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Gonadal function in men treated for acute leukaemia

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Abstract

Gonadal function was assessed in eight men in remission of leukaemia who had completed treatment eight months to eight years previously. All four men treated for acute myeloid leukaemia had normal sperm counts and motility, compared with only one of the four with acute lymphatic or undifferentiated leukaemia. Hormonal studies indicated that the sterility resulted from gonadal failure rather than pituitary dysfunction after cranial irradiation.

These findings are important in the counselling of patients with leukaemia.

Introduction

Complete remission may now be induced in most young adults with acute leukaemia, and the proportion continuing without recurrence at five years is roughly one third. Thereafter relapse is rare and cure must be considered to be probable. As with other malignancies for which the rate of cure is appreciable, attention must be given to long term complications. We performed this study to assess gonadal function after the treatment of acute leukaemia in adults.

Patients and methods

We investigated eight of 21 men aged under 50 in remission of leukaemia who had completed treatment. Their mean age at presentation was 23.6 years (range 15 to 33 years) and at follow up 29.2 years

(range 20 to 38 years). The treatment free interval ranged from eight months to eight years. Table I gives details of treatment.

Seminal analysis was performed after a minimum of three days'

TABLE I—Details of treatment

Case No	Leukaemia	Induction agents and total dosage	Maintenance agents and dosage
1	Acute myeloid	Adriamycin 620 mg Cytarabine 5.6 g Thioguanine 16.8 g	
2	Acute myeloid	Daunorubicin 1.68 g Cytarabine 27.6 g Thioguanine 9.2 g	
3	Acute myeloid	Adriamycin 900 mg Cytarabine 15.18 g Thioguanine 15.18 g	
4	Acute myeloid	Adriamycin 900 mg Cytarabine 8.4 g Thioguanine 13.4 g	
5*	Acute lymphatic	Vincristine 12 mg Adriamycin 270 mg Colaspase 210×10^3 IU	Cyclophosphamide 18.75 g Methotrexate 1.875 g Mercaptopurine 43.75 g
6*	Acute lymphatic	Vincristine 8 mg Adriamycin 200 mg Colaspase 16.5×10^3 IU	Cyclophosphamide 22.5 g Methotrexate 2.34 g Mercaptopurine 52.5 g
7*	Acute lymphatic	Vincristine 12 mg Adriamycin 640 mg Colaspase 252×10^3 IU Cyclophosphamide 3.6 g	Cyclophosphamide 4.5 g Methotrexate 4.5 g Mercaptopurine 78.75 g
8*	Acute undifferentiated	Vincristine 8 mg Adriamycin 200 mg Colaspase 102×10^3 IU	Cyclophosphamide 18.75 g Methotrexate 2.5 g Mercaptopurine 43.5 g

*Cranial irradiation of 2400 rads given.

abstinence. At 9 am, after basal blood specimens had been obtained for estimation of concentrations of prolactin (mean of three measurements), sex hormone binding globulin, testosterone, and 17β -oestradiol, a standard test was performed in which luteinising hormone releasing hormone (100 μ g) was given. Follicle stimulating hormone, luteinising hormone, and prolactin concentrations were measured by specific double antibody radioimmunoassay using Medical Research Council standards 69/104, 68/40, and 71/222 respectively. After ether extraction testosterone and oestradiol concentrations were measured by tritiated radioimmunoassay. Progesterone concentration was measured by tritiated radioimmunoassay after hexane extraction. Concentrations of sex hormone binding globulin were measured by saturation radioimmunoassay.¹

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Results

Seminal analysis (table II)—All patients treated for acute myeloid leukaemia had normal sperm counts (mean count 180×10^6 sperm/ejaculate, range $57-253 \times 10^6$ sperm/ejaculate) and motility. Only one of four patients treated for acute lymphatic or undifferentiated leukaemia had a normal sperm count (50×10^6 sperm/ejaculate), the rest being azoospermic. Active spermatogenesis was unrelated to the treatment free interval. Six conceptions occurred after chemotherapy: four were congenitally normal (although one child had severe epilepsy), one resulted in a spontaneous abortion, and one resulted in a child with anencephaly. No conceptions were achieved by patients treated for acute lymphatic or undifferentiated leukaemia.

TABLE II—Results of seminal analysis

Case No	Leukaemia	No of children (and any abnormality)		No of spontaneous abortions after treatment	Sperm count ($\times 10^6$)
		Before treatment	After treatment		
1	Acute myeloid	0	1	0	187
2	Acute myeloid	0	2	0	57.6
			(1 anencephaly, 1 epilepsy)		
3	Acute myeloid	1	0	1	225
4	Acute myeloid	1	2	0	253
5	Acute lymphatic	0	0	0	0
6	Acute lymphatic	0	0	0	50
7	Acute lymphatic	1	0	0	0
8	Acute undifferentiated	0	0	0	0

Hormonal changes (table III)—All patients with normal sperm counts had normal or marginally raised basal gonadotrophin concentrations. In each of them a subnormal response of luteinising hormone and an exaggerated response of follicle stimulating hormone followed

TABLE III—Hormonal concentrations

	Acute myeloid leukaemia		Acute lymphatic and acute undifferentiated leukaemia		Normal range
	Range	Mean	Range	Mean	
Luteinising hormone (U/L):					
Baseline	2.5-5.3	3.9	7.6-30	18.0	1.4-9.7
Time after 100 µg LHRH:					
20 mins	8.4-10.7	9.4	15.6-45	29.4	13.1-57.6
60 mins	9.4-10.5	10	14.2-52	31.2	11-47
Follicle stimulating hormone (U/L):					
Baseline	4.2-10.8	68	5.2-15	8.3	1-7
Time after 100 µg LHRH:					
20 mins	47-53	51	27.6-62	41.3	1-7
60 mins	37.5-50	44	19-77	40.4	0.8-5.2
Progesterone (nmol/l)	3.7-8.7	6.2	3.2-7.7	5.2	<12
17β-Oestradiol (pmol/l)	130-200	175	130-200	155	<30-128
Sex hormone binding globulin (nmol/l)	24-41	32	21-51	30.9	17-50
Testosterone (nmol/l)	8-34	19.3	13.3-19	16.3	10-38
Mean prolactin (mU/l)	115-246	170	263-391	336	<360

LHRH = Luteinising hormone releasing hormone.

Conversion: SI to traditional units—Progesterone: 1 nmol/l $\approx$ 0.31 ng/ml. 17β-Oestradiol: 1 pmol/l $\approx$ 0.27 pg/ml. Sex hormone binding globulin: 1 nmol/l $\approx$ 0.05 µg/ml. Testosterone: 1 nmol/l $\approx$ 0.29 ng/ml.

injection of 100 µg luteinising hormone releasing hormone. Two of the three patients with azoospermia had raised basal serum gonadotrophin concentrations; all three had normal dynamic responses of luteinising

hormone but exaggerated responses of follicle stimulating hormone to the injection of luteinising hormone releasing hormone. All of the patients had normal or marginally raised serum concentrations of progesterone, sex hormone binding globulin, and 17β-oestradiol. Two patients, who had been treated for acute lymphatic and acute undifferentiated leukaemia, had marginally raised serum prolactin concentrations. All but one patient had normal serum testosterone concentrations.

Discussion

These results show that relatively short term cyclical combination chemotherapy for acute myelogenous leukaemia comprising adriamycin, cytarabine, and thioguanine does not necessarily cause azoospermia. By contrast, treatment for acute non-myelogenous leukaemia (induction of remission with adriamycin, vincristine, prednisolone, and colaspase followed by cranial irradiation and then three years' maintenance treatment with cyclophosphamide, mercaptopurine, and methotrexate) usually does.

Differences in both the schedule and the individual drugs used may have accounted for these findings. The hormonal studies suggest that sterility results from gonadal failure rather than from pituitary dysfunction after cranial irradiation. The most likely causal agent, absent from the treatment given for acute myelogenous leukaemia, is cyclophosphamide.²

The finding of gonadal failure as a consequence of successful treatment of acute lymphatic or undifferentiated leukaemia and the observation of normal spermatogenesis in men treated for acute myeloid leukaemia have important implications for the counselling of patients with leukaemia.

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ONE HUNDRED YEARS AGO The recent New York legislation gives a man very complete far-reaching and apparently retrospective rights to possess himself in pieces as well as in peace, and under the most adverse circumstances. "A person," says section 305, "has the right to direct the manner in which his body shall be disposed of after his death, and to direct the manner in which any part of his body which becomes separated therefrom during his life-time shall be disposed of." Such claims might, it is thought in America, seriously affect the pathological museums of the hospitals, for which dismembered and morsels of humanity have hitherto been appropriated without legal leave asked or permission granted. It is feared that some fortunate possessors of rare pathological growths may set an unreasonably high value on their morbid peculiarities, when once they discover that they are their legal property and have a marketable value. A man's bones may become of more worth than himself, and his little finger of more value than all the rest of his body. (*British Medical Journal* 1883;i:167.)