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Hypothyroidism in children treated with Chemotherapy and Radiotherapy: A single institution study from Kuwait

Rakesh Mittal, MD[1], Nisreen Khalifa, MD[1], Sahar Omar, MD[1], Saadeldin Mahmoud, MD[3], Abraham Varghese, MD[2], Saroj Vasishta, MD[2]

(1) Unit of Pediatric Oncology, Department of Medical Oncology, Kuwait Cancer Control Centre, Kuwait
(2) Department of Radiation Oncology, Kuwait Cancer Control Centre, Kuwait
(3) Department of Nuclear Medicine, Kuwait Cancer Control Centre, Kuwait

✉ *Corresponding Author: Dr. Rakesh Mittal, MD*
Consultant & In charge, Pediatric Oncology, Department of Medical Oncology, Kuwait
E mail: rakeshmittal55@hotmail.com

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Abstract

Objectives: This retrospective study was undertaken to evaluate the cases of thyroid related complications, with emphasis on hypothyroidism in children with Hodgkin's disease who were treated with combined modality protocols.
Methods: Sixty three children with Hodgkin's disease, who were treated at the pediatric oncology unit of Kuwait Cancer Control Centre from January 1998 to December 2007, were included in the study. Forty children were treated on combined modality protocol (chemotherapy + involved field radiotherapy). After treatment, they were followed with serial measurement of thyroid function test (TFT) and neck ultrasound (US). Patients with two consecutive reading of high TFT were started on replacement therapy with L-Thyroxin.
Results: In our series 40 children received combined modality therapy. ABVD (**A**driamycin, **B**leomycin, **V**inblastin, **D**acarbazine) chemotherapy was used in 39 children and 37 children received radiotherapy to the neck and chest. The radiotherapy dose varied from 15 Grays to 25 Grays. At a median follow-up of 6 years, 21 children (56.7%) developed hypothyroidism at a median duration of 24 months (range: 5 months – 57 months). There was no correlation between age and dose to the development of hypothyroidism. All children received replacement therapy with L-thyroxin. We did not find any case of hyperthyroidism, or thyroid malignancy.
Conclusions: Significant number of children developed hypothyroidism after receiving radiation to the neck and chest area and chemotherapy, necessitating lifelong replacement therapy. It will be interesting to see if elimination of radiation with the help of risk and response adapted protocols using FDG- PET may reduce the event of hypothyroidism in treated Hodgkin's disease cases.

Introduction

Treatment of Hodgkin's disease (HD) is a major success story; almost 90 % of children achieve long term survival. Challenge today is – how to reduce the long term complications related to the treatment of HD. Number of publications (1-5) suggest that atleast some of the complications are due to radiotherapy. In the late effect study group, Bhatia et al (6) reported cumulative incidence of second malignancy to be as high as 26.3 % at 30 years. Since chemotherapy has emerged as the most effective therapy for HD, attempts are to reduce the dose and field of radiotherapy without compromising the outcome in terms of long term survival (7, 8). More recent trials; risk and response adapted, use radiotherapy only if complete response (CR) is not achieved. In this direction, availability of Positron Emission Tomography (PET) has served a useful purpose, as this imaging modality helps evaluation of early response, accurately (9-11).

The reduction of late treatment complications is one of the main objectives for treatment of HD in the 21st century. Radiation to the neck and upper chest has been reported to lead to several late complications, such as growth retardation, second malignant neoplasms, cardiomyopathy and hormonal and metabolic complications including thyroid dysfunctions (1-6). The thyroid gland plays an important role in the growth and metabolism, particularly, among growing children.

Kuwait Cancer Control Centre (KCCC) is the only comprehensive cancer centre existing in Kuwait. Its pediatric oncology unit (part of medical oncology department), is responsible for the treatment of children with solid tumors, as well as lymphomas. This centre has recently adopted the new protocol for treatment of HD as per the CCLG guidelines. Earlier, however, children were being treated with chemotherapy followed by involved field radiotherapy (IFRT). Though effects of radiotherapy on thyroid gland are well documented, we present here retrospective analysis of treatment of HD from KCCC. This study has focused on the effects of combined protocol using chemotherapy and radiotherapy on thyroid gland. We have specifically evaluated the problem of hypothyroidism and thyroid neoplasms in treated HD.

Methods

All children with previously untreated HD who were treated at the pediatric oncology unit of KCCC from 1998 to 2007 were included in the study. The study was retrospective and analyzed the case notes of 63 children with regards to age, gender, nationality, symptoms, staging, histopathology, lactate dehydrogenase level (LDH), treatment regimens, response to therapy, toxicity, follow-up and outcome. The imaging for staging purpose was done by X ray of the chest, US

of neck and abdomen, CT scan of neck, chest, abdomen & pelvis, and gallium scan. Bone marrow aspiration biopsy was performed in patients who had "B" symptoms or had clinically advanced disease. In all the cases, the diagnosis was proved by histopathology and staging was carried out according to the Ann Arbor system [12]. Patients were assigned to low risk group if they had stage I A, I B, or II A, intermediate risk were those with stage II B or III A, rest others were staged as high risk. The disease was described as "bulky", if peripheral lymphnodes were more than 6 cms or the mediastinal widening was more than 1/3rd of maximum chest diameter.

A Combined modality approach was used for the treatment of the majority of children. The most commonly used chemotherapy combination was ABVD. The initial response assessment was done after completion of 2 cycles. For low risk patients, 4 cycles of ABVD cycles were used, while for intermediate or high risk patients, 6 cycles of ABVD with or without IFRT was administered. Radiotherapy was delivered to involved field only and was given after completion of chemotherapy. Majority of the children received a dose of 2100 cGy in 14 fractions over a 3 weeks period. Response to treatment was defined on the basis of resolution of clinical, radiological and radioisotopic resolution of disease at completion of therapy. Complete remission (CR) was defined as complete resolution of all the previously present clinical, radiological and radioisotopic lesions, or reduction of initial tumor volume to more than 70% but gallium positive lesions should become negative. Partial remission (PR) was defined reduction in the tumor mass between 50 – 70% with positive or negative gallium scan. Progressive disease (PD) was described as appearance of new lesions during course of treatment and children with less than 50% reduction in tumor size were described as non – responders. Patients were regularly called for follow-up after completion of treatment. They were called every 2 months in first year, every 3 months in the 2nd year, 4 monthly in 3rd and 4th years, and 6 monthly subsequently. For children who received radiation, thyroid function test (TFT) was performed at six month interval along with US of the neck region. A high thyroid stimulating hormone (TSH) value for consecutive 2 readings was taken as evidence of hypothyroidism and they were started on replacement therapy. This study was aimed at finding the incidence of clinical or biochemical hypothyroidism and other thyroid abnormalities. All the treatment was administered after taking due consent from the family. Since it is a retrospective analysis, ethical approval was not required.

Results

The median follow-up was 6 years (range 3 years to 13 years). The baseline epidemiological data is summarized in Table 1. Chemotherapy was the main modality of the treatment. Radiotherapy was used as the combined modality therapy in 40 (63%) children. The treatment details are depicted in table 2. At the time of last follow-up 53 children were alive without any evidence of disease. There were 4 documented deaths; two deaths were due to therapy related complications, while others died due to progressive disease, while 6 were lost to follow-up.

Thyroid toxicity data:

This study was aimed at documenting the incidence of thyroid related toxicities. The details are summarized in table 3. In the radiotherapy group, there was significant more number of male patients (70%) as compared to females (30%). Thirty seven children (92.5%) received radiation to the neck and mediastinum. Majority of the children (67.5%) received radiation dose between 20 to 25 Grays.

Hypothyroidism:

None of the children had clinical signs and symptoms of hypothyroidism. However, biochemical hypothyroidism was documented in 56.7% of children who received radiation to the neck and mediastinum. The median time to develop hypothyroidism was 24 months (range: 5 -57 months). Though the numbers are small, but there was no relation between dose of radiation and development of hypothyroidism. All children required replacement with L-thyroxin. Their growth parameters were within normal range during the time of follow-up.

Thyroid Nodule: Thyroid nodules were picked by serial US of the neck during follow-up period. There were no clinically palpable nodules. Five children had single or multiple nodules with size ranging from 2 mm to the maximum of 11 mm. These nodules developed much later than the development of biochemical hypothyroidism. They are being monitored regularly and are stationary in size.

There were no documented cases of hyperthyroidism, thyroid malignancy or any other second primary tumor.

Discussion

The reported incidence of thyroid dysfunction in children mentioned in the literature varies from 37% (5) to as high as 88% (13). This wide variation in the reported incidence could be explained by different techniques of radiotherapy, and duration of follow-up. In our series, the incidence of hypothyroidism was 52% for all the patients who received radiation therapy, but it was 56.7% for the patients who received radiation to neck and mediastinum. The hypothyroidism developed at a median duration of 24 months (5 months – 57 months). Only 2 patients developed hypothyroidism within 12 months of completing the radiation therapy. Bhatia et al (6, 14) reported 6 years as median time to develop hypothyroidism after initiation of treatment, which is much longer than observed in our series. There is no possible explanation for the shorter time for the development of hypothyroidism in our series as dose of radiations in her series was much higher. In her series, there were large number of children (56/89) who were treated only with radiotherapy and the incidence of hypothyroidism reported was 65%. In our series, no child was treated with "radiotherapy alone" protocol. All our patients were treated on "combined modality" protocol or "chemotherapy only" protocol, but there are no studies to suggest that children treated on combined modality protocol develop hypothyroidism early.

It has been established in the literature that chemotherapy has no effect on development of hypothyroidism (13, 15), hence those patients who were treated with "chemotherapy only" protocol, were not subjected to measurement of thyroid function post therapy. Hence we have no comparative data for the two groups.

Effect of the age at the time of giving radiation therapy has been a subject of controversy, with some authors (5, 16) reporting increased incidence at younger age, while others (17) reported higher incidence with increasing age, probably due to higher doses. But like many other studies (18, 19), we did not find any relation with age and incidence of hypothyroidism.

The dose of radiation has been directly implicated in the development of hypothyroidism (6). Though lower radiation dose is desirable but no dose can be considered safe for the development of thyroid related complications. Exposure to as low dose as 100 – 700 cGy during initial 3-4 years of life has been associated with 1-7% incidence of thyroid cancer at 10-30 years (20). It has been suggested to try radiation fields which can avoid radiation to the thyroid gland (21), but it is very difficult, as in majority of the cases, lower cervical lymph nodes are involved, which necessitate encompassing the thyroid gland in

the radiation field. In our study, we did not find any correlation between radiation dose and development of hypothyroidism. But in our study the numbers are small to reach any definite conclusion.

The replacement therapy with L- thyroixin was initiated in all the patients who developed biochemical evidence of hypothyroidism. The dose was titrated according to the TSH level. None of the patient who was started on replacement therapy could be weaned off the therapy after any length of treatment. The replacement therapy should be started early in these patients, as longer duration of raised TSH can lead to thyroid focal abnormalities (22)

Thyroid Nodular Disease: Five children were found to have very small thyroid nodules, which were not clinically palpable. These nodules were picked up by the US of neck during routine follow-up studies. The maximum size of the nodule recorded was 11 mm, while minimum was 2 mm. Bhatia et al (1, 6) reported 5 cases of clinically palpable thyroid nodules, which were subjected to surgery, and found one case of papillary carcinoma. In our series, the nodules were too small to warrant any surgical intervention. Brignardello et al (23) have recommended serial US examination for all patients who receive radiation to the neck area for early diagnosis of thyroid malignancy. Bossi et al (24) reported a close association between reduced thyroid volume post radiation and hypothyroidism.

Conclusion

This study once again confirms the serious side effect of radiation on the functioning of the thyroid gland, which is very vital for the normal growth and development of the children. The only answer to this problem is to develop protocols which avoid radiation wherever possible. In our institute, we adopted the protocol, which avoid radiation to those children who become PET negative after 2 cycles of chemotherapy. After adopting this protocol, we have treated more than 20 children without any radiation (not included in the analysis). Looking back at our data for the patients who were treated on old protocol of combined modality therapy with significant incidence of hypothyroidism, and subsequent patients who were treated with no radiation therapy without compromising the long term cure, we can safely say that efforts should continue towards reducing the use of radiation therapy, or to find techniques of radiation which can minimize the long term side effects in children with Hodgkin's Disease.

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Tables

Table 1: Baseline Characteristics of Patients

Median Age (range)	10 years (3-15 years)
Gender (%)	
Male	37 (59%)
Female	26 (41%)
Nationality (%)	
Kuwaitis	44 (70%)
Non-Kuwaitis	19 (30%)
B Symptoms (%)	
No	43 (68%)
Yes	20 (32%)
Histopathology (%)	
Nodular Sclerosis	29 (46%)
Mixed Cellularity	21 (33%)
Lymphocyte Predominant	08 (13%)
Unclassified	05 (8%)
Disease Status (%)	
Bulky	28 (44%)
Non-bulky	35 (56%)
Stage (%)	
I	03 (5%)
II	38 (60%)
III	08 (13%)
IV	12 (19%)
DNK	02 (3%)
Lactate Dehydrogenase, LDH (%)	
Normal	49 (78%)
High	10 (16%)
DNK	04 (6%)

DNK = Data Not Known

Table 2: Treatment Details

Chemotherapy (%)	
ABVD	39 (62%)
Others	17 (27%)
ABVD + Others	05 (8%)
DNK	02 (3%)
Median Number of Cycles (range)	6 (2-8)
Disease Status after Chemotherapy (%)	
CR	53 (84%)
PR	05 (8%)
PD	02 (3%)
Not Evaluated	03 (5%)
Type of Radiotherapy (%)	
Involved Field Radiotherapy	34 (85%)
Mini Mantle	01 (3%)
Mantle	02 (5%)
Inverted	03 (7%)
Outcome (%)	
CR	55 (87%)
PR	02 (3%)
PD	03 (5%)
Not Evaluated	03 (5%)

ABVD = Doxorubicin (Adriyamycin), Bleomycin, Vinblastine, Dacarbazine

Table 3: Thyroid Toxicity Data

Number who received RT	40
Gender (%)	
Male	28 (70%)
Female	12 (30%)
RT to the neck & Mediastinum	37 (92.5%)
RT dose	
25 Grays or more	6 (15%)
20 – 24.5 Grays	27 (67.5%)
< 20 Grays	7 (17.5%)
Thyroid Toxicity	
Hypothyroidism	21 (56.7%)
Hyperthyroidism	Nil
Thyroid Nodule	05
Thyroid Malignancy	Nil
Other Second malignancies	Nil
Hypothyroidism	
Biochemical Hypothyroidism	21
Clinical hypothyroidism	Nil
Interval between RT and hypothyroidism I	Median time 24 months (range: 5 – 57 months)
< 12 months	02 (9.52%)
12 months – 24 months	11 (52.38%)
> 24 months	08 (38.09%)
Replacement Therapy	21 (100%)