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Clinical characteristics and therapy outcome of pediatric Hodgkin's lymphoma - a single centre experience from the west part of Turkey

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ABSTRACT

The aim of this study was to evaluate the epidemiologic and clinicopathological characteristics and treatment outcome of pediatric Hodgkin's lymphoma (HL) cases treated in our institution. The patient records were reviewed retrospectively. Thirty-eight patients were eligible out of 51. The median age was 10 years and M:F ratio was 1.7:1. The major histological subtype was nodular sclerosis. The treatment regimen was COPP and/or ABVD + involved-field radiotherapy (IFRT) in 24, and GPOH-HD 90 + IFRT in 13 patients. Median follow-up was 105 months. At 5 and 10 years event-free survival rates were 77% and 73%; overall survival rates were 96% and 92%, respectively. Survival rates were comparable with the other studies from Turkey. No prognostic factor could be determined owing to the limited patient number. The epidemiologic and clinical features of pediatric HL may show considerable differences even between the regions of a country. We need large scale national trials to determine our own risk factors and design risk-based therapy regimens accordingly [Turk J Cancer 2007;37(3):98-108]

KEY WORDS:

Hodgkin's Lymphoma, childhood, clinical characteristics, therapy outcome

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INTRODUCTION

The incidence rates for childhood Hodgkin's Lymphoma (HL) displays some characteristic epidemiological, clinical and histopathologic features according to various geographic areas, particularly according to the socio-economic status of a given population (1). The pediatric HL series from Turkey presents a similar sex, age and subtype distribution with other developing countries: younger age at presentation, high male-to-female ratio, presence of constitutional symptoms, and predominance of mixed cellular type which is called epidemiological Type 1 HL (2-6). The region where our center is located is at the extreme west part of Turkey. The socio-economic status of the Aegean region is relatively high when compared to the rest of the country. The distribution of childhood malignant disease in this region shows a considerable difference from the general national figures, mostly resembling a developed country pattern (7). In this study, we aimed to evaluate the epidemiological, clinical and pathological characteristics and treatment outcome of pediatric HL cases treated in our institution.

PATIENTS AND METHODS

We retrospectively reviewed the records of children and adolescents with Hodgkin's lymphoma treated consecutively from June 1988 to June 2007 at our institution.

In addition to general hospital patient charts, pediatric oncology department records that used to contain oncological details for diagnosis, treatment course and follow up were analyzed for this study. Inclusion criteria were: i) children and adolescents ≤18 years of age with histologically proven HL, ii) Pathological diagnosis either done at our center or confirmed by our pathology department, iii) All the anticancer treatment and follow-up to be completed at our center. Disease staging was done according to Ann-Arbor classification system. Histopathological subtypes of tumors were defined using Rye criteria. Diagnostic investigations included biopsy of a clinically involved lymph node, chest X-ray, computed tomography (CT) scan of thorax, abdominopelvic ultrasonography and CT scan, bone marrow aspirates and biopsies and bone scintigraphy for clinically advanced disease. None of the patients underwent staging laparotomy. The diagnosis, staging and treatment decisions for all patients had been carried out by our center's multidisciplinary Pediatric Oncology Group.

Laboratory tests included a complete blood count, erythrocyte sedimentation rate (ESR), liver and renal chemistries, serum lactate dehydrogenase (LDH). The clinical and laboratory findings evaluated for prognostic significance on event-free survival (EFS) and overall survival (OS) were: Age, gender, stage (I-II vs. III-IV), histology, presence of mediastinal bulky disease (a mediastinal mass of >one third of the transthoracic diameter on an upright chest radiograph) and/or peripheral bulky disease (peripheral lymph node of >6 cm in maximal axial diameter), presence of B symptoms, number of involved nodal areas (<3 vs. ≥3), hemoglobin level (<11 g/dl vs. ≥11 g/dl), WBC (<13.500/mm^3 vs. ≥13.500/mm^3), ESR (<20 mm/h vs. ≥20 mm/h), serum lactate dehydrogenase level (LDH: <500 IU/L and ≥500 IU/L) and type of chemotherapy (GPOH 90 vs. COPP-ABVD based regimen). Presence of extranodal disease was not included in this analysis because of small number of patients. The number of the patients with other histological types was small, so histology was analyzed as nodular sclerosis (NS) vs. mixed cellular (MC) subtype only.

Treatment protocol

The primary chemotherapy regimens according to the stages are shown at table 1. The chemotherapy regimens were COPP (cyclophosphamide, vincristine, prednisone, procarbazine) or MOPP (mechlorethamine, vincristine, prednisone, procarbazine) and/or ABVD (adriamycin, bleomycin, vincristine, dacarbazine) based in 24 patients (63%). Since 1989, we used standard COPP/ABVD based regimens, and then we started to treat our patients according to the GPOH 90 protocol (8) in 1997. Thirteen (31.5%) patients received GPOH 90 regimen until 2000. However, five out of these 13 (39%) cases experienced relapse including three early relapses (≤18 months). Therefore, we returned to use the COPP/ABVD-based regimens after 2000. Only one patient with an early stage nodular lymphocyte-predominant HL received CHOP regimen.

In our pediatric HL treatment protocol, low dose (1980-2520 cGy) radiotherapy was administered in patients with complete response after chemotherapy. When there was initial bulky disease, 540 cGy boost dose was given to the bulky site. Doses higher than 3060 cGy were delivered to patients having residual disease after chemotherapy or progressive disease. Dose levels up to 4140 cGy were tailored according to the response to initial chemotherapy. Radiotherapy was delivered with megavoltage units (6 MvX or Co60) to the involved field in early or to the bulky site in advanced stage patients. Parallelly opposed, antero-posterior isocentric fields were simulated in all patients and critical structures were shielded with individual cerrobend alloy blocks. 1980 to 4140 cGy was delivered with 180 cGy per fraction to the reference isodose encompassing the treatment volume calculated in computerized treatment planning system. The whole lymphatic region of initially involved lymph node was irradiated in early stage patients.

Statistical analysis

EFS was determined from the date of diagnosis to the date of event (relapse, progression, death, or the most recent follow-up examination). OS was calculated from the initiation of the treatment to the date of death or was censored at last follow-up. Clinical factors at diagnosis were investigated with univariate analysis using log rank test. Kaplan-Meier product-limit method was used to determine survival probabilities for both EFS and OS at 5 and 10 years. All calculations were performed with SPSS version 11.0 statistical software.

RESULTS

The records of 550 patients with lymphoma and solid tumors were analyzed for this study. The number of childhood leukemia cases treated by the pediatric oncology department during the same period was 194. The most common childhood malignant disease was leukemia (26%),

Table 1
The primary chemotherapy regimens according to the stages

Primary chemotherapy	Stage I-IIA n: 20 (52%)	Stage IIB-IIIA n: 9 (24%)	Stage IIIB-IV n: 9 (24%)	Total n:38 (100%)
COPP – ABVD based regimens				**24**
COPP	5*	1*	1	7
ABVD	8	-	2	10
COPP / ABVD alternating	1	2*	4	7
GPOH 90 treatment protocol				**13**
OEPA (male) or OPPA (female)	3	-	-	3
OEPA + COPP	-	3	-	3
OPPA + COPP	2	3	2	7
CHOP	1	-	-	**1**
Total	**20**	**9**	**9**	**38**

*One of the patients received MOPP instead of COPP
COPP: cyclophosphamide, vincristine, prednisone, procarbazine; MOPP: mechlorethamine, vincristine, prednisone, procarbazine; ABVD: adriamycin, bleomycin, vincristine, dacarbazine; OEPA: vincristin, etoposide, prednisone, and adriamycin; OPPA: vincristin, procarbazine, prednisone, and adriamycin; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone

followed by central nervous system (CNS) tumors (21%) and malignant lymphomas (14%). Children with HL constituted 48% of the lymphoma cases and 6.9% of all malignant pediatric diseases (n:744) treated at our center.

There were 51 children and adolescents with HL. Thirteen patients were excluded due to following reasons: patients who had been still on anticancer treatment (n:4), patients who were admitted because of relapse HL (n:2) or primary resistant disease (n:1), patients whose diagnosis and/or some part of the treatment protocol was given elsewhere (n:1), patients who had to complete part of their treatment in other centers (n:5).

A total of 38 patients were included in the analysis. The median age was 10 years (range: 2-18 years) and there were 24 boys and 14 girls, and the M:F ratio was 1.7. The most common histological subtype was nodular sclerosis (55.3%) followed by mixed cellular (31.6%). Twelve patients had B symptoms (31.6%). There were 23 patients (60%) with Stage I-II and 15 patients (40%) with Stage III-IV disease. Some patient characteristics are shown at table 2.

The number of involved lymph node regions was <3 in 22 (58%) patients, and ≥3 in 16 cases (42%). The most common nodal sites involved were cervical (n:32, 84%) and mediastinal (n:27, 71%). Five of 38 (13%) children had extranodal disease at diagnosis. Anatomical locations involved were lungs (n:3) and liver (n:2). Bulky disease was present in 25 (66%) patients during the diagnosis. Nine (36%) of them had mediastinal and 12 (48%) had peripheral bulky disease, and four (16%) patients had both mediastinal and peripheral bulky disease. Five (13%) of 38 children had extranodal disease at diagnosis. Anatomical locations mostly involved were lungs (n:3) and liver (n:2).

Table 2
Some clinical and demographic characteristics of study population

	n	%
Sex		
Male	24	63
Female	14	37
M:F ratio	1.7:1	
Age (years)		
<5	4	10.5
5-10	18	47.3
>10	16	42.1
Histologic subtype		
Lymphocyte predominant	4	10.5
Nodular sclerosis	21	55.3
Mixed cellular	11	31.6
Lymphocyte depletion	-	-
Nodular lymphocyte-predominant	1	2.6
Clinical stage		
IA	9	23.7
IB	1	2.6
IIA	10	26.3
IIB	3	7.9
IIIA	4	10.5
IIIB	3	7.9
III_SA	2	5.2
III_SB	2	5.2
IVA	1	2.6
IVB	3	7.9
Total	38	100

The number of chemotherapy courses according to the stage were as follows: 2-4 courses for stage I-IIA patients (n:20), 4-6 courses for stage IIB-IIIA patients (n:9), 6-8 courses for stage IIIB-IV patients (n:9).

All patients except one stage IVSB were irradiated initially with doses between 1980 to 3960 cGy to the primary site.

Relapse patterns

There were nine treatment failures. One patient with Stage IVsB HL developed refractory disease. There were eight patients (21%) who developed relapse in this study group. The time to relapse was the first 18 months (9-18 months) for 5 patients and 55, 74, 77th month of diagnosis for the other three cases. Table 3 shows some clinical features and treatment details for patients with relapse disease. Among these, one patient (patient no:8) had only a true infield recurrence in the irradiated site. He was initially staged as IB left cervical disease. He recurred at the initial site despite 3600 cGy bilateral cervical and 3960 cGy to the left cervical area. He is alive after 6 cycles of COPP without evidence of disease.

Patient no:3 had a mediastinal recurrence just on the lower border of the treatment field. Before this marginal relapse, he was initially irradiated to the cervical and mediastinal area with a dose of 3400 cGy. He is in complete remission after 6 cycles of chemotherapy.

In another patient (no:5) with stage IIA, infield mediastinal relapse was associated with an outfield axillary relapse after 2520 cGy of modified mantle, including cer-

Table 3
Some clinical features and treatment details for patients with relapsed disease

Patient no	Age, gender	Histology	Stage	Primary CT	Primary RT	Time to relapse (mos)	Site of relapse	Salvage treatment	Outcome
1	8 y, F	MC	IVA	COPP (4) / ABVD (4)	Mediastinal 25.2 Gy	9	OPTS *(abdominal paraaortic & renal)*	NHL BFM 95 regimen and paraaortic RT	Alive, CR
2	10 y, M	NS	IIISA	OEPA (2) / COPP (2)	Cervico-mediastinal 25.2 Gy	10	PTS *(abdominal paraaortic, spleen)*	Splenectomy, MOPP(3)/ ABVD(3) paraaortic RT	LFU after 40 mos
3	5 y, M	NS	IIA	ABVD (3)	Cervico-mediastinal 34 Gy	14	PTS *(mediastinal)*	COPP (3) / ABVD (3)	LFU after 136 mos
4	16 y, F	NS	IVSB	OPPA (2) / COPP (6)	(-)	18	PTS *(abdominal mediastinal, cervical)*	ABVD (3) & Mantle+inverted Y RT & ABMT	Alive, CR
5	16 y, M	NS	IIA	OEPA (2) +RT	Cervico-mediastinal 25.2 Gy	18	PTS (cervical) & OPTS (axillary)	COPP (3) / ABVD (3)	Alive, CR
6	5 y, M	MC	IIIA	OPPA (2) / COPP (1)	Cervico-mediastinal 25.2 Gy + 9 Gy cervical boost	55	PTS *(supraclavicular)* & OPTS *(axillary)*	ABVD (6) & axillary RT	Alive, CR
7	12 y, M	LP	IIIA	OEPA (2) / COPP (3)	Mantle + para-aortic 25.2 Gy	30	PTS *(abdominal paraaortic) &* OPTS *(pelvic, spleen)*	ABVD (3) / COPP (3) & RT (pelvic) ABMT for 2nd relapse	CR for 6 mos Died with disease
8	7 y, M	NS	IB	ABVD (3)	Cervical 39.6 Gy	77	PTS *(cervical)*	COPP (6)	Alive, CR

CT: chemotherapy; Mos: months; M: male; F: female; MC: mixed cellularity; NS: nodular sclerosing; LP: lymphocyte predominant; COPP: cyclophosphamide, vincristine, prednisone, procarbazine; MOPP: mechlorethamine, vincristine, prednisone, procarbazine; ABVD: adriamycin, bleomycin, vincristine, dacarbazine; OEPA: vincristin, etoposide, prednisone and adriamycin; OPPA: vincristin, procarbazine, prednisone and adriamycin; IFRT: involved field radiotherapy; PTS: primary tumor site; OPTS: out of primary tumor site; ABMT: autologous stem cell transplantation; CR: complete remission; LFU: lost to follow up; LCAL: large cell anaplastic lymphoma

Table 4
Epidemiologic and histopathologic data from some Turkish pediatric HL series

	Patient (n)	Median age (years)	Sex M / F	Histopathology MC	Reference (no)
Ertem et al.	82	NA	5.3:1	56.1	2
Cavdar et al.	175	7.8*	3.1:1	58.3	3
Buyukpamukcu et al.	210	8	2.96:1	69.6	4
Oguz et al.	69	7	3:1	38	5
TPOG Data	1823	8	2.54:1	46.5	6
Current study	38	10	1.7:1	31.6	-

*mean age,
NA: not available

vical, supraclavicular and mediastinal lymphatics. He remains in complete remission after 3 cycles of COPP and 3 cycles of ABVD.

One patient (no:7) with Stage IIIA HL, lymphocyte predominant histology experienced two relapses. He was initially treated with 5 cycles of chemotherapy followed by mantle and para-aortic (2520 cGy) radiotherapy. The first relapse (para-aortic at the irradiated and pelvic-spleen at the unirradiated site) was at 30th month of diagnosis and he reached CR with salvage therapy including ABVD (3)/ COPP (3) and pelvic 3060 cGy RT. He remained in continuous complete remission since he developed a second relapse at 6th year of diagnosis where autologous bone marrow transplantation (ABMT) was done after achieving a partial response with second salvage treatment. However, he eventually died with progressive disease.

Cervico-mediastinal radiotherapy at a dose of 2520 cGy was effectuated to the patient no:6 after 3 cycles of

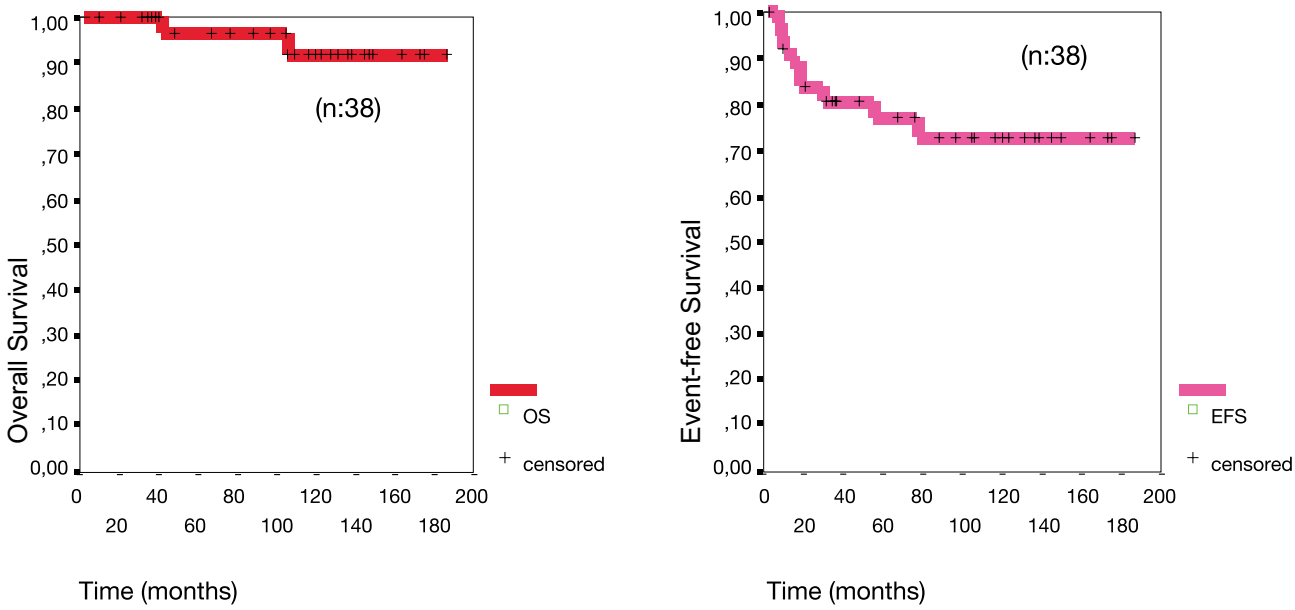

Fig 1. OS and EFS for the whole study group

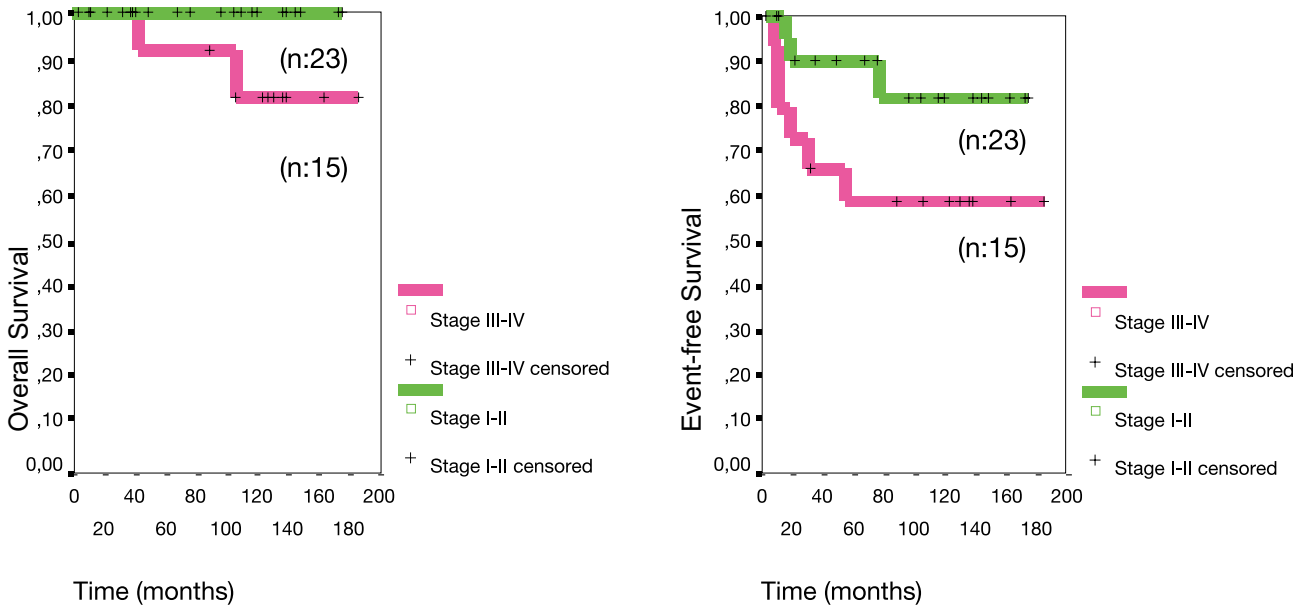

Fig 2. OS and EFS in Stage I-II vs. Stage III-IV disease

chemotherapy. He also received 900 cGy boost dose to the bilateral cervical region. He had infield supraclavicular and outfield axillary relapse. He is alive with complete remission after 6 cycles of ABVD and axillary radiotherapy.

Patient no:4 with stage IVsB was not initially irradiated because of inexistence of bulky disease. She had cervical, mediastinal and para-aortic recurrence after 8 cycles of chemotherapy. She received 3 cycles of ABVD, mantle and inverted Y irradiation and ABMT as salvage treatment and is in complete remission.

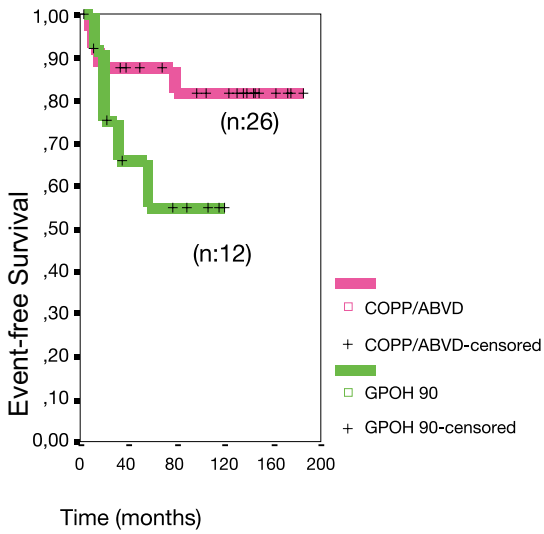

Fig 3. EFS according to the therapy regimen (COPP-ABVD based vs. GPOH 90)

In patient no:1 with stage IVA, mediastinal and para-aortic irradiation was planned after 8 cycles of chemotherapy. She experienced an abdominal relapse during the mediastinal irradiation. After accelerating the mediastinal irradiation, the patient received chemotherapy and para-aortic radiotherapy as salvage treatment. She is alive with complete remission.

The last patient (no:2) with initial stage IIIsA received 2520 cGy cervico-mediastinal radiotherapy after 4 cycles of chemotherapy. He had para-aortic and splenic recurrence and after splenectomy he received 6 cycles of chemotherapy and para-aortic radiotherapy.

Survival rates

Median follow-up time was 105 months (range: 3-186). The 5-year EFS and OS rates for the whole study group were 77% and 96%, respectively (Figure 1). The 10-year EFS and OS rates were 73% and 92%, respectively. The prognosis for early disease (Stage I-II) vs. advanced disease (Stage III-IV) patients was as follows:

- Stage I-II patients: EFS was 90%, and 82%, at 5 and 10 years, respectively. OS was 100% at both 5 and 10 years (Figure 2).

- Stage III-IV patients: EFS was 59 % at 5 and 10 years. OS was 92% at 5 year and 81% at 10 year (Figure 2).

Univariate analysis

None of the pretreatment prognostic factors was found significant (p >0.05) for EFS and OS.

The EFS and OS rates also did not show any significant difference between Stage I-II disease and Stage III-IV disease (p=0.09 and p=0.10, respectively) (Figure 2). Moreover, there was no significant difference between the OS and EFS rates of patients who received GPOH 90 regimen and COPP-ABVD based regimens (p=0.55 and 0.11, respectively) (Figure 3).

Late Effects

Only one patient developed therapy-related AML after ABMT. Another patient developed two osteochondromas; one within and one outside the RT field. None of the patients experienced pulmonary or chronic cardiotoxicity. A male patient is infertile due to procarbazine. Two female patients gave birth to healthy children.

DISCUSSION

There are substantial variations between regions of the world in the incidence of all childhood cancers combined and of the principal diagnostic groups (9). In affluent countries, the most common childhood cancer types are leukemias, followed by CNS tumors and lymphomas (9). In our series, the distribution of childhood cancer was similar with this pattern: most common childhood malignant diseases were leukemias (26%), CNS tumors (21%) and malignant lymphomas (14%). Hodgkin's lymphoma constituted 6.85% of all malignant diseases and 48% of lymphomas enrolled in our institution.

The incidence rates for 1073 children with lymphoma and solid tumors registered to the Turkish Pediatric Oncology Group (TPOG) Pediatric Tumor Registry 2002 revealed that lymphomas (26.8%) were the most common pediatric malignant disorder excluding leukemias, followed by CNS tumors (21.1%) (10). The data including childhood leukemias was only available after the collaboration of the Turkish Pediatric Oncology Group (TPOG) and Turkish Pediatric Hematology Associations in 2005. The national data from these two associations showed the distribution of the most common cancer types in 1435 children as follows; leukemia 27.2%, lymphomas & reticuloendothelial system (RES) 16.7% (Hodgkin's lymphoma 9.9%), CNS/intracranial/intraspinal 11.6% (11). These results were consistent with a developing country pattern. The incidence of lymphoma tends to be higher in the Middle East Cancer Consortium (MECC) countries than in Europe (12). However, our own data showed similar figures with the developed countries (9). Although we didn't have an analysis on socio-economic status of this patient population, this striking difference can be explained with different socio-economic and cultural profile of our patients or may be due to some genetic differences. In accordance with our incidence rates, the results from the İzmir Cancer Registry shows that the childhood cancer patterns in İzmir region mostly resembles the western population's figures; leukemias (30.6%) followed by CNS tumors (21.3%), and lymphomas (15%) were the most common malignant diseases in İzmir (7). In our region, besides the ranking of tumors, the total and site specific incidence rates are very close to the developed countries (12,13).

The median age of our patients was 10 years. The most recent data on pediatric HL in Turkey showed a median age lower (8 y) than in developed countries (6). Previously published data from the other regions of Turkey were also consistent with this result (Table 4). We had only four patients (10%) younger than 5 years of age during the initial diagnosis. In other series from Turkey, this ratio was higher: 29.7% was ≤ 5 years of age; 17.6% was <5 years of age and 32.3% was <7 years of age, respectively (3-5). Reports from other developing countries show that pediatric HL occurs at a younger age with as many as 15 to 30% of cases occurring before 5 years of age, against some 5% in developed countries (1,8, 14-17)

In this study group, M:F ratio was 1.7:1. The other series reported a higher M:F ratio up to 5.3 (Table 4). Pediatric HL presents a slight male predominance in Western countries with an M:F ratio close to 1.5:1. However, there is a large male excess in less economically developed countries, with an M:F ratio between 2.5:1 and 5:1 (1).

In contrast to the general national figures as well as the data from other developing countries, which all showed a MC predominant histopathologic subtype, the predominance of NS (NS) histology (55%) was the most prominent feature of our study population. However, 31% of our cases had MC histology, a proportion higher than the incidence observed at the developed countries (9,18,19).

Distribution of HL cases over age, gender, geographical areas and socio-economic settings have long suggested multiple etiologically distinct entities for HL, rather than a single disease. The prevalent type in developing

countries is the MC histological subtype, predominates in young children, particularly in males, mostly presents as advanced stage disease. These features could be partly explained by the hypothesis of an etiologic role of EBV in the pathogenesis of HL. Studies have shown a causal relationship between infectious mononucleosis and subsequent Epstein-Barr virus (EBV)-positive HL (20-25). Çavdar et al. (3) showed the high frequency of EBV-related LMP-1 positivity (73.6%) in pediatric HL cases. Childhood Hodgkin's lymphoma in developed countries affects mainly older children, mostly presenting as NS histological subtype and might be explained with a delayed exposure to common infectious agents as there is an increased male susceptibility to viral and bacterial infection in childhood, which is more marked in the first five years of life (1,18).

Most of the data coming from the other centers, as well as the TPOG data including 1823 children from 22 different centers from all over the country is consistent with a developing country pattern of HL (type I) characterized by a high incidence of MC histological subtype, a younger median age and a male predominance (Table 4). Our data, reflecting the figures from the extreme west part of our country was more consistent with the data from affluent countries (18, 26-29). The higher socio-economic and cultural status of this geographical area may be a contributing factor for this striking difference.

Nine patients had (23%) treatment failures in our study, one of them being resistant disease (Table 3). This patient with Stage IVsB HL with extensive pulmonary metastasis during the initial presentation developed resistant disease after 6 courses of COPP. She received three courses of ABED (Adriamycin, Bleomycin, Etoposide, Dacarbazine) and mediastinal radiotherapy, followed by BEAM protocol (Carmustin, Etoposide, Ara-C, Melphalan) and autologous stem cell transplantation. She reached complete remission but developed therapy related AML at 39th month of ABMT and died with progressive disease.

Five of these relapse cases had NS histology. They all initially achieved complete remission but relapsed at a median of 18 months. Four relapses occurred at the primary site (two in the irradiated, two in the unirradiated site), two occurred at both the primary and out-of-primary sites and only one occurred at out of the primary site (Table 3). All relapsed patients, except one with stage IVSB HL, were initially irradiated with doses between 1980 to 3960 cGy to the primary site. It should be noted that these doses were adequate for controlling disease.

The 5-year EFS was 77% and OS was 96% in this patient group. The 10-year EFS and OS rates were 73% and 92%, respectively. Even though it was not statistically significant, EFS and OS rates in advanced disease were lower than in the early stage disease. These survival rates are comparable with some other series from Turkey (4-6). Although no significance could be shown, The EFS in patients receiving GPOH 90 protocol was lower (5 and 10 year EFS was 55%) than the patients who received COPP/ABVD based regimens (5 and 10 year OS were 100% and 83% respectively). Our results with GPOH-HD 90 protocol were less satisfactory as compared with those reported by DAL/GPOH-HD study groups of OS and EFS 98% and 91% for all stages (8). Inferior survival rates, compared with the results of the GPOH-HD group, has been reported in Iranian children who also received German-Austrian DAL-HD 85-90 protocol (5 and 16 year OS 94.4% and 88.1%, EFS 79.2% and 75.4%, respectively) (30). Although the number of patients was not enough to draw a conclusion, one should consider some other poor prognostic factors which could not be shown with this patient size, such as the high number of patients with bulky disease (66%.) There might also be some undetermined histological risk factors such as subtypes of NS histology (NS1 vs. NS2). A recent large scale study from the DAL-HD-90 group showed that NS2 histology had a major negative impact on treatment outcome in HL (29). Another pediatric study from Turkey showed that NS histologic subtype resulted in a significant decrease ($p=0.02$) in EFS (49.2 months for NS and 72.2 months for the other subtypes), however they did not have any subclassification of NS subtype since it had not been a common practice in pediatric HL (5). At another center in Turkey, treatment protocol had been tailored according to the histological subtype, long before the industrialized countries have started to search for risk-based treatment regimens: they used to give ABVD+IFRT (involved field RT) for stage I-II patients with NS and lymphocyte depletion subtypes, where other stage I-II patients were given COPP+ IFRT between June1984 and December 1992 (4).

Beside histological subtypes, many other factors could be contributing on the outcome of HL patients. Saunders et al. (19) showed that EFS rate of patients with unfavorable disease was lower in underprivileged countries as compared to that at the industrialized countries, even when the same therapy regimen was used. Each population has its own characteristics, so any therapy regimen resulting

in an excellent outcome under given conditions does not necessarily lead to the same outcome under different conditions. Considerable differences have been shown in the distribution of histological types as well as the survival rates of pediatric HL among the regions of Europe (18). These variables may also be differing within the different geographic regions of a large country.

The outcome of children with HL has greatly improved with 5-year overall survival rates greater than 95%, and 5-year EFS greater than 90% for all stages for the last two decades (1-5). Treatment results have shown considerable improvement even in developing countries. The main challenge today is finding a balance between maximizing cure and minimizing the late effects (31). Therefore, emphasis is now on tailoring therapy according to the risk groups which should be based on well-defined prognostic factors. Several study groups from the developed countries have been searching for the efficacy of risk-based therapies using risk factors determined in their own populations (27-29, 32-34). Since epidemiologic and clinicopathologic features of HL show considerable variations even within our country, we need to define our own prognostic factors. This major objective could only be achieved with multicentric national clinical trials.

References

1. Dinand V, Arya LS. Epidemiology of childhood Hodgkin's disease: is it different in developing countries? Indian Pediatr 2006;43:141-7.
2. Ertem U, Duru F, Dagdemir A, et al. Hodgkin's disease in 82 Turkish children diagnosed over a 10-year period: epidemiological, clinical, and histopathologic features and prognosis with prolonged chemotherapy. Pediatr Hematol Oncol 1997;14:359-66.
3. Cavdar AO, Pamir A, Gozdasoglu S, et al. Hodgkin disease in children: clinicoepidemiologic and viral (Epstein-Barr virus) analyses. Med Pediatr Oncol 1999;32:18-24.
4. Buyukpamukcu M, Atahan L, Caglar M, et al. Hodgkin's disease in Turkish children: clinical characteristics and treatment results of 210 patients. Pediatr Hematol Oncol 1999;16:119-29.
5. Oguz A, Karadeniz C, Okur FV, et al. Prognostic factors and treatment outcome in childhood Hodgkin disease. Pediatr Blood Cancer 2005;45:670-5.
6. Buyukpamukcu M., on behalf of the Turkish Society of Pediatric Oncology Group. Hodgkin's Lymphoma in Turkey. J Pediatr Hematol Oncol 2007;29 Suppl 1: S5.
7. Eser S. 1997-2002 Childhood Cancer Incidence in Izmir, Turkey. J Pediatr Hematol Oncol 2007;29 Suppl 1:S6
8. Schellong G, Potter R, Bramswig J, et. al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: the German-Austrian multicenter trial DAL-HD-90. The German-Austrian Pediatric Hodgkin's Disease Study Group. J Clin Oncol 1999;17:3736-44.
9. International Agency for Research on Cancer. ACCIS: automated childhood cancer information system. Available at: http://www-dep.iarc.fr/accis.htm [Last Accessed: 11/03/2006].
10. Kutluk T. First national pediatric cancer registry in Turkey: a Turkish pediatric oncology group study (abstract). Ped Blood & Cancer 2004;43:452.
11. Kutluk T, Yesilipek A, on behalf of Turkish Pediatric Oncology Group (TPOG) and Turkish Pediatric Hematology Society (TPHD). Pediatric Tumor Registry for 2002-2005 in Turkey. J Pediatr Hematol Oncol 2007;29 Suppl 1:S12-3.
12. Cavdar AO, Kutluk T. Childhood Cancer. Freedman LS, Edwards BK, Ries LAG, Young JL (eds). Cancer Incidence in Four Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) Compared with US SEER. National Cancer Institute, 2006. NIH Pub. No. 06-5873. Bethesda, MD.
13. Stiller CA, Marcos-Gragera R, Ardanaz E, et al. Geographical patterns of childhood cancer incidence in Europe, 1988-1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:1952-60.
14. Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, et al. Cancer in children and adolescents in Europe: Developments over 20 years and future challenges. Eur J Cancer 2006;42:2183-90.
15. Baez F, Ocampo E, Conter V, et al. Treatment of childhood Hodgkin's disease with COPP or COPP-ABV (hybrid) without radiotherapy in Nicaragua. Ann Oncol 1997;8:247-50.

16. Sackmann-Muriel F, Zubizarreta P, Gallo G, et al. Hodgkin disease in children: results of a prospective randomized trial in a single institution in Argentina. Med Pediatr Oncol 1997;29:544-52.

17. Arya LS, Dinand V, Thavaraj V, et al. Hodgkin's disease in Indian children: outcome with chemotherapy alone. Pediatr Blood Cancer 2006;46:26-34.

18. Clavel J, Steliarova-Foucher E, Berger C, et al. Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): Report from the Automated Cancer Information System project. Eur J Cancer 2006;42:2037-49.

19. Saunders CH, Metzger ML, Hudson MM, et al. Comparison of treatment outcomes of childhood Hodgkin Lymphoma in two US centers and a Center in Recife, Brazil. Pediatric Blood Cancer 2007;49:139-44.

20. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med 2003;349:1324-32.

21. Kuppers R, Schmitz R, Distler V, et al. Pathogenesis of Hodgkin's lymphoma. Eur J Haematol Suppl 2005;(66):26-33.

22. MacMahon B, Cole P, Newell GR. Hodgkin's disease: one entity or two? Lancet 1971;1:240-1.

23. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus associated Hodgkin's disease: epidemiologic characteristics in international data. Int J Cancer 1997;70:375-82.

24. Weiss LM, Movahed LA, Warnke RA, et al. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. N Engl J Med 1989;320:502-6.

25. Pamir A, Cavdar AO, Vonlanthen R, et al. Epstein-Barr virus latent membrane protein expression and distribution of viral subtypes in Turkish Hodgkin's disease (A comparative study with nonneoplastic lymphoid hyperplasia). Med Pediatr Oncol 1995;25:260.

26. Chow LM, Nathan PC, Hodgson DC, et al. Survival and late effects in children with Hodgkin's lymphoma treated with MOPP/ABV and low-dose, extended-field irradiation. J Clin Oncol 2006;24:5735-41.

27. Donaldson SS, Link MP, Weinstein HJ, et al. Final results of a prospective clinical trial with VAMP and low-dose involved-field radiation for children with low-risk Hodgkin's disease. J Clin Oncol 2007;25:332-7.

28. Shankar AG, Ashley S, Radford M, et al. Does histology influence outcome in childhood Hodgkin's disease? Results from the United Kingdom Children's Cancer Study Group. J Clin Oncol.1997;15:2622-30.

29. Dieckmann K, Potter R, Hofmann J, et al. Does bulky disease at diagnosis influence outcome in childhood Hodgkin's disease and require higher radiation doses? Results from the German-Austrian Pediatric Multicenter Trial DAL-1993HD 90. Int J Radiat Oncol Biol Phys 2003;152:21-3.

30. Alebouyeh M, Moussavi F, Haddad-Deylami H, et al. Successful ambulatory treatment of Hodgkin's disease in Iranian children based on German-Austrian DAL-HD 85-90: single institutional results. Ann Oncol 2005;16:1936-40.

31. Thomson AB, Wallace WHB. Treatment of paediatric Hodgkin's disease: a balance of risks. Eur J Cancer 2002;38:468-77.

32. Landman-Parker J, Pacquement H, Leblanc T, et al. Localized Childhood Hodgkin's Disease: Response-Adapted Chemotherapy With Etoposide, Bleomycin, Vinblastine, and Prednisone Before Low-Dose Radiation Therapy - Results of the French Society of Pediatric Oncology Study MDH90. J Clin Oncol 2000;18:1500-7.

33. Friedmann AM, Hudson MM, Weinstein HJ, et al. Treatment of unfavorable childhood Hodgkin's disease with VEPA and low-dose, involved field radiation. J Clin Oncol 2002;20:3088-94.

34. Dorffel W, Luders H, Ruhl U, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. Klin Padiatr 2003;215:139-45.