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Children Fathered by Men Treated with Chemotherapy for Testicular Cancer

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In a study designed to assess the potential teratogenic effect of paternal chemotherapy, information was obtained on 131 children fathered by 107 men treated for metastatic testicular cancer. Of this group, first born children fathered by 96 chemotherapy patients were compared with 96 children fathered by matched controls. There was no excess of malformations (relative risk 1.0, 95% confidence intervals 0.41 and 2.40).

In addition, the rates for specific malformations in the total cohort of 131 children were compared with the general population. There were no significant differences from national rates although the rate for congenital heart disease was higher than expected.

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INTRODUCTION

TESTICULAR CANCER is the most common malignancy in men aged 20–34 in England and Wales [1]. Cure rates have improved dramatically over the past 15 years due to the introduction of effective chemotherapy (see [2] for review). The effect of treatment on fertility and the identification of any risk to children fathered after chemotherapy becomes of crucial importance in a predominantly young patient population. It is now clear that a substantial proportion of men treated with platinum containing chemotherapy for testicular cancer recover spermatogenesis [3–5] and a proportion subsequently father children [6]. Since chemotherapy usually has a profound suppressive effect on spermatogenesis frequently with a delay in recovery from 1–3 years, it has been suggested that damage to the germinal epithelium may result in viable but defective spermatozoa capable of fertilizing the ovum but producing abnormalities in the foetus. Indeed, in some cases pregnancies have been terminated on the grounds that foetal malformations might occur.

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Our preliminary results [6] suggested that treatment for testicular cancer should not constitute a reason for advising termination of pregnancy, but numbers were too small to detect a relative risk of less than 3.2. The present multicentre study was designed to provide further information on whether there is evidence of an increased risk of congenital malformation in children conceived after paternal exposure to chemotherapy.

SUBJECTS AND METHODS

Identification of fathers and control subjects

Through the Medical Research Council Testicular Tumour Working Party, contact was made with clinicians in 25 centres in England and Wales. Men who had received treatment for histologically proven non-seminomatous germ cell testicular tumours (NSGCTT) between 1970 and 1986 and who were known to have fathered at least one child after starting treatment were notified to the coordinating centre. Treatment details were provided on a standardized form. Close contact was maintained with a liaison person in each centre to identify eligible men when they attended for follow-up. Since all testicular tumour patients are reviewed regularly, the majority of eligible men are likely to have been identified over the 2-year period of the study. Each patient was sent a letter asking for permission to obtain information on their children; of the 111 contacted, 107 agreed to participate; one patient could not be traced.

A total of 96 men who fathered at least one child after chemotherapy were matched with controls for age (within 2 years), ethnic group, and social class. The control group included 44 men with Stage 1 NSGCTT who had never received chemotherapy but who fathered a child following orchiectomy (surveillance controls). Since numbers in the latter group were insufficient, 52 community controls were also chosen by requesting the general practitioner of each chemotherapy patient to select the next man on this practice list fulfilling the matching criteria, who had fathered at least one living child. There remained 11 cases for whom no matched controls were found.

Identification and assessment of children

Information was collected on all children (131) fathered after chemotherapy; the index child (107 in total) was defined as the first child conceived after the start of treatment. For the surveillance controls, the first child conceived after orchiectomy was included, and for community controls, the child closest in age to the corresponding index child was selected.

The general practitioner was contacted after family consent had been obtained and the infant was at least 3 months of age. They were asked to supply general medical information about the children and to complete a standardized form relating to presence or absence of specific congenital malformations (squint, congenital heart disease, inguinal hernia, undescended testes, etc.). Detailed examination of 36 of the children showed that completion of the questionnaire by the general practitioner was sufficient for the identification of abnormalities sought [6].

The outcome variable was the presence of one or more congenital malformations. These included major structural malformations, such as congenital heart defects, and minor abnormalities, such as squint and inguinal hernia. In addition, attention was given to the presence of cryptorchism.

To ensure that the three groups were comparable with regard to maternal age, parity, social class and sex of the child, these variables were analysed with one-way analysis of variance and chi-square where appropriate.

Treatment of patients

Details of the overall approach to management have been reviewed elsewhere [2]. During the period of the study, several chemotherapy protocols were employed, however, almost 90% of men received platinum based chemotherapy (see Results).

RESULTS

Description of populations

The study included 107 men treated with chemotherapy and 96 controls (44 surveillance controls and 52 community controls). Analysis of variance showed no significant differences between the three groups in mother's age at birth of the index child ($P > 0.10$). Nor was there a significant difference between the three groups in father's social class (as determined from the Registrar General's Scale), sex of the index child, or birth order of the index child, by chi-square analysis ($P > 0.10$). Analysis of variance showed that the chemotherapy and surveillance groups were similar in age at time of treatment ($P > 0.10$), but there was a statistically significant difference ($P < 0.005$) in the time from completion of treatment to the birth of the index child, with a mean of 2.99 years in the chemotherapy group and 1.95 years in the surveillance group. At the time of examination the mean age of the index children was 1.7 years with a mean age in the controls of 2.4 years.

Chemotherapy

Chemotherapy received by the patients (number of patients is in parentheses) was as follows: PVB* (39), PVB + EP (2), PVB + VB + EP (1), PVB + ADR + MEL (1), BEVP (6), VB (7), VB + ADR + DTIC (1), POMB/ACE (6), C + O (1), C +

Table 1. Congenital defects in index children fathered by men treated with chemotherapy for testicular cancer and controls

Index children with matching controls
Ventricular septal defect
Total anomalous pulmonary venous drainage
Sagittal synostosis (surgically corrected)
Strabismus
Laryngomalacia
Talipes equinovarus and testicular maldescent
Inguinal hernia (2)
Marfan's syndrome (familial)
Index children unmatched
Cor biloculare (neonatal death)
Inguinal hernia
Strabismus
Community controls
Coarctation of the aorta and ventricular septal defect
Strabismus and posterior cataract
Malformed ureter, with hydronephrosis and renal failure
Surveillance controls
Testicular maldescent
Inguinal hernia (2)
Hydrocele
Cavernous hemangioma
Capillary hemangioma

Table 2. Children fathered by men treated with chemotherapy for testicular cancer: observed and expected congenital malformation rates

Disorder	National rate/ 1000	Observed in study	Observed rate/1000 (95% confidence interval)
Strabismus	38	2/131	15.3 (1.85–53)
Maldescent	26	1/65	15.4 (4.2–80)
Inguinal hernia	10	3/131	22.9 (4.66–67)
Congenital heart disease	6.6	3/131	22.9 (4.66–67)

DTIC (1), MIT (1), AMD (1), EP (7), BEP (28), VB + EP (1), VB + BEP (2), VEP (1).

Of the chemotherapy group, 95 (89%) patients received platinum containing chemotherapy.

Congenital defects

There were 96 cases for whom controls were identified. In the comparison of chemotherapy and control groups only the first child conceived after treatment was included in the analysis. Nine children in the chemotherapy group, six in the surveillance group and three community controls were noted to have malformations (Table 1). As there were no differences between the two groups of controls in malformation rate (chi-square for homogeneity of proportions $P = 0.33$), they have been combined in subsequent analyses.

When the 96 surveillance and community control families were combined to make an unexposed group and compared with the matched chemotherapy group of 96, the relative risk of malformations was 1.00 with 95% confidence intervals of 0.41 and 2.40.

In addition, the rates for specific malformations in the complete cohort of children conceived after chemotherapy were compared with known national rates [7]. A total of 131 children of 107 men treated with chemotherapy was included. Although the observed rate for congenital heart disease was higher than expected, none of the observed rates were statistically different from the national rates ($P > 0.05$) (Table 2).

Congenital malformations in relation to type of chemotherapy are shown in Table 3. There was no statistically significant difference in time from completion of chemotherapy to birth between children with and without malformations

Table 3. Children fathered by men treated for testicular cancer: malformations in relation to type of chemotherapy

Diagnosis	Treatment	Completion of treatment to conceptions (months)
Strabismus	Cisplatin, vinblastine, bleomycin	2
Cor biloculare	Bleomycin, etoposide, vinblastine, cisplatin	8
Inguinal hernia	Bleomycin, etoposide, cisplatin	17
Inguinal hernia	Bleomycin, etoposide, vinblastine, cisplatin	17
Laryngomalacia	Cisplatin, vinblastine, bleomycin	25
Talipes and testicular maldescent	Actinomycin	27
Ventricular septal defect	Cisplatin, vinblastine, bleomycin	35
Total anomalous pulmonary venous drainage	Cisplatin, vinblastine, bleomycin	38
Sagittal synostosis	Cisplatin, vinblastine, bleomycin	47
Kyphosis and marfanoid features	Vinblastine and bleomycin	64
Strabismus*	Bleomycin, etoposide, vinblastine, cisplatin	56
Inguinal hernia*	Bleomycin, etoposide, cisplatin	17

*Second child fathered after treatment.

(Mann–Whitney U test $P = 0.44$) (Table 3). Indeed, the mean time between chemotherapy and birth was shorter in the group of children without malformations.

DISCUSSION

Little information is available in testicular cancer patients regarding children fathered after the remaining gonad has been exposed to chemotherapy. Although several reports have documented apparently healthy normal children fathered by testicular tumour patients successfully treated with chemotherapy [8–11], no study has been designed to look specifically for evidence of an increase risk of congenital malformation. To our knowledge, our previous report [6] represents the only published data specifically addressing the possible teratogenic effect of paternal chemotherapy. In the present study there was no evidence that chemotherapy for testicular cancer was associated with an increased risk of malformation.

Testicular cancer is a curable disease predominantly of young men who are unlikely to have completed their families prior to treatment. The information derived from this study provides the basis for counselling patients regarding the potential risk to children conceived after paternal exposure to chemotherapy. There was an increase in the rate of congenital heart defects between the cases and national rates; however, this did not reach statistical significance. There is no obvious pathophysiological explanation for such an increase, but it should be borne in mind for further investigations involving larger numbers of children.

Although there was no evidence for an increase in malformations when the children fathered by chemotherapy patients were compared with the two control groups, the smallest risk which could have been detected with a sample this size was 2.6 using a 2-tailed Fisher exact test with $P < 0.05$. In view of the findings we would not consider prior chemotherapy for testicular malignancy a reason for advising termination of pregnancy.

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*Abbreviations: P, cisplatin; B, bleomycin; V, vinblastine; E, etoposide, Adr, Adriamycin®; MEL, melphalan; DTIC, imidazole carboxamide; C, carboplatin; O, vincristine; M, methotrexate; C, cyclophosphamide; MIT, mithramycin; AMD, actinomycin D.

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Enhancement of Adriamycin® Cytotoxicity in a Multidrug Resistant Chinese Hamster Ovary (CHO) Subline, CHO-Adr^r, by Toremifene and its Modulation by Alpha$_1$ acid Glycoprotein

Mittali Chatterjee and Adrian L. Harris

The effects of a new antioestrogen, toremifene, on multidrug resistance have been studied in a Chinese hamster ovary parental line, CHO-K1, and in a multidrug resistance subline, CHO-Adr^r. Toremifene at subinhibitory concentrations increased the cytotoxic effectiveness of Adriamycin® in both cell lines. The degree of potentiation was greater in the CHO-Adr^r lines for any given concentration of toremifene. Toremifene is 99.7% bound to human serum proteins (Sipila *et al. Pharmacol Toxicol* 1988, 63, 62–64), which includes binding to an acute phase plasma protein, alpha$_1$ acid glycoprotein (AAG). Since AAG is normally absent from tissue culture media, we have assessed the effect of AAG on toremifene mediated potentiation of Adriamycin® cytotoxicity. In the presence of increasing concentrations of AAG, there was a dose-related reversal of the effect of toremifene on Adriamycin® cytotoxicity in both cell lines. These results show that toremifene is effective in enhancement of Adriamycin® cytotoxicity in CHO-K1 and CHO-Adr^r cell lines, and this modulation can be altered by AAG. The clinical implication is that patients should be selected for such therapy by measurement of AAG levels.
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