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Testicular Function after Chemotherapy for Osteosarcoma

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Testicular volume, sperm count and four hormones were measured in 18 patients 1–13 years after chemotherapy for osteosarcoma. The testicles were small in 13 patients. 17 patients gave semen samples: 10 were azoospermic and 2 were oligozoospermic. Testicular volume and sperm count were possibly associated with the type of chemotherapy. Of the 7 patients who had received cisplatin-containing chemotherapy, 6 had small testes and azoospermia; 1 was oligozoospermic with normal-sized testes. In 3 of the 11 patients whose chemotherapy had not included cisplatin, testicular size and sperm count were normal.
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INTRODUCTION

SINCE ADVANCES in chemotherapy have dramatically increased the survival of young patients with Hodgkin's disease, testicular cancer, acute leukaemia and osteosarcoma, attention has been focused on potential normal tissue injury, including gonadal damage, after chemotherapy. Almost all men with Hodgkin's disease treated with mechlorethamine, vincristine, procarbazine and prednisone are sterile [1–5]. In most patients with testicular cancer spermatogenesis recovers in the third year after cessation of cisplatin-containing chemotherapy [6–8]. Multidrug chemotherapy for acute lymphoblastic leukaemia is associated with significant impairment of reproductive function in adult men, with early and complete recovery [9]. The prognosis for fertility in boys with acute lymphoblastic leukaemia is not well documented, but may be inferior to that of adult males with leukaemia [10]. Reversible testicular injury has been suspected in patients undergoing adjuvant chemotherapy for soft-tissue sarcoma with doxorubicin, cyclophosphamide and high-dose methotrexate. However, these agents, in combination with radiotherapy to the thigh or abdomen, may result in permanent testicular failure [11]. Our aim was to evaluate the impact of combination chemotherapy on reproductive and endocrine function in long-term male survivors of high-grade osteosarcoma.

PATIENTS AND METHODS

Patients

The series comprised 18 men over the age of 18 who had been treated for osteosarcoma at Helsinki University Hospital. The mean (median) age at diagnosis was 18 (17) years, range 9.4–33. 4 patients were under 15-years-old at diagnosis. Of the 18 patients, 17 had osteosarcoma in an extremity.

Chemotherapy

All patients had received chemotherapy according to the Scandinavian osteosarcoma protocol [12], a modification of the Rosen T-10 scheme. Before surgery all patients received four weekly infusions of methotrexate 8–12 g/m^2 and after surgery, a 2 day course of bleomycin 15 mg/m^2, cyclophosphamide 600 mg/m^2 and dactinomycin 0.6–1.25 mg/m^2 (BCD) (all per day), a 3 day course of doxorubicin (30 mg/m^2) per day and two additional infusions of methotrexate. In patients with a poor tumour response the infusions of methotrexate were replaced with cisplatin (120 mg/m^2) and doxorubicin, given with BCD (regimen A). Patients with a favourable tumour response continued to receive chemotherapy (BCD with doxorubicin and methotrexate infusions) in three cycles for 30 weeks (regimen B).

Of the 18 patients, 7 received regimen A and 11 received B. The age at diagnosis was 14–25 years (median 18) in patients receiving regimen A and 9–33 years (16) for B. The ages at which the study was done were 18–31 years (23) for A and 20–40 years (24) for B. The time from completion of chemotherapy to study was 1–6 years (4) for regimen A and 2–13 years (6) for B.

Follow-up

The medical history included detailed information on sexual behaviour and pairing. Testicular size was measured as length and breadth in millimetres. An estimate of testicular volume was made by Hansen and With's formula: 0.52 × longitudinal axis × squared transverse axis [13]. The reference group consisted of 34 healthy medical students, aged 22–25 years.

For each patient the serum concentrations of follicle stimulating hormone (FSH), luteinising hormone (LH), testosterone and prolactin were measured by radioimmunological methods from blood samples drawn in the morning. The reference values were below 10 IU/l, below 10 IU/l, above 15 IU/l and below 400 μmol/l, respectively.

A semen sample was obtained from 17 of the 18 patients; 2 cases initially refused, but donated the sample later and 1 patient had been sterilised.

RESULTS

The mean (median) testicular size was 18.8 (15.5) ml in the patient group compared with 28 (26) ml in the reference group ($P < 0.001$, t test). In 13 out of 18 patients, the size was below 20 ml, which was the lower limit of the 95% range in the reference group (upper limit 40 ml) (Fig. 1).

Serum FSH, LH, testosterone and prolactin concentrations were normal in 7 patients. The abnormalities included a high concentration of FSH (7 cases) (Fig. 1), LH (8) or prolactin (1), or a low concentration of testosterone (8).

An association between sperm count and testicular volume

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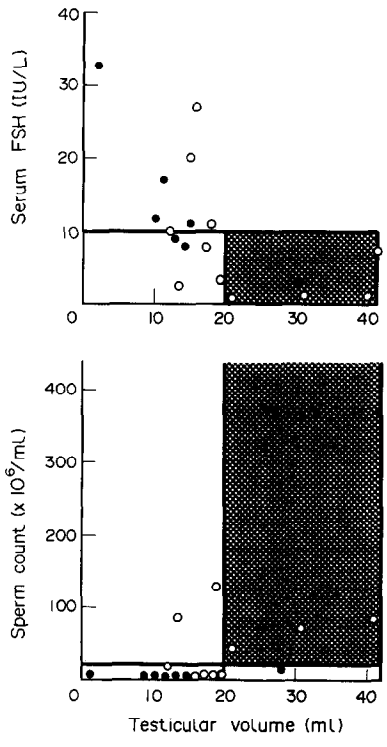

Fig. 1. Serum FSH and sperm count in patients with osteosarcoma treated with combination chemotherapy with (●) or without (○) cisplatin. Shaded area = normal range.

was dependent on the chemotherapy regimen (Fig. 1). Of the 7 patients who received regimen A, which included cisplatin, 6 had small testes and azoospermia and 1 had normal testicular volume but was oligozoospermic. In contrast, those who received regimen B had both abnormal and normal values for sperm count and testicular volume (Fig. 1). Of the 11 patients, 3 had both sperm count and testicular size within normal limits. The mean testicular size was smaller ($P = 0.061$) and the mean sperm count ($P = 0.043$) was significantly lower in patients who received regimen A than in those who received regimen B (t tests). An association was also observed between the serum concentration of FSH and testicular volume; this was independent of the regimen (Fig. 1).

Of the 18 men, 3 were married. 1 had married and had 2 children before his illness; the other 2 had no children of their own. Half of the men reported an active sex life: intercourse more than twice a week. However, a third of the men had an inactive sex life or none. Sexual activity was similar in patients who had received chemotherapy regimens A or B. Of the 18 men, only 1 had an active sex life, a normal sperm count, normal concentrations of all four hormones and normal-sized testicles.

DISCUSSION

In boys or men treated for osteosarcoma, gonadal damage was common, as indicated by small or reduced-sized testicles, abnormal serum levels of one or more hormones, impaired sperm production and decreased sexual activity. The results also indicated that identical chemotherapeutic regimens result in a wide pattern of gonadal damage which is unpredictable within individuals but may be a feature when groups are analysed. Furthermore some patients tolerated treatment without any evidence of gonadal damage.

Although the number of patients was small our findings suggest that the use of cisplatin is associated with an enhanced damaging effect on spermatogenesis. After cisplatin-containing chemotherapy in patients with testicular cancer, there is a return of spermatogenesis in 50–80% of patients 2–3 years after initiation of treatment [6–8]. However, the dose of cisplatin used has been smaller (200–600 mg/m^2) and the duration of treatment shorter (2–6 months) than that in patients with osteosarcoma (720 mg/m^2 and 11 months). Cisplatin is generally given at 20 mg/m^2 over 5 consecutive days in patients with testicular cancer, compared with a single infusion of 120 mg/m^2 in those with osteosarcoma. Thus, the mode of administration, total dose and duration of cisplatin therapy could have had an influence on the degree of impairment of spermatogenesis.

The combination of cisplatin and cyclophosphamide may be associated with an increase in gonadal toxicity, since cyclophosphamide was not included in the testicular cancer treatment protocols from which there are gonadal toxicity data [6–8]. Cyclophosphamide induces reversible dose-related germinal injury when used alone in adolescent boys treated for nephrosis [14] or as a component in multidrug therapy for acute leukaemia [9]. In the acute leukaemia study cyclophosphamide was one of several drugs in a protocol that excluded cisplatin. A dose of 650 mg/m^2 was given four times during induction therapy (weeks 1–8) and once during consolidation therapy (weeks 20–26), up to a total dose of 2600 mg/m^2. In comparison the total dose of cyclophosphamide in our osteosarcoma protocol was 4800 mg/m^2. Probably as the result of the differences in dose the recovery of spermatogenesis after chemotherapy was reported to be complete in the patients with leukaemia but incomplete in our patients with osteosarcoma. In our group spermatogenesis did not recover in the patients receiving both cisplatin and cyclophosphamide.

High-dose methotrexate may be less harmful to the gonads as seen in our patients who were not treated with cisplatin. Also, in patients with soft-tissue sarcoma treated with a combination of cyclophosphamide, doxorubicin and high-dose methotrexate, testicular damage was reversible and age-related [11].

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Comparison of Mass Spectrometry and Radioimmunoassay to Measure Medroxyprogesterone Acetate in Patients with Endometrial Cancer

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Serum medroxyprogesterone acetate (MPA) was measured by radioimmunoassay (RIA) and gas chromatography-mass spectrometry (GC-MS) in patients with endometrial cancer. Samples were obtained 3, 6 and 24 h after the oral administration of 100 or 200 mg MPA once a day. The levels obtained by GC-MS were lower (median 16–29%) than those obtained by RIA, which is probably attributable to the presence of metabolites interfering with the RIA. Two commercial MPA formulations gave different MPA serum levels by both RIA and GC-MS. The levels obtained by GC-MS were so low that frequently only partial saturation of the endometrial progesterone receptor may be achieved which may explain why high oral doses are needed to produce optimum therapeutic response.
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INTRODUCTION

THE DAILY doses of medroxyprogesterone acetate (MPA) in breast and endometrial carcinoma range from 100–200 mg to several grams per day. Significant dose–response effects have been reported even between such high doses as 500 and 1500 mg per day [1]. However, in many other well-controlled studies no differences have been found between various high-dose regimens. It is therefore possible that above a certain threshold differences in drug concentration are unimportant.

The commonest method for measurement of MPA in serum is radioimmunoassay (RIA). High serum levels have been measured by RIA after oral and parenteral administration in volunteers [2, 3] and in patients undergoing high-dose treatment [4, 5]. However, since none of the available antisera are completely specific for MPA, the results are influenced by MPA metabolites. The gas chromatography (GC) methods give lower plasma levels than RIA and the differences can be remarkable [6]. Extraction with non-polar solvents such as hexane or petroleum ether [2–5, 7] has been used to reduce interference in RIA.

Wide inter-individual variation in serum MPA levels occurs with RIA [2–5]; similar results were obtained with high-pressure liquid chromatography (HPLC) [9, 10] and GC [6, 11–13], which could both be expected to be more specific than RIA. Different commercial MPA formulations can produce different serum levels according to RIA [4] and HPLC [10].

GC-mass spectrometry (GC-MS) in the selective ion monitoring (SIM) mode is generally regarded as the most specific method for measuring serum levels of hormones and drugs. MS methods for MPA and megestrol accetate have been reported [3, 14–18], but are little used clinically. Serum levels obtained by GC-MS and RIA have been compared in two studies. In one report [3] GC-MS gave MPA levels 8–87% of those obtained by RIA after petroleum ether extraction [3]. However, in another study [16], only small differences were seen. In both of these studies the same type of antiserum was used.

We have studied serum MPA levels by both RIA and GC-MS in patients with endometrial cancer during continuous oral therapy with two commercial MPA formulations at two dosages.

PATIENTS AND METHODS

Two series of patients with stage I–II endometrial cancer were investigated. All patients had undergone hysterectomy or

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