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Long-term survivors of ovarian malignancies after cisplatin-based chemotherapy: cardiovascular risk factors and signs of vascular damage

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Abstract

Male germ cell tumour patients treated with cisplatin-based chemotherapy frequently develop cardiovascular risk factors and disease, but sparse information is available about long-term complications of this type of chemotherapy in women. We investigated the prevalence of cardiovascular risk factors and vascular damage in 21 women (median age 39 years; range 26–57 years) with an epithelial or germ cell tumour of the ovary cured by cisplatin-based chemotherapy after a median follow-up of 14 years (range 3–21 years). Hypercholesterolaemia was present in 62%, obesity in 24%, hypertension in 14%, insulin resistance in 14%, and microalbuminuria in 24% of patients. Microalbuminuria was more frequent in long-term cancer survivors than in a female background population with a similar age (23.8 versus 3.2%; $P < 0.05$). A substantial portion of young female patients cured by cisplatin-based chemotherapy are likely to develop cardiovascular risk factors and signs of endothelial damage at an early stage.

Keywords: Germ cell tumour; Ovaries; cis-Platinum; Cardiovascular diseases; Endothelium

1. Introduction

Malignant germ cell tumours of the ovaries are most often diagnosed in young females. In the past two decades, the prognosis of patients with advanced disease has improved significantly as a result of advances in systemic treatment with cisplatin-containing chemotherapy. The first platinum-containing regimen used for advanced ovarian germ cell tumours was PVB (cisplatin, vinblastine, bleomycin) [1]. Subsequent experience in testicular germ cell tumours indicated that substitution of etoposide for vinblastine (BEP) produces less toxicity and perhaps a better outcome in patients with bulky disease [2,3]. As a result, BEP for three or four courses has become the standard regimen for patients with advanced ovarian germ cell tumours, resulting in long-term survival in most cases [4,5]. Improved survival has resulted in an increase in the number of cured patients.

Substantial data exist regarding the late effects of cisplatin-based therapy in men with testicular cancer. However, sparse information is available about long-term surviving women with ovarian germ cell tumours. We have reported long-term cardiovascular toxicity and cardiovascular risk factors in male survivors of testicular cancer who had been treated with cisplatin-based chemotherapy [6,7]. We wondered whether these adverse effects were also observed in long-term survivors of ovarian tumours following cisplatin combination chemotherapy. Therefore, the objective of the current study was to investigate cardiovascular risk factors and signs of cardiovascular damage in this group of long-term female survivors.

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2. Patients and methods

In 2001, the charts of all patients treated at the University Hospital, Groningen, with salpingo-oophorectomy followed by cisplatin-containing chemotherapy because of a tumour of the ovary were reviewed. Patients who were less than 40 years of age at the time of treatment and had attained a disease-free survival of at least three years were eligible. Twenty-one patients fulfilled these criteria. Patients' characteristics are shown in Table 1. Most patients were still under surveillance at our outpatient clinic when they were asked to participate in this study. Written informed consent was obtained from each patient.

2.1. Follow-up investigations

A detailed medical history was obtained with the help of a questionnaire on the day of the follow-up investigations. This questionnaire included questions regarding actual and previous cardiac function, cardiovascular risk factors, presence of complaints known to be related to chemotherapy, and use of medication. A full physical examination was performed and blood pressure was measured with a standard mercury sphygmanometer at both arms in a sitting position after a resting period of 10 min. Hypertension was defined as a systolic pressure >150 mmHg or a diastolic pressure >95 mmHg or the use of antihypertensive medication. Body mass index (BMI) was calculated by dividing the body weight (in kg) by height (in m) squared. A BMI >27.8 kg/m^2 was considered to indicate the patient was overweight [8].

Table 1
Patients' characteristics

Number of subjects	21
Age (years) at start of chemotherapy	
Median (range)	26 (15–37)
Age (years) at follow-up	
Median (range)	39 (26–57)
Follow-up duration (years)[a]	
Median (range)	14 (3–21)
Diagnosis (*N*,%)	
Germ cell tumour of the ovary	17 (81)
Epithelial carcinoma of the ovary	4 (19)
Chemotherapeutic regimen[b] (*N*,%)	
BEP or EP	10 (48)
PVB	5 (24)
CAP-5	4 (19)
Other cisplatin-containing	2 (9)

[a] Years since start of chemotherapy.
[b] (B)EP: bleomycin, etoposide, cisplatin; PVB: cisplatin, vinblastine, bleomycin; CAP-5: cyclophosphamide, doxorubicin, cisplatin.

Blood samples collected after an overnight fast were analysed for serum lipid levels (total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol). Cut-off points for lipid levels were used as recommended by the American National Cholesterol Education Program Adult Treatment Panel III (ATP III) [9]. Hypercholesterolaemia was defined as elevated fasting total serum cholesterol (>5.2 mmol/l) or use of cholesterol-lowering medication.

Urinary albumin excretion was determined in a 24-h urine collection. Microalbuminuria was defined as a urinary albumin excretion of 30–300 mg/24 h. Creatinine excretion in 24-h urine samples was determined to estimate renal function. Magnesium was measured in serum and 24-h urine samples.

Measurements of endothelial and inflammatory marker proteins were also performed: fibrinogen was measured using the Clauss functional assay (reference values 1.7–3.5 g/l). Von Willebrand factor (vWF; Dako A/S, Glostrup, Denmark; reference values 50–150%), plasminogen activator inhibitor type 1 antigen (PAI-1; reference values 4–43 ng/ml), and tissue-type plasminogen activator antigen (t-PA; reference values 1–10 ng/ml) were measured using an enzyme-linked immunosorbent assay (ELISA) (Asserachrom, Diagnostica Stago, Asnieres-sur-Seine, France).

Serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels were measured using a fluoroimmunoassay (AutoDelfia, Perkin Elmer/Wallac Oy, Turku, Finland) to exclude hypothyroidism as the cause of hypercholesterolaemia. Fasting serum insulin and glucose levels were determined to investigate the presence of insulin resistance. Insulin-to-glucose ratio (IGR) was calculated by dividing fasting serum insulin (pmol) by fasting serum glucose (mmol). An IGR >22 was considered to indicate insulin resistance.

Platinum levels were measured in serum and urine samples by a sensitive procedure during which high pressure decomposition of samples is followed by an adsorptive voltammetric measurement [10]. Detection limits of platinum were 6 and 3 pg/g for serum and urine samples, respectively. The coefficient of variation and day-to-day variation were 6% and 5%, respectively.

Data on cardiovascular risk factors and urinary albumin excretion from 2926 women (age range 30–56 years), a selection from the Dutch Prevention of Renal and Vascular ENd-stage Disease (PREVEND) population study (all inhabitants of the city of Groningen) [11], were used to estimate the prevalence of cardiovascular risk factors and microalbuminuria in the general female population, using an adjusted weighting approach in which non-response was taken into account [12]. Variance estimation was performed using the jack-knife procedure [12].

2.2. Statistical analysis

Categorical variables were compared using the Chi-square test. Pearson's correlation coefficient and Spearman's rank test were used to calculate correlations between variables. Double-sided P-values <0.05 were considered to indicate significance.

3. Results

Twenty-one patients had a median follow-up of 14 years. During follow-up, none of the patients developed a cardiovascular event, although one patient developed periodic cardiac arrhythmia without signs of ischaemic heart disease. Eight patients developed complaints of Raynaud's phenomenon, which subsided in most patients after a longer follow-up. Five patients complained of prolonged paresthesiae during follow-up. Three patients used antihypertensive medication, one patient used cholesterol-lowering medication, and 18 patients used either hormonal replacement therapy or oral contraceptives.

3.1. Cardiovascular risk factors

Frequencies of cardiovascular risk factors are shown in Table 2. An increased total cholesterol and LDL cholesterol occurred in 62% of patients. Twenty-nine percent of patients had a decreased HDL cholesterol, while 38% had an increased total cholesterol/HDL cholesterol ratio. Comparison of the cardiovascular risk factors with the Dutch background population revealed that microalbuminuria occurred more frequently in the long-term cancer survivors. Table 3 shows additional markers of endothelial damage and inflammatory proteins, which were increased in a few patients.

Table 2
Cardiovascular risk factors in long-term survivors of tumours of the ovary after chemotherapy ($n=21$)

	Normal value	Chemotherapy patients $N=21$ Number with abnormal value % (95% CI)	Controls $N=2926$ Number with abnormal value % (95% CI)
Blood pressure	150/95 mmHg/24 h	3 14.3 (1–29.3)	2.6 (1.9–3.3)
Total cholesterol (fasting)	<5.2 mmol/l	13 61.9 (41.3–82.7)	46.7 (44.3–49.0)
Body mass index (BMI)	<27.8 kg/m^2	5 23.8 (5.6–42.0)	17.8 (16.0–19.6)
24-h Urinary albumin excretion	<30 mg/24 h	5 23.8 (5.6–42.0)[a]	3.2 (2.6–3.8)

[a] Chemotherapy patients versus controls $P<0.05$.

Table 3
Cardiovascular risk factors and endothelial damage parameters in long-term survivors of tumours of the ovary after chemotherapy ($n=21$)

Risk factor	Normal value	Mean±S.D. (range)	Number (%) of patients with abnormal result
Dyslipidaemia			
Total cholesterol	<5.2 mmol/l	5.6±1.2[a]	13 (62)[b]
HDL cholesterol	>0.9 mmol/l	1.2±0.4[a]	6 (29)[b]
LDL cholesterol	<3.4 mmol/l	3.9±1.0[a]	13 (62)[b]
Total cholesterol/HDL cholesterol-ratio	<5.0	5.0±1.3[a]	8 (38)[b]
Triglycerides	<2.3 mmol/l	1.6±1.7[a]	2 (10)[b]
Marker proteins			
Fibrinogen	⩽3.5 g/l	3.0[c] (1.9–4.1)	9 (43)
vWF	⩽150%	108[c] (28–296)	1 (5)
PAI-1	⩽43 ng/ml	26.5[c] (3–183)	3 (14)
t-PA	⩽10 ng/ml	7.6[c] (1.5–21.0)	1 (5)

vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor type 1 antigen; t-PA, tissue-type plasminogen activator antigen; S.D., standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Patients using cholesterol-lowering medication not included.

[b] Patients using cholesterol-lowering medication included.

[c] Median.

3.2. Hormonal and renal parameters

Five patients were overweight with a BMI above 27.8 kg/m^2. All but one patient had a normal thyroid function with normal TSH and FT4. Signs of insulin resistance were found in 3/21 (14%) of patients. Four (19%) patients had a decreased serum magnesium level, while urinary excretion of magnesium was normal in all patients. Serum magnesium levels correlated inversely with the insulin resistance parameter IGR ($r = -0.548$; $P = 0.015$).

3.3. Platinum levels

All patients had detectable serum platinum levels. An extremely long-lasting retention of platinum in serum, up to 21 years after cisplatin treatment, was accompanied by excretion of platinum in the urine. Serum levels of platinum correlated inversely with the duration of follow-up ($r = -0.56$; $P = 0.009$) and 24-h creatinine clearance ($r = -0.61$; $P = 0.003$). Furthermore, serum platinum levels correlated strongly with amounts of platinum excreted over 24 h ($r = 0.82$; $P < 0.001$). For patients with a follow-up of more than 10 years, the mean amount of platinum excreted over 24 h was 1.26 ± 0.50 μg.

4. Discussion

Patients with advanced germ cell tumours of the ovary can be cured by cisplatin-based chemotherapy. Nowadays, most patients are treated with a combination of bleomycin, etoposide and cisplatin. Most data on cisplatin-based chemotherapy and its long-term side-effects arise from studies in male patients with testicular germ cell tumours, while in female patients only small studies have been reported. Since the prognosis of female patients with germ cell tumours of the ovary is comparable to the prognosis in cisplatin-treated male patients, long-term side-effects are equally relevant. Studies in testicular cancer patients have shown that long-term survivors often develop cardiovascular risk factors, like dyslipidaemia, hypertension and microalbuminuria, and are at an increased risk of cardiovascular events more than ten years after treatment [6,7,13].

The current study in long-term female survivors of cisplatin-based chemotherapy showed hypercholesterolaemia and microalbuminuria in 62% and 24% of patients, respectively. Increased urinary loss of albumin can be viewed as an important sign of generalised endothelial damage. Compared with the female background population, the prevalence of microalbuminuria in cancer survivors was significantly higher, which is an important finding in these young patients, since microalbuminuria is a predictor of cardiovascular events [11]. Compared with male germ cell cancer patients, treated with a similar chemotherapeutic regimen, the prevalence of microalbuminuria after long-term follow-up is comparable [6]. Although a direct comparison has not been made, cardiovascular risk factors are equally or somewhat less pronounced in ovarian germ cell survivors compared with testicular cancer survivors [6,7,13,14]. However, follow-up is too short and the number of female patients too small to conclude that female cancer survivors have a greater risk of cardiac events, as observed in male testicular cancer survivors [6,13].

The development of a metabolic syndrome-like state has been suggested in long-term testicular cancer survivors [15,16]. In the current study, 24% of patients were found to be overweight, while an increased insulin-to-glucose ratio and hypertension were both found in 14% of the patients.

The pathogenesis of cardiovascular risk factors in cancer survivors is still not clear. Hypomagnesaemia, due to renal tubular damage, is a common acute side-effect of cisplatin [17]. Low serum magnesium levels have also been found in 20% of cisplatin-treated testicular cancer patients after a median follow-up of 58 months [14]. Furthermore, testicular cancer patients treated with both surgery and chemotherapy have been reported to have lower levels of serum magnesium than testicular cancer patients treated with surgery only five or more years after therapy, although serum magnesium levels were still within the normal range [18]. Magnesium has been suggested to be involved in the regulation of insulin sensitivity, lipid metabolism, and vascular tone [19,20]. In the present study, a decreased serum magnesium was present in 19% of patients and serum magnesium correlated negatively with the insulin-to-glucose ratio. Therefore, magnesium homeostasis may play a role in the development of a metabolic syndrome in female survivors after cisplatin-based chemotherapy.

Platinum can be detected in small amounts in serum and urine more than ten years after cisplatin therapy. Since cardiovascular risk factors and disease develop gradually over a period of more than 10 years [6], these complications may be related to this prolonged retention of platinum in the body. In this small group of female patients cured by cisplatin-based chemotherapy for up to 21 years, we have measured serum platinum levels with a sensitive assay. In all patients, serum platinum levels were above the lower limit of detection. Serum platinum levels correlated with both the duration of follow-up and renal function. These data indicate that patients who have received a cumulative cisplatin dose of 400 mg/m^2 may be exposed to platinum for over 20 years. Whether chronic circulating platinum in these women has direct toxic or mutagenic effects, which may induce late toxicity or secondary malignancies, is unknown. However, direct contact between platinum and endothelial cells for a long time may induce untoward effects.

Previous studies in women receiving cisplatin-based chemotherapy have demonstrated that, although ovarian dysfunction or failure is a risk of platinum-based chemotherapy, most women will resume normal ovarian function and be able to conceive healthy children [21,22]. Ten women in the present study used oestrogen replacement therapy, while eight patients used oral contraceptives. Oestrogens have been described to have beneficial effects on lipid levels, fibrinolytic capacity, and vascular tone in observational studies [23,24], while adverse effects have been reported on the occurrence of microalbuminuria [25]. Therefore, the findings of the present study may have been influenced by most of the patients taking oestrogen supplementation.

The current data show that, just as in male patients treated with cisplatin-based chemotherapy, female patients are likely to develop cardiovascular risk factors and signs of vascular damage at a young age. With an excellent prognosis once patients have reached a durable complete remission, development of cardiovascular risk factors is an important issue. More research on intervention strategies aimed at the elimination of risk factors like hypertension and hypercholesterolaemia is needed for these cancer survivors.

5. Conflict of Interest Statement

No conflicts of interest

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