Endocrinologic Late Effects of Chemoradiotherapy in Pediatric Acute Leukemia

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ABSTRACT

This study intends to describe growth and endocrine disorders secondary to chemotherapy among long-term survivors of pediatric acute leukemia. Sixteen patients including 14 ALL and 2 AML entered the study. Four were females and 12 were males with the mean age of 17.38 ± 3.81 years. Following the completion of their therapy, the mean follow up period of the patients was 62.43 ± 41.11 months. Somatic growth, sexual maturation, hypothalamic- pituitary-thyroid axis and hypothalamic-pituitary-gonadal axis were evaluated in all the patients. Two out of 16 had pathologic short stature (12.5%) and 3 patients had enuchoid status (18.75%) with antrophometric measurements. Eleven patients had normal thyroid gland dimensions and homogeneous thyroid tissue on ultrasonographic examination. One patient had Ia and another four patients had Ib diffuse goitre according to WHO criteria. Two out of 16 patients were diagnosed as subclinic primary hypothyroidism (12.5%), and three of them were diagnosed as subclinic central hypothyroidism (18.75%) according to TRH testing. Three patients were subclinic subtle central hypothyroidism. Thyroid auto-antibodies were in normal range in all patients. Eight patients (66.6%) out of 12 male subjects revealed impaired HHG axis. Hypergonadotropic hypogonadism (Leydig and Sertoli dysfunction) were observed in five of them and isolated Sertoli dysfunction was detected in three of them. Azoospermia was encountered in all patients with isolated Sertoli dysfunction. Testicular biopsy was obtained from only one of them and atrophic testicular tissue was detected. Female patients show normal pubertal development and gonadal functions. Conclusion: Subclinic subtle primary and subclinic central hypothyroidism were found in 31.2%, impaired Sertoli and Leydig with Sertoli cell function in 66.66% of long-term survivors pediatric acute leukemia and testicular tissue was more sensitive to adverse effects of chemotherapy than ovarian tissue.

Key Words: Chemoradiotherapy, Acute leukemia, Late effects, Endocrine.

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INTRODUCTION

The overall cure rate for childhood cancer is now over 60% and is over 80% for some tumours. It has been estimated that at least 1: 900 young adults will have been cured of childhood cancer by the year 2000[1]. Treatment advances in acute leukemia have led to significant improvements in patient survival. However, successfully treated patients are at risk of important late complications of therapy including on endocrine system. Radiation therapy may directly impair hypothalamic, pituitary, thyroid and gonadal function or, alternatively, it may induce the development of thyroid adenomas or carcinomas. Cytotoxic chemotherapy may damage the gonads. Both irradiation and cytotoxic chemotherapy may interfere with the normal growth of bone. Most treament protocols combine chemotherapy and irradiation, but chemotherapy becomes an important and sometimes exclusive form of treatment in many conditions[2,3]. Clinical endocrine problems following childhood cancer treatment are short stature, lack of pubertal development, precocious puberty, hypothyroidism, thyroid tumours, gynaecomastia, infertility and hypopituitarism[2,4]. The aim of this study was to investigate the hypothalamic-pituitary-thyroid axis and hypothalamic-pituitary-gonadal axis disorders secondary to chemoradiotherapy in pediatric acute leukemia.

MATERIALS and METHODS

Growth and endocrine disorders secondary to chemoradiotherapy among long-term survivors of pediatric acute leukemia were studied in 16 patients. Sixteen patients including 14 ALL and 2 AML entered the study. Four were females and 12 were males with the mean age of 17.38 ± 3.81 years. Following the completion of their therapy, the mean follow up period of the patients was 62.43 ± 41.11 months.

All the patients were investigated according to somatic growth by anthropometric measurement (height, height standard deviation score for Neyzi's Turkish standards), sexual maturation by Tanner-Marshall's criteria[5,6]. Thyroid gland volume was measured by thyroid ultrasonography. Hypothalamic-pituitary-thyroid axis was evaluated by assessing thyroid function tests (total T_3, total T_4, freeT_3, free T_4 and basal TSH) and TRH testing. Thyroid auto-antibodies (anti-M, anti-Tg) were measured by RIA[7]. Hypothalamic-pituitary-gonadal axis was evaluated by assessing basal gonadotropins (LH, FSH) and gonadal hormones in all patients. Baseline and human chorionic gonadotropin (hCG) stimulated testosterone levels were determinated in male patients with delayed sexual maturation to assesing Leydig cell function. Hormonal levels were measured by chemiluminescent immunoassay methods as described before[7,7a]. Also spermiogram was performed in patients whose sexual maturation was over P3 and testicular biopsy was planned in azoospermic patients.

RESULTS

The clinical characteristics of sixteen patients including sex, diagnosis, age at diagnosis, present age, duration period without treatment, and antropometric characteristics are given at Table 1. Two out of 16 patients had short stature (12.5%) and three patients had enuchoid status (18.75%) with anthropometric measurements. The characteristics of hypothalamic-pituitary-thyroid axis are summarized at Table 2. Eleven patients had normal thyroid gland dimensions and homogeneous thyroid tissue. One patient had Ia and another four patients had Ib diffuse goitre according to WHO criteria. Total T_3, total T_4 levels and free T_3 and free T_4 levels were measured as 1.36 ± 0.37 ng/dL and 9.18 ± 2.29 µg/dL; 6.08 ± 1.18 pmol/L and 16.59 ± 3.45 pmol/L, respectively. Basal TSH levels were found as 2.1 ± 1.09 mIU/mL in sixteen patients. Results of the TRH stimulation tests were found as follows: Peak TSH= 13.60 ± 8.09 mIU/mL and D TSH= 11.85 ± 7.46 mIU/mL. The characteristics of five patients with thyroid dysfunctions are shown at Table 3. All the patients with thyroid dysfunction had received prophylactic cranial irradiation. Two out of 16 patients were diagnosed as subclinic primary hypothyroidism (12.5%) with TRH stimulating test. Three patients were subclinic central hypothyroidism (18.75%) (Figure 1). Thyroid auto-antibodies were in normal range in all patients.

Hypothalamic-pituitary-gonadal axis is summarized at Table 4. The mean age was 16.87 ± 4.03 years and 18.89 ± 3.00 years in twelve boys and four girls respectively. Sexual maturation of male patients were as follows: 1: P1, 2: P2, 7: P3, 1: P4, 1: P5 (Table 4). Five patients revealed hypergonadotropic hypogonadism and three out of 16 patients had isolated Sertoli dysfunction (Table 5). Totally, eight patients had pathological findings in hypothalamic-pituitary-gonadal axis

Table 1. Clinical characteristics of the patients

No	Sex	Diagnosis	Age at diagnosis (years)	Chemotherapy	No	Radiotherapy Field	Dose (cGy)	Treatment duration (months)	Duration without treatment (months)	Present AGE (year)	Mean H_{SDS}**	Mean Span-total height
16	4 F	14 ALL	7.96	Combined	15	13 cranial	2400-5	47.43	62.43	17.38	+ 0.87	- 4.44
	12M	2 AML	± 3.43	chemotherapy			3000-1	± 22.44	± 41.11	± 3.81	± 1.18	± 3.88
							1800-7				Short	Patients with
						6 testicular	1200-1				patients:	Enuchoid
							1500-3				n: 2	status n: 3
							2400-2				(12.5%)	(18.75%)

* Mean ± SD

** H_{SDS}: Height Standard Deviation Score

Table 2. Hypothalamic-pituitary-thyroid axis

No	**Age (year)**	**Goitre n**	**(WHO)**	**Mean TT_3* (ng/dL)**	**Mean TT_4* (µg/mL)**	**Mean fT_3* (pmol/L)**	**Mean fT_4* (pmol/L)**	**Mean bTSH* (mIU/mL)**	**TRH stimulation test Mean pTSH****	**Mean DTSH*****
16	17.38	11	0	1.36	9.18	6.08	16.59	2.10	13.6	11.85
	± 3.81	1	Ia	± 0.37	± 2.29	± 1.18	± 3.45	± 1.09	± 8.09	± 7.46
		4	Ib							
		(Diffuse)								

* Mean ± SD

** pTSH: peak TSH

*** DTSH: pTSH-bTSH

(66.66%). Azoospermia was encountered in all patients with isolated Sertoli dysfunction. Testicular biopsy was obtained from only one of them and atrophic testicular tissue was shown. Pubertal stage was P5 in all the female patients. Females had normal pubertal development and gonadal functions.

DISCUSSION

Decreased linear growth is a common problem during therapy in children with cancer. Although catch-up may occur, such that the premorbid growth status is regained, in some instances short stature is permanent or even progressive. Factors that may influence growth in a child with a malignant disease include the disease itself, irradiation, cortisone and cytotoxic drug treatment, infection and poor nutrition[1,8]. External cranial irradiation for the treatment of malignant diseases has become a frequent cause of growth hormone deficiency (GHD). The timing of occurrence and the frequency of GHD are related to the hypothalamic- pituitary irradiation dose. Frequency varies from 50% in leukemia (2400 cGy) to 75% in face and neck tumours or medulloblastoma (2500-4500 cGy). The incidence of GHD in such children will depend on the number of fractions, fraction size and duration of the irradiation schedule[2]. The minimum harmful irradiation dose is probably close to 1800-2000 cGy[10]. Radiation-induced GHD is common[11]. On the other hand there is in vitro evidence that cytotoxic chemotherapy may affect growth mechanisms and in vivo evidence affect on growth[11].

In our study, thirteen patients were treated with prophylactic cranial irradiation and combination cyto-

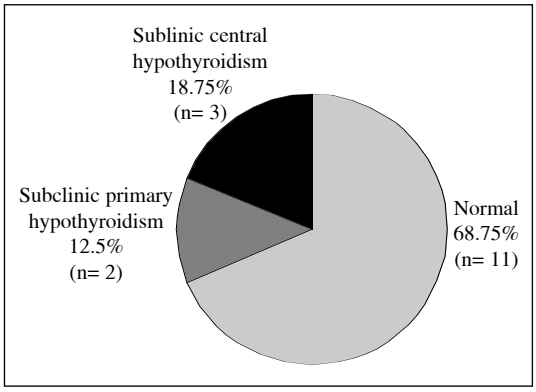

Figure 1. Distribution of the patients according to thyroid functions.

Table 3. Characteristics of the patients with thyroid dysfunction

No	Cranial RT(cGy)	Age (year)	TT_3 (ng/dL)	TT_4 (µg/dL)	fT_3 (pmol/L)	fT_4 (pmol/L)	bTSH (mIU/mL)	TRH stimulation test pTSH	TRH stimulation test DTSH	Comment
1.Ş.K.	2400	23.06	1	11.30	5.10	19.00	1.90	6.50	5.20	SCH
2.M.K.	3000	11.00	1.3	10.60	5.70	14.30	1.60	7.59	6.11	SCH
3.S.G.	2400	20.43	1.5	7.20	5.10	22.00	0.74	5.10	4.30	SCH
4.R.M.	1800	16.27	1	5.00	5.00	22.00	4.80	27.10	24.13	SPH
5.B.C.	1800	17.8	0.88	10.10	5.30	23.42	3.40	34.58	31.20	SPH

SCH: Subclinic central hypothyroidism.
SPH: Subclinic primary hypothyroidism.

Table 4. Hypothalamic-pituitary-gonadal axis

Sex	Age* (year)	Pubertal stage		Regular menses	Comment
Female n= 4	18.89 ± 3.00	4/4	P5	4/4	Normal pubertal development and gonadal functions
		1/12	P1		
Male n= 12	16.87 ± 4.03	2/12	P2		66.66% (n= 8) pathologic findings in HPG axis
		7/12	P3		
		1/12	P4		
		1/12	P5		

toxic chemotherapy (Table 1). Cranial prophylactic irradiation doses were 1800 cGy in seven; 2400 cGy in five; 3000 cGy in one patient. Two out of 16 patients had short stature and two other had enuchoid status with anthropometric measurements. Yamada et al reported the growth of 89 patients who were long-term survivors of pediatric acute leukemia and lymphoma. Eight patients with CNS relapse had a greater decrease in height standard deviation score (H_{SDS}) after the relapse than 81 patients without CNS relapse. Two patients who received cranial irradiation when they were younger than 2 years of age demonstrated a marked decrease in H_{SDS} more than 3.0 SD. In endocrine studies, all eight patients with CNS relapse failed to show the normal growth hormone response to arginine, growth hormone-releasing factor and glucagon-propranolol tests, while spontaneous growth hormone secretion during sleep was normal. Magnetic resonance imaging revealed small pituitary glands in seven patients with CNS relapse. Authors suggested that in leukemia and lymphoma patients with CNS relapse, growth hormone secretion was impaired at the hypothalamic level, resulting in a secondary atrophy of the pituitary gland[12]. Selected endocrinologic tests with magnetic resonance imaging may help to clarify the mechanism of growth impairment in these patients who were treated with cranial irradiation.

The most important complications of irradiation to the thyroid gland are hypothyroidism and thyroid tumours. An estimated dose of 9 cGy was linked to a four-fold increase of malignant tumours and a two-fold increase of benign tumours[1,2,13,14]. Hypothyroidism is the most common late effect involving this gland and almost always is due to irradiation to the neck. Between 1.5 and 6 years after irradiation doses of 1500 to 7000 cGy, laboratory evidence of primary hypothyroidism has been demonstrated in 40% to 90% of patients with Hodgkin's and non-Hodgkin's lymphomas[1]. The first detectable abnormality of the hypothalamic- pituitary- thyroid axis is an exaggerated response of TSH to TRH stimulation, indicating increased pituitary TSH reserve. This is followed by a raised resting TSH levels, the thyroxine remaining within normal limits (compensated thyroid dysfunction) and then by frank hypothyroidism with increased TSH and reduced thyroxine levels[2,4].

Leiper et al, found that at a mean of 2.2 years after receiving 900-1000 cGy in preparation for bone marrow transplantation, 10 of 17 children showed abnormalities of TSH response to TRH, of whom 4 were hypothyroid[4]. Robinson et al, reported that 17 patients had abnormalities of thyroid function 7 years after treatment of whom 5 were hypothyroid and 8 showed only transient dysfunction among 175 long-term survivors of childhood acute lymphoblastic leukemia who had received either 1800 or 2400 cGy of prophylactic cranial or craniospinal irradiation[15].

In this study, subclinic primary hypothyroidism and subclinic central hypothyroidism were observed in 2 and 3 patients respectively. Eleven patients had normal thyroid functions. Thyroid dysfunction was found in 2 out of 8 patients who have received 1800 cGy prophylactic cranial irradiation, on the other hand in 3 out of 5 patients having received 2400 cGy prophylactic cranial irradiation.

Table 5. Characteristics of the patients with gonadal dysfunction

No	Age at diagnosis	Sex	Testicular RT(cGy)	Present age (year)	Pubertal stage	Testicular size (mL)	LH (U/L)	FSH (U/L)	Testosterone (ng/dL)	hCG TEST	Spermiogram	Leydig cell dysfunction	Sertoli cell dysfunction	Relase of gonadotropin
1. H.E.	16	M	1500	18.20	P2	4	50	61.00	100.00	190.00	-	+	+	H.H.
2. S.G.	7	M	1500	20.70	P3	12	37.80	64.00	378.00	-	Oligosp.	+	+	H.H.
3. M.Ö.	3	M	-	18.40	P3	10	12	26.00	223.00	589.00	Asperm. Atrophia	+	+	H.H.
4. B.C.	10	M	1500	17.80	P3	12	3.20	8.80	400.00	581.00	Asperm.	-	+	ISD
5. R.M.	10	M	-	16.20	P3	12	4.50	12.00	200.00	-	Asperm.	-	+	ISD
6. H.S.	8	M	2400	25.20	P4	20	7.30	14.60	612.20	1185.00	Asperm.	-	+	ISD
7. V.B.	4	M	1200	15.60	P3	15	39.40	47.80	129.70	-	-	+	+	H.H.
8. Ö.A.	4	M	-	18.00	P5	25	20.00	40.00	35.30	-	-	+	+	H.H.
			Mean	18.76		13.70	21.70	34.20	232.00					
			± SD	± 2.80		± 5.90	± 17.00	± 20.60	± 182.00			5/8	8/8	5/8 HH 3/8 ISD

H.H.: Hypergonadotropic hypogonadism
ISD: Isolated sertoli dysfunction

Thyroid functions in three patients who have not received cranial irradiation were found normal. These findings show that the hypothalamic-pituitary-thyroid axis is more effected by irradiation.

Radiation therapy to the gonads and alkylating agent chemotherapy, either alone or in combination, impair actual fertility in survivors of childhood and adolescent cancers. Males are particularly affected by alkylating agents such as cyclophosphamide, chlorambucil, nitrosourea, procarbazine, vinblastine, cytosine arabinoside and cisplatinum. The normal adult testis is extremely sensitive to the effects of external irradiation[1,2,4,16]. Prophylactic cranial irradiation may also be associated with impaired growth and pubertal development in boys with ALL. In irradiated women the response of the ovary involves a pool of oocytes which was once destroyed and can not be replaced.

Surprisingly, children who have received cranial irradiation may present with early or true precocious puberty. Early puberty occurred essentially in girls after cranial irradiation for leukemia, and the children who had been irradiated when very young tended to have the earliest puberty[3].

Testicular function in 25 boys treated with a modified LSA2L2 protocol, severe testicular damage was reported. LSA2L2 protocol consisted of 10 cytotoxic agents including cyclophosphamide and cytosine arabinoside for 3 or 4 years. In 24 testicular biopsies assessed at the time of completion of chemotherapy there was an absence of germ cells in thirteen and the germ cells were markedly depleted in the remaining eleven. Raised basal FSH levels and exaggerated FSH response to an acute bolus of GnRH were reported in the majority boys who were pubertal[18].

Cyclophoshamide and cystosine arabinoside depress the tubular fertility index. Boys treated for ALL at ages between 3.5 and 15 years had reduced tubular fertility indices on testicular biopsies, with 41% having a severely depressed value[4]. Gonadal function was assessed in 15 boys with ALL who had received testicular irradiation. All of those who had received 12 or 15 Gy had normal Leydig cell function, although high levels of gonadothropins showed subclinical Leydig cell damage[19].

Leydig cell function in 21 boys with ALL who had

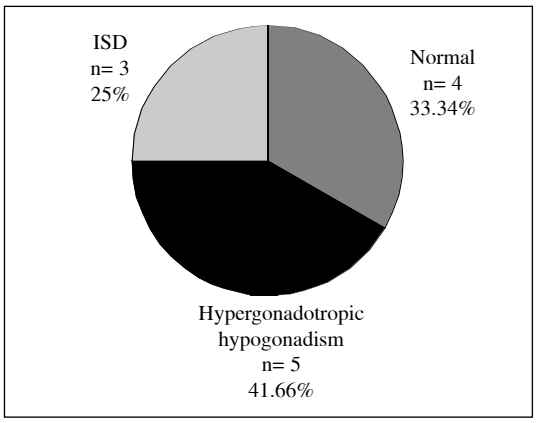

Figure 2. Gonadal functions in males.

been treated with testicular irradiation was prepubertal. Leydig cell insufficiency, indicated by a low plasma testosterone response to chorionic gonadotropin and/or an increase in basal level of plasma luteinizing hormone was observed in 19/21 patients[2,4].

Hypothalamic-pituitary-gonadal axis was evaluated in twelve boys and four girls. In this study the mean age was 16.87 ± 4.03 years in males. Sexual maturations were as follows: 1: P1, 2: P2, 7: P3, 1: P4 and 1: P5. Five patients revealed hypergonadotropic hypogonadism and four out of 16 patients had elevated FSH levels. Six out of 12 patients received testicular irradiation in addition to their combined chemotherapy. All the nine male patients had gonadal dysfunction. lncreased FSH levels were the common characteristics in these cases. In spermiogram, one out of the five patients had oligospermia, in the other four patients azoospermia was found. These findings clarify that the effect of chemotherapy on testis is found especially in Sertoli cells. Testicular and ovarian functions were assessed in 11 patients with Hodgkin's disease, all of whom showed elevated serum FSH levels and 2 azoospermia[20].

Quigley et al, reported a high incidence of ovarian damage in 20 girls treated with a modified LSA2L2 protocol. Basal and peak FSH levels after administration of GnRH were significantly higher. Serum inhibin concentration, a granulosa cell product, was undetectable in these children. Despite evidence of primary ovarian damage, all the children had reached puberty and oestradiol levels were normal[18]. A premature menopause remains a possibility if significant follicular depletion has occurred at the time of cytotoxic treatment[19].

ln our study, pubertal stage was P5 in all the females. Females had normal pubertal development and gonadal functions and one cured patient had a healthy son. Hypothalamic-pituitary gonadal axis is more influenced in male patients than females. Periodical controls are essential for those patients especially to determine the candidates for hormonal replacement therapy and psychosocial support.

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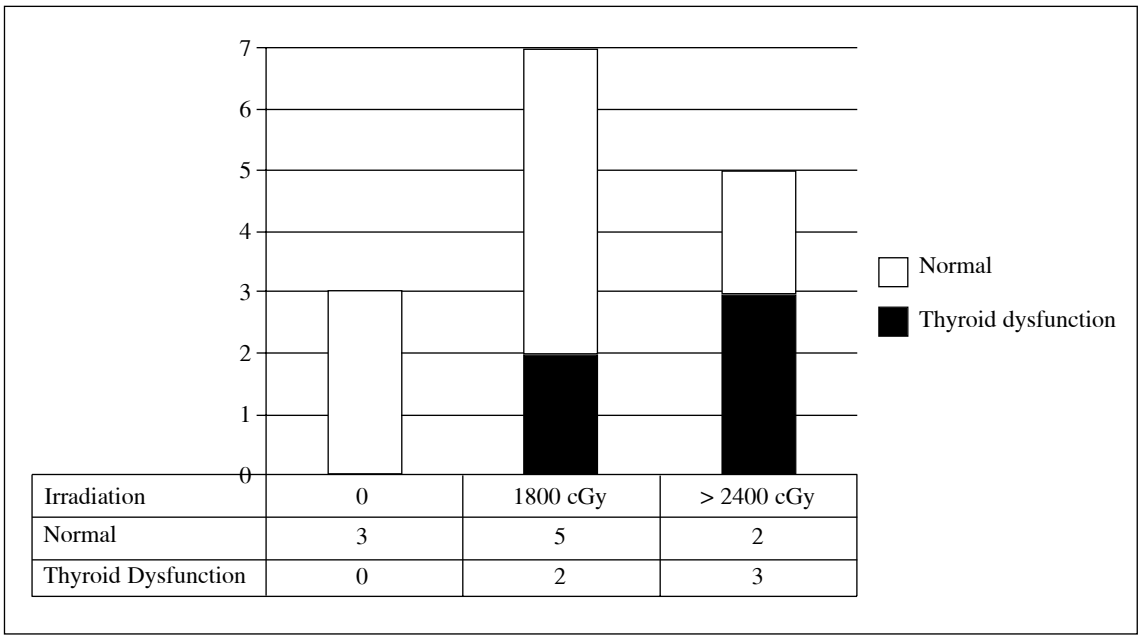

Irradiation	0	1800 cGy	> 2400 cGy
Normal	3	5	2
Thyroid Dysfunction	0	2	3

Figure 3. Thyroid functions according to cranial irradiation doses.

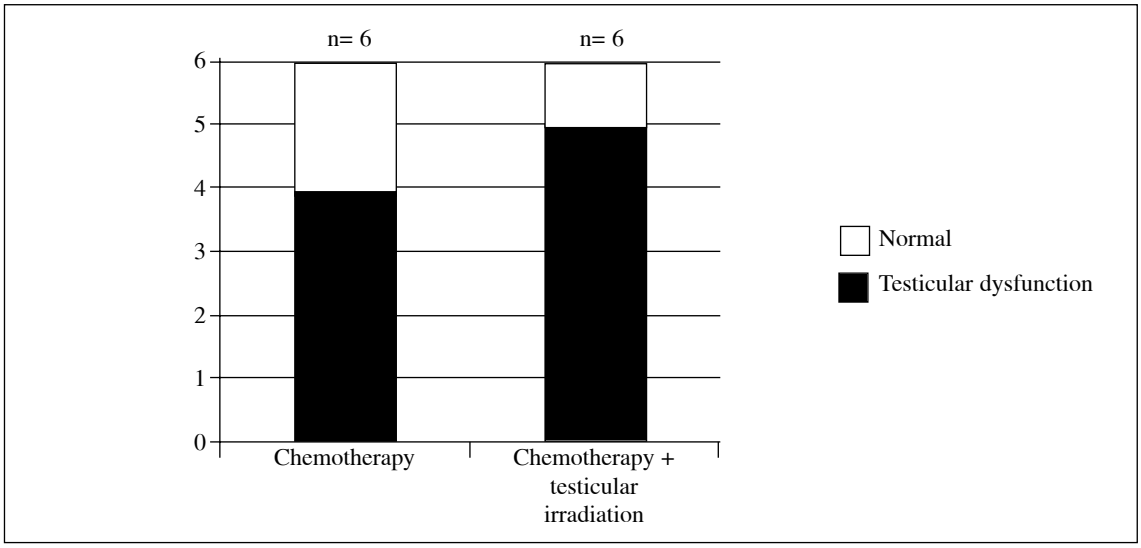

Figure 4. Therapy and testicular functions.

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