Eur J Cancer Clin Oncol, Vol. 22, No. 3, pp. 289–294, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00

Chronic Gonadal Toxicity in Patients with Testicular Cancer after Chemotherapy

ERNST D. KREUSER, UTE HARSCH, WULF D. HETZEL and WOLFGANG SCHREML
Department of Internal Medicine, University of Ulm, Steinhövelstraße 9, 7900 *Ulm/Donau, F.R.G.*

Abstract—*Forty-five patients with disseminated testicular cancer treated with cisplatin, vinblastine and bleomycin ± adriamycin (PVB ± A) were studied to establish the impact of chemotherapy on hormonal and reproductive functions. Data on FSH, LH, testosterone, prolactin, semen analyses and sexual functions were obtained before, during and* 1–6 yr *after chemotherapy. Mean LH, testosterone and prolactin levels were within normal limits before, during and after chemotherapy. Twenty per cent* (4/20) *of the patients revealed pathologically elevated FSH levels due to pretreatment gonadal dysfunction. Germinal aplasia occurred in all patients in the first year after chemotherapy, as* 100% *rendered azoospermic and* 95% *showed statistically significant elevated FSH values* (P= 0.001). *In the third year after chemotherapy* 80% (8/10) *of the patients showed normalization of FSH levels and* 100% (7/7) *recovery of sperm production but with a high degree of immotile sperms. Although these results emphasize the restitution of spermatogenesis in the third year after cessation of PVB-regimen, the minority of these patients fathered children, probably due to reduced sperm motility.*

INTRODUCTION

SINCE the introduction of antineoplastic chemotherapy long lasting clinical remissions have been obtained for many patients with certain types of neoplastic diseases, e.g. Hodgkin's disease, acute leukemia and testicular cancer. As a consequence of this therapeutic success, concerns have arisen about persistent or delayed toxicity of cancer chemotherapy that may become clinically significant for long term survivors. Drugs used for cancer chemotherapy are well known to produce acute toxic side effects on multiple organ systems. Most commonly affected are those organs containing self-renewing cell populations such as bone marrow, gastrointestinal tract, mucosal membranes and hair follicles. However, potential gonadal injury after chemotherapy has been studied only in a limited number of malignant diseases including Hodgkin's disease [1–5], malignant lymphoma [3, 4, 6], leukemia [7, 8] and soft tissue sarcoma [9, 10]. In part this lack of attention has stemmed from the absence of any immediate or life-threatening symptoms resulting from gonadal injury. It seems worth mentioning that the documentation of gonadal toxicity is not recommended in the *WHO-Handbook for Reporting Results* [11]. The implications of cytotoxic-induced gonadal dysfunction go beyond the observation of infertility. The real importance of such findings lies in the impact of the changes in sexuality on the quality of life. Little information is available about injury and recovery of spermatogenesis induced by cytotoxic drugs in patients with testicular cancer [12–15]. Therefore we undertook a prospective study to establish the impact of chemotherapy by cisplatin, vinblastine and bleomycin (± adriamycin) on hormonal regulation and reproductive functions in 45 patients with testicular cancer.

Accepted 11 September 1985.
Address for correspondence and reprints: Ernst D. Kreuser, Department of Internal Medicine, University of Ulm, Steinhövelstr. 9, 7900 Ulm/Donau, F.R.G.

MATERIAL AND METHODS

Patients

From January 1984 to January 1985, 45 patients with testicular cancer were studied. Due to the fact that some patients were referred after initial therapy and others were followed at their local hospitals, the data sets of individual patients are not complete in some cases. Characteristics of the patient population are summarized in Table 1.

Therapy

The PVB-regimen included cisplatin 20 mg/m^2 i.v. day 1–5, vinblastine 6 mg/m^2 i.v. day 1 + 2, bleomycin 12 mg/m^2 i.v. day 1–5. The VB/AP-sequentially alternating regimen consisted of vinblastine 0.2 mg/kg i.v. day 1 + 2, bleomycin

30 mg i.v. day 1–5; adriamycin 60 mg/m^2 i.v. day 1 and cisplatin 100 mg/m^2 i.v. day 2. No patient received maintenance therapy.

Hormonal analyses

Blood samples were tested for follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone and prolactin by radioimmunoassay (Serono) before treatment, before each cycle and 1–6 yr after cessation of chemotherapy. Normal values in our laboratory are as follows: FSH 175–700 ng/ml, LH 25–100 ng/ml, testosterone 300–900 ng/100ml and prolactin 5–15 ng/ml.

Semen analyses

Semen analyses were done on freshly produced specimens before and 1–6 yr after chemotherapy. Ejaculates for analyses were obtained after a suggested 5 days abstinence. Sperm evaluation from antegrade ejaculation included sperm density, motility, volume, pH, liquefication time, % vital spermatozoa, % normally motile spermatozoa, % abnormal forms, % macrocephalic forms, % multiple-tailed spermatozoa, % headless tails and % tailless heads. Normozoospermia was defined as sperm density greater than 20 x 10^6/ml. The criterion for normal motility was greater than 50%. In patients with supposed retrograde ejaculation 100 ml urine, obtained after masturbation, were centrifuged 10 min with 3000 U/min and the sediment was analyzed. In patients revealing no ejaculation at all retrograde ejaculation was induced by alpha-sympathomimetics (5 mg Midodrin-hydrochlorid i.v.).

Questionnaire

Following informed consent the patients were asked to answer questions regarding previous fertility, contraception, marital status, future fertility wishes and children fathered after chemotherapy. Informations on libido, erection, ejaculation and orgasm were obtained before and after chemotherapy.

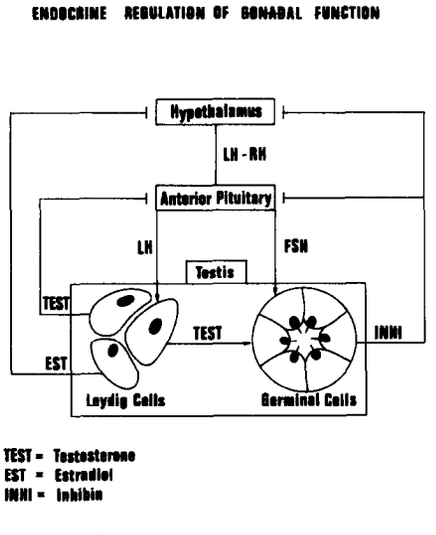

Fig. 1. Endocrine regulation of gonadal function.

Statistical analyses

Chi-square statistics were used to calculate the significance of differences of serum hormone levels.

RESULTS

Hormonal analyses

Before chemotherapy 20% (4/20) of the patients revealed pathologically elevated serum FSH levels (mean: 460 ng/ml), during chemotherapy 79% (11/14) (mean: 1060 ng/ml). In the first year after cessation of chemotherapy 95% (18/19) of the patients showed elevated FSH levels (mean: 1380 ng/ml), in the second year 56% (5/9) (mean: 820 ng/ml), and in the third year or later 20% (2/10) (mean 520 ng/ml) (Fig. 2). Statistical analyses using chi-square test revealed a statistically significant difference between pathologically elevated FSH levels before chemotherapy and during chemotherapy ($P = 0.01$), before chemotherapy and 1 yr after chemotherapy ($P = 0.0001$). There was no statistically significant difference comparing FSH levels before and two years after chemotherapy or later (Table 2).

Before treatment 5/20 patients showed falsely increased LH levels due to cross reactivity with β-HCG. During chemotherapy 86% (12/14) of the patients showed normal LH values (mean: 70 ng/ml), in the first year after chemotherapy 90% (17/19) mean: 60 ng/ml), in the second year or later 100% (19/19) (mean: 38 ng/ml) (Fig. 2). Comparing elevated LH levels before and at various time points after chemotherapy chi-square test showed no statistically significant difference (Table 2).

Testosterone and prolactin mean levels were within normal range before, during and after chemotherapy (Fig. 2). Statistical analyses comparing elevated testosterone and prolactin values revealed no significant difference.

Semen analyses

Thirty-three specimens of 25 men were analyzed. The results of sperm counts according to chemotherapy are shown in Fig 3. Four out of six patients showed oligozoospermia before chemotherapy with a sperm density of 1–25 × 10^6/ml. Twelve out of twelve patients revealed azoospermia 1–2 yr after completion of chemotherapy. Seven out of seven patients investigated in the third year or later after chemotherapy showed sperm counts between 6 and 60 × 10^6/ml reflecting

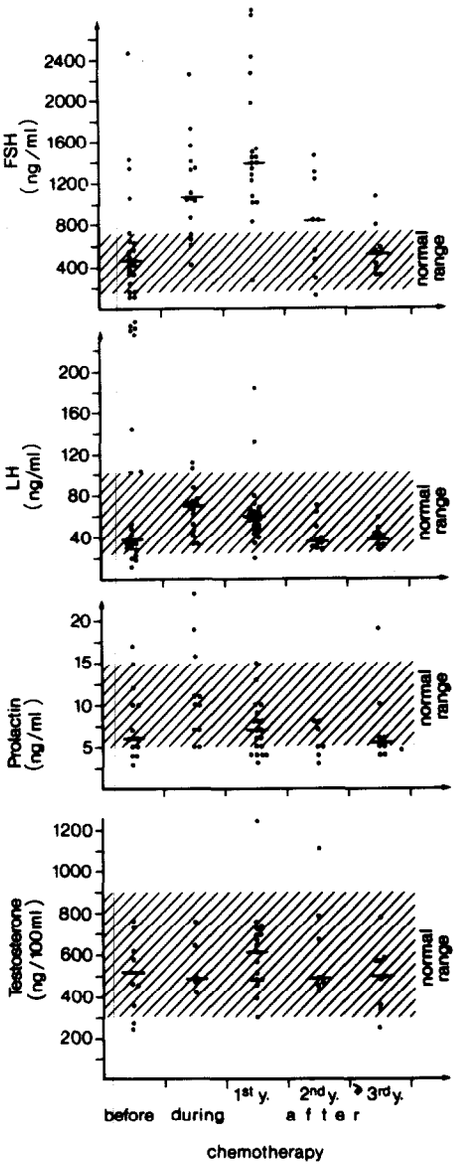

Fig. 2. Serum FSH, LH, prolactin and testosterone levels before and after chemotherapy.

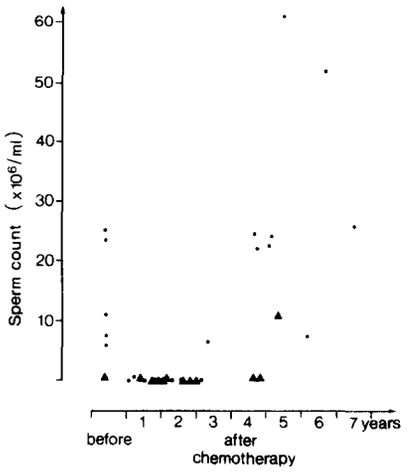

Fig. 3. Sperm count in 25 patients with testicular cancer before and after chemotherapy. ●, Antegrade ejaculation; ▲, retrograde ejaculation.

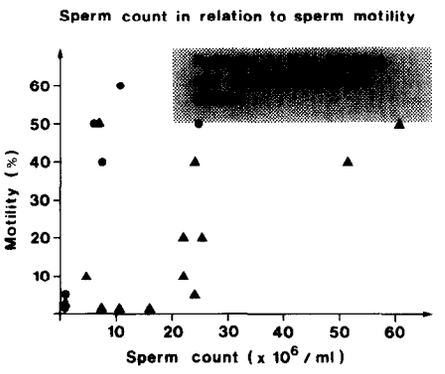

Fig. 4. Sperm count in relation to sperm motility. ●, Before chemotherapy; ▲, 3 yr or later after chemotherapy.

restitution of spermatogenesis in all patients (Fig. 3). However, analyses of sperm motility revealed pathologically decreased numbers of immotile forms in 3/6 patients before chemotherapy and in 6/8 patients 3 yr or later after chemotherapy with PVB ± A-regimen (Fig. 4).

In two patients with retrograde ejaculation sperm count could be improved from less than 1 × 10^6/ml to 10.8 and 22 × 10^6/ml by alpha-sympathomimetics.

Questionnaire

Thirty-six patients completed the questionnaire. Before chemotherapy 81% (29/36) and after chemotherapy 86% (31/36) of the patients reported to have future fertility wishes. Twenty-two per cent (8/36) fathered children before chemotherapy, one patient fathered two healthy girls 18 and 48 months after treatment with six cycles of the VB/AP-regimen. Libido, erection and orgasm were present in 100% (36/36) of the patients before and after chemotherapy (Table 3). Seventy-three per cent (33/45) of our patients were treated by retroperitoneal lymph node dissection (RLND). In 24/33 patients primary RLND and in 9/33 delayed RLND was performed (Table 1). The ejaculation was disturbed in 57% (19/33) of these patients due to radical RLND.

DISCUSSION

Testicular function in men is particularly susceptible to injury by cytotoxic drugs. Chemotherapy-induced gonadal toxicity and recovery of spermatogenesis may be related to the type of drugs, the total dose and the duration of therapy [16]. For the drugs studied to date, the primary histopathological lesion is a progressive, dose-related depletion of germinal epithelium. Germinal aplasia is characterized by the absence of spermatocytes and spermatogonia in the tubular lumen. The pituitary gland and the gonads function in a feedback cycle.

Table 1. *Characteristics of patient population*

No.	45 patients	
Median age	29 years	
Range	18–67 years	
	%	*n*
Histology (WHO)		
Tumors with one histologic pattern	80%	(36/45)
Seminoma	11%	(4/36)
Embryonal carcinoma	47%	(17/36)
Malignant teratoma	33%	(12/36)
Choriocarcinoma	8%	(3/36)
Tumors with more than one histologic pattern	20%	(9/45)
Classification		
Stage		
I	2%	(1/45)
II A/B	27%	(12/45)
II C/D	20%	(9/45)
III	2%	(1/45)
IV	40%	(18/45)
Treatment		
Orchiectomy	90%	(44/45)
Retroperitoneal lymphadenectomy	73%	(33/45)
primary	73%	(24/33)
secondary	27%	(9/33)
Chemotherapy	91%	(41/45)
PVB – regimen	73%	(30/41)
VB/AP – regimen	27%	(11/41)

mine drug-related infertility. Besides these endocrinological and andrological methods, the reproductive potential should be identified by a sexual questionnaire.

Almost all patients with Hodgkin's disease treated with nitrogen mustard, vincristine, prednisone and procarbazine (MOPP) or nitrogen mustard, vinblastine, prednisone and procarbazine (MVPP) are sterile. It could be shown that only one or two cylces of MVPP-therapy were required to produce aplasia of germinal epithelium [1, 17]. Reversible testicular injury has been demonstrated in patients undergoing adjuvant chemotherapy for soft tissue sarcomas with doxorubicin, cyclophosphamide and high-dose methotrexate. However, these agents in combination with adjuvant radiotherapy to thigh or abdomen produced permanent testicular failure [10]. The prognosis for fertility in boys with acute lymphoblastic leukemia is not known [8], although administration of antileukemic chemotherapy in boys with acute leukemia can be compatible with normal gonadal development [7].

Our studies demonstrate that pretreatment gonadal dysfunction occurs in patients with testicular cancer. Pathologically elevated FSH levels in 20% (Fig. 2) and oligozoospermia with reduced sperm motility in 60% (Fig. 3, 4) of the patients before chemotherapy reflect the impairment of germinal epithelium. Primary dysgenesis of germinal epithelium, benign testicular lesions, endocrinological or immunological neoplastic effects are discussed to be responsible for this pretreatment gonadal dysfunction [18]. However, we assume that rather tumor effects may induce the reduction of pretreatment fertility than preexistent testicular lesions, because 22% of our patients fathered children before a testicular tumor was diagnosed (Table 3). The effects of chemotherapy with the PVB ± A-regimen in the first year after che-

Table 2. *Statistical analyses of serum FSH and LH before, during and after chemotherapy*

	FSH					LH				
	No. of pathologically elevated serum hormone levels									
Before chemotherapy	5/20					6/20				
During chemotherapy	11/14	$P=0.01$	$P=0.0001$	$P=0.10$	$P=0.80$	2/14	$P=0.30$	$P=0.20$	$P=0.10$	$P=0.10$
1st year after chemotherapy	18/19					2/19				
2nd year after chemotherapy	6/10					0/10				
3rd year after chemotherapy	2/10					0/10				

In men with normal spermatogenesis, an inhibitor (INHI) of FSH is assumed to be produced by the testes (Fig. 1). When the germinal epithelium is impaired, e.g. by cytotoxic drugs, FSH blood levels rise. The Leydig-cells produce testosterone in a feedback cycle with LH. In complete Leydig-cell failure, levels of LH rise and testosterone levels fall (Fig. 1). Therefore FSH and LH levels reflect the state of germinal epithelium and Leydig-cells. Furthermore, semen analyses are required to deter-

Table 3. Marital status, children and sexual functions of 36 patients with testicular cancer before and after chemotherapy

	Before chemotherapy		After chemotherapy	
Unmarried	78%	(28/36)	64%	(23/36)
Married	22%	(8/36)	34%	(12/36)
Divorced	–	(0/36)	3%	(1/36)
Children	22%	(8/36)	25%	(9/36)
Future fertility wishes	81%	(29/36)	86%	(31/36)
Libido	100%	(36/36)	100%	(36/36)
Erection	100%	(36/36)	100%	(36/36)
Ejaculation	50%	(18/36)	50%	(18/36)
Orgasm	100%	(36/36)	100%	(36/36)

motherapy were substantial, as 100% of our patients rendered azoospermic (Fig. 3) and 95% revealed statistically significant elevated FSH values ($P = 0.0001$) (Fig. 2, Table 2). During the follow up there was a continuous decrease of FSH levels. In the third year or later after chemotherapy 80% of the patients showed normalization of FSH levels and 100% recovery of sperm production indicating the restitution of spermatogenesis in most patients 3 yr after therapy with PVB ± A-regimen (Fig. 2, 3).

Although these results emphasize the recovery of spermatogenesis, the minority of our patients fathered children after chemotherapy probably due to reduced sperm motility (Fig. 4). Since serum LH and testosterone levels were not statistically significantly altered before, during and after chemotherapy (Fig. 2, Table 2), Leydig-cells obviously were not injured by cytotoxic drugs. According to the normal testosterone levels, libido, erection and orgasm were not disturbed in all patients after chemotherapy (Table 3). Our sexual questionnaire underlines the real importance of protection of fertility, since 86% of our patients reported to have future fertility wishes (Table 3). Nevertheless, RLND caused most probably irreversible infertility in 57% of our patients. Although sperm count could be improved by alpha-sympathomimetics (Fig. 3), fathership in patients with loss of ejaculation has been observed only exceptionally [12].

In conclusion, our studies document that fertility is a major problem in this patient population of young men with testicular cancer and a high probability of cure.

We have shown that PVB ± A-regimen causes germinal aplasia in all patients. Although our data emphasize recovery of spermatogenesis in most patients in the third year after cessation of chemotherapy the minority only fathered children after chemotherapy probably due to reduced sperm motility. Future efforts should be directed to treatment modalities which supplement more conservative surgical measures and protect spermatogenesis during chemotherapy, thus improving the quality of life for the cured patients.

REFERENCES

1. Chapmen RM, Sutcliffe SB, Malpas JS. Male gonadal dysfunction in Hodgkin's disease. *JAMA* 1981, **245**, 1323–1328.
2. Dein RA, Mennuti MT, Kovach P, Gabbe SG. The reproductive potential of young men and women with Hodgkin's disease. *Obstr Gyn Surg* 1984, **39**, 474–482.
3. Roeser HP, Stocks AE, Smith AJ. Testicular damage due to cytotoxic drugs and recovery after cessation of therapy. *Aust N Z J Med* 1978, **8**, 250–254.
4. Sherins RJ, DeVita VT. Effect of drug treatment for lymphoma on male reproductive capacity. *Ann Int Med* 1973, **79**, 216–220.
5. Sherins RJ, Olweny CLM, Ziegler JL: Gynecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkin's disease. *N Engl J Med* 1978, **299**, 12–16.
6. Richter P, Calamera JC, Morgenfeld MC, Kierszenbaum AL, Lavieri JC, Mancini RE. Effect of chlorambucil on spermatogenesis in the human with malignant lymphoma. *Cancer* 1970, **25**, 1026–1030.
7. Blatt J, Poplack DG, Sherins RJ. Testicular function in boys after chemotherapy for acute lymphoblastic leukemia. *N Engl J Med* 1981, **304**, 1121–1124.
8. Lendon M, Hann IM, Palmer MK, Shalet SM, Morris Jones PH. Testicular histology after combination chemotherapy in childhood for acute lymphoblastic leukemia. *Lancet* 1978, **2**, 439–441.
9. Rosenberg SA, Kent H, Costa J. Prospective randomized evaluation of the role of limbsparing surgery, radiation therapy and adjuvant chemoimmunotherapy in the treatment of adult soft tissue sarcomas. *Surgery* 1978, **84**, 62–69.
10. Shamberger RC, Sherins RJ, Rosenberg SA. The effects of postoperative adjuvant chemotherapy and radiotherapy on testicular function in men undergoing treatment for soft tissue sarcoma. *Cancer* 1981, **47**, 2368–2374.
11. *WHO-Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO Offset Publication No. 48, 1979.

12. Fossa SD. Fertility and testicular cancer. Second Germ Cell Tumors Conference, Leeds, 15–19 April, 1985 (Abstract).
13. Lange PH, Narayan P, Vogelzang NJ, Shafer RB, Kennedy BJ, Fraley EF. Return of fertility after treatment for non-seminomatous testicular cancer: changing concepts. *J Urol* 1983, **129**, 1131–1135.
14. Tachil JV, Jewett MAS, Rider WD. The effects of cancer and cancer therapy on male fertility. *J Urol* 1981, **126**, 141–145.
15. Oliver RTD. Recovery of fertility after chemotherapy for germ cell tumors. Second Germ Cell Tumors Conference, Leeds, 15–19 April, 1985 (Abstract).
16. Drasga RE, Einhorn LH, Williams SD, Patel DN, Stevens EE. Fertility after chemotherapy for testicular cancer. *J Clin Oncol* 1983, **1**, 179–183.
17. Chapman RM. Effects of cytotoxic therapy on sexuality and gonadal function. *Semin Oncol* 1982, **9**, 84–94.
18. Kießling M, Haselberger J. Struth B. Fertilität und Sexualfunktionen vor und nach Therapie. In: Weißbach L, Hildenbrand G, eds. *Register- und Verbundstudie für Hodentumoren*, Bonn. München, Zuckschwerdt, 1982, 366–377.