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Hodgkin Lymphoma in Childhood and Adolescence: A Single-Institution Experience

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Abstract

Objective: Historical assessment of HL treatment shows a successful model of combining therapies and achieving excellent outcomes. Centers with reporting epidemiologic knowledge, treatment schedules, and survival rates will make progress regarding their prognostic factors. So, we aimed to report treatment schedules and survival rates of pediatric Hodgkin lymphoma patients treated 20 years ago.

Methods and Materials: A single-center, retrospective study was performed on patients with pediatric Hodgkin lymphoma who underwent chemotherapy, radiotherapy, or both between 1988 and 2002. The demographic and clinical characteristics of the patients were recorded. Survival rates, including disease-free and overall, were calculated.

Results: There were 96 patients with a median age of 10 years. All stage I-II and IIIA patients who received combined or alone ChT and RT were in complete remission at the end of the RT, except one patient who did not receive RT was disease-free at the time of analysis. 5 and 10 years, disease-free survival rates were 95 % and 95 %. Also, for 5 and 10 years, overall survival rates were 99 % and 95 %.

Conclusion: HL has had higher survival rates with particularly effective treatment modalities over the years. So, in this study, pediatric HL patients also had been observed with high response rates and prolonged survival.

Keywords: Hodgkin Lymphoma, pediatric cancers, radiotherapy, chemotherapy

Introduction

With the advances in radiotherapy (RT) and chemotherapy (ChT), dramatic changes in treatment modalities in pediatric Hodgkin lymphoma (HL) have been observed for years. From the first description in 1832 by Thomas Hodgkin till the 1960s, HL was an incurable disease **[1,2]**. Later, Kaplan and his group defined classic extended field RT (EFRT) and high doses for HL, so RT had taken a significant part in treatment, and HL became one of the best curable diseases **[2]**. However, cure is often associated with substantial delayed effects of therapy, especially in children **[3,4]**. Stanford investigators reported the most severe growth retardation in children who had received more than 33 Gy **[5]**. RT techniques and doses were similar in children and adults. Successful results with ChT in patients who had relapsed prompted the first combined modality trials. The correlation between the size of radiation fields and late complications has been demonstrated in patients with early-stage unfavorable HL in a European trial **[6]**. This led to the concept of involved field RT (IFRT), and with effective ChT, IFRT was shown to be sufficient **[6]**. In the 1990's doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) were considered the standard ChT for HL treated with IFRT **[7]**. Later recurrences occurred in initially involved nodes treated with ChT alone. Patients have started treatments with the affected node RT (INRT) approach **[8,9]**. INRT is radiating specific lymph nodes initially involved and giving the mission of elimination of microscopic diseases. This approach increased the importance of pretreatment imaging technologies, and trials will report details of INRT soon. Pediatric HL trials recently focused on minimizing toxicity and improving survival rates by combining different treatment modalities and schedules. Data on prognostic factors influencing outcomes divide patients into groups and establish a new approach, risk-adapted therapy **[10-13]**. According to these factors that differ between institutions, favorable/unfavorable or low, intermediate, and high-risk groups have been defined, and treatment intensity is varied to limit late effects or increase survival rates.

Historical assessment of HL treatment shows a successful model combining therapies and achieving excellent outcomes. Centers with reporting epidemiologic knowledge, treatment schedules, and survival rates will make progress regarding their prognostic factors. So, pediatric HL patients treated at Istanbul University Oncology Institute were analyzed retrospectively since 1988 and aimed to report survival rates.

Methods and Materials

Study design

Archive records of HL children (aged < 18 years) diagnosed and treated at Istanbul University Oncology Institute between January 1988 and December 2002 were obtained for analysis. All cases had biopsy-proven disease, and pathological evaluation was performed due to the World Health Organization (WHO) subtype classification. Data collected included demographic and clinical information, initial symptoms, histology, staging investigations, the situation of B symptoms, and treatment modalities. The staging was assigned according to the Ann-Arbor staging system **[14-16]**. Staging evaluation included medical history, chest radiography, ultrasound (USG), computed tomography (CT) scan, and gallium-67 scintigraphy. Staging laparotomy was performed on 7 patients with stage III-IV. Laboratory studies were recorded, including initial lactate dehydrogenase (LDH), erythrocyte sedimentation rate, and a complete blood count.

Treatment strategies

Treatment groups such as ChT alone, RT alone, or combined-modality treatments were performed according to the stage and age of patients. Cht regimes were OPPA/COPP, ABVD, MOP/ABV, and COPP. RT fields and doses after ChT were decided by evaluating remission status with clinical and imaging assessments. RT techniques included IFRT, EFRT, total nodal radiation, and initially bulky region radiation. Radiation doses were 15, 20, or 25 Gy as determined by the child's bone age was 5 years or less, 6 to 10 years, or more than 10 years, respectively. Boosts of radiation were reserved for those who failed to achieve a complete response with the planned therapy or for those who had bulky disease at the time of presentation.

Response criteria

Response assessment was carried out at the end of treatment, and patients were grouped into four categories: complete response (CR), good partial response (GPR), partial response (PR), and progressive disease (PD). GPR was defined as a reduction of 50% or more significant in any axis of a measurable nodal mass, while PR was defined as shrinkage of measurable disease that did not achieve a 50% or more substantial reduction in any one axis. Patients were deemed to have progressive disease if there was an increase in any one axis of a measurable nodal mass.

Statistical analysis

Disease-free survival (DFS) and overall survival (OS) estimates were calculated by Kaplan-Meier analysis (17). The DFS period was defined from the date of pathological diagnosis to the date of recurrence, death, or last disease-free visit (months). OS period was determined from the date of pathological diagnosis to the date of death or last visit (months). Differences between groups were assessed by the log-rank statistic (18). Multivariate analysis was done using the Cox stepwise regression analysis to determine the independent contribution of each prognostic factor (19). p - values < 0.05 were considered significant.

Results

Patients

96 pediatric patients treated between 1988 and 2002 were evaluated for analysis. Patient characteristics are summarized in **(Table 1)**. Median age was 10 years (range 3-18 years), and a slight male predominance (male/female ratio, 2.7) was observed. According to WHO pathological classification, there were 47(49 %) patients with mixed cellularity, 39(41 %) with nodular sclerosis, 7(7 %) with lymphocyte predominance, and 3(3 %) with lymphocyte depletion. According to Ann Arbor classification, there were 57(59 %) patients with early-stage (stage I-II), and 21(22%) of these included B symptoms. Twenty-five (26 %) patients were presented with stage III, and 14(15 %) patients were given with stage IV disease.

Table 1: Patient characteristics

Features	n	%
Age		
<6	17	18
6-10	35	36
11-17	44	46
Sex		
Male	70	73
Female	26	27
Histologic subtypes		
Mixed cellularity	47	49
Nodular sclerosis	39	41
Lymphocyt predominance	7	7
Lymphocyte poor	3	3

Stage		
I	10	10
II	47	49
III	25	26
IV	14	15
Systemic B symptoms		
Yes	44	45
No	52	55
Localization of Disease		
Supradiaphragmatic	55	57
Infradiaphragmatic	4	4
Both	37	39

Table 2: Chemotherapy regimens

Schema	**n**	**%**
OPPA/COPP	20	28
ABVD	22	31
MOPP/ABV	20	28
COPP	9	13

Table 3: Radiotherapy fields

Field	**n**	**%**
Involved field	39	60
Extended field	10	15
Totally nodal	2	3
Bulky	14	22

Treatment outcome and response

Of the 96 patients with HL, two patients with stage IA did not have ChT and were treated only with RT. 44 of 94 patients with stage I-II and IIIA who received combined or alone ChT or RT were all in CR at the end of treatment, and all of them, except one patient who did not receive RT, were disease-free at the time of analysis. 20 of 31 patients with stage IB and IV had CR. 3 patients, one stage IV and two-stage II, had PD after ChT, and 2 stage II patients had CR with RT. Patients who had PR 29, and with RT, 24 had CR, and 5 had PR. 2 of these PR patients died due to progression. 1 stage IV patients with PD after ChT also died of the disease. Totally 10 of 96 patients did not receive RT, and the details of treatments were summarized in **(Tables 2, 3 and 4)**.

On univariate analysis, age above 11 years, stage IIIB, and IV have significance for DFS. Stage was found to be the only factor for DFS on multivariate analysis. The entire group's 5-year and 10-year DFS and OS were 95 %, 95 %, 96 % and 95 %, respectively. 84 patients were alive without or with disease **(Table 5)**. A total of 7 patients died to date at the analysis, but only 4 of them died because of progression. Of 3 of 7 patients, one was treatment-related death. The two patients died from non-disease-related factors. During the last follow-up, information on 5 patients needed to be included.

Table 4: The response rates of patients

	No RT (n)	**RT Response (n)**			Total (n)
		CR	**PR**	**PD**	
Response after ChT					
CR	8	54	-	-	62
PR	1	23	5	-	29
PD	1	2	-	-	3

Table 5: The status of patients

Current Status	n	%
Alive after CR	74	77
Alive after relapse/progression	10	10
Died to disease	4	4
Died to other cause	3	3

Discussion

HL comprises 6 % of childhood cancers with a range of 40 % among lymphomas, and for more than 40 years, treatment strategies geared to the specific problems in children with HL have been tested by different pediatric oncologic groups **[20,21]**. In these approaches, high priority was given to the reduction of late effects caused by RT and CT next to the goal of achieving high survival rates. Combined modality therapy results have been reported to improve outcomes such as relapse-free survival rates of 90 % to 95 % in patients with early-stage disease and 70 % to 90 % in patients with advanced-stage disease **[22-24]**.

The other important sequence of studies is refining the extent of staging. Staging was reduced from systemic use of laparotomy to routine clinical stage **[25]**. When patients were to be treated by RT alone, a precise anatomic notation of the sites involved was critical to designing radiation portals. When all patients begin to receive CT, clinical staging has had successful treatment results. The clinical stage limits the potential immunosuppressive effects of splenectomy and other complications associated with staging laparotomy in patients with HL.

Strategies that have been used over the years to reduce side effects have included the following: reduction in the number of cycles of mustard, oncovin, procarbazine, and prednisone (MOPP), or doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) administered; reduction in the amount of radiation delivered; use of CT instead of RT; and the development of new combinations of CT drugs, with plans to use such combinations instead of MOPP or in alternation with MOPP **[25,26]**. MOPP, the first of the successful CT combination, is often associated with the development of amenorrhea in women, infertility in both sexes, and the occurrence of secondary leukemia **[25,27-32]**.

In the 1990s, ABVD was considered the standard care for advanced HL and was replaced by MOPP treatment in combined therapy modality for early-stage HL **[33]**. RT has been a therapeutic mainstay for several decades, particularly for early-stage HL; nevertheless, high-dose RT is likely to produce skeletal growth retardation, thyroid dysfunction, cardiac diseases, and gonadal dysfunction when the relevant tissues are included in the treatment field. In addition, high-dose RT may contribute to the development of secondary malignancies. Radiation dose and area have been reduced by enhanced reliance on CT. Low-dose rather than standard dose (36-40 Gy) RT in children presumably reduces morbidity and long-term toxicity, such as growth disturbances and organ dysfunction. IFRT was as effective as EFRT in combined therapy approaches **[34-36]**.

Risk-adapted combined-modality therapy is now the standard approach for children with Hodgkin's disease, although risk categories vary slightly from one protocol to another. This approach aims to limit exposure to the most toxic agents among favorable risk patients while intensifying treatment among high-risk patients to improve disease control. So, patients with HL were divided into two or three groups based on factors shown to influence outcome by current trials **[10-13]**. According to these, favorable/unfavorable or low/intermediate/high-risk groups were defined. Mainly, agreement was supplied that low risk/bright patients include those with clinical stage I or II disease, no B symptoms or bulky nodal involvement, and disease in fewer than three nodal regions. Intermediate-risk conditions include bulky nodal involvement and sometimes stage IIIA disease, with criteria that vary from trial to trial. High-risk patients are those with background IIIB, IVA, and IVB disease.

Newer approaches advocate for early dose intensity to limit cumulative therapy using response-based paradigms. This means modifying treatment according to the response to the initial few cycles of CT and limiting toxicity by selecting patients who respond early to treatment and sparing them additional therapy. This is called response-adapted therapy. This approach was found safe and efficacious by preliminary results of prospective trials **[11,13,37-40]**. Some questions, like treatment strategy for slow responders, remain for response-adapted therapy. Ongoing studies may give a chance to define the outlines of this approach. Targeting molecular mechanisms specific to the Reed-Sternberg cell may allow for less toxic and more efficacious treatments.

For three decades, combined CT-RT has been preferred in most of the studies on childhood HL because combined modality is the precondition for reducing the radiation dose, reducing the radiation fields, shortening chemotherapy, omitting splenectomy and laparotomy, and thus, for optimizing the benefit/risk ratio between cure rates and late effects. This small sample study showed long-term high survival rates with all these effective ChT schemas and RT approaches.

Conflict of Interest: The author declares no conflict of interest.

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