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Non-Hodgkin's Lymphomas in Turkey: Eighteen Years' Experience at the Hacettepe University

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In this retrospective study, 470 patients with non-Hodgkin's lymphoma (NHL) who had been followed in the Hacettepe University Medical Oncology Department between 1973 and 1990, were evaluated to establish their epidemiologic, clinical and therapeutic characteristics. Out of 470 patients, 302 (62.2%) were male and 168 (37.8%) were female. The ages ranged from 16 to 85, with a median of 44 years. Constitutional symptoms were present in 46.4% of the patients. According to the Working Formulation, low, intermediate, and high-grade lymphomas comprised 33.4%, 54.9%, and 12.7%, respectively. The most common extranodal presentation was gastrointestinal. The chemotherapy regimens most commonly used were CVP (cyclophosphamide, vincristine, prednisone), BCNOP (bleomycin, cyclophosphamide, mitoxantrone, vincristine, prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CHOP-Bleo (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin). The response rates and the survival figures attained with these regimens were not statistically significantly different ($P > 0.05$). In the Cox multivariate model, pathologic grade, leukopenia, responsiveness to chemotherapy, bone marrow involvement and age were the important factors influencing the disease-free survival, while responsiveness to chemotherapy, age, presence of constitutional symptoms, pathologic grade, extranodal presentation and stage were the important factors influencing the overall survival. The distribution of NHL according to grade and stage was similar to that in western societies, while constitutional symptoms and lymphomas of the small intestine including immunoproliferative small intestinal disease were more common in Turkey.

Key words: Non-Hodgkin's lymphoma — Chemotherapy — Immunoproliferative small intestinal disease

Particular subtypes of non-Hodgkin's lymphomas (NHLs) are more common in different parts of the world. The high incidence of "T" cell lymphomas in Japan and Burkitt lymphomas in Africa are two well established examples. Turkey is located in the Mediterranean region where immunoproliferative small intestinal disease (IPSID) is more common.[1)] NHL constitutes 3% of all malignancies seen in western countries. Lymphomas in Turkey account for 8.9% of all the malignant diseases of men and 6.7% of those of women.[2)] With a relative frequency of 7.9%, Turkey has a higher NHL incidence than other western countries.[3)]

NHL may vary from rapidly growing tumors which are fatal within a few years, to more indolent tumors which may show many years of slow growth before evolving into a more malignant phase. The Working Formulation (WF) is still the most widely used pathologic classification in NHL. Although it lacks immunologic properties, it is quite simple to use as it depends solely on morphologic criteria.[4)] In the WF, NHLs are divided into three subgroups according to their histologic grades, namely low, intermediate and high. Low-grade lymphomas have an indolent course, while high-grade lymphomas show a rapid downhill course unless aggressively treated. Chemotherapy and radiotherapy are the two major modalities in lymphoma treatment. Bone marrow transplantation is an alternative approach particularly in refractory lymphomas.[5–8)] Results with biologic response modifiers have been encouraging, although it is too early to draw definitive conclusions.[9)]

This study was designed to analyze the clinical features, stages, pathologic subtypes, response to therapeutic modalities, and the factors influencing the outcome of patients with NHL who had been followed at the Hacettepe University Department of Medical Oncology between January 1973 and December 1990. Comparative analysis of our results with previously published series from the Middle East and Mediterranean region as well as from western countries may improve our understanding and future management of NHLs.

MATERIALS AND METHODS

In this retrospective study, 470 (302 male and 168 female) Turkish patients who had been followed at the Hacettepe University Department of Medical Oncology between January 1973 and December 1990, were evaluated. This department serves as one of the major

oncology referral centers in Turkey. The ages of the patients ranged from 16 to 85 years.

The data drawn from each patient were: age, sex, profession, province in which she/he lived, presence of "B" symptoms (fever, night sweats, and/or unexplained loss of 10% of body weight in the 6 months preceding admission), lymphatic-extralymphatic presentation, complete blood counts, erythrocyte sedimentation rate (ESR), blood chemistry, radiologic studies, bone marrow examination, pathologic subtype, clinical stage (according to the Ann Arbor staging system), therapeutic modalities, response to the treatment, complications encountered during therapy, response to the treatment, infections during the course and the causes of death. Mediastinal adenopathy of greater than one-third of the widest internal diameter of the chest or any tumor mass greater than 10 cm in diameter are defined as "bulky" disease.

Complete remission is defined as the total regression of disease 2 months after completion of the last therapeutic cycle. Partial remission is defined as more than 50% reduction in measurable disease in the same manner. Disease-free survival (DFS) and overall survival (OAS) were evaluated by utilizing the Cutler-Ederer method.[10] Univariate associations between the patients' characteristics and survival (e.g., DFS and OAS) were evaluated with a log-rank test. Numeric prognostic variables were analyzed by using variance analysis. Multivariate analysis using the Cox proportional hazards model was performed to determine the importance and the predictive value of the prognostic factors.[11] The criterion of statistical significance in both univariate and multivariate models was a P value less than or equal to 0.05.

RESULTS

In this study, 302 male (64.3%) and 168 female (35.7%) patients with NHL were retrospectively analyzed. The male to female ratio was 1.8/1. The ages ranged from 16 to 85 (median, 44 years). The major presenting symptoms are listed in Table I. Fever, night sweats, and/or weight loss (constitutional symptoms) were present in 218 cases (46.4%). The most common "B" symptom in our study group was weight loss. The proportion of patients having constitutional symptoms was found to increase with advancing stage (Mantel-Haenszel test for linear association, $P=0.00011$).

The clinical presentation was nodal in 278 (59.1%) and extranodal in 192 (40.9%) patients. Among nodal presentations, involvement of the cervical lymph nodes was the most common. The extranodal sites of presentation are shown in Table II. Gastrointestinal (GI) lymphomas were the most common (55.2%) occurrences among the extranodal presentations. The small intestine was the most common localization among the GI lymphomas (22 out of 106 patients with GI lymphomas had IPSID). Gastric lymphomas were the second most common among all GI lymphomas.

Anemia was the most common (42.6%) hematological finding, whereas only 3% of patients exhibited autoimmune hemolytic type. Thrombocytopenia and leukopenia were seen in 8.3% and 5.6% of the patients, respectively. The average ESR was 43.83 ± 36 mm/h with a median of 32 mm/h. Bone marrow involvement was detected in 25.8% of the patients with bone marrow aspiration and it increased to 32.2% in the group who also had bone marrow biopsy.

Prior to 1982, the Rappaport Classification was the preferred method for pathologic subgrouping. Since then

Table I. Major Presenting Symptoms on Admission

Presenting symptoms	Number	Percent
"B" symptoms[a)]	218	46.4
Lymphadenopathies	196	41.7
Gastrointestinal	69	14.6
Neurologic	16	3.4
Dermatologic	12	2.5
S.V.C.S.[b)]	10	2.1
Orthopedic	9	1.9
Genital	4	0.8

a) Patients having one or more of the following symptoms: fever, weight loss and night sweats.
b) S.V.C.S.: Superior vena cava syndrome.

Table II. Extranodal Presentations

Localization	Number	Percent
Central nervous system[a)]	12	6.3
Head and neck[b)]	10	5.2
Lung and pleura	4	2.0
Stomach	40	20.8
Small intestine[c)]	58	30.2
Large intestine and rectum	8	4.2
Bone	13	6.8
Bone marrow	20	10.4
Skin	13	6.8
Breast	6	3.1
Genitourinary tract[d)]	5	2.6
Other localizations	3	1.6
Total	192	100.0

a) Brain, basis cranii (base of the cranium), cranial nerve, meninx, and epidural mass.
b) Paranasal sinus, nasal mucosa, soft palate, parotid gland, salivary glands, thyroid, and mandible (jaw).
c) Immunoproliferative small intestinal disease (IPSID) accounted for 22 out of 58 cases.
d) Ovary, uterine cervix, prostate, and testes.

Table III. Pathologic Subgroups of Non-Hodgkin's Lymphomas According to Rappaport Classification and Working Formulation[a)]

Pathologic subgroup	Number	Percent
Low grade	134	33.4
Nodular well dif.[b)] lymphocytic (NWDL)	20	5.0
Diffuse well dif. lymphocytic (DWDL)	67	16.7
Nodular poorly dif. lymphocytic (NPDL)	30	7.5
Nodular mixed lymphohistiocytic (NML)	17	4.2
Intermediate grade	216	53.9
Nodular histiocytic (NH)	11	2.8
Diffuse poorly dif. lymphocytic (DPDL)	92	23.0
Diffuse mixed lymphohistiocytic (DML)	34	8.5
Diffuse histiocytic (DHL)	79	19.7
High grade	51	12.7
Diffuse histiocytic (immunoblastic)	17	4.2
Lymphoblastic	19	4.7
Diffuse undifferentiated	15	3.7
Total	401	100.0

a) The patients whose pathologic preparations were not available for re-evaluation were not included in this table.
b) Differentiated.

the Working Formulation has been used. Pathologic preparations were available for 401 patients out of 470 patients for re-evaluation and the slides were re-examined according to both classifications (Table III). Diffuse poorly differentiated lymphocytic lymphoma (DPDL) (23.0%), diffuse histiocytic lymphoma (DHL) (19.7%) and diffuse well differentiated lymphoma (DWDL) (16.7%) were the most common pathologic subtypes according to the Rappaport Classification, whereas the intermediate-grade lymphomas (53.9%) were the most common group according to the Working Formulation. Patient distribution according to grade and stage is presented in Table IV. The Ann Arbor staging system was used. "Bulky" disease was present in 39 patients.

As it was hardly ever possible to attain complete remission in low-grade lymphomas, the relationship between the grade and survival was investigated in terms of OAS. There was a prominent decrease in OAS with increasing grade (log-rank test, $P=0.00004$). The median OAS was found to be 180+, 170+, and 50 months for low-grade, intermediate, and high-grade lymphomas, respectively. The life table according to the grade is presented in Fig. 1. There was an inverse relationship between advancing stage and survival (in both DFS and OAS) (log-rank test, $P<0.00001$). The life table according to the stage is shown in Fig. 2.

First, second, third and fourth-line chemotherapies were given to 432, 185, 79, and 30 cases, respectively. One hundred and ninety-four cases received radiotherapy, mostly in combination with a chemotherapy regimen. CVP (cyclophosphamide, vincristine, prednisone), BCNOP (bleomycin, cyclophosphamide, mitoxantrone, vincristine, prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CHOP-Bleo (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) were the most commonly used regimens. As our study group covered all the patients after 1973, CVP was the most commonly utilized combination. Table V shows the results achieved with the first-line treatments. When these four regimens were compared in terms of response and survival, no statistically significant difference was found (log-rank test, $P>0.05$). The overall complete remission rate attained with the first-line chemotherapies was 53.3%. This rate fell to 36.2%, 16%, and 8% in patients receiving second (185 cases), third (79 cases) and fourth-line (30 cases) salvage chemotherapies. Nausea, vomiting, alopecia and bone marrow suppression were the most commonly encoun-

Table IV. Patient Distribution According to the Grade and Stage (401 Patients)[a)]

Grade	Stage				Total
	I	II	III	IV	
Low	23	31	16	64	134
Intermediate	61	59	35	61	216
High	9	10	7	25	51

a) The patients whose pathologic preparations were not available for re-evaluation and the patients with undetermined pathologic grades were excluded.

tered side effects. Avascular necrosis of the femoral head was observed in three patients receiving corticosteroids (two of them had received radiotherapy, as well). Febrile neutropenic episodes had an important impact on mortality. Infections were the most common cause of death (28/60, 46.7%). Progressive disease, bleeding and cardiopulmonary complications were the next most common reasons.

There were 7 patients (1.5%) with second malignancies in our study group. A case with simultaneous NHL and hypernephroma was accepted as "double primaries." One patient developed acute myeloblastic leukemia and the remaining four had carcinomas of the prostate, colon, anus and stomach. The earliest occurrence was 5 months and the latest was 8 years following the completion of treatment of NHL.

The prognostic factors affecting the DFS and OAS according to univariate analysis are presented in Table VI: age, pathologic grade, anemia, thrombocytopenia, bone marrow involvement, responsiveness to chemotherapy and radiotherapy were the important prognostic factors affecting both the DFS and OAS. ESR and lactic dehydrogenase (LDH) levels were found to be important prognostic factors for OAS but not DFS. When listed according to P values, responsiveness to chemotherapy, stage, anemia, thrombocytopenia and pathologic grade were the most important prognostic factors in decreasing order.

After the univariate analysis, Cox multivariate survival analysis was performed, as this method offers the advantage of examining all the prognostic factors when they are together in a single model. According to the multivariate analysis, pathologic grade, leukopenia, responsiveness to chemotherapy, bone marrow involvement and age were the most important factors influencing the DFS; while responsiveness to chemotherapy, age, presence of "B" symptoms, pathologic grade, extranodal presentation and stage were the important factors influencing the OAS.

DISCUSSION

The male to female ratio was found to be 1.8/1, and the median age was 44 years. These findings were in accordance with the literature, as NHL is more common

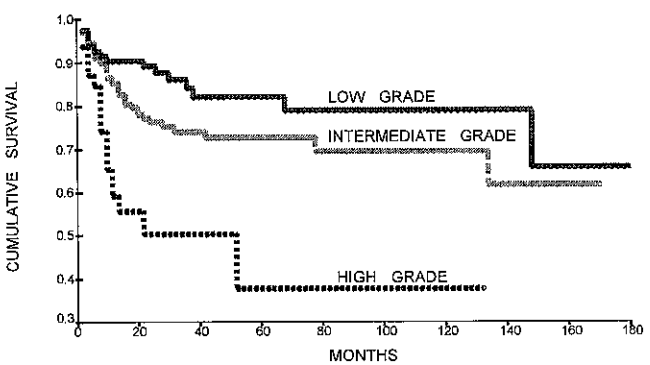

Fig. 1. Survival according to grade. There was a prominent decrease in the overall survival with increasing grade (log-rank test, $P=0.00004$).

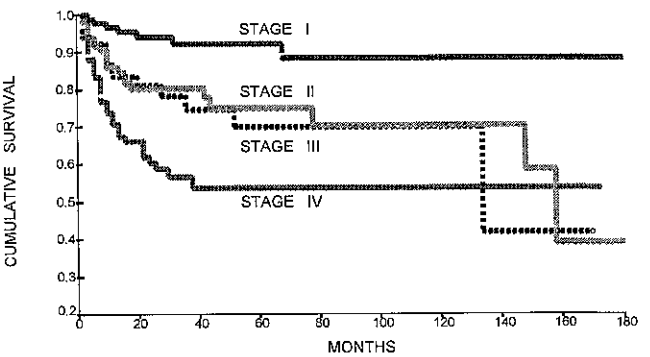

Fig. 2. Survival according to stage. There was an inverse relationship between advancing stages and survival (log-rank test, $P<0.00001$).

Table V. Results Achieved with the First-line Chemotherapies

Regimen	Complete remission	5-Year		10-Year	
		DFS	OAS	DFS	OAS
CVP[a)]	49.7%	67.3%	74.2%	53.7%	70.3%
BCNOP	67.4%	61.8%	74.6%		
CHOP	56.8%	43.2%	68.0%	43.2%	60.4%
CHOP+Bleo	55.0%	43.6%	83.3%		

CVP: Cyclophosphamide, vincristine, prednisone; BCNOP: Bleomycin, cyclophosphamide, mitoxantrone, vincristine, prednisone; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-Bleo: Cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin.
a) The results achieved with first-line CVP in low, intermediate and high-grade lymphomas.

Table VI. Prognostic Factors in Non-Hodgkin's Lymphoma (Univariate Analysis)

Prognostic factor	Statistical method	*P* value	
		DFS[a]	OAS[b]
Sex	log-rank	>0.05	>0.05
Age	correlation	<0.001	<0.01
"B" symptoms	log-rank	>0.05	>0.05
Extranodal presentation	log-rank	>0.05	>0.05
Grade	log-rank	<0.05	=0.00004
Stage	log-rank	<0.00001	<0.00001
"Bulky" disease	log-rank	>0.05	>0.05
Sedimentation rate	correlation	>0.05	<0.05
Lactic dehydrogenase	log-rank	>0.05	<0.01
Anemia	log-rank	<0.05	<0.00001
Leukopenia	log-rank	>0.05	>0.05
Thrombocytopenia	log-rank	<0.005	<0.00001
Bone marrow involvement	log-rank	<0.01	<0.05
Response to the chemotherapy	log-rank	<0.00001	<0.00001
Radiotherapy	log-rank	<0.05	<0.05

a) DFS: Disease-free survival. *b*) OAS: Overall survival.

in males and tends to increase at the end of the fourth and at the beginning of the fifth decades.[12, 13]

Turkey is divided into seven geographical regions. When the NHL admissions were analyzed according to geographical regions, we noted that 62% of the patients were inhabitants of Central Anatolia and the Black Sea regions. After the Chernobyl nuclear reactor accident in 1986 and the radiation fall-out in the Black Sea region, we were all curious about the early and late effects of radiation in the countries neighboring Russia. We were not able to find any difference in the number of cases coming from the Black Sea region before and after the accident. Our study was terminated as of 1990, and it may be too early to draw any definitive conclusions since malignancies secondary to radiation may occur even decades after the exposure.

Constitutional symptoms were present in 46% of the patients. This is a very high percentage compared with the literature. Most series from western countries give figures of about 20%.[13, 14]

In our series there were four cases with autoimmune diseases, who had later developed NHL. Lymphoma of the salivary glands and lymphoma of the breast were observed in two cases with Sjogren's syndrome. Lymphoma of the thyroid developed in a patient with Hashimoto's thyroiditis. We had a case with systemic lupus erythematosus, who developed NHL three years later.

Presentation was nodal in 59.1% and extranodal in 40.9% of the patients. The vast majority of the extranodal presentations (55.2%) were in the GI system (Table II). This finding is in agreement with reports from Turkey and other countries.[15–17] For GI lymphomas, the small intestine was the most common site of disease (54.7%). IPSID is seen more frequently in the Mediterranean region and Middle East than in other parts of the world.[1] Turkey is located in this area, so that a high incidence of IPSID is expected. There were 22 patients with IPSID in our series, which constituted 4.9% of all lymphomas and 21% of the GI lymphomas. This finding is not in accordance with another Turkish study, which reported a high incidence of gastric lymphomas (43%) and the absence of IPSID.[15] In the former study, there were 185 patients and all the patients were inhabitants of the south and southeastern regions of Turkey. The present study includes 470 referred patients from all regions of Turkey. The differences in the size and composition of the populations could explain the discrepancy between the results obtained in the two studies. Gastric lymphomas were the second most common among all gastrointestinal lymphomas (37.8%) in our series. Gastric lymphomas accounted for 25%, 34%, and 35% of the GI lymphomas in Lebanon, Jordan and Kuwait, respectively.[1, 18, 19]

Out of 47 cases with head and neck lymphomas, the initial sites of presentation were tonsils and nasopharynx in 37 and the remaining 10 had lymphomas of the extranodal sites. In a large series of head and neck lymphomas it has been found that approximately one-third of head and neck lymphomas arise from the extralymphatic tissues.[20] In our series, 64% of the tonsillary lymphomas were of DPDL and histiocytic types. More than half of the cases (58.3%) with nasopharyngeal lymphomas were of diffuse histiocytic type. Lymphomas of the parotid gland were the most common extralymphatic localizations in the head and neck lymphomas, where 3 cases out of 4 had low-grade histologies. Histiocytic and poorly differentiated lymphocytic lymphomas are the most common pathologic subtypes in all head and neck lymphomas (72.3%) and our findings were in concordance with the literature.[21, 22]

When the laboratory findings were analyzed, anemia (42.6%), hypoalbuminemia (32%) and LDH elevation (30.7%) were the most common changes. Mean ESR was 48.83±36 mm/h. In a series of 317 patients with NHL, anemia was reported to be the most common (44%) hematologic alteration, showing a close resemblance to our series.[23] Currently, LDH is considered to be one of the most important prognostic factors as it reflects the tumor cell burden.[24–29] The OAS rate was adversely affected by high LDH values in our series (log-rank test, $P<0.01$). Bone marrow involvement was documented in 25.8% and 32.2% of patients in whom bone marrow aspiration and biopsy were performed, respectively.

According to the Rappaport Classification DPDL, DHL and DWDL were the most common histologic subtypes (Table III). DHL, DPDL and NPDL were reported to be the most common subtypes in the United States.[13, 14] The only important difference was the relatively low incidence of NPDL in our series. When the same analysis according to the Working Formulation was done, intermediate, low and high grades were seen in decreasing order with percentages of 53.9, 33.4, and 12.7, respectively (Table III). These findings were quite similar to the previously reported series.[30, 31]

Distribution according to the stages revealed that approximately half of the cases were in early stages (I & II), while the other half were in later stages (49.7% versus 50.3%). When the stage distribution according to the grades was taken into consideration, a propensity of low-grade and high-grade lymphomas to be in later stages was observed (Table IV).

As complete remissions were hardly ever attained, low-grade lymphomas were discarded before analysis of the relationship between the pathological grade and the DFS. A significant decrease in OAS rate was found with increasing grade (log-rank test, $P=0.00004$) (Fig. 1). This finding was in concordance with the literature.[32, 33] An inverse relationship between the stage and the OAS was documented (log-rank test, $P<0.00001$) (Fig. 2). Most of the series from Europe and the United States had similar results.[26, 27, 34, 35]

CVP, BCNOP, CHOP and CHOP-Bleo were the regimens most frequently employed. CVP had been utilized in patients who were not suitable candidates for the "watch and wait" policy and in patients with poor bone marrow reserve. It was also administered to patients with aggressive lymphomas in the 1970's. BCNOP, CHOP and CHOP-Bleo regimens were chosen only for intermediate and high-grade lymphomas. We were not able to show any superiority of alternative chemotherapy regimens over CHOP.

In this study complete remission rates were 36.2%, 16%, and 8.7% with the second, third, and fourth-line chemotherapies, respectively. ProMACE-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide-mechlorethamine, vincristine, procarbazine, prednisone), BCNOP, and CHOP-Bleo were the best second-line regimens, with complete remission rates of about 50%. It has been estimated that 25% of the patients with relapsing lymphomas might enjoy a long-term disease-free interval.[36] The lymphoma cells may have or acquire multidrug resistance (MDR) genes and may become refractory to many different chemotherapeutic agents.[37, 38] Second malignancy was observed in 7 cases (1.5%). Lymphoma and hypernephroma occurred concomitantly in one patient, and were considered as "double primaries." After excluding the patient with double primaries, the frequency of second malignancy was 1.3% (6/470), comparable to other series.[39, 40]

Univariate and multivariate comparisons of the prognostic factors were done. In univariate analysis, the most important prognostic factors in decreasing order were responsiveness to chemotherapy, stage, anemia, thrombocytopenia and pathological grade (Table VI). In multivariate analysis, pathologic grade, leukopenia, responsiveness to chemotherapy, bone marrow infiltration and age were the most important factors for DFS, while responsiveness to chemotherapy, age, presence of constitutional symptoms, pathologic grade, extranodal presentation and stage were the most important ones for OAS. These observations were in accordance with those in most of the published series.[24, 26, 34, 41–43]

These results obtained in Turkish patients show similar stage and grade distribution of NHL to those in western countries, while lymphomas of the small intestine including IPSID were more common in the population studied. Much remains to be learned concerning the factors responsible for the geographic variations in this entity.

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