These results are closely comparable to several studies conducted in the Middle East region, where the incidence of HL 29.5% in Jordan, 33% in Bahrain, 27% in Saudi Arabia. In comparison with other studies from the Far East and Western countries, the results were intermediate. Notably, the Far East incidence of HL ranges between 5%-10% [7].

Nodular sclerosis was the commonest histology of HL which comprises 70% of all cases followed by NLPHL (17.5%) then MC (6.5%). NS was reported to be the commonest subtype of adult HL in many regional (Jordan) and western studies; there is no significant difference with our results. While MC is slightly more frequently seen in US (25%), in Jordan MC is less

common than US and comprise only 14% of all HL [15]. The etiology of HL is an unresolved issue but is likely complex and may vary depending on the different subtypes [21].

DLBCL was the most common subtype of NHL and constitutes 63% of all adult NHL, followed by lymphoplasmacytic lymphoma (9%). Notably, FL, the second most common adult NHL in most regional and western studies, was encountered in only 2% of all our cases. In comparison to the results of the other studies, there is a significant difference in the incidence of different entities of NHL between our region and other neighboring and developed countries. For example, DLBCL comprised 30-40% of all NHL in the US, 85% of cases in Jordan, 47% in Kuwait [14]. On the other hand, FL is the second most common NHL in the almost all other studies worldwide, 22% in the US, 11% in Jordan, 15.5% in Kuwait [14, 22].

Regarding HL treatment pattern in our region, we found that 17% of these cases has been treated by combined modality treatment (chemotherapy and radiation therapy). The remaining 83% treated by chemotherapy alone. Most patients who were treated by combined modality therapy were either stage I or II diseases. Fifteen patients (41%) received RT after achieving complete remission by chemotherapy as a consolidation therapy. The other 21 patients RT have been given to initial bulky or residual diseases.

Long-term toxic sequelae of irradiation especially in younger patients, has diminished enthusiasm for the combined modality approach. It had emerged as the most prominent competing cause of death after treatment for limited-stage HL [23]. Combined-modality therapy, compared with chemotherapy alone for patients with stage III to IV disease, who achieve a complete response to a full course of conventional chemotherapy, have no proven benefit [24]. In all patients with HL who received RT during the period of our research, only five patients had stage III or IV disease.

NHL is a heterogeneous group of the disease that could affect any part of the body. They are characterized by a tendency to present or progress to generalized disease. Therefore, optimal systemic therapy is paramount [7]. In this study we concentrated on the treatment modality of DLBCL, because it is the commonest subtype of NHL and its treatment is the area of intensive debate among medical and radiation oncologists.

Among 262 patients with DLBCL, only 45 patients received RT as a part of their treatment. Unlike HL, sixteen patients received RT for symptomatic palliation; the remaining 29 patients received RT with the curative intent as a part of combined modality treatment. Four patients had stage III disease.

A decreasing use of consolidation RT after multi-agent chemotherapy has been observed over last 15 years. In recent large retrospective study in US, two thirds of patients with early stage DLBCL are now treated with (immuno-)chemotherapy alone; the authors observed a decline in the use of consolidation RT from a peak of 47 % in 2000 to a nadir of 32 % in 2012 ($p < 0.001$) [25]. The omission of radiotherapy and abandonment of combined-modality approaches in current clinical practice worldwide including our region might not always be fully evidence-based.

In conclusion, Hodgkin lymphoma in the West is basically a disease of young adults. In the underdeveloped world, children are the main victims. In our study all the ages are involved. Distribution and pattern of lymphoma vary between different geographical areas. Among our study population, there is meager dissimilarity in the incidence of different histological types of HL, while NHL pattern shows more evident difference in comparison with the neighboring and developed countries. As mentioned, follicular lymphoma is a clear example of that difference. Although, combined modality approach is still standard of care in lymphoma, treatment of lymphoma with rituximab and/or combination chemotherapy have led to the premise that RT might be obsolete. In our region, most of our patients have been treated with chemotherapy alone.

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