

GONADAL, ADRENAL, ANDROGEN AND THYROID FUNCTIONS IN ADULTS TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Background and Methods. The limited and controversial data available regarding endocrine function in adults treated for acute lymphoblastic leukemia (ALL) prompted us to study the influence of chemotherapy on gonadal, adrenal androgen and thyroid function. Forty-eight ALL adults (30 men and 18 women) in first complete remission (CR) were investigated.

Results. Severe reproductive function impairment was detected in 10/12 males receiving treatment, while endocrine function was affected in only 1 case. All but one off-therapy male showed normal reproductive function; moreover, endocrine function was impaired in only one male. Eight of 10 females receiving treatment showed hypergonadotropinemia and decreased estrogen levels. All off-therapy women reported regular menses, even though mild hypergonadotropinemia persisted in only 2 cases. Adrenal androgen function was depressed in 12/22 on-therapy patients in both sexes, and in 6/17 off-therapy males. All off-therapy females recovered completely. Dihydroepiandrosterone-sulfate (DHEA-S) serum levels were significantly correlated to the length of time-off therapy ($p=0.003$), and inversely correlated to the age at diagnosis ($p < 0.0001$) in off-therapy males. All patients remained euthyroid, although 4 patients showed subclinical impairment of thyroid function.

Conclusions. Our experience suggests that long-term prospective studies for ALL adults are necessary in order to better define the magnitude and duration of influence the chemotherapy has on endocrine function.

Key words: ALL, adults, chemotherapy, endocrine function

Although improvements in the management of adult acute lymphoblastic leukemia (ALL) have lagged behind those seen in the treatment of children, 70-85% of adults achieve complete remission (CR) and an increasing number remain in continuous remission, with a significant proportion (15-35%) of long-term survivors after five years.¹

The prolonged disease-free survival of adults with ALL has focused attention on the side effects of chemotherapy with regard to endocrine function. Radiation and many chemotherapeutic agents are known to produce severe side effects, including long-term

endocrine toxicity.^{2,3}

Up to now the data concerning endocrine function in adults treated for ALL have been very limited.³⁻⁵ This lack of attention has stemmed not only from the small percentage of long-term adult ALL survivors, but also from the absence of acute or life-threatening symptoms due to endocrine injury.

Most of these studies analyzed gonadal endocrine and reproductive function with controversial results. Opinion also diverges on the relative susceptibility of females to gonadal damage as compared to males.

This retrospective study was carried out to

evaluate the influence of chemotherapy on gonadal, adrenal androgen and thyroid function in adult males and females treated for ALL.

Patients and methods

Forty-eight patients, 30 men and 18 women, with ALL were assessed after informed consent was obtained. All patients were tested in first CR: 22 during consolidation or maintenance chemotherapy, 26 at different times after discontinuation of therapy.

Clinical features of all patients examined are summarized in Table 1.

Patients tested after having discontinued therapy had been treated according to the GIMEMA ALL 0183 protocol⁶ and those tested during treatment were receiving the GIMEMA ALL 0288 protocol.⁷

All patients received intrathecal methotrexate, associated with cranial irradiation (1800 rads) in 13 (10 off-therapy), for CNS prophylaxis. None had evidence of any coexisting illness likely to impair endocrine function.

Hormone determinations by specific radioimmunoassays, sperm analysis and interviews were used for diagnostic evaluation.

To evaluate gonadal function in males, blood

samples were tested for serum levels of follicle-stimulating hormone (FSH), interstitial cell-stimulating hormone (ICSH), 17 B-estradiol (E2) and testosterone. In addition, semen analyses were performed on freshly produced specimens after a suggested five-day abstinence. The samples were analyzed for sperm density, morphology and motility.

In women, serum values of FSH, luteinizing hormone (LH), E2, progesterone (during the luteal phase for cycling women) and testosterone were determined.

Furthermore, in both sexes the following hormones were tested: androstenedione and dihydroepiandrosterone-sulfate (DHEA-S) to assess adrenal androgen function; triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) to evaluate thyroid function.

Normal values are as follows: FSH, 5 to 14 mUI/mL for both men and women in the follicular or luteal phase; LH, 5 to 15 mUI/mL; ICSH, 5 to 20 mUI/mL; E2, 22 to 50 pg/mL for men and 50 to 300 pg/mL for women; progesterone 4.5 to 20 ng/mL; testosterone, 3.5 to 11.5 ng/mL for men and 0.20 to 0.80 for women; DHEA-S, 1500 to 3900 ng/100 mL for men and 1500 to 3460 ng/mL for women; androstenedione, 1500 to 2400 pg/mL for men and 1500 to

Table 1. Clinical features of 48 adults treated for acute lymphoblastic leukemia.

	males		females	
	on therapy	off therapy	on therapy	off therapy
No. of patients	12	18	10	8
Age at diagnosis (years)				
median	28	20	30	17
range	18-53	16-55	21-41	15-37
Age at evaluation (years)				
median	29	29	31	25
range	19-53	22-57	22-42	19-41
Duration of treatment (months)				
median	6	19	6	18
range	2-25	13-36	5-24	13-32
Time off therapy (months)				
median	–	53	–	48
range	–	2-129	–	20-103

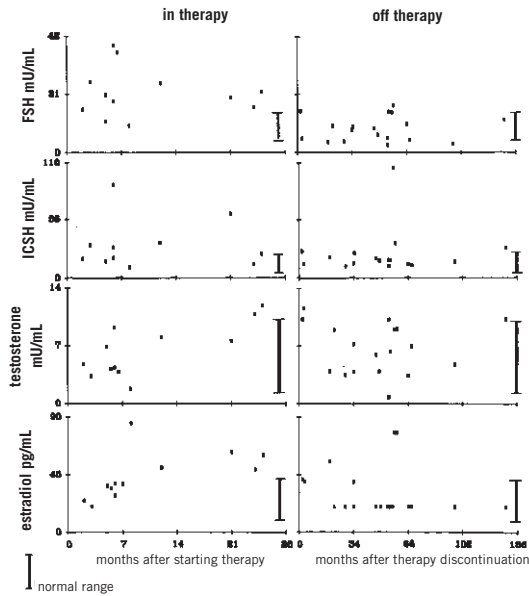


Figure 1. Gonadotropin and sex steroid serum levels in treated ALL men.

2800 pg/mL for women; T3, 0.6 to 2 ng/mL; T4, 45 to 115 ng/mL; TSH, 0.5 to 4.5 uIU/mL.

Patients were asked to answer questions regarding previous fertility, future fertility wishes, sexual function, pregnancies, use of oral contraceptives and/or hormonal replacement therapy and premature menopausal symptoms.

None of the patients used oral contraceptives or hormonal replacement therapy during this study.

Results

Gonadal function

Gonadotropin and sex steroid values in ALL men (12 studied during treatment and 18 after therapy discontinuation) are given in Figure 1.

Severe reproductive function impairment was detected in 10 out of 12 men receiving treatment. FSH serum levels in each of the 10 men were markedly elevated and associated with oligo azoospermia. ICSH serum levels were markedly elevated in 2 patients and within the

normal range or at its highest limit in the remaining men. Testosterone serum levels were normal in 11 patients, including the 2 with high ICSH values; only one male, on-therapy for 8 months, showed a significant decrease in testosterone levels with impairment of sexual function. E2 values were within the normal range in 9 and increased in the other 3.

Out of 18 men tested after having stopped therapy, only one showed severe reproductive function impairment with high E2 values and abnormal FSH serum levels associated with oligospermia. ICSH serum values were within the normal range or at its highest limits in all but one patient who showed normal testosterone levels. E2 serum values were within the normal range in all but 2 men. Testosterone serum levels were within the normal range in all but one patient, who had normal gonadotropin levels.

Gonadotropin and sex steroid values in ALL (stopping therapy) are given in Figure 2. Hyper-

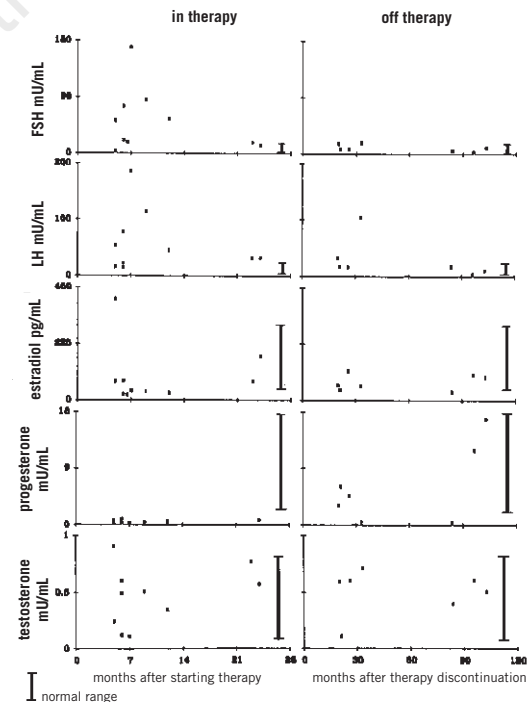


Figure 2. Gonadotropin and sex steroid serum levels in treated ALL women.

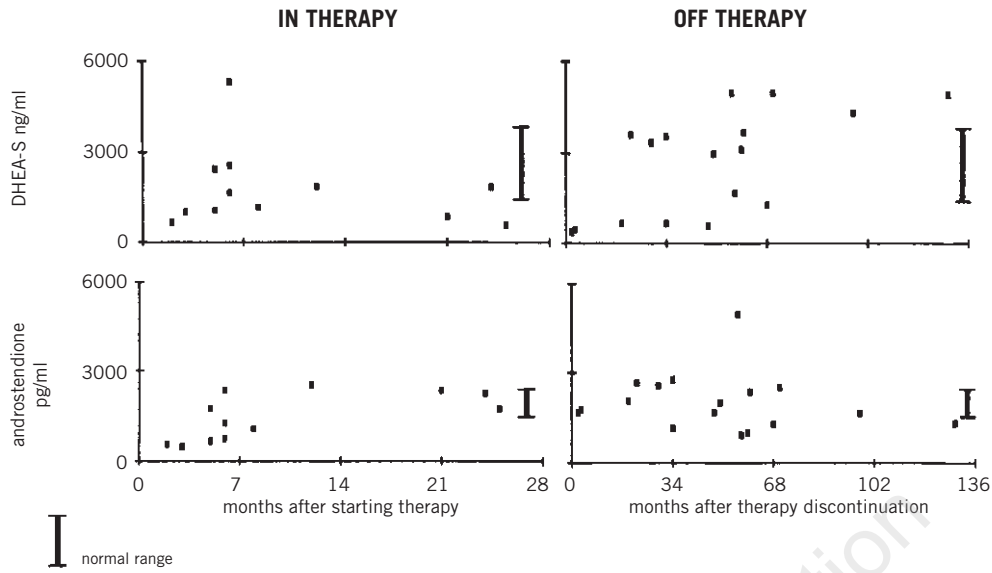


Figure 3. Adrenal androgen serum levels in treated ALL men.

Table 2. Thyroid hormones serum values in 48 evaluated adults.

hormones	males		females	
	in therapy	off therapy	in therapy	off therapy
T3 (ng/mL)				
median±SD	1.61±0.57	1.73±0.82	1.4±0.34	1.36±0.37
range	0.8-2.9	1-4.9	0.8-1.8	0.8-1.8
T4 (ng/mL)				
median±SD	95.36±15.5	97.29±24.4	90.78±19.35	99.85±12.33
range	70-120	55-145	73-130	79-115
TSH (uU/mL)				
median±SD	1.4±0.82	2.14±0.83	2.58±2.65	1.87±0.62
range	1.1-2.4	0.7-4	0.4±8.96	1.2±3

Abbreviations: SD: standard deviation.

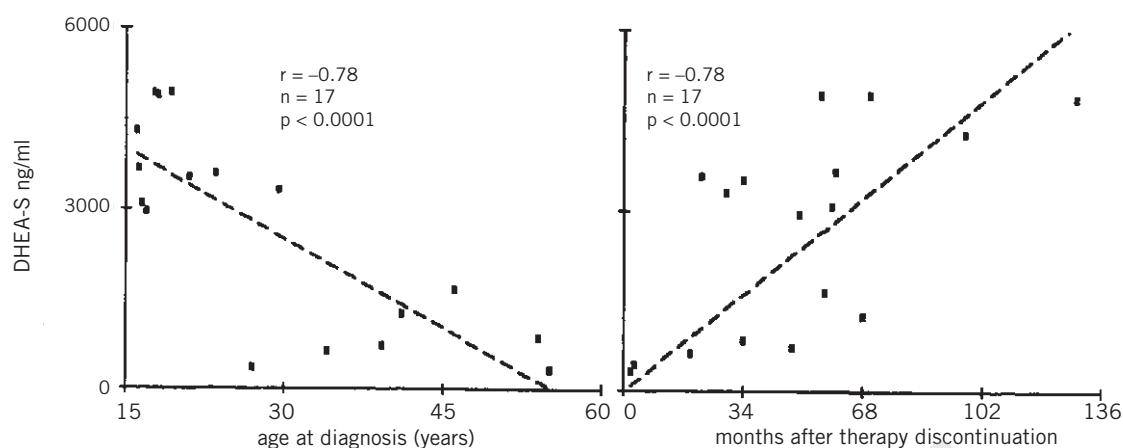


Figure 4. Off-therapy ALL men: DHEA-S serum levels correlate to age at diagnosis and length of time off therapy.

($p=0.003$) (Figure 4). Androstenedione synthesis was decreased in 6/12 on-therapy and in 4/17 off-therapy men (Figure 3).

As shown in Figure 5, adrenal androgen synthesis was depressed in 5 of 10 females on therapy, while it was normal in all these off therapy.

Thyroid function

Forty-six patients were tested for thyroid function. All of them remained euthyroid. T3, T4 serum levels were within the normal range in all 46 patients. TSH values were elevated in 1 and at the highest normal limit in 2 of 9 females on therapy; they were at the highest normal limit in 2 of 18 off-therapy men (Table 2).

Discussion

In this retrospective study significant impairment of reproductive function was found in both sexes (men: $p<0.0001$; women: $p=0.002$), during therapy, independently of the treatment phase.

Severe reproductive function impairment was detected in 10/12 (83%) males receiving treatment, while endocrine function was affected in only 1 case, although ICSH levels were elevated in 9. FSH serum levels were within the normal

range in 2 patients tested during and immediately after consolidation phase, respectively. These data are partially in contrast with those reported by Kreuser et al., who demonstrated markedly elevated FSH values in all men with ALL tested immediately after consolidation therapy; FSH levels in that study returned to the normal range during the second year of maintenance.⁴ Similarly, Kreuser et al. reported unimpaired endocrine gonadal function in all men during intensive chemotherapy.⁴

In our experience, after stopping therapy all but one man recovered normal reproductive function, although 4 patients showed FSH levels at highest normal limit; moreover, endocrine function was impaired in only 1 man.

Reproductive function was impaired in 8/10 (80%) females receiving treatment: they manifest hypergonadotropinemia and decreased estrogen levels with hypoamenorrhea, a premature menopause type condition. These findings are similar to those reported by Keilholz et al. in women submitted to autologous bone marrow transplantation (ABMT).² After therapy discontinuation, all females reported regular menses, even though mild hypergonadotropinemia persisted in only 2 cases. It is important to note that two off-therapy patients delivered healthy

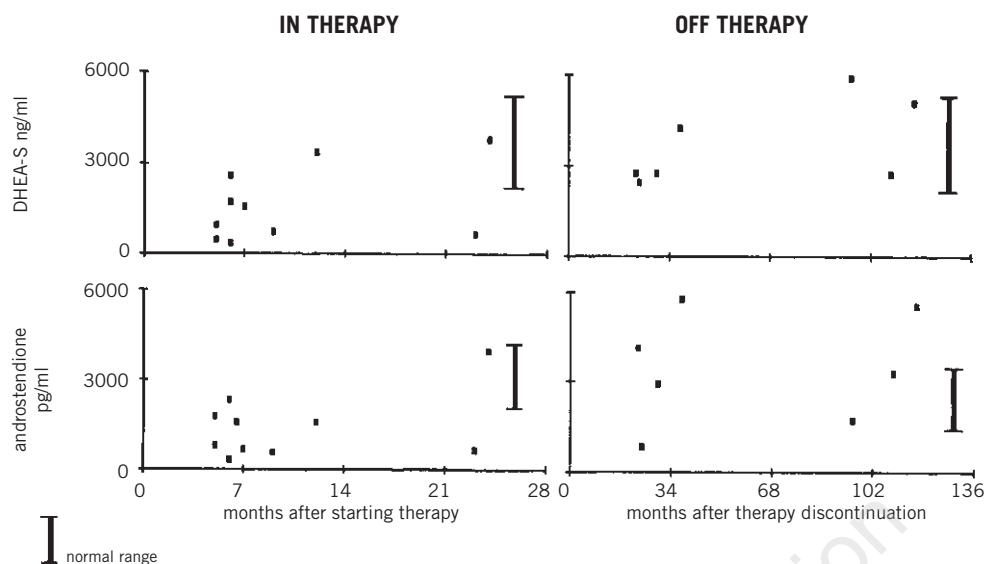


Figure 5. Adrenal androgen serum levels in treated ALL women.

children. These data suggest that the reproductive and endocrine function damage caused by ALL chemotherapy is reversible, with recovery of normal ovarian function after therapy is terminated. In contrast, Kreuser et al. reported unaffected ovarian function, with normal gonadotropin and gonadal steroids values, in all women tested during intensive chemotherapy for ALL.⁴ Previously, Wang et al. had reported normal FSH, LH and estradiol in women treated for malignant lymphoma and acute myeloid leukemia.⁸

Adrenal androgen function was impaired in 60% of all patients receiving chemotherapy. After therapy was finished, all females recovered completely, while 35% of the men continued to have adrenal androgen function. In the men off therapy there was a significant inverse correlation between age at diagnosis and reduced endocrine function ($p < 0.0001$) and a direct correlation between endocrine activity and the length of time from end of therapy ($p = 0.003$).

Few data on adrenal androgen function are reported in patients treated with antineoplastic drugs. Keilholz et al. reported moderate toxicity to the adrenal cortex, more pronounced in women than in men submitted to myeloablative

therapy followed by ABMT.² These contrasting findings require further evaluation to elucidate adrenal androgen production in patients treated with intensive chemotherapy.

Detailed studies on thyroid function, mostly in irradiated patients, have been published. Thyroid dysfunction was found by Sklar et al. in 10 of 23 long-term survivors after allotransplantation (compensated hypothyroidism in eight and primary thyroid failure in two).⁹ In contrast, Keilholz et al. did not find any abnormalities in thyroid function in patients submitted to ABMT.²

In our experience all patients remained euthyroid, although 4 (2 women on therapy and 2 men off therapy) showed subclinical impairment of thyroid function. All patients who received cranial irradiation showed normal thyroid function.

Our experience suggests that prospective studies for patients treated with the same therapeutic protocol are important to better define the influence of chemotherapy on endocrine function in adults treated for ALL.

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