

Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer

D. Strumberg*, S. Brüggel, M. W. Korn, S. Koeppen¹, J. Ranft², G. Scheiber³, C. Reiners^{4†}, C. Möckel⁵, S. Seeber & M. E. Scheulen

Department of Internal Medicine (Cancer Research), West German Cancer Center, ¹Department of Neurology, ²Department of Angiology, ³Department of Anesthesiology, ⁴Clinic for Nuclear Medicine and ⁵Department of Otorhinolaryngology, University of Essen, Essen, Germany

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Background: Because of the increasing number of long-term survivors of metastatic testicular germ-cell cancer, a general concern has been secondary morbidities, especially cardiovascular risk factors.

Patients and methods: Thirty-two patients treated with cisplatin- and doxorubicin-containing chemotherapy ≥ 13 years before the time of analyses were evaluated for neuro-, oto-, pulmonary-, vascular- and gonadal toxicity including evaluation of myocardial damage and cardiovascular risk factors and analysis of microcirculation.

Results: Thirty percent of the patients showed abnormal left ventricle function. Elevated follicle stimulating hormone (FSH) and luteinising hormone (LH) levels in 75% of patients were often associated with low testosterone levels. Elevated total cholesterol levels were found in 82% and higher triglyceride levels in 44% of patients, most of them were overweight. About 25% of the patients developed diastolic arterial hypertension after chemotherapy.

Reduced hearing was confirmed in 23% of patients, especially at frequencies higher than 3000 Hz. Moreover, 53% of patients presented transient evoked otoacoustic emissions.

In 38% of patients non-symptomatic neuropathy was detected, in 28% symptomatic neuropathy, and in 6% disabling polyneuropathy. In 80% of patients with neuropathic symptoms additional morphological and functional abnormalities were found by nailfold capillary videomicroscopy, compared to only 57% of the patients without neuropathic symptoms.

Conclusions: Patients cured by cisplatin-based chemotherapy for metastatic testicular cancer have to be cognizant of their unfavorable cardiovascular risk profile, that might be a greater risk than developing a relapse or second malignancy.

Key words: cardiovascular risk, chemotherapy, cisplatin, long-term toxicity, testicular cancer

Introduction

Testicular cancer is the most common cancer disease among 20–35-year-olds, with incidence rates still on the increase [1]. Although some patients can be cured by orchidectomy alone or orchidectomy followed by retroperitoneal lymph node dissection, approximately 50–70% of patients with non-seminomatous testicular tumours need systemic treatment [2–5]. The prognosis of advanced testicular cancer has improved considerably in the past 25 years, hence approximately 70–80% of patients with metastatic disease will

achieve a durable complete remission after three to four cycles of a combination therapy with cisplatin (P), etoposide (E), and bleomycin (B) followed by secondary surgery [6].

The improved prognosis of testicular germ-cell cancer has brought the long-term toxicity of the treatment and life-quality after treatment into focus. Especially in patients with good-risk testicular cancer, the development of new treatment strategies has focused on reducing treatment toxicity while maintaining efficacy.

On the other hand, aggressive high-dose chemotherapy regimens are becoming increasingly used in poor-risk patients [7]. Hence, although supportive measures may control the acute toxicities of chemotherapy, the danger of potential long-term alterations remains or might even increase. Thus, a decreased quality of life, increased risk for secondary morbidity, and the use of economic resources to treat late sequelae

*Correspondence to: Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen, Hufelandstraße 55, 45122 Essen. Tel: +49-201-723-2027; Fax: +49-201-723-5988; E-mail: dirk.strumberg@uni-essen.de

†Present address: Clinic for Nuclear Medicine, University of Würzburg, Germany.

might be avoided by a reduction of therapy-induced late toxicity.

Numerous clinical studies on long-term toxicity after treatment for testicular cancer have been published. However, late effects of treatment may be underestimated in many cases, for many studies focused on a particular class of late toxicity, such as hormonal alterations, cardiovascular morbidity and secondary malignancies. Furthermore, refined methods may detect long-term effects in view of improved sensitivity.

This study evaluated the extent and reversibility of long-term toxicity after chemotherapy treatment in long-term survivors of testicular germ-cell cancer, including myocardial perfusion scintigraphy, *in vivo* capillary videomicroscopy of post capillary vessels and transient evoked otoacoustic emission screening procedures. In addition, the influence of the type and dose of therapy used and of patient characteristics on the frequency of late toxicity have been assessed. We performed a subtle large-scale examination concerning neuro-, oto-, pulmonary-, vascular-, cardio- and gonadal toxicity including self-reported state of health.

Patients and methods

All 55 long-term survivors (being in complete remission for at least 12 months), out of 143 patients that had been treated for testicular cancer from 1977 to 1981, were invited to be interviewed and examined with regard to the detection of possible late toxicities following chemotherapy. All of these 55 patients were seen during the study period for the investigation of late toxicity and were monitored through the oncological out-patient clinic at Essen University Medical School. Thirty-two out of the 55 patients agreed to participate and gave their written informed consent. The median age at the time of our study was 40 years (range 30 to 59 years) and the median follow-up duration was 15 years (range 13 to 17 years). Further characteristics of the 32 patients (all of them were stage IIIa–c according to the nomenclature recommended by the Workshop for Staging and Treatment of Testicular Cancer [8]) are listed in Table 1. Data on tumour stage, laboratory values and individual treatment variables were extracted from the patients' charts.

For the statistical analysis, patients were stratified into appropriate subgroups of chemotherapy treatment, according to the single or cumulative doses of cytotoxic agents used, use of additional medications and other patient characteristics, e.g. active or former smoking history.

All patients had participated in a study investigating successive alternating chemotherapy in patients with pulmonary metastasis due to non-seminomatous testicular germ-cell cancer [9]. Regimen A contained vinblastine (0.4 mg/kg split into two injections on days 1 and 2) in combination with bleomycin [30 units given daily by continuous i.v. infusion over 24 h for 5 consecutive days (days 1–5)], q21days. Regimen B contained adriamycin (60 mg/m² i.v. on day 1) in combination with cisplatin (20 mg/m²/day for 5 consecutive days (days 1–5), q21days. Patients were randomly assigned to either schedule ABBAB or BBAABB. In case of no response or relapse, patients received a salvage therapy containing ifosfamide (40 mg/kg i.v. daily for 5 consecutive days) in combination with etoposide (120 mg/m² orally daily for 5 consecutive days) [9]. The cumulated doses of applied cytotoxic agents are shown in Table 1.

On the study day, blood samples were taken, after a rest period of at least 15 min, at a standardized time to gain comparable interindividual

Table 1. Patient characteristics

Number of patients	32
Age at time of chemotherapy, years	
Median	25
Range	17–42
Duration of follow-up, years	
Median	15
Range	13–17
Treatment	
Cumulated dose of cytotoxic agents (mg/m ²)	median (range)
Cisplatin	407 (45–1200)
Doxorubicin	227 (58–480)
Bleomycin	296 (74–457)
Vinblastine	59 (12–245)
Etoposide	443 (116–1756)
Ifosfamide	16 200 (3100–59 500)
Surgery (retroperitoneal lymphadenectomy) after chemotherapy	24/32 patients
Radiation after chemotherapy	8/32 patients

values of circadian fluctuating sex hormones. All blood samples were analyzed according to laboratory standards at Essen University Medical School and standard normal ranges were used. Hepatic and renal function, plasma electrophoresis, electrolytes including magnesium and phosphate, lactate dehydrogenase, as well as total serum cholesterol, HDL cholesterol and low-density lipoprotein (LDL), triglycerides, apolipoprotein A1 and a complete blood cell count were determined. Cut-off points for lipid levels were used as recommended by the American National Education Program [10]. In addition, the following serum hormone levels were quantitatively determined using commercially available kits: follicle-stimulating hormone (FSH), luteinizing hormone (LH) (fluoroimmunoassay), testosterone, human β -choriogonadotropin and α -fetoprotein (radioimmunoassay).

The body mass index, defined as body weight (kg) divided by height squared (m²), was used as a measure of corpulence [11].

A thorough medical history of all 32 patients was obtained. Patients were interviewed based on the standardized questionnaire SCL-90-R [12] that is characterized by 90 symptom-oriented questions including such that were related to main organ functions (heart, lung, kidney, etc.). Another questionnaire [13] focussed on symptoms related to cancer disease and anticancer chemotherapy, their influence on social behaviour, anxiety concerning tumour-relapse as well as comfort with the present life situation. Patients were asked about smoking and drinking habits, exposure to noise, possible toxins at work, and regular use of medication.

All patients received a full physical examination and a number of special investigations of organ-specific long-term toxicity, as detailed below.

Pulmonary toxicity

Lung function was tested by measurements of total lung capacity (TLC), vital capacity (VC), forced expiratory volume in one second (FEV1), and diffusion capacity for carbon monoxide (Tlco). The diffusion capacity for carbon monoxide was assessed by the single breath technique as

described [14, 15], corrected for abnormal values of serum haemoglobin [16].

Cardiotoxicity

Patients underwent an exercise ECG using a bicycle ergometer according to a standard protocol to evaluate the existence of silent myocardial ischemia [17]. Since all patients received adriamycin, we performed further evaluation of possible long-term cardiotoxicity by standard stress and rest myocardial perfusion scintigraphy using ^{99m}Tc -Ery i.v. [18]

Neurotoxicity

Patients underwent a standardized examination including assessment of vibratory (VDT) and cooling (CDT) detection thresholds. The neuropathy symptom score (NSS) according to Dyck et al. [19] was used for standardized quantification neuropathy-associated symptoms: grade I, non-symptomatic neuropathy; grade II, symptomatic neuropathy; grade III, disabling polyneuropathy.

Ototoxicity

Pure-tone audiometry was performed using a Beomat 500 audiometer (Ollmann, Germany). Air and bone conduction thresholds were determined at 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 kHz. The extent of threshold reduction necessary to be classified as significant hearing loss was defined to be at least 10 dB at two or more frequencies. A potentially P-reducing hearing loss was assumed if significant unilateral or bilateral hearing loss increased toward higher frequencies. Since detection of transient evoked otoacoustic emissions is a sensitive, objective method for detecting cochlear damage in cisplatin-treated patients and probably more reliable than pure-tone audiometry or evoked acoustic potentials [20], we also analyzed transient evoked otoacoustic emissions in the patients of our study group as previously described [21].

Vascular toxicity

Digital blood pressure measurements were performed using a continuous-wave Doppler velocity meter at all digital palmar arteries. Measurements were repeated directly and 1 min after exposure of both hands to cold water. The results of technical investigations and the clinical findings were evaluated separately by independent investigators. Only gross amplitude pulse curve reduction ≥ 30 mmHg compared to the blood pressure before cold provocation, as well as amplitude pulse curve reduction until 0–10 mmHg, in addition to a history of classical finger discoloration accompanied by dysaesthesia were the mandatory criteria for the diagnosis of Raynaud's phenomenon [22].

In vivo capillary videomicroscopy is one of the few noninvasive and clinically useful direct methods for evaluating the microcirculation of normal and ischaemic areas. Nailfold capillary abnormalities in the patients of our study group were analyzed with the capillary microscope GLK 154 Microscan under immersion oil at magnifications of $\times 60$ and $\times 400$ according to Ranft and Heidrich [23].

Statistics

Statistical analyses were performed using SPSS (Chicago, IL) software. Mean or median values of different groups or subgroups were compared with an unpaired Student's *t*-test or Mann-Whitney *U*-test when indicated. Categorical variables were compared using the χ^2 test. Pearson's correlation coefficient and the Spearman rank-sum tests were applied when indicated. Multiple-linear regression analysis was performed to

evaluate the effect of different cumulative cytotoxic dosages or cytotoxic administration on a number of organ-specific parameters with adjustment for potential confounding factors. All tests were two-tailed and significance was accepted at the $P < 0.05$ level.

Results

Cardiotoxicity

One patient (3%) with a positive smoking history suffered a myocardial infarction 11 years after chemotherapy at the age of 46 years. None of the other 31 patients reported cardiac events during follow-up after completion of chemotherapy. Exercise ECG did not indicate the presence of myocardial ischaemia in any patient. One patient out of 32 (3%) showed supraventricular arrhythmia. Additional investigation of 30 patients by standard stress and rest myocardial perfusion scintigraphy using ^{99m}Tc -Ery confirmed a regular systolic left ventricular function in 21 patients (70%) [ejection fraction (EF) $\geq 50\%$; increase of EF under stress $\geq 5\%$ compared with EF at rest]. All patients received doxorubicin, which is no longer used as standard therapy in this setting. The cumulative dose of doxorubicin in these patients was 222 mg/m² (median, range 0–480 mg/m²). However, nine out of 30 patients (30%) showed pathological findings: in six of these patients the EF was inadequate under stress conditions and in three patients the EF at rest was $< 50\%$. The cumulative dose of doxorubicin in the nine patients with abnormal results was 207 mg/m² (median, range 58–280 mg/m²); hence, presenting no correlation between the results of myocardial perfusion scintigraphy and cumulative doses of doxorubicin.

Ototoxicity

Thirty patients were examined for ototoxicity. Based on self-estimation of symptoms, 20 patients (63%) reported no experience of ototoxic symptoms, neither before nor after chemotherapy. Ten patients (31%) noted hearing impairment since chemotherapy, but none of these patients required a hearing aid as yet. According to the medical history of these 10 patients with clinical hearing loss, one patient suffered from diabetes mellitus, four patients had previous, chronic noise exposure without adequate protection, and two patients reported a history of otitis media. In addition, 10 patients (31%) noted periodic tinnitus, six of those in combination with hearing impairment.

Pure-tone audiometry confirmed no audiometric changes in nine out of 30 patients (30%). In seven patients (23%), hearing was unilaterally reduced by 5–35%, especially at higher frequencies (starting at 3000 Hz). In six of these seven patients audiometric changes matched with self-reported clinical hearing loss. In 14 out of 30 patients (47%) pure-tone audiometry revealed a bilateral hearing reduction of 5–45%, again predominantly at higher frequencies. Six of these 14 patients experienced either clinical hearing loss or tinnitus, or both, and three of them had a history of chronic noise exposure. In

our study group, we could not confirm a significant correlation between hearing loss and previous cumulative dose of cisplatin during chemotherapy, since cumulative doses of cisplatin were ≥ 400 mg/m² in 10/14 (71%) and < 400 mg/m² in 11/16 patients (69%) exhibiting hearing loss by pure-tone audiometry. Although four out of five patients with previous noise exposure compared to six out of 25 patients (24%) without, complained of hearing impairment, no significant correlation between noise exposure and hearing loss could be demonstrated in our study group.

Because pure-tone audiometry is subject to a patient's compliance, we also utilized transient evoked otoacoustic emissions for non-invasive evaluation of otoacoustic emissions that have been evaluated as a means of monitoring cochlear function in patients receiving cisplatin. In previous studies, evaluation of transient evoked otoacoustic emissions was shown to be a sensitive method for detecting ototoxicity in cisplatin-treated patients and probably more reliable than pure-tone audiometry or evoked acoustic potentials [20]. However, other studies were different in that the measurable changes in transient evoked otoacoustic emissions occurred later than changes in the pure-tone audiometry for these patients [24].

In our study, 16 out of 30 patients (53%) presented transient evoked otoacoustic emissions (four patients bilateral, 12 patients unilateral). Only three patients out of those with positive transient evoked otoacoustic emissions, complained of hearing reduction with/without tinnitus. However, in 14 out of 30 patients (47%) no transient evoked otoacoustic emissions were detectable. This in particular is interesting since nine of these 14 patients showed significant hearing loss by pure-tone audiometry, either unilateral (two patients) or bilateral (seven patients).

Taken together, in our study 10 out of 30 patients (33%) complained of clinical hearing reduction. In 21 patients (70%) hearing loss was detectable by pure-tone audiometry without significant correlation to either cumulative dose of cisplatin or previous noise exposure. Positive transient evoked otoacoustic emissions were detectable in 16 patients that did not match with hearing loss by pure-tone audiometry.

Gonadal toxicity and fertility

Elevations of FSH (FSH > 11 mU/ml) were observed in 24 out of 32 patients (75%). Fifteen of these (47%) had concomitantly elevated LH levels (LH > 5.8 mU/ml), four (12%) of which were accompanied by low testosterone levels (testosterone < 2.5 ng/ml). Only two of these four patients had one remaining testicle, since the other two patients had secondary testicular cancer in the remaining testicle and were on hormone supplementation.

These results indicate that almost half of the examined testicular cancer patients treated with chemotherapy will develop compensated (35%) or even decompensated (12%) Leydig cell insufficiency. The degree of FSH elevation corre-

lated with the cumulative doses of cisplatin ($P = 0.001$) in contrast to the degree of LH elevation.

After chemotherapy, 13 out of 32 patients (41%), who wanted pregnancy, reported a history of infertility, defined as more than 2 years' attempt by the couple to achieve pregnancy without success. Nine of these had previous retroperitoneal lymphadenectomy due to residual testicular cancer, five of those with concomitantly FSH elevation. However, six out of 32 patients (19%) reported the birth of healthy children after chemotherapy, four of these had previous retroperitoneal lymphadenectomy and five showed elevated FSH levels with or without concomitant elevation of LH levels, two patients even had FSH levels > 20 mU/ml. A significant correlation between previous retroperitoneal lymphadenectomy and/or elevated FSH/LH levels, respectively, with clinical infertility could not be detected, although six out of 24 patients (25%) with previous retroperitoneal lymphadenectomy have since complained of dry ejaculation.

Cardiovascular risk factors

In addition to the changes in sex hormones as potential factors of influence on cardiovascular risk [16 patients (50%) showed testosterone-levels < 4 ng/ml], elevated cholesterol levels were found in a proportion of patients which were higher than expected in comparison with standard age-matched control groups [25]. Twenty-five out of 31 analyzed patients (81%) had total serum cholesterol levels > 200 mg/dl after chemotherapy in contrast to total serum cholesterol levels that had been in the normal range before chemotherapy in the same patients. In nine patients (36%) elevation of total serum cholesterol was accompanied by sonographic features of steatosis hepatis. A significant correlation between total serum cholesterol and cumulative doses of cisplatin could not be demonstrated in our patients. Furthermore, in 12 out of 31 patients (44%), we found elevated levels of triglycerides (> 200 mg/dl), two of these even with levels > 400 mg/dl. Apolipoprotein A1 levels were elevated in one patient and levels for HDL-cholesterol were < 30 mg/dl in four patients (15%).

Obesity was assessed in 31 patients by calculation of the body mass index. Based on a cut-off value ≥ 25 , 15 patients (48%) were considered overweight, 13 of these (87%) in combination with elevated total serum cholesterol levels and seven patients presented a combination of body mass index ≥ 25 , cholesterol elevation and smoking history.

Examination of arterial blood pressure, according to the Riva Rocci (RR) method, showed development of diastolic arterial hypertension after chemotherapy in eight out of 32 patients (25%) (defined as diastolic blood pressure ≥ 95 mm Hg) compared with pretreatment measurements of blood pressure, while systolic pressure was not altered. Furthermore, six of these patients had a smoking history, four had a body mass index > 25 and three showed an additional elevation of total serum cholesterol.

A positive smoking history was reported in 18 out of 32 patients (56%). Apart from myocardial infarction in one patient, the other patients of our study group did not report episodes of angina and none received regular cardiac medication. There were no cerebrovascular incidents in our study group.

Taken together, approximately half of the patients in our study group presented an unfavorable cardiovascular risk profile with a significantly increased risk for occurrence of cardiovascular events.

Vascular toxicity

Eleven out of 32 patients (35%) experienced symptoms of a classic Raynaud's phenomenon after chemotherapy, yet with varying intensity and frequency of attacks. However, two patients judged the intensity as severe, with an impact on their daily life. Five of these symptomatic patients showed morphological abnormalities in nailfold capillary videomicroscopy.

Digital Doppler flow measurements showed a reduction in blood pressure ≥ 30 mmHg compared with the pressure before cold provocation in 20 out of 26 patients (77%). Furthermore, the cumulative dose of bleomycin was positively correlated to the occurrence of Raynaud's phenomenon in these patients ($P < 0.05$). However, none of the patients presented pulse curve reduction until 0–10 mmHg. It is noteworthy that in six patients (23%), digital blood pressure before cold provocation was reduced ≥ 30 mmHg, compared with the systemic blood pressure in these patients.

Nailfold capillary videomicroscopy was performed in 22 patients. Regarding morphology, in 20 patients (90%) one or more remarkable findings were determined. In 11 patients (50%) the capillary density was reduced (< 7 capillaries/mm² nailfold), in eight patients (36%) the apical limb width was abnormal and 13 patients (59%) presented capillary tortuosities. Moreover, disordered capillary blood flow was detected in six patients (27%). However, the cumulative dose of bleomycin was neither correlated with morphological abnormalities nor with reduced capillary blood flow in our study group.

Neurotoxicity

Sixteen out of 32 patients (50%) did not report any neuropathic symptoms. The 16 symptomatic patients reported persisting peripheral neuropathy (predominantly typical paresthesias) since chemotherapy. The onset of symptoms varied considerably among the patients, ranging from the first course of chemotherapy until months after the end of treatment. However, none of the patients with remaining complaints reported severe interference with their daily activities or work. Despite the fact that 13 out of 16 symptomatic patients received cumulative doses of cisplatin of more than 400 mg/m², there was no significant correlation between cumulative doses of cisplatin and neurotoxicity according to the neuropathy symptom score

(NSS) [19] that was used for standardized quantification neuropathy-associated symptoms. Twenty-three out of 32 patients examined (72%) had neuropathic symptoms: 12 (38%) with non-symptomatic neuropathy (NSS grade I), nine (28%) with symptomatic neuropathy (NSS grade II) and two (6%) with symptoms of disabling polyneuropathy (NSS grade III).

Fifteen out of 23 patients (65%) with neuropathic symptoms were further analyzed by nailfold capillary videomicroscopy. In 12 of these patients (80%) morphological and functional abnormalities were found. In contrast, only four out of seven patients (57%) without neuropathic symptoms had abnormalities.

Pulmonary toxicity

Thirty patients were assessed for pulmonary function, 19 of these (63%) reported active smoking or a smoking history. None of the 30 patients reported symptoms of respiratory dysfunction.

Pulmonary toxicity was not detectable in 11 patients (37%) without a smoking history. Lung function tests were abnormal in 13 patients (43%), all of them active smokers or patients with a smoking history. Obstructive disease was found in five patients (17%), whereas restrictive defects were demonstrated in six patients (20%). Results in seven patients (23%) indicated emphysema of the lung, two of these had additional symptoms of obstructive disease. The cumulative dose of bleomycin was 268 mg/m² (median, range 74–457 mg/m²). Evaluation of lung diffusion capacity did not show abnormalities in our study group.

Secondary malignancies

To the time of the present study, neither clinical symptoms nor investigation results indicated the presence of secondary malignancies in the 32 patients of our study group. Eight patients received additional radiotherapy after previous chemotherapy. Two patients reported contralateral secondary testicular cancer, that was treated by orchidectomy and subsequent radiotherapy. Other secondary malignancies, such as solid tumours or leukaemia, were not reported.

Self-reported state of health

The 32 men comprising our study group reported physical and social well-being. All but three men were employed in a wide range of different jobs and all men denied any limitations in their social or working life related to the previous cancer disease or its treatment. Although various clinical symptoms related to long-term toxicity after chemotherapy treatment were reported (e.g. peripheral neuropathy, Raynaud's phenomenon, hearing reduction), patients became accustomed to their symptoms since chemotherapy. In this way it is noteworthy that none of the patients had been consulting a doctor for their symptoms before this study.

Discussion

Because of the increasing number of long-term survivors of metastatic testicular germ-cell cancer treated with cisplatin-containing chemotherapy, a general concern has been that chemotherapy-induced side-effects could increase the age-related risk of different secondary morbidities. Especially the impact of an increased incidence of cardiovascular risk factors has become a matter of great concern.

Although the total number of patients in this study is limited and direct comparisons with the local normal population were not made, our findings confirm previous studies suggesting an increased occurrence of cardiovascular risk factors in patients cured by chemotherapy from disseminated testicular cancer [26–30]. Hence, one cardiac event occurred 11 years after chemotherapy in our study group. Moreover, nine out of 30 patients (30%) showed abnormal function of the left ventricle by myocardial perfusion scintigraphy, suggesting early-stage cardiac dysfunction. These observations are in agreement with recent investigations using echocardiograms, showing that 33% of the patients treated by chemotherapy without anthracyclines have abnormal function of the left ventricle [26]. According to our study, the increase in risk factors persists up to 17 years after chemotherapy. However, the reason why these patients develop this unfavorable cardiovascular risk profile is still unknown. The chemotherapy administered, especially the cumulative doses of doxorubicin and cisplatin, were not considered to be an important causal factor in our study, which is consistent with previous investigations [26]. However, secondary hormonal and metabolic changes were observed in our patients that may play a role in the development of cardiovascular morbidity [28]. Elevated FSH and LH levels were found in the majority of patients (75%), indicating persisting Leydig cell dysfunction in a large portion of patients associated with low testosterone levels. Moreover, our study group presented elevated total cholesterol levels (82% of patients) and higher triglyceride levels (44% of patients) than would be expected in an age-matched control group [25]. In addition, about half of our patients were overweight, most of them in combination with elevation of total cholesterol levels. Beside metabolic abnormalities, about 25% of our patients developed diastolic arterial hypertension after chemotherapy. The role of small-vessel abnormalities as a risk factor for cardiovascular disease is not clear. Besides abnormal digital Doppler flow measurements, we found remarkable morphological alterations by nailfold capillary videomicroscopy in the vast majority of our patients. Although the cause–effect relationship between bleomycin and Raynaud’s phenomenon is well established [27, 31], the cumulative dose of bleomycin was neither correlated with morphological abnormalities nor with reduced capillary blood flow in our study group.

All patients in our study were orchidectomised prior to chemotherapy, most of them had resection of a residual tumour after chemotherapy and eight had additional radio-

therapy. All these treatment modalities may contribute to the effects on gonadal toxicity and fertility. The effects of chemotherapy regimens, including cisplatin, on testicular function have been shown to be dose-dependent [28, 32] [this study]. Another frequent reason for impaired fertility is previous retroperitoneal lymphadenectomy due to a residual tumour, because alteration of thoracolumbal sympathetic nerve function often results in retrograde, dry ejaculation. A modified retroperitoneal lymphadenectomy that preserves sympathetic nerve function was shown to improve the rate of antegrade ejaculation without an impact on the surgical result [33].

It has previously been shown that cisplatin and vinblastine treatment cause a dose-dependent sensory type of peripheral neuropathy in the majority of patients [27, 31, 34–39]. However, the relationship between drug doses and neurotoxicity has been discussed controversially [40, 41]. Previous studies reported up to 76% neurophysiological abnormalities after chemotherapy for testicular cancer [39]. In our study, 50% of the patients reported typical paresthesias as symptoms of persisting peripheral neuropathy since chemotherapy. It is as yet unclear whether cisplatin-induced peripheral neuropathy may also indirectly contribute to the observed abnormalities in microcirculation in 80% of our patients with neuropathic symptoms.

The incidence of ototoxicity, similar to that of neurotoxicity, varies considerably according to the diagnostic methods used [42–46]. Thirty-one percent of our patients, comparable to the reported frequencies of between 11% and 33%, had symptomatic ototoxicity [27, 40, 47]. Noise exposure seems to be especially related to the development of ototoxicity. Besides pure-tone audiometry, transient evoked otoacoustic emissions have been evaluated as a means of monitoring cochlear function in patients receiving cisplatin and carboplatin. It has been suggested that detection of transient evoked otoacoustic emissions is not only a sensitive method for detecting ototoxicity in cisplatin-treated patients but also more reliable than pure-tone audiometry [20]. However, other reports indicate that measurable changes in transient evoked otoacoustic emissions occurred later than changes in the pure tone audiogram for the cisplatin group [24]. In our study, 53% of the patients presented transient evoked otoacoustic emissions, but only 10% out of these complained of hearing reduction. In contrast, in 14 out of 30 patients (47%), no transient evoked otoacoustic emissions were detectable, but in nine of these 14 patients (64%), a significant hearing loss was shown. Hence, although not dependent on patients’ compliance, transient evoked otoacoustic emissions did not demonstrate diagnostic advantage in our study with regard to early detection of cisplatin-induced ototoxicity.

Two out of 32 patients (6%), comparable to the reported frequencies of between 3% and 5%, reported contralateral secondary testicular cancer resulting from contralateral carcinoma *in situ*, already present at the time of diagnosis of the first tumour, which is considered a biological association. Therapy-related malignancies, such as solid tumours or

leukaemia, did not occur in our study group. A number of investigations on therapy-related malignancies following treatment of germ-cell cancer have been reported [48–50]. Therapy related solid tumours are associated mainly with the use of radiation therapy, with an increased risk of about 2- to 3-fold compared with the general population [48]. However, modern radiation techniques are likely to lower the expected therapy-related tumour rate substantially. Therapy-related leukaemias are associated predominantly with chemotherapy, particularly with the use of alkylating agents and topoisomerase-II inhibitors, such as etoposide [49, 50]. According to recent studies, the cumulative incidence in general is low with 0.5% and 2% at 5 years of follow-up for patients receiving etoposide at cumulative doses <2 g/m² and >2 g/m², respectively [48]. In our study group none of the patients received more than 2 g/m² cumulative dose of etoposide.

In conclusion, our study demonstrates that patients cured by cisplatin-based combination chemotherapy for metastatic testicular germ-cell cancer generally are physically well and live a normal social life. Thus, it confirms previous clinical examinations [27, 31, 32]. Nonetheless, patients have to be cognizant of their unfavorable cardiovascular risk profile. Therefore, the development of cardiovascular disease might be a greater risk to these patients than developing a relapse or a second malignancy. This aspect has particular consequences concerning, for example, the control of body weight, regulation of hypertension and cholesterol levels, as well as the prevention of further risk factors such as smoking.

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