Effects of Radiation on Testicular Function in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childrens Cancer Study Group

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Testicular function was evaluated in 60 long-term survivors of childhood acute lymphoblastic leukemia (ALL). All the patients were treated on two consecutive Childrens Cancer Study Group protocols and received identical chemotherapy and either 18 or 24 Gy radiation therapy (RT) to one of the following fields: craniospinal plus 12 Gy abdominal RT including the gonads (group 1); craniospinal (group 2); or cranial (group 3). The median age at the time of their last evaluation was 14.5 years (range, 10.5 to 25.7), which took place a median of 5.0 years (range, 1 to 10.3) after discontinuing therapy. The incidence of primary germ cell dysfunction as judged by raised levels of follicle-stimulating hormone (FSH) and/or reduced testicular volume was significantly associated with field of RT; 55% of group 1, 17% of group 2, and 0% of group 3 were abnormal ($P = .002$). Leydig cell function, as assessed by plasma concentrations of luteinizing hormone (LH) and testosterone, and pubertal development, was unaffected in the majority of subjects regardless of RT field. These data indicate that in boys undergoing therapy for ALL, germ cell dysfunction is common following testicular irradiation and can occur following exposure to scattered irradiation from craniospinal RT. In contrast, Leydig cell function appears resistant to direct irradiation with doses as high as 12 Gy.

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ABNORMALITIES of gonadal function have been reported following the treatment of a variety of childhood cancers.[1] Gonadal dysfunction can result from either direct damage to the gonad by chemotherapy and radiation therapy (RT) or from damage to the hypothalamic-pituitary unit as a consequence of cranial irradiation. The latter appears to be a relatively infrequent cause of gonadal failure and develops most commonly following high-dose (> 35 Gy) cranial RT for CNS tumors.[2,3] Thus, for most children undergoing treatment for a malignancy including acute lymphoblastic leukemia (ALL), ultimate gonadal damage is dependent on the type of chemotherapy used and the proximity of the gonads to the field of RT. While information is available regarding the gonadal toxicity of various chemotherapeutic agents,[4,5] much less is known concerning the effects of radiation on the developing gonad.[1,5-7]

In the current study, we have evaluated testicular function in a unique group of long-term survivors of ALL. These subjects had been treated with identical chemotherapy, but three different radiation fields (cranial, craniospinal, and craniospinal plus abdominal including the testes). Since the chemotherapy used in this study has low potential for gonadal toxicity,[8,9] abnormalities of gonadal function detected in these patients are likely to be secondary to RT. Based on our recent evaluation of ovarian function in girls treated under identical conditions,[10] we anticipated a high incidence of gonadal dysfunction in the boys who received testicular irradiation.

PATIENTS AND METHODS

Between June 1972 and February 1975, a total of 936 pediatric patients with ALL were entered in Childrens Cancer Study Group treatment protocols CCG-101 and

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CCG-143. Eligibility requirements were the same for entry into both studies and have been described previously.[10] All patients received the same induction therapy of vincristine, prednisone, and asparaginase. Patients successfully attaining remission were randomized to one of the following CNS intensification regimens: 24 Gy craniospinal RT plus 12 Gy extended abdominal field including the gonads; craniospinal RT (24 Gy or 18 Gy); cranial RT (24 Gy or 18 Gy) plus intrathecal methotrexate; intrathecal methotrexate alone. Patients treated with the latter regimen were noted to have a high rate of CNS relapse. Consequently, these patients received additional CNS prophylaxis consisting of either craniospinal RT (24 Gy) or cranial RT (24 Gy) plus intrathecal methotrexate. The details of the RT have been reported previously.[10,11] Treatments were delivered in five 120 to 200 cGy tumor dose fractions per week. For subjects receiving craniospinal RT, the scattered dose reaching the testes, assuming they were located 3 to 5 cm from the lower end of the spinal field, was estimated at 10% to 15% of the spinal dose for patients treated with cobalt 60 and 2% to 3% of the spinal dose for patients treated with megavoltage irradiation, giving a range of 36 to 360 cGy (Faiz M. Kahn, personal communication). All patients received identical maintenance therapy consisting of daily mercaptopurine, weekly methotrexate, and monthly pulses of vincristine and prednisone. Patients were randomized to receive either 3 or 5 years of maintenance therapy.

In 1979, protocol CCG-101L was developed to investigate the sequelae of childhood ALL and its treatment. Of the 22 institutions originally involved in protocols CCG-101 and CCG-143, 15 agreed to participate in CCG-101L. No significant differences were observed in the characteristics of eligible survivors included or not included in the study.[10]

Testicular Evaluation

Testicular evaluation commenced at either 12 years of age or 7 years postdiagnosis of leukemia (whichever was earlier), and included data on Tanner pubic hair and genital stages,[12] testicular volumes as estimated with a Prader orchidometer[13] and plasma determinations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. Testicular volume was not used as a determinant of pubertal stage. Institutional normal ranges were obtained for FSH, LH, and testosterone. Although the original protocol requested semen analyses on all subjects who had completed their pubertal development, the number of studies reported was insufficient to provide meaningful information. Primary germ cell damage was considered present if the testicular volume (mean of the two measurements) was reduced in size (below 10th percentile)[13] in relation to age and pubertal stage and/or basal FSH level was elevated above institutional norms.

Patient Characteristics

Sixty male patients were evaluated, representing approximately 70% of eligible patients. Their median age at diagnosis was 5.4 years (range, 0.7 to 16.5) and median age at last evaluation was 14.5 years (range, 10.2 to 25.7). At the time of their last evaluation, patients had been off therapy for a median of 5.0 years (range, 1 to 10.3). Thirty-three of the subjects were evaluated on two or more occasions, while the remaining 27 were evaluated only once. Fifteen of the 60 subjects had been treated initially with intrathecal methotrexate only and were recalled for CNS irradiation. A total of three patients experienced a CNS relapse; two were from the intrathecal methotrexate only group prior to CNS irradiation, while the third patient had originally received 24 Gy cranial RT. The latter patient subsequently received additional treatment with intrathecal methotrexate following his CNS relapse. None of the patients included in the study had experienced a testicular or bone marrow relapse. None of the patients had evidence of hypothyroidism. The patients were divided into three groups based on the type of CNS prophylaxis they had received: group 1 (n = 11), craniospinal RT plus extended abdominal field; group 2 (n = 23), craniospinal RT alone (19 received 24 Gy, four received 18 Gy); group 3 (n = 26), cranial RT (21 received 24 Gy, five received 18 Gy).

Statistical Analysis

Factors associated with abnormal testicular function were assessed using the χ^2 test of homogeneity of proportions (categorical variables) and the Student's *t*-test (continuous variables).[14] Probability values are based on two-sided tests of significance. A number of pairwise comparisons were made to test the hypothesis that the extent of radiation exposure to the gonads is associated with abnormal testicular function. The conclusions regarding statistical significance in the current study are unchanged, whether or not a multiple comparison adjustment is made for all pairwise comparisons. The results for primary germ cell and Leydig cell function are reported using the data available from the 60 patients in this study. An analysis, restricted to the subgroup of 36 patients with data on all parameters (LH, FSH, testosterone, Tanner staging, and testicular volume) yielded the same results.

RESULTS

Plasma Levels of LH and FSH

Gonadotropin determinations were available in 53 of the subjects; six patients (11%) had elevated plasma concentrations of FSH, one of whom (group 1 patient) also had the single elevated plasma level of LH. The field of RT was significantly associated with elevated levels of FSH with an incidence of raised levels of FSH of 50% (four of eight) in group 1, 10% (two of 20) in group 2, and 0% (zero of 25) in group 3 ($P = .005$) (Table 1). Pair-wise comparisons demonstrated that elevated FSH levels were significantly higher in group 1 versus group 3 ($P = .002$). Although there was a fivefold difference between groups 1 and 2, this difference was not statistically significant at the .05 level ($P = .07$), while group 2 did not differ from group 3 ($P = .37$). Age at diagnosis, time since radiation, or duration of maintenance chemother-

Table 1. Patient Data

Treatment	N	Follicle-Stimulating Hormone			Testicular Volume			Germ Cell Function		
		n	Elevated	%	n	Reduced	%	n	Abnormal*	%
Group 1										
Craniospinal plus extended abdominal RT	11	8	4	50	10	5	50	11	6	55
Group 2										
Craniospinal RT	23	20	2	10	17	2	12	23	4	17
Group 3										
Cranial RT	26	25	0	0	17	0	0	26	0	0
Significance			$P = .005$			$P = .014$			$P = .002$	

*Abnormal germ cell function is defined as a raised level of follicle stimulating hormone and/or reduced testicular volume for age and pubertal status.

apy did not prove to be significantly related to raised levels of FSH.

Testicular Volume

An assessment of testicular volume was available in 44 of the subjects; eight patients (18%) had testicular volumes below the 10th percentile for age (Fig 1). In seven of the eight patients, testicular volume was also reduced for stage of pubertal development. The one patient whose testicular size was reduced for age but not for his pubertal status was a 14.5 year old from group 3 who was prepubertal by examination, had normal levels of LH and FSH, and a reduced testosterone level for age (see below). This patient most likely has a central cause for his delayed puberty and small testes and is, therefore, not considered to have primary germ cell dysfunction. Abnormally reduced testicular volume was significantly related to the field of RT ($P = .014$), with the highest incidence occurring in patients in group 1 (five of 10) (Table 1). Pair-wise comparisons demonstrated that the incidence of reduced testicular volume was significantly higher in group 1 versus group 3 ($P = .007$). The difference between groups 1 and 2 approached statistical significance with $P = .08$, while groups 2 and 3 did not differ ($P = .47$). Reduced testicular volume was not related to age at diagnosis, time since radiation, or duration of chemotherapy.

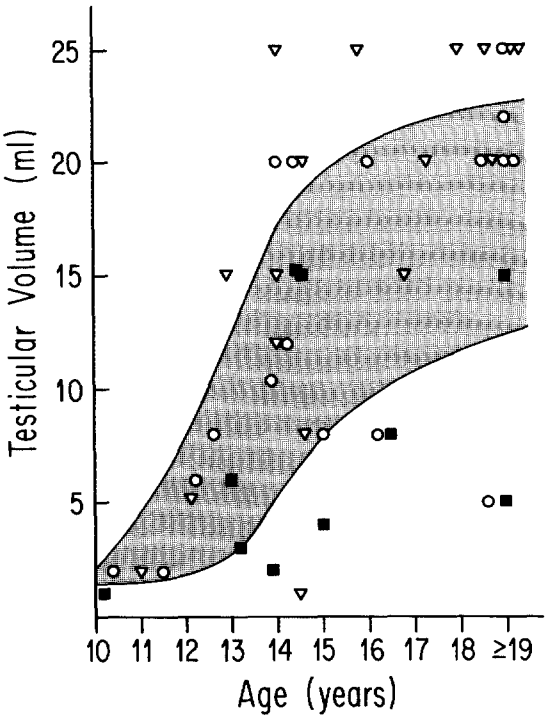

Fig 1. Testicular volume versus chronologic age. (■) Group 1 received craniospinal plus extended abdominal RT; (○) group 2 received craniospinal RT and; (▽) group 3 received cranial RT. Shaded area represents normal range (10th to 90th percentiles) for testicular volume.

The overall incidence of primary germ cell damage was 17% (10 of 60 patients) and was significantly associated with the field of RT ($P = .002$) (Table 1). The results of pairwise comparisons demonstrated that the incidence of germ cell dysfunction was significant between groups 1 and 3 ($P < .001$), while the difference between groups 1 and 2 ($P = .07$) and groups 2 and 3 ($P = .09$) approached statistical significance. All four subjects from group 2 with primary testicular damage had received 24 Gy craniospinal RT and three had been treated with cobalt 60. The mean age at diagnosis, time since radiation, age at last evaluation, and duration of chemotherapy did not differ between the subjects who manifested evidence of germ cell dysfunction and those who did not.

Pubertal Maturation

Data on Tanner stage of pubic hair and genital development[12] were available in 57 patients. Six patients were considered to have delayed development (> 2 SD below mean),[15] although serial data were available in four of the six and showed that all four patients ultimately achieved full sexual maturity. Five of the six boys had normal basal gonadotropin levels, suggesting that their slow development was due to a constitutional or central delay. The one boy from group 1 with delayed puberty also had persistent elevations of LH and FSH. Although he did eventually achieve normal adult sexual development, the initial lag in his puberty may have been due to primary testicular dysfunction. The frequency of delayed puberty was similar among the three treatment groups; 9% (one of 11) in group 1; 9% (two of 22) in group 2; and 13% (three of 24) in group 3, exhibited delayed development. None of the patients exhibited precocious sexual development.

Plasma testosterone levels were available in 50 subjects whose ages ranged from 10.2 to 23.7 years (median, 14.5 years). Testosterone values were appropriate for age and pubertal status in 48 of 50 subjects tested, including the one patient with an elevated level of LH. Two patients (one each from groups 1 and 3) had reduced testosterone levels for age. These patients were 14.5 and 16.5 years of age. The former patient also demonstrated delayed puberty. None of the subjects required testosterone replacement therapy.

DISCUSSION

In the present study, we have evaluated testicular function following the use of three different radiation regimens in boys treated for ALL. Since all study subjects received cranial RT and identical chemotherapy, the differences in gonadal function noted between the various treatment groups are most likely due to differences in the RT fields that were used. Evidence of gonadal dysfunction in our study was confined to patients whose testes were either directly in the RT field (group 1) or situated close to the margins of the RT field (group 2). The patients treated with chemotherapy and cranial irradiation alone (group 3), in contrast, did not exhibit evidence of testicular dysfunction. This is consistent with the data of others who have evaluated testicular function following the use of cranial RT and similar chemotherapy, which did not include alkylating agents.[8,9]

The most prominent findings noted among the patients with gonadal dysfunction were raised levels of FSH and reduced testicular volume. Both of these are considered sensitive indices of germ cell damage and correlate with impaired spermatogenesis and infertility.[4,16,17] Previous data, primarily in adult males, indicate that the extent of germ cell dysfunction and the time to recovery following testicular irradiation are dose dependent.[5,7,18] Dosages of radiation in excess of 400 to 600 cGy are known to cause azoospermia in all adult patients, which can persist for 5 or more years.[18] Shalet et al reported evidence of germ cell dysfunction in 10 of 10 adult males who had received testicular irradiation during childhood with total doses ranging from 268 to 983 cGy.[19] In our study, approximately half of the patients treated with 1,200 cGy direct testicular irradiation (group 1) were found to manifest signs of primary germ cell damage, an incidence lower than anticipated. Most likely, the true incidence of gonadal damage sustained by our patients has been underestimated in this study. Many of the patients were evaluated during early adolescence and often only on one occasion. It is well documented that it may be extremely difficult to establish a diagnosis of germ cell dysfunction during the peripubertal period.[20,21] This is especially true in boys since their gonadotropin levels are less reflective of gonadal dysfunction than they are in girls.[22] This sexual dimorphism in the gonadotropin response to primary gonadal damage may account, at least in part, for the higher incidence of elevated gonadotropins noted in girls following 12 Gy extended abdominal RT.[10] Serial testing with advancing age generally allows for more precise delineation of testicular function.[21] As FSH levels may remain in the normal range during this developmental stage despite the coexistence of severe dysfunction or even absence of germinal elements,[22,23] our gonadotropin data must be interpreted with caution.

The data obtained from the subjects who received craniospinal irradiation (group 2) suggest that the scattered dose of radiation reaching the testes was sufficient to cause damage to the germinal epithelium in some of the patients, particularly those who received 24 Gy from a

cobalt 60 source. This is consistent with data on adults indicating that transient germ cell dysfunction can occur following irradiation with doses as low as 35 cGy,[18] as well as that of data by Brown et al[24] on children receiving craniospinal irradiation as therapy for brain tumors. In contrast, neither Ahmed et al[25] nor Livesey and Brook[3] found evidence of primary testicular damage following craniospinal irradiation during childhood with doses to the spine in the range of 29 to 33 Gy. Since the scattered dose of radiation to the testes during craniospinal irradiation is dependent upon several variables, including the type and total dose of radiation, the direction of the radiation beam, and the distance of the testes from the margin of the RT field, it is not surprising that different investigators have reported conflicting results. Although the chemotherapy used in our study did not appear to cause direct gonadal damage, we cannot exclude the possibility that, when combined with spinal irradiation, the chemotherapy had an additive or synergistic adverse effect on gonadal tissue.

There was little evidence of Leydig cell dysfunction in our study subjects. Puberty progressed in an age-appropriate manner, and plasma levels of LH and testosterone were normal in the vast majority of patients, including those who received 12 Gy testicular irradiation (group 1). Shalet et al[19] noted that Leydig cell function was preserved in a group of adult males who as children received testicular irradiation with doses up to 9.8 Gy. Children who receive testicular irradiation with doses greater than 20 Gy, by contrast, frequently develop both clinical and hormonal evidence of Leydig cell failure.[26-28] The threshold dose beyond which the majority of young subjects will develop clinically significant Leydig cell dysfunction is not yet known; however, the current data suggest that it is greater than 12 Gy but less than 20 Gy.

Recently, several investigators have reported early or precocious puberty in children who received cranial RT for leukemia prophylaxis or as treatment for a CNS tumor.[10,29] Preliminary data suggest that girls are affected more often than boys and that the incidence is higher among subjects treated with doses $\geq$ 24 Gy.[30] We did not observe such a trend in our male patients, all of whom received cranial RT. At the time of their initial assessment, many subjects were already in puberty, and thus the precise age at the onset of puberty was not known. It is possible, therefore, that some of the subjects did enter puberty at an early age, but this was obscured by our study design.

In summary, the results of our study indicate that (1) most boys with ALL who receive cranial RT combined with chemotherapy not including alkylating agents appear to retain normal testicular function, (2) germ cell dysfunction is common following testicular irradiation during childhood and can occur following exposure to scattered irradiation from craniospinal RT, and (3) Leydig cell function appears relatively resistant to direct irradiation with fractionated doses as high as 12 Gy. At the present time, the natural history of our patients' gonadal dysfunction is unknown, and we are not able to fully assess their chances of fertility. In order to obtain this information, follow-up studies, which include direct measurements of spermatogenesis, will be necessary.

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APPENDIX

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