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Gonadal function after testicular radiation for acute lymphoblastic leukaemia

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SUMMARY Pubertal maturation, growth, and gonadal function were assessed in 13 boys with acute lymphoblastic leukaemia who had received direct testicular irradiation three to nine years earlier as treatment for testicular relapse or prophylaxis against this complication. Six boys had reached Tanner stage III–V puberty, five of whom had normal growth velocities and bone ages equivalent to chronological age. One boy exhibited maturational arrest on entering stage IV. The remaining seven children (54%) showed evidence of complete pubertal delay or arrested development in stage II, with absence of the pubertal growth spurt and often with delayed bone age. Basal gonadotrophins were abnormally high in all 13 boys, and those with delayed puberty had prepubertal concentrations of testosterone.

Testicular irradiation given before puberty causes permanent Leydig cell damage in a high proportion of subjects, necessitating testosterone supplementation. The extent of damage may be related to the age at which radiation is delivered.

As treatment of acute lymphoblastic leukaemia has led to prolonged survival, testicular relapse has become more common, usually occurring within two years of stopping treatment.[1] As this complication is potentially curable when treated with further intensive chemotherapy and local testicular irradiation, the long term effects of treatment become important.

We recently reported that testicular irradiation in 11 prepubertal boys with acute lymphoblastic leukaemia caused severe Leydig cell damage, as shown by an appreciable decline in the plasma testosterone response to human chorionic gonadotrophin stimulation, six months after radiotherapy.[2] Brauner *et al* found similar changes in 12 patients who had received local testicular irradiation 10 months to 8½ years earlier.[3]

The purpose of this study was to assess pubertal maturation and gonadal function in 13 boys who had received previous testicular irradiation, thus enabling us to ascertain whether Leydig cell damage in these patients is permanent or whether there is capacity for recovery.

Patients and methods

Between 1974 and 1982, 20 boys with acute lymphoblastic leukaemia developed testicular relapses (found on biopsy) and were treated by local radiation and chemotherapy. Unilateral orchidectomy was also performed in two early cases before standardisation of treatment. A further two boys had prophylactic testicular irradiation as part of the UKALL VI protocol. All patients were prepubertal at the time of radiotherapy. Nine of the 22 boys were excluded either because they were less than 10 years of age or had died, leaving 13 available for assessment. Seven of these were included in our previous study using the human chorionic gonadotrophin test.[2]

Table 1 shows clinical and treatment data, including details of radiation, in these 13 boys. Eleven had received 24 Gy of radiation to the testes in 10 fractions, accompanied by a reinduction and consolidation regimen consisting of vincristine, prednisolone, asparaginase, cyclophosphamide, cystosine arabinoside, and, in some, daunorubicin. Ten had completed treatment and one was still receiving standard maintenance therapy at the time of the study. This consisted of 6-mercaptopurine, methotrexate, vincristine, and prednisolone. One boy (patient 12) had received two courses of irradiation to a total dose of 36 Gy. One further boy (patient 11) received 15 Gy of prophylactic testicular

Table 1 *Initial chemotherapy protocol, relapse status, and radiation data on 13 boys with acute lymphoblastic leukaemia receiving testicular irradiation*

Patient no	*Initial treatment protocol*	*Relapses*	*Age at irradiation (years)*	*Interval between testicular irradiation and study (yrs)*	*Dosage testicular irradiation (Gy)*	*Dosage cranial irradiation (Gy)*
1	IV	T	8·9	4·9	24	24
2	VI	CNS+BM	10·6	4·8	15	24+24 CrSp
3	II	T+CNS+BM	9·7	7·6	24	24+24 CrSp
4	V	T*	11·0	5·1	24	24
5	UKCCSG	T	11·9	3·3	24	24
6	V	T	7·6	5·6	24	24
7	V	T	9·6	4·7	24	24
8	GOS	T+CNS+BM	7·6	5·5	24	24+24 CrSp
9	V	T	8·4	4·6	24	24
10	II	T	6·4	6·2	24	24
11	V	T	8·7	8·7	24	24
12	III	T*	5·5+9·3	8·4+4·6	36	24
13	III	T+CNS+BM	9·7	3·2	24	24+24 CrSp

*Patients with single testis.
CrSp=craniospinal; T=testicular; CNS=central nervous system; BM=bone marrow.
Protocols II and III contain cyclophosphamide±adriamycin in addition to 6-mercaptopurine, methotrexate, vincristine, cytosine arabinoside, and prednisolone.
UKCCSG T cell protocol contains thioguanine, CCNU in addition to above.

irradiation and was still on treatment. Before testicular relapse all patients had been treated using standard chemotherapy protocols and cranial prophylaxis comprising 24 Gy cranial irradiation and intrathecal methotrexate (Table 1). Four boys had received a second course of craniospinal irradiation and prolonged treatment with intrathecal methotrexate for central nervous system relapse (Table 1).

All patients were assessed regularly as outpatients with respect to growth velocity and pubertal progression (Tanner).[4] As testicular growth is impaired after irradiation,[3] testicular volume could not be used as an index of pubertal development and penile growth, scrotal rugosity, and distribution of pubic hair were the parameters used.

Basal values for plasma testosterone luteinising hormone, and follicle stimulating hormone were measured by radioimmunoassay. Bone age was estimated by the method of Greulich and Pyle.[5]

Results

Clinical findings. The findings for pubertal status and growth velocity are summarised in Table 2, which also gives the results for bone age, plasma testosterone, plasma luteinising hormone, and follicle stimulating hormone.

Six boys aged 13·3 to 17·3 years at the time of the study showed stage III–V pubertal development. One of the six received 15 Gy prophylactic irradia-

Table 2 *Growth data, pubertal status, and biochemical data including plasma testosterone, luteinising hormone (LH), and follicle stimulating hormone (FSH) on 13 boys with acute lymphoblastic leukaemia after testicular irradiation*

Tanner stage	*Patient no*	*Chronological age (yrs)*	*Bone age (yrs)*	*Height velocity (cm/yr)*	*Puberty stage genitalia*	*FSH (U/l)*	*LH (U/l)*	*Testosterone (nmol/l)*
Stage III–V	1	13·8	14	8	III	>40	25·5	3·5
	2	15·4	15	8	IV	12·0	7·3	12·0
	3	17·3	16–17	6	IV	>40	20·9	15·5
	4	16·1	16	9	V	>40	35·7	6·8
	5	15·2	15–16	2	IV	36	28·4	14·5
	6	13·3	13·5	7	IV	12·2	9·3	4·8
Stage II	7	14·2	10–11	3	II	34·2	24·0	0·9
	8	13·0	10	2·5	II	34·7	23·0	1·3
Stage I	9	13·0	13·5	4	I	>40	21·1	1·9
	10	12·6	12·5	3	I	32·6	21·9	0·5
	11	14·2	13	2·5	I	34·2	20·2	1·6
	12	13·9	12·6	3	I	>40	20·0	1·3
	13	12·9	10–11	1·5	I	31·9	21·5	1·5

tion at the age of 10·6 years and the remainder had 24 Gy at an average age of 9·8 years (range 7·6 to 11·9 years). One had had a unilateral orchidectomy. Five of the six had shown a normal adolescent growth spurt and had normal bone ages. One boy had remained in stage IV puberty for 19 months and had failed to show adolescent acceleration of growth. His bone age was also normal.

Two boys aged 13 years and 14·2 years showed early pubertal changes (stage II) with some penile growth; one had scant pubic hair. Neither boy had shown progression in his pubertal development or acceleration of growth over the previous 12 months. Bone age was delayed by three to four years in both boys. These two patients were irradiated at the ages of 7·6 and 9·6 years respectively.

Five boys aged 12·6 years to 14·2 years showed no evidence of pubertal development or accelerated adolescent growth. Bone age was delayed by 1·2 years to 1·9 years in three of them. These patients received testicular irradiation at a mean age of 7·8 years (range 5·5 to 9·7 years), while one of them had a second course of irradiation (total dose 36 Gy) and unilateral orchidectomy.

Puberty stage *versus* age at irradiation was subjected to linear regression analysis (Figure).

Endocrine findings. All the patients showed raised basal follicle stimulating hormone values ranging from 12·2 U/l to over 40 U/l. Basal values in normal boys of this age are usually less than 7·8 U/l. In addition, basal concentrations of luteinising hormone were greater than 20 U/l in all but two boys, both of whom had shown pubertal progression. Normal values for luteinising hormone at this age are usually less than 3·3 U/l.

In the five boys with normal progression, basal testosterone values ranged from 3·5 nmol/l to 15·5 nmol/l (mean 8·5 nmol/l). The one boy in whom puberty seemed to have been arrested in stage IV had a plasma testosterone value of 14·5 nmol/l. The two boys with slight pubertal development had basal plasma testosterone values of 0·9 and 1·3 nmol/l. These values are in the normal prepubertal range. The five boys with no evidence of pubertal development had basal plasma testosterone values between 0·5 nmol/l and 1·9 nmol/l.

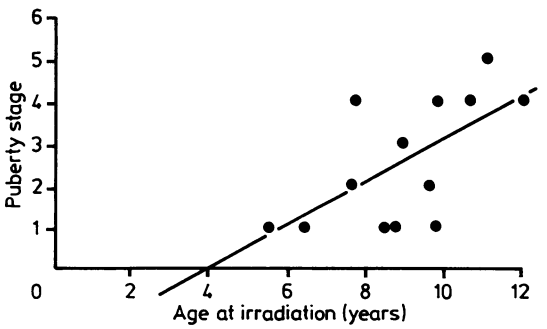

Figure *Regression analysis of the puberty stage and age at irradiation.*

Puberty stage=0·5 (age at irradiation) −2·1 (r=0·63; P=0·02).

Five of the seven children previously studied six months after irradiation (patients 1 and 6 to 11) and found to have poor plasma testosterone responses to human chorionic gonadotrophin stimulation continued to show abnormally low peak plasma testosterone values (less than 2 nmol/l) when tested two to four years later. These five patients (patients 7 to 11) subsequently exhibited pubertal delay and growth failure. The remaining two boys (patients 1 and 6) showed recovery of testicular function two and three years after irradiation with peak plasma testosterone values of 4·6 nmol/l and 6·8 nmol/l respectively. They have exhibited normal virilisation and adolescent growth.

Discussion

Endocrine disturbance seems to be relatively uncommon in patients who receive uncomplicated treatment for acute lymphoblastic leukaemia. Growth hormone deficiency assessed by conventional stimuli after prophylactic cranial irradiation is rare, but becomes frequent with increasing radiation dosage.[6] A normal growth pattern, however, is often preserved despite biochemical abnormalities.[7] Gonadotrophin deficiency is not usually found,[6] but abnormalities of thyroid stimulating hormone and corticotrophin secretion have been reported without clinical evidence of endocrine disorder.[6] Although standard chemotherapy consisting of vincristine, prednisolone, 6-mercaptopurine, and methotrexate reduces the number of germ cells of the testis as measured by the tubular fertility index,[8] Leydig cell function seems to remain intact,[9] and most boys undergo normal virilisation.[10] Cytosine arabinoside and cyclophosphamide further reduce the tubular fertility index[8] but do not impair testosterone secretion.[9]

This picture seems to be changing with the treatment of testicular relapse. It is evident from our results that the Leydig cell sustains severe and often permanent damage after fractionated testicular radiotherapy, shown by complete failure of virilisation in five boys and by arrest of pubertal growth and development in a further three (two in stage II and one in stage IV). All but one of these boys had received 24 Gy of local irradiation, while the other

had received a total dose of 36 Gy to his remaining testicle after orchidectomy. Of the five patients showing normal progression, one had received a lower dose of 15 Gy for prophylaxis, while the others had received the standard treatment dose of 24 Gy. They attained stage II puberty at a mean of 12·7 years.

Damage to the Leydig cell was suspected in our previous study when we found impaired testosterone responses to human chorionic gonadotrophin six months after radiotherapy.[2] In two of the seven boys common to both studies, recovery of function was found when repeat human chorionic gonadotrophin tests were performed two to four years later. This has subsequently been corroborated by the finding of normal pubertal progression in these two boys, while testosterone responses to human chorionic gonadotrophin remained impaired in the five others who failed to mature.

The absolute dose of radiation at which recovery of the Leydig cell does not occur is unknown. It would seem to be greater than 24 Gy, and may be dependent on the age at which irradiation is given. It is of interest that boys showing normal adolescent development received testicular radiotherapy at a mean age of 9·8 years compared with 7·9 years in those progressing no further than stage II. Although we cannot draw any firm conclusions from this, it strongly suggests that there may be a greater risk of permanent Leydig cell failure if radiation is given during early childhood. Linear regression analysis confirms this impression. This point is well illustrated by the boy who received 24 Gy of local radiotherapy at 11 years of age, and despite unilateral orchidectomy exhibited normal pubertal maturation.

Adequate pubertal concentrations of testosterone have only been achieved in those successfully undergoing virilisation by virtue of a compensatory rise in luteinising hormone to abnormal values. All of those exhibiting little or no spontaneous development had testosterone concentrations in the prepubertal range. Both gonadotrophins reached abnormally high values in this group of patients excluding a diagnosis of 'simple delay' or radiation induced pituitary failure. Growth hormone deficiency was also ruled out in the two boys treated for meningeal leukaemia with a second course of cranial irradiation, showing abnormal growth patterns.

In conclusion, not only does testicular irradiation cause germ cell damage and subsequent sterility, but there is a considerable risk that it will impair Leydig cell function and that testosterone replacement treatment will be required to achieve virilisation at the normal time of adolescence. Nonetheless in a minority of children, Leydig cell recovery occurs sufficiently to allow pubertal progression and this may be related to the age at which radiotherapy is given. These findings emphasise the need for vigilant long term follow up of all patients treated with local testicular radiotherapy. If testosterone replacement is found to be necessary it is advisable to start treatment before these boys suffer further psychological trauma through short stature and immature development. Thirteen to 14 years of age seems to be a suitable time in most cases, although individual needs should always be taken into account.

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