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Childhood Hodgkin Lymphoma in Iran; survival and outcome

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ABSTRACT

Background: Staging has an important role in both defining the prognosis of Hodgkin lymphoma (HL) and choosing the best treatment protocol. This study was designed to evaluate the features of HL and estimate the survival rate in patients referred to MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC) for continuing their treatment or as a new pediatric case of cancer.
Materials and methods: 119 patients <19 years of age diagnosed with HL at MPCTRC from 2008 to 2018 were enrolled. Staging, demographic findings, treatment protocols and outcomes were studied and analyzed for possible correlation between various parameters.
Results: In our study, the mean age of patients was 10.2 years (SD±3.5), and included 65.5% (n = 78) male and 34.5% (n = 41) female patients. Fifty-eight percent of patients were treated with ABVD protocol and 38.7% with Hybrid routine protocol. There was a significant association between coughing as a symptom and high stage of the disease (p = 0.044). The 5-year event-free survival (EFS) and overall survival (OS) rate for patients were 65% and 93.8% respectively. Bone marrow transplantation (p < 0.001), stage of the disease (p = 0.001) and treatment protocol (p = 0.034) had direct impact on OS.
Conclusion: Treatment modalities based on staging is important for improving outcomes in HL. In the limited settings, ABVD and other treatment protocols supplemented with BMT in relapsed cases is associated with good outcomes.

1. Introduction

Hodgkin Lymphoma (HL) is a type of neoplasm which occurs across different age groups including childhood, adolescence and young adulthood and old age [1,2]. According to World Health Organization (WHO), the incidence of HL in children aged 0–19 is the 4th in ranking of all common childhood cancers of Asia and Iran. During year 2018, according to the estimated number of HL crude rate in Iran for 0–19 years of age patients, the incidence, prevalence and mortality per 100,000 children were 0.69 (male: 0.86 and female: 051), 1.8 (male: 2.1 and female: 1.4) and 0.06 (male: 0.07 and female: 0.06), respectively [3,4].

Additionally, the overall survival (OS) rate has improved dramatically over the past decades for HL [5]. Although long term follow up of patients with HL show >90% survival, there are late effects seen because of treatment such as cardiopulmonary disturbances and second malignancies [6–8]. In spite of high OS in patients with HL, the current treatment strategies aim to improve the EFS and the late effects.

The risk ratios for death from HL is overtaken by the risk of other causes of death [9]. The 5-year relative survival rate (aged ≥ 18 years) in the United States improved approximately from 70% in 1975 to just over 88% in 2006 [10]. Furthermore, the one-year and five-year survival rates for all patients of any age diagnosed with HL are 92 and 86 percent respectively [11].

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Fortunately, the treatment of HL is usually effective and many patients are successfully cured [12–14]. The combination of chemotherapy and radiotherapy can increase the survival from HL(age range of 20–84 years) by more than 80% [15], although such treatment depends on the stage of the disease and pathology of the HL [16].

Mahak Pediatric Cancer Treatment and Research Center (MPCTRC) that is sponsored by Mahak charity society to support children with cancer, provide free therapeutic and diagnostic services throughout Iran and other countries.

The aim of designing this study was to evaluate HL (in patients younger than 19 years of age) according to their age, treatment plan, and contributing risk factors. Also survival and outcomes in enrolled patients had been considered by this study too.

2. Materials and Methods

2.1. Population

This retrospective study was conducted on 119 individuals younger than 19 years old who were diagnosed with HL in MPCTRC from 2008 to 2018. The study excluded those patients who refused treatment after the diagnosis. The study was approved by the human investigations ethics committee of MPCTRC and was performed in accordance with the revised Helsinki Declaration.

2.2. Data collection

A designed questionnaire according to the aims of the study had been validated by MPCTRC's medical committee. This unique questionnaire included demographic information such as sex, age, consanguinity (parental familial marriage), etc. Also, specialized and pathologic information including Type of cancer, stage of the disease, bone marrow transplantation (BMT), laboratory tests, radiotherapy, treatment protocols, etc. were collected from related departments of MAHAK Children Hospital.

2.3. Treatment modalities

Chemotherapy protocols that had been administrated for considered patients are as below:

1. Hybrid regimen consisted of:
   - Cyclophosphamide 600 mg/m^2; iv; day 0
   - Vincristine 1.4 mg/m^2; iv; day 0
   - Prednisolone 40 mg/m^2/day; P.O; day 0–13
   - Procarbazine 100 mg/m^2/day; P.O; day 0–6
   - Doxorubicin 35 mg/m^2; i.v; day 7
   - Bleomycin 10 U/m^2; i.v; day 7
   - Vinblastine 6 mg/m^2; i.v; day 7

The hybrid regimen administered as 4 and 6 cycles for low risk and high-risk patients respectively.

2. ABVD regimen consisted of:
   - Doxorubicin 25 mg/m^2; i.v; day 0, 14
   - Bleomycin 10 U/m^2; i.v; day 0, 14
   - Vinblastine 6 mg/m^2; i.v; day 0, 14
   - Decarbazine 375 mg/m^2; i.v; day 0,14

The ABVD regimen administered as 4 and 6 cycles for low risk and high-risk patients respectively.

At the time of diagnosis all of the patients with HL, evaluated by PET-scan. Following chemotherapy regimens, the response assessment to chemotherapy had been considered by PET-scan after every two cycles. Computed Tomography (CT) scan according to the tumor location was another choice if PET-scan was not accessible. Finally, at the end of the treatment, the patient was evaluated one more time by PET-scan.

Decision making about radiotherapy eligibility had been done by PET-scan or CT-scan (based on tumor location). PET-scan could metabolically and morphologically evaluate the residue. If there was report of residue after the 4th cycle of chemotherapy, then the patient had eligibility of radiotherapy modality. The external radiotherapy had been locally done based on the tumor location.

Patients who conferred with relapse, had been administered by chemotherapy regimen. Then tumor markers of the patient had been checked for remission. If there was not any report of residue by PET-scan and also if there were negative tumor markers, then the patient had eligibility of autologous Bone Marrow Transplantation (BMT) with Bucy conditioning regimen. Patients who relapsed were given salvage chemotherapy with ICE regimen.

2.4. Statistical analysis

Statistical analysis was performed using Mann-Whitney, Spearman correlation coefficient, Kaplan-Meier, Log Rank, Cox regression via SPSS-23.0. The p-value less than 0.05 were considered statistically significant.

3. Results

Demographic data and treatment protocol of 119 cases of HL (M/F: 6.5/3.5) were analyzed. In this study 85.7% (n = 102) of patients were Iranian and the mean age ± SD was 10.2 ± 3.5 years.

The clinical stage of disease was determined as which are shown in Table 1. For treatment process, 50.4% (n = 57) were under radiotherapy, 58% (n = 69) of patients were treated by ABVD protocol, 38.7% (n = 46) of patients were treated by Hybrid protocol and 3.3% (n = 4) of patients were treated by other routine protocols.

In 34.5% (n = 41) of all cases, relapses were seen, among whom, 61% (n = 25) were treated by ABVD protocol and 34.1% (n = 14) were treated by Hybrid protocol and 26.8% (n = 11) administered by external radiotherapy. Results showed that 34.1% (n = 14) and 65.9% (n = 27) of patients had early and late relapse respectively. Patients who had recurrence less than 6 months after diagnosis categorized as early relapse. Late relapse group consisted of patients who had relapse more than 6 months after the diagnosis.

Out of enrolled patients 26.1% (n = 31) had BMT. BMT was done in 71% (n = 22) and 25.8% (n = 8) of cases after the first and second relapse respectively. One child had BMT and never conferred with relapse. He had been cured and is alive without any complication.

In general, eight patients died, four of them were during treatment by ABVD protocol, three of them were during treatment by Hybrid protocol, and one patient was treating by other protocols who died because of bleeding. Other 7 patients died out of MPCTRC in their residential cities.

3.1. Association of HL symptoms with stage of the disease

There was no significant association between the stage and any of the symptoms, including fever, night sweats, bone pain, weight loss, and pruritus, and dyspnea. However, coughing had a significant relationship with the stage of the disease (p = 0.044) (Table 2). Out of 10 patients who had cough as a symptom, five children had mediastinal mass and one case had pulmonary involvement.

3.2. Correlation of laboratory parameters with stage of the disease

The correlation between stage of the disease and laboratory

Table 1
Distribution of characteristics of patients with Hodgkin Lymphoma in MAHAK Children Hospital, Tehran, Iran.

Characteristics	n	percent
Gender		
Female	41	34.5
Male	78	65.5
Age(years)		
<5	8	6.7
5–9.9	47	39.5
10–14.9	58	48.7
≥15	6	5.0
Stage at diagnosis		
IA or IB	24	20.2
IIA or IIB	38	31.9
IIIA or IIIB	45	37.8
IVA or IVB	12	10.1
BMT		
+	31	26.1
-	88	73.9
CD15		
+	55	67.1
-	27	32.9
CD20		
+	39	54.9
-	32	45.1
CD30		
+	88	97.8
-	2	2.2
Radiation		
+	57	50.4
-	56	49.6
Relapse		
+	41	34.5
-	78	65.5
Treatment Protocol		
ABVD	69	58.0
Hybrid	46	38.7
ABVE/PC	3	2.5
Others	1	0.8

Table 2
Distribution of symptoms according stage of disease in Hodgkin Lymphoma patients.

Symptoms	Stage								p-value
	IA or IB		IIA or IIB		IIIA or IIIB		IVA or IVB		
	n	%	n	%	n	%	N	%	
Fever									
+	3	12.5	13	34.2	12	26.7	2	16.7	0.689
-	21	87.8	25	65.8	33	73.3	10	83.3	
Cough									
+	0	0	2	5.3	7	15.6	1	8.3	
-	24	100	36	94.7	38	84.4	11	91.7	0.044
Night Sweat									
+	2	8.3	5	13.2	5	11.1	2	16.7	
-	22	91.7	33	86.8	40	88.9	10	83.3	0.607
Bone Pain									
+	1	4.2	0	0	1	2.2	3	25	
-	23	95.8	38	100	44	97.8	9	75	0.054
Weight Loss									
+	1	4.2	9	23.7	7	15.6	2	16.7	
-	23	95.8	29	76.3	38	84.4	10	83.3	0.474
Pruritus									
+	0	0	4	10.5	2	4.4	1	8.3	
-	24	100	34	89.5	43	95.5	11	91.7	0.632
Dyspnea									
+	1	4.2	2	5.3	1	2.2	2	16.7	
-	23	95.8	36	94.7	44	97.8	10	83.3	0.490
BM Involvement									
+	0	0	0	0	0	0	2	16.7	
-	24	100	38	100	45	100	10	83.3	0.709

parameters was only statistically significant in four of 18 parameters. Furthermore, there was a direct and significant correlation between the stage of the disease and Erythrocyte Sedimentation Rate (ESR; $r = 0.299$, $p = 0.005$), Ferritin ($r = 0.287$, $p = 0.015$) and Prothrombin Time (PT; $r = 0.247$, $p = 0.019$). There was also a significant and indirect relationship between the stage of the disease and Hgb ($r = -0.\ 0.254$, $p = 0.008$). Cut off hemoglobin level was 14.0–17.5 g/dL for males and 12.2–14.0 g/dL for females.

3.3. Treatment protocol

Limited stages (or low risk) include stage I and II and advanced stage (or high risk) includes stage III and IV. Fig. 1 shows the treatment plan for HL with different stages in this study. During the treatment of HL, 41 patients experienced relapse, 31 of whom were underwent BMT. Approximately all of the BMT-cases (97%) except one of them were successfully cured and got their recuperation, which means that BMT could be an effective treatment for relapse HL (Table 1).

3.4. Overall survival rate

The overall survival (OS) rate, 2-years, 3-years, 4-years, 5-years and 10-years were 98.9%, 95.4%, 95.4%, 93.8% and 92%, respectively (Fig. 2). The median time of follow up in considered patients was 4.87 years (interquartile range (IQR): 5.13 years).

Additionally, the survival rate based on treatment protocol and risk of the disease was evaluated and results are shown in Table 3. It seems that ABVD protocol (RR = 0.81, 90% CI: 0.009–0.708, $p = 0.057$) and radiotherapy (RR = 0.021, 90% CI: 0.002–0.254, $p = 0.011$) have reduced the risk of death, while higher stage of HL increases the risk of death ($p = 0.008$).

To be more precise, the risk of death in patients with stage IV is 155.4 times higher than that of those with stage I (RR = 155.4, 90% CI: 10.7–2257.0, $p = 0.002$).

3.5. Event-free survival rate

The Event-free survival (EFS) rate, 2 -years, 3- years, 4- years, 5-years and 10-years were 76%, 74.7%, 70.5%, 65% and 65%, respectively (Fig. 3).

In addition, the EFS rate based on treatment protocol and risk of the disease was evaluated and results are shown in Table 3. Bone marrow transplants (RR = 7.81, 95% CI: 3.94–15.50, $p < 0.001$), treatment protocol (RR = 0.39, 95% CI: 0.19–0.81, $p = 0.034$) and stage of disease ($p = 0.001$) had a significant relationship with EFS.

HL patients with relapse who received BMT had higher OS in comparison with those who only received chemotherapy and radiotherapy. Also, the risk of recurrence or death in patients with stage IV of disease is 4.55 times higher than that of patients with stage I of disease (RR = 4.55, 95% CI: 1.81–11.45, $p = 0.007$).

The choice of treatment protocol did not statistically affect OS and EFS across the risk groups (Table 3).

4. Discussion

From year 2008–2018, approximately 3500 children were registered with cancer diagnoses in MPCTRC, and 119 of them were diagnosed with HL. HL is usually more prevalent at younger ages, and the average age of patients in the countries with a young population is expected to be relatively lower [11,17]. In our study, the mean age of patients was 10.2.

According to a systematic review study, incidence rates of HL varies geographically, which seems to be the lowest among Asian population [17]. According to the latest WHO reports, India is the

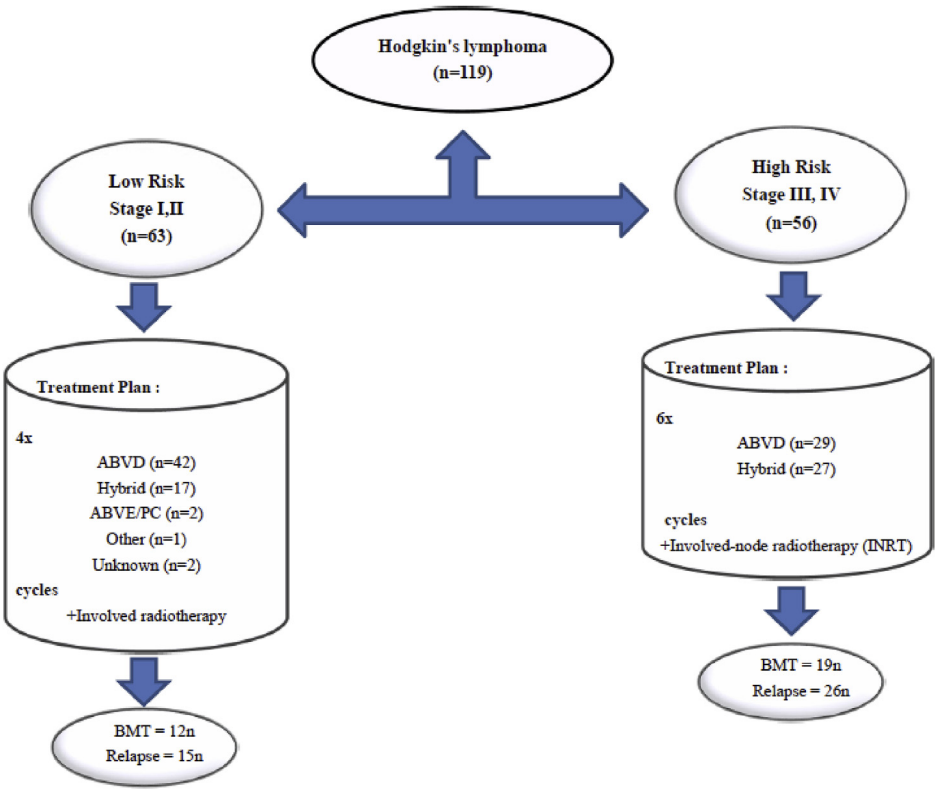

Fig. 1. Treatment plan for Hodgkin Lymphoma.

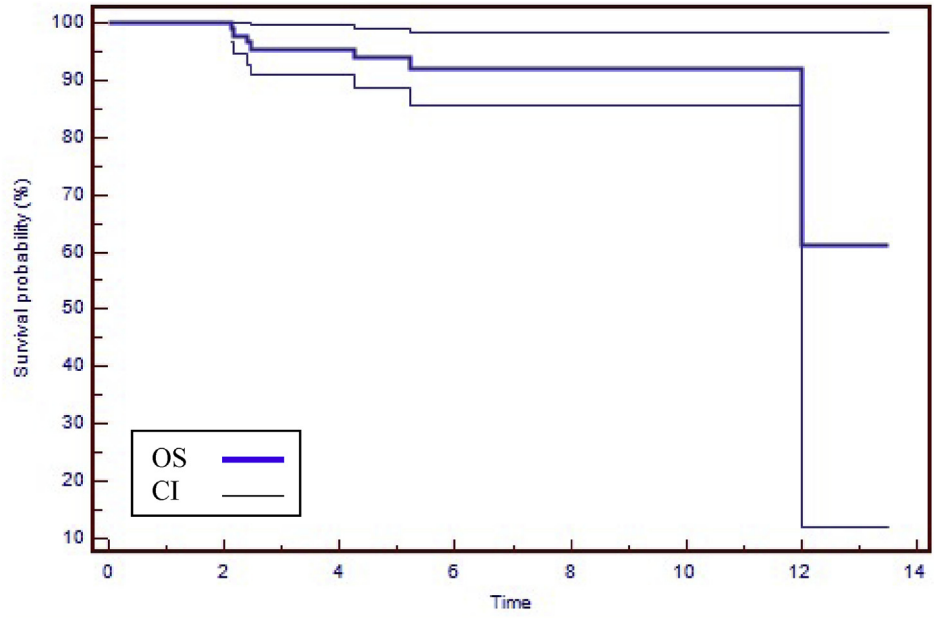

Fig. 2. Overall survival (years) and 95% Confidence Interval (CI) of patients with Hodgkin lymphoma in MAHAK Children Hospital, Tehran, Iran.

first Asian country for high incidence of childhood HL [18,19], while Iran ranks as the 7th. Fortunately, HL responds well to treatment, and in most Iranian medical centers including MAHAK children hospital, appropriate and advanced therapeutic methods are available. In this regard according to international agency for research on cancer by World Health Organization (WHO), mortality due HL in Iran (0.07) is very low in comparison with other Asian countries (0.10) [20]. In addition, in our study, 119 of 3500 children diagnosed with cancer had HL, which is almost similar to the HL incidence reported by the GLOBOCAN.

Due to poor data collection system and lack of diagnosis methods such as PET scan in the past, we failed to have access to accurate HL staging system, but this problem has been solved recently with the advent of these vital systems [11,15]. In our study,

Table 3
Overall Survival and Event-free Survival rate based on treatment protocol and risk of disease.

	3 years	5 years	10 years	p-value	3 years	5 years	10 years	p-value
Low Risk	95.7%	95.7%	95.7%	–	84.1%	78.4%	71.2%	–
ABVD	100%	100%	100%	0.065	88.5%	85.2%	76.3%	0.273
Hybrid	90%	90%	90%		78.8%	63%	63%	
High Risk	94.9%	91.5%	87.4%	–	63.7%	47.5%	47.5%	–
ABVD	96.2%	86.7%	86.7%	0.897	62.2%	43.6%	–	0.480
Hybrid	92.9%	92.9%	92.9%		71.1%	71.1%	71.1%	

***The statistical Log Rank test was used to compare the survival of ABVD and Hybrid protocol.

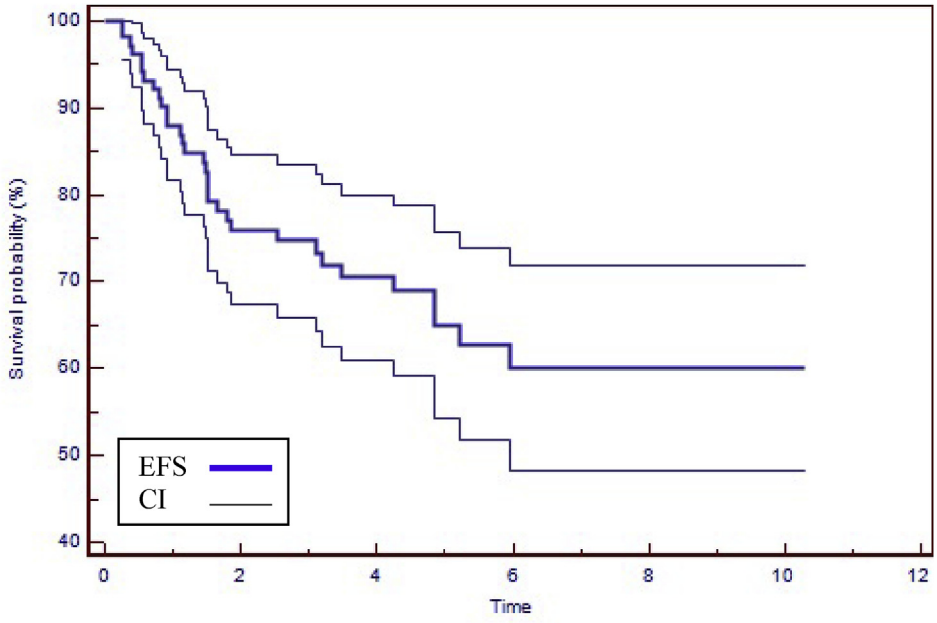

Fig. 3. Event Free survival (years) and 95% Confidence Interval (CI) of patients with Hodgkin lymphoma in MAHAK Children Hospital, Tehran, Iran.

like several other studies, more than half of patients were at stages I or II [2,21,22]. A 2017-published article illustrates that the incidence of disease increases directly with high stages of HL [2]. In other studies, symptoms such as fatigue, fever and lymphadenopathy are very common in children with HL, which was similar to what we obtained in this study [11,23]. Additionally, as a great number of our patients were diagnosed with mediastinal masses which are related to higher HL stages, coughing has shown a significant relationship with the stage of disease. In a retrospective cohort study of 469 newly diagnosed HL patients, cough has been reported significant among patients [24].

In most of studies, BMT is suggested as a treatment of cancer relapse, and can reduce the likeliness of further relapses and also mortality [14,25–27]. Unlike other studies, the appropriate response to BMT was higher in this study, which can be due to this fact that in our center, BMT has been usually performed after the first relapse. Results revealed that 71% of cases undergone BMT after the first relapse.

In pediatric patients ABVD is a therapeutic choice [22]. Adult studies have shown that ABVD is effective for limited (5- year OS 96%–98%) [28–30] and advanced stages (5-year OS 84%–90%) of disease [31,32]. In our retrospective study on Patient younger than19 years of age, we similarly reported 3- years, 5-years and 10-years OS and EFS. Ten-year EFS for low and high-risk groups were 71.2% and 47.5%, respectively, while 10-year OS were 95.7% and 87.4%, for both groups respectively.

5. Conclusion

Treatment modalities based on staging is important for improving outcomes in HL. In the limited settings, ABVD and other treatment protocols supplemented with BMT in relapsed cases is associated with good outcomes.

Declaration of competing interest

The authors taking part in evaluation and writing the manuscript have not any conflict of interest for this report.

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