

Original Article

Treatment of Childhood Hodgkin's Disease in Kuwait

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ABSTRACT

Objectives: To assess the efficacy of radiotherapy (low and high dose) and/or the different regimens of chemotherapy in the treatment of children with Hodgkin's disease.

Setting: Kuwait Cancer Control Centre

Methods: This is a retrospective study. The case records of all children treated by radiotherapy and/or chemotherapy were studied and the data analyzed.

Results: Between November 1988 and December 1997, 25 patients were treated for Hodgkin's disease (HD). Age at diagnosis ranged from 5 to 17 years; 14 were males, and 11 were females. The most common histological type seen was mixed cellularity (MC) in 11 patients (44%), followed by nodular sclerosis (NS) in eight (32%), lymphocyte predominant (LP) in three (12%) and nodular sclerosis/mixed cellularity in one (4%). The histology was not done in two (8%) children. Stage IIA HD was seen in nine (36%) patients, followed by Stage IA and IVB

in four (16%) each, Stage IIIA and B in three (12%) each and Stage IIB in two patients (8%) only.

Children were treated according to different types of schemes: ABVD, MOPP/ABVD, VAMP, VEPA, COPP/ABVD and high-dose radiotherapy (HDRT): 30–41 Gy (n=6) or low-dose radiotherapy (LD RT): 20–25 Gy (n=9), chemotherapy only (n=6) or radiotherapy only (n=3).

A total of 20 patients (80%) achieved complete remission, and four patients, one of them after surgery (16%), achieved a second remission. One boy died due to disease non-response. The median follow-up was 4 years 8 months; range was 17 months to 11 years 1 month.

Conclusions: We have found that patients treated with LDRT and chemotherapy (CT) have done just as well as those treated with HDRT plus CT in terms of overall survival and local control.

KEYWORDS: children, Hodgkin's disease, Kuwait

INTRODUCTION

The five-year survival rate of children with Hodgkin's disease (HD) is 80-90%^[1,2]. While the cure rate has improved since the 1960s, with long-term follow up late complications of therapy have also become evident^[3]. For this reason, many institutions have modified the treatment of HD and used reduced doses of radiation therapy (15–25 Gy) to limited fields in conjunction with chemotherapy^[2, 4-10].

Our department has had two defined treatment strategies for this disease during two periods. From 1988 to 1993, most children received high-dose radiotherapy (HDRT) (30–40 Gy) with chemotherapy (CT), mainly using the scheme MOPP/ABVD. During the second period, from 1994 to 1997, low-dose radiotherapy (LDRT) with 20–25 Gy with CT, using the schemes VAMP, VEPA and ABVD was followed. So far, we have not found any secondary tumors, such as leukemia or non-Hodgkin's lymphomas, which were the most frequent secondary malignant diseases following

therapy with alkylating agents. The results of our experience with pediatric HD have not been published before.

SUBJECTS AND METHODS

This is a retrospective observational study including 25 patients with a diagnosis of HD. They were admitted to our department between November 1988 and December 1997 (Table 1). There were 14 males and 11 females. Median age at the time of diagnosis was nine years with a range of 5-17 years. Mixed cellularity was the most frequent histology subtype. Disease staging was determined with the Ann Arbor staging classification^[11]. "B" symptoms were present at the time of initial diagnosis in nine (36%) children.

TREATMENT PLAN

Three patients received RT alone, 15 received combined modality therapy (CT + RT), six children received chemotherapy alone, and one was treated by surgery only.

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Radiotherapy only: Two of the patients treated by irradiation alone had extended-field RT, 35 and 36 Gy, respectively, and both were classified as Stage IA(neck). The third patient with Stage IIA received 30 Gy.

High-dose radiotherapy and chemotherapy: Six patients, diagnosed between 1988 and 1993, were treated by HDRT (30–40 Gy) and CT (Table 2). Three of them received six courses COPP/ABVD, two received six courses MOPP/ABVD, and one was treated by six courses Ch1VPP.

Low-dose radiotherapy and chemotherapy: Nine children, diagnosed between 1994 and 1997, received LDRT (20–25 Gy) and CT (Table 2). Three of them received six courses VEPA, two children received six courses ABVD, one child was treated by six courses VAMP, one patient by six courses VAMP/VEPA, and two received six courses MOPP/ABVD. All children received limited field RT.

Chemotherapy: CT alone was used as the sole therapy in six children (Table 1). RT was indicated for and advised for all these patients, but their parents refused it.

Surgery: One child underwent only surgery outside Kuwait, and no another oncology treatment was given at the time. Further treatment was given one year later.

RESULTS

Only 25 of the children diagnosed and treated for HD during the period from 1988 to 1997 were available for this report. The general characteristics of the patients, including age, gender, clinical stage and histopathology, are shown in Table 1. The majority of patients were males (56%). The mean age was nine years and ranged from 5-17 years. Analysis of clinical stages revealed that Stage II and IV predominated (68%) in this study. "B" symptoms were positive in 36% of the patients. The distribution of histologic subtypes showed a relatively high frequency of MC, accounting for 44% of the patients. Eight cases (32%) were NS, and three patients (12%) were LP. One child was diagnosed as suffering from miscellaneous type (NS/MC). In addition, two patients were treated without ascertaining the histologic subtypes because diagnosis was done by fine needle biopsy only. In all cases, therapy was carried out as scheduled per treatment scheme.

Radiation therapy

Two patients are in first complete remission (CR), 8 years and 10 years, respectively. One child, treated by 30 Gy, had a recurrence three years after RT with local progression and dissemination to liver, spleen and paraaortic lymph nodes. He

underwent CT of four courses of MOPP/ABVD, and is now seven years into his second CR.

High-dose radiotherapy and chemotherapy

Four of six children achieved first CR, with median of four years six months and range of 1.5-8.25 years. One patient had a recurrence two years and seven months after completion of therapy (MOPP/ABVD and 30 Gy), and was treated by six courses of ABVD as a second line CT. He is now eight months into his second CR. One patient died due to progression of the disease. He did not reach complete remission during therapy; his mediastinal mass showed partial regression only. Also second line CT by BEAM scheme had a minimal effect.

Low-dose radiotherapy and chemotherapy

Eight of nine children are in first CR, with a median of four years and range of one year 10 months – six years four months. One patient had a recurrence five months after completion of therapy (VEPA and 25 Gy). He is one year five months into his second CR after second line therapy by DECAL and COPP.

Chemotherapy

All six patients treated by chemotherapy alone achieved first CR, with median of four years five months and range of one year seven months–six years six months.

Surgery

The patient, who underwent surgery for lymph nodes on the neck, developed local progression one year later. He was treated by six courses of VEPA, and he is 3.5 years in CR.

DISCUSSION

During the long first period of this study, patients were treated with a variety of CT regimens. To share our experience in the treatment of HD, we are including all patients in this study. Though there was a relatively low number of patients in the nine-year period, it should be pointed out that some children were treated in other departments as the pediatric oncology unit was not established until 1996.

At our institution, no staging laparotomy with splenectomy in children with HD has been done because of reports of hyperacute infections in up to 10% of the children undergoing splenectomy in the late 1970s^[12].

The histological patterns of Hodgkin's disease also vary from country to country^[13]. For example, in both Africa and South America there is a relative predominance of MC and LD subtypes^[14,15]. Similarly, in India MC is the most common subtype,

Table 1
Characteristics of the study population

No	Age at dg	Sex	Histo-logy	Symp A/B	Stage	RT	HDRT +CT	LDRT +CT	Surg.	CT	Out-come	Length of follow-up	Note
1	8.5y	M	LP	A	I		35Gy				1stCR	8y 1m	relapse
2	4y	M	MC	A	I	36Gy					1stCR	10y 1m	after
3	5.5y	M	MC	A	II	1)30Gy				2) 4xMOPP/ ABVD	2ndCR	11y 1m	3y 8m
4	14y	M	MC/NS	B	IV		41.4Gy 4xCOPP/ ABVD 2xBEAM				Died	1y 5m	
5	15y	M	NS	B	IV		30Gy 1)4xMOPP/ ABVD 2)6xABVD				2ndCR	3y 8m	relapse after 1.5y
6	13y	F	MC	B	IV		30Gy 6xMOPP/ ABVD				1stCR	1y 5m	
7	7y	M	MC	A	II		30Gy 7xMOPP/ ABVD				1stCR	8y 3m	
8	5y	M	NS	B	II		30Gy 6xCh1VPP				1stCR	5y 8m	
9	6y	M	LP	A	I		40Gy 6xCOPP/ ABVD				1stCR	6y 9m	
10	7y	F	Non-Spec.	B	III			22.3Gy 6xMOPP/ ABVD			1stCR	6y 4m	
11	14y	F	MC	A	II			25Gy 6xVAMP			1stCR	3y 3m	
12	17y	F	NS	A	III			25Gy 6xVEPA			1stCR	2y 9m	
13	6y	F	MC	A	I			20.8Gy 6xABVD			1stCR	4y 4m	
14	5y	M	NS	A	II			20Gy 6xABVD			1stCR	5y 1m	
15	8y	F	NS	A	III			1)25Gy 6xVEPA		2) 5xDECAL 6xCOPP	2ndCR	3y 1m	relapse after 7m
16	14y	M	NS	B	III			23.4Gy 6xVAMP/ VEPA			1stCR	1y 10m	
17	9y	F	NS	A	II			25Gy 6xMOPP/ ABVD			1stCR	3y 6m	
18	7y	F	Non-spec	B	III			22Gy 6xMOPP/ ABVD			1stCR	6y 4m	
19	5y	M	MC	A	II				1)	2) 6xVEPA	2ndCR	4y 7m	relapse after 1y
20	5.5y	F	MC	B	II					6xCh1VPP	1stCR	5y	
21	16y	M	MC	A	III					6xABVD	1stCR	4y 3m	
22	14y	F	LP	A	II					6xVAMP	1stCR	4y 2m	
23	14y	M	NS	B	IV					8xABVD	1stCR	1y 7m	
24	8y	M	MC	A	II					6xCh1VPP	1stCR	5y 4m	
25	7y	F	MC	A	II					6xMOPP/ ABVD	1stCR	6y 6m	

1) primary therapy
2) therapy of relapse

Table 2
Combined modality therapy

	High-dose RT+ Chemotherapy	Low-dose RT+ Chemotherapy
COPP/ABVD	3	-
MOPP/ABVD	2	2
VEPA	-	3
ABVD	-	2
VAMP	-	1
VAMP/VEPA	-	1
Ch1VPP	1	-
Total	6	9

Note. Doses: COPP, cyclophosphamide 600 mg/m² intravenously (IV) days 1 and 8; vincristine 1.5 mg/m² IV days 1 and 8; procarbazine 100 mg/m² orally days 1 to 14; prednisone 40 mg/m² orally days 1 to 14 for courses 1 and 4 only; ABVD, doxorubicin 25 mg/m²; vinblastine 6 mg/m²; bleomycin 10 mg/m²; dacarbazine 350 mg/m²; all administered IV on days 1 and 15 of each 28 day cycle. MOPP, nitrogen mustard 6mg/m² IV days 1 and 8; vincristine 1.4mg/m² IV days 1 and 8; procarbazine 100mg/m² orally days 1 to 14; prednisone 40mg/m² orally days 1 to 14, repeated every 28 days. VEPA, vinblastine 6 mg/m² IV days 1 and 15; etoposide 200 mg/m² IV days 1 and 15; prednisone 40 mg/m² orally days 1 to 14; adriamycin 25 mg/m² IV days 1 and 15; repeated every 28 days. VAMP, vinblastine 6 mg/m² IV day 1 and 15; adriamycin 25 mg/m² IV days 1 and 15; methotrexate 20 mg/m² IV days 1 and 15; prednisone 40 mg/m² orally days 1 to 14; repeated every 28 days. Ch1VPP, chlorambucil 6 mg/m² orally days 1 to 14; vinblastine 6 mg/m² IV days 1 and 8; procarbazine 100 mg/m² orally days 1 to 14; prednisone 40 mg/m² orally days 1 to 14; repeated every 28 days.

with NS being extremely rare^[16]. The majority of children in Europe and North America, though, present with NS subtypes. In our study, MC was the most frequent subtype. This is the same as seen in Africa and India.

Shanker et al^[13] found that in a group of 331 children with HD, MC subtype had the highest relapse rate, but this difference was statistically significant only in Stage I patients who received local irradiation alone. Similarly, in our study one patient having MC/NS subtype died due to progression of disease, while two patients developed relapse with MC subtype and two children with NS one.

As is well established, surgery alone is not sufficient therapy for HD. One patient developed local recurrence one year after operation, but regular CT was later fully effective. Interestingly, six children who received only CT have fared extremely well, and the median of their first CR is four years five months.

In analyzing our patterns of failure in the patients treated by RT alone, there was one patient with recurrence. His HD involved the neck, with a histologic diagnosis of MC. He received 30 Gy but developed recurrence two years ten months after completion of RT, and a complete work up revealed dissemination in the liver, spleen and paraaortic lymph nodes. The question of the reason for recurrence remains. Was it either in-field and/or marginal failure or primary microscopic dissemination of HD

followed by an insufficient first-staging procedure?

One of six children who relapsed following HDRT and CT did so without an irradiated field. In addition, this is the same reason for recurrence in one of nine children treated by LDRT and CT. The rate of recurrence is 11% and 16%, respectively, however, this is a small group of patients regarding regular analysis of data. Local relapse rate for sites that received between 17.5 and 22.5 Gy plus CT was 7% by Maity^[2] and 3% by Donaldson and Link^[17]. Regarding disease sites receiving 35 to 40 Gy, Kaplan^[18] reported a 4% local failure rate, Thar^[19] reported 3% for sites irradiated with 34 Gy and more, and Maity^[2] reported 5%.

Lou and Pinkerton^[20] assessed the effects of RT, CT or combined RT and CH on relapse-free survival (RFS) and overall survival (OS) rates in children with Hodgkin's disease stage I and IIA. There is little evidence from randomized controlled trials to evaluate the consensus approach of short course CT and local RT compared with other approaches. In one randomized trial, no statistically significant difference in survival between involved field and extended field RT was observed. Our group of patients with stage I or IIA disease is very heterogeneous and small. It is, therefore, insufficient to make a decision regarding optimal therapy.

In summary, we have found that children treated at our department with LDRT and CT have done just as well as those treated by HDRT with CT in terms of overall survival and local control. Although we had excellent outcomes in the group of six patients with CT alone, these results cannot justify omission of RT in the treatment scheme of HD in children. The early outcomes of this study suggest that all these regimens of CT followed by LDRT may be effective and safe therapies for children with HD.

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