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Secondary Raynaud's Phenomenon and Other Late Vascular Complications Following Chemotherapy for Testicular Cancer

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182 patients treated with cisplatin-based chemotherapy for testicular cancer at Hannover University Medical School who were in complete remission (CR) for more than 1 year after therapy were randomly selected for the evaluation of late vascular toxicity. 90 patients with a mean age of 28 years (19–53) and a median follow-up of 57.9 months (15–159) participated in this examination. Patients were examined clinically and digital photoelectric pulse plethysmography (PP) and Doppler-flow of the digital arteries after cold exposure were performed. Thirty seven per cent of patients developed symptoms of Raynaud's phenomenon (RP) after chemotherapy, which were transient in 7%. PP proved to be highly diagnostic for RP with a sensitivity of 95% and a specificity of 100%. As significant risk factors for the development of RP, the cumulative dose of bleomycin ($P < 0.05$) and the use of bleomycin in combination with vinblastine (PVB-regimen) instead of etoposide (PEB-regimen) ($P < 0.01$) were found. A trend for an increased frequency of RP was observed in patients who received bleomycin as a bolus instead of continuous infusion. No significant correlation was seen with the cumulative or single doses of cisplatin, etoposide or vinblastine, serum magnesium levels during or after chemotherapy or a history of smoking. RP was not associated with the occurrence of neuro- or ototoxicity. All 7 patients with hypertensive blood pressure before chemotherapy developed RP. Furthermore, the median postchemotherapy diastolic blood pressure had increased by 8 mmHg compared to prechemotherapy values, leading to significant hypertension in 8 patients (>20 mmHg increase). 2 patients developed major vascular events with myocardial infarctions at 4 years and 5 years after chemotherapy, respectively. No cerebral infarction was registered. In summary, RP is the main late vascular toxicity affecting one third of patients after curative chemotherapy for testicular cancer. However, the incidence of RP following PEB-therapy in contrast to PVB-therapy appears to be lower. Major vascular events seem to be rare. The prospective evaluation of late toxicity should be part of current chemotherapy treatment for testicular cancer, and long-term follow-up of surviving patients is recommended.

Key words: testicular cancer, bleomycin, late toxicity, vascular toxicity, chemotherapy, Raynaud's phenomenon, photoelectric plethysmography

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INTRODUCTION

WITH THE introduction of chemotherapy containing vinblastine and bleomycin [1] and later cisplatin [2] (PVB), the chances of cure for patients with metastatic testicular cancer have increased tremendously. Today, approximately 80% of patients with metastatic disease can be cured by three to four cycles of the combination of cisplatin, etoposide and bleomycin (PEB). With the success of cytotoxic treatment, the possible development of long-term side effects in this young patient population has become increasingly important. Most patients currently treated can expect to live another 30–50 years after successful treatment, thus making the impact of possible late toxicity very relevant to the individual. In recent years, several studies have been conducted concerning late toxicities after chemotherapy for testicular cancer such as neurotoxicity, fertility impairment, ototoxicity, renal damage and vascular toxicity [3–13]. Vascular toxicity after treatment for testis cancer was first reported in 1977 by Carol Teutsch in a 17-year-old patient who developed Raynaud's phenomenon (RP) 12 weeks after the start of chemotherapy with vinblastine and bleomycin [14]. After discontinu-

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ation of chemotherapy, the symptoms of RP slowly resolved completely. Consecutive studies have reported varying frequencies of vascular toxicity after chemotherapy for testicular cancer with a range from 1 to 50%. This may be related to the considerable differences in the drug regimens used in these studies (e.g. substitution of etoposide for vinblastine in PVB-therapy), the different dosages and modes of drug application (e.g. bolus versus continuous infusion of bleomycin), the additional medication given as part of the supportive treatment (particularly diuretics, steroids and electrolyte substitution) and to different individual risk factors of the patients treated. Therefore, the comparison of published data appears to be difficult, and data for larger series are mainly available for patients treated with PVB-therapy, but not for PEB-therapy, which is currently considered the standard combination therapy regimen for metastatic germ cell tumours. It was the aim of this study to investigate the frequency of late vascular toxicity in patients successfully treated for testicular cancer by platinum-based combination chemotherapy at Hannover University Medical School between 1976 and 1987. Furthermore, we tried to analyse the impact of different risk factors on the occurrence and the severity of long-term vascular problems in this young patient group.

PATIENTS AND METHODS

Patients

182 randomly selected patients treated for testicular cancer at Hannover University Medical School between 1976 and 1987 were invited to be interviewed and examined concerning the detection of possible late toxicities following chemotherapy. Only patients who had been in complete remission at the time of examination for at least 12 months were included in the analysis. Access to the patients' data had been gained through the routine follow-up programme at the oncological outpatient department. 90 of the 182 (49%) patients responded to the invitation and agreed to participate in a clinical examination and a personal interview. The characteristics of these 90 patients are given in Table 1. The patients' tumour stage, laboratory values before and during chemotherapy, and treatment variables including the regimens used, cumulative drug dosages, modes of application, additional medications (particularly steroids, diuretics, intravenous fluids and electrolyte substitution) were extracted from the patients' charts. The standardised questionnaire contained a large variety of questions about clinical complaints possibly related to chemotherapy-induced late toxicity. With respect to vascular toxicity, emphasis was placed on the symptoms of RP, particularly time of occurrence, severity, duration period, reversibility and on the subjective importance of these complaints (Appendix). In addition, the patient's medical history was evaluated with respect to risk factors for vascular disease.

Table 1. Characteristics of 90 patients treated with chemotherapy for testicular cancer who were evaluated for late vascular toxicity

	Number of patients	(%)
Primary tumour		
Gonadal	81	(90%)
Extragonadal	9	(10%)
Histology		
Seminoma	7	(8%)
Non-seminoma	83	(92%)
Stage (Lugano classification)		
I	9	(10%)
II a/b	19	(21%)
II c/d	10	(11%)
III	52	(57%)
Treatment		
Chemotherapy		
PVB	30	(33%)
PEB	26	(29%)
PEB + Vcr	10	(11%)
PEB + Vbl or PVB + PE	11	(12%)
Other	13	(14%)
Retroperitoneal lymphadenectomy	57	(63%)
Radiotherapy (abdominal)	10	(11%)
Risk factors for vascular disease		
Smoker	38	(42%)
Non-smoker	37	(41%)
Former smoker/occasional smoker	15	(17%)
Overweight	9	(10%)
Diabetes mellitus	2	(2%)
Hypertension	7	(8%)
Prior ischaemic heart disease	1	(1%)
Patients		Range
Mean age at time of chemotherapy (years)	28	19–53
Median duration of complete remission (months)	57.9	15–159

PEB = cisplatin, etoposide, bleomycin; PVB = cisplatin, vinblastine, bleomycin; Vbl = vinblastine, Vcr = vincristine.

Methods

For the clinical evaluation of vascular toxicity, blood pressure at both arms was registered according to the Riva–Rocci method in a sitting position after a 10 min rest period in all patients. To investigate abnormal vasospastic responses to cold provocation, photoelectric plethysmography (PP) was used to record volume pulses of all 10 fingers. Pulse curves were obtained by attaching two photoplethysmographic sensors simultaneously to the fingertips of corresponding fingers of both hands. Volume pulse curves were registered for each pair of corresponding fingers for approximately 10 s. This procedure was followed by digital blood pressure (DF) measurement using a portable continuous-wave Doppler velocity meter to detect the systolic blood pressure at the digital palmar arteries I, III and V. Registration was performed after in- and deflation of a 2.5 cm digital cuff applied to the proximal phalanx of each finger. The first appearance of the Doppler signal after gradual deflation from suprasystolic pressures in each finger was recorded as the respective digital systolic blood pressure. Both investigations were performed before, directly after and 10 min after exposure of both hands to water at a temperature of approximately 10°C. The finding of RP was evaluated separately for each of the methods of investigation ((1) pulse plethysmography, (2) digital blood pressure, (3) history). The registered pulse curves of the PP-investigation were analysed by an independent investigator who was not informed about the patients' symptoms. Only "gross amplitude reduction" with near to nil blood flow or "fragmented down-stroke" plus very low amplitude as typical signs of vasospastic abnormalities after cold provocation [15], when occurring in patients with a normal pulse wave before cold exposure, were classified as positive for RP. Slight decreases or increases of the pulse wave were considered as normal. Registered curves with other than the described abnormalities or disturbance through artefacts were considered not eligible for analysis. For DF

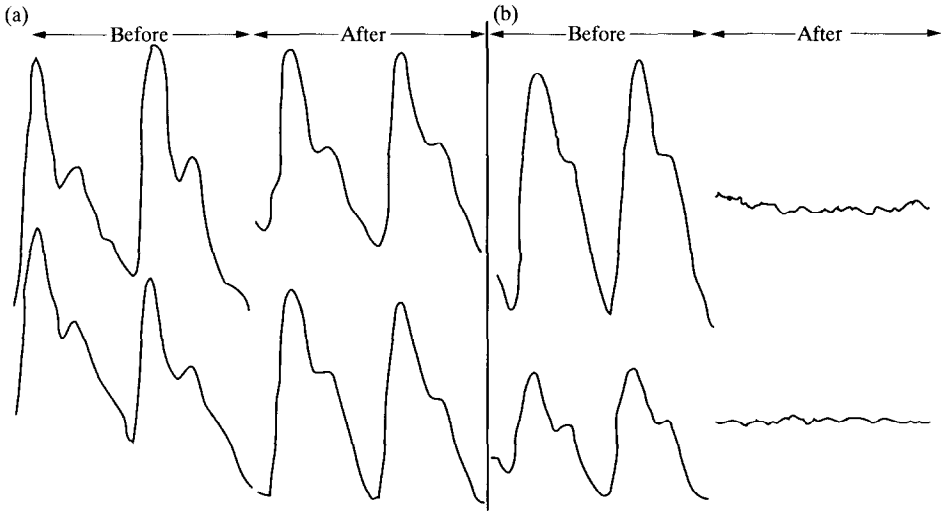

Figure 1. Digital photoelectric plethysmography of the small fingers (Dig. V) before and immediately after cold exposure of both hands. Normal blood flow reaction (a) and near to nil flow (b) after cold exposure. (a) Patient 1, normal blood flow before and after (b) patient 2, normal blood flow before, near to nil blood flow after cold exposition (top: right finger V, bottom: left finger V).

measurements, vasospasm was only diagnosed in those patients without any measurable Doppler signals after cold exposure in more than one finger, because of individually differing time spans between the end of cold provocation and digital blood pressure measurements. In the patients' interview, the mandatory criterion for the diagnosis of RP was a localised discolouration of the fingers accompanied by dysaesthesia after exposure to cold. In addition, the patient's history was evaluated for additional severe vascular problems, such as ischaemic heart disease, hypertension and cerebral vascular accidents. Finally, a serum analysis was performed at the time of our scheduled examination to measure serum concentration of electrolytes including magnesium, creatinine, uric acid, glucose and cholesterol levels, liver enzymes, full blood count, protein electrophoresis and sex hormone status.

RESULTS

Clinical frequency of Raynaud's phenomenon (RP)

33 of 90 eligible patients (37%) reported a history of Raynaud's phenomenon (RP) postchemotherapy. 24 patients (27%) complained of persisting symptoms with only little variation during the course of time. 6 patients (7%) reported experiencing episodes of RP for a mean period of 36 months (range: 3–72 months) after chemotherapy, after which the symptoms had gradually subsided; 3 further patients (3%) mentioned symptoms of decreased intensity, but still experienced RP attacks after exposure to cold. 50 patients (56%) had not experienced symptoms of RP, and in 7 patients (8%) symptoms similar to RP had already been present before chemotherapy or the symptoms described were non-specific and could not be classified. The localisation of the symptoms varied between only two fingers affected up to manifestation of RP in both hands including the wrists and occasionally the feet. Symptoms were bilateral in all patients. The severity of symptoms ranged from tingling of the fingers caused by exposure to cold temperature (26%) to severe pain in the hands when touching cold water in the summer (11%). The majority of patients (63%) found the attacks annoying but tolerable. The individual episodes of RP lasted between several minutes and more than one hour. The onset of symptoms also varied; 2 patients (2%) noticed symptoms of RP during chemotherapy, while most patients developed RP long after the end of therapy, noticing the first symptoms particularly in the first winter after chemotherapy. 99% of the patients experienced their first episode of RP during the first year following chemotherapy.

Photoelectric plethysmography (PP) and digital blood pressure measured by Doppler-flow (DF)

The results of digital blood flow measured by PP (71 patients investigated) before and after cold provocation were normal in 40 patients (56%). 20 patients (28%) had abnormal results showing typical vasospastic pulse curves after cold provocation,

Table 2. Sensitivity and specificity of digital light plethysmography (PP) and digital blood pressure measurement by Doppler-flowmetry (DF) in correlation to a history of clinical symptoms of Raynaud's phenomenon (RP). (Only patients with clearly diagnostic PP-diagrams were noted)

Method	Clinical symptoms	Result of investigation	Validity
PP	21 patients with RP	20 recognised as vasospastic	Sensitivity 95%
PP	39 patients without RP	39 with normal evaluable PP	Specificity 100%
DF	23 patients with RP	20 recognised as vasospastic	Sensitivity 87%
DF	39 patients without RP	36 with normal DF	Specificity 92%

Table 3. Development of secondary Raynaud's phenomenon in relation to chemotherapy

		Raynaud's phenomenon*		
	No. patients	Persistent	Transient	None
No. eligible patients	90	27 (30%)	6 (7%)	50 (56%)
Mean age at time of chemotherapy (years)	28	28	32	28
Median duration of CR (months)	57.9	63.1	78.9	52.3
Chemotherapy regimens				
PVB	30	11 (37%)†	6 (20%)†	11 (37%)†
PEB	26	7 (27%)†	0 (0%)†	19 (73%)†
PEB + Vcr	10	2 (20%)	0 (0%)	7 (70%)
PEB + Vbl or PVB + PE	11	4 (36%)	0 (0%)	6 (55%)
Other	13	3 (23%)	0 (0%)	7 (54%)
No. patients with P containing therapy	86	26 (30%)	6 (7%)	48 (56%)
Median cumulative dose of P (mg/m²)	442	506	330	444
No. patients with B containing therapy	85	27 (32%)‡	6 (7%)‡	47 (55%)‡
Median cumulative dose of B (mg/m²)	164	199	210	145
No. patients with E containing therapy	50	13 (26%)	0 (0%)	32 (64%)
Median cumulative dose of E (mg/m²)	1800	1700	0	2000
No. patients with Vbl containing therapy	46	17 (37%)	6 (13%)	21 (46%)
Median cumulative dose of Vbl (mg/m²)	52	51	51	50
No. patients with Ifo containing therapy	18	2 (11%)	1 (6%)	10 (56%)
Median cumulative dose of Ifo (g/m²)	16	18	21	22
No. patients with Vcr containing therapy	11	3 (27%)	0 (0%)	6 (55%)
Median cumulative dose of Vcr (mg/m²)	6	3	0	8

B = bleomycin; E = etoposide; Ifo = ifosfamide; P = cisplatin; PEB = cisplatin, etoposide, bleomycin; PVB = cisplatin, vinblastine, bleomycin; Vbl = vinblastine, Vcr = vincristine.
* Note that 7 patients were not classified due to non-specific symptoms; † Statistically significant difference ($P < 0.01$); ‡ Statistically significant difference ($P < 0.05$).

and in 11 patients (15%) the diagrams were not clearly diagnostic. A good correlation between the evaluable PP-diagrams (85% of all registered PPs) and clinical symptoms of RP was found: all 20 "vasospastic" diagrams were registered in patients with clinical RP, and only one of the PP examinations of a patient with a history of clinical symptoms of RP failed to show a curve alteration after cold provocation (sensitivity: 95%; specificity: 100%). Even when the clinical inspection of the hands after cold exposure did not detect a typical RP, the abnormal PP correlated well with the reported history. A typical example of abnormal flow during PP investigation in a patient with RP is shown in Figure 1.

The detection of RP through digital blood pressure measurement in our setting proved to be slightly less sensitive and specific compared to PP. Of the 62 patients evaluated by this method, 39 (63%) showed normal digital blood pressure after cold provocation despite three positive clinical histories of RP. In one of these 3 cases, PP had also shown a normal pulse curve

Table 4. Frequency of Raynaud's phenomenon (RP) in testicular cancer depending on the mode of application (continuous infusion versus bolus) and cumulative dose of bleomycin (B)

Regimen	No. patients	Median dose of B	No. patients with RP
All regimens	90	165 mg/m²	33 (37%)
	20	≥165 mg/m²	10 (50%)
	70	<165 mg/m²	23 (33%)
PVB-bolus	16	150 mg/m²	11 (69%)
	10	≥150 mg/m²	8 (80%)
	6	<150 mg/m²	3 (50%)
PVB-continuous infusion	14	255 mg/m²	6 (43%)
	6	≥255 mg/m²	5 (83%)
	8	<255 mg/m²	1 (13%)

and the 2 other cases were not clearly diagnostic by PP. 20 patients (32%) presented without a measurable Doppler signal immediately after cold provocation, a finding typical of RP, however 2 of these patients had never experienced RP, and both PP and the clinical examination showed no pathological findings. In 3 patients (5%), DF measurements were already abnormal prior to cold provocation (individual fingers were without flow signals), correlating with positive RP histories and pathological PP examinations in 2 of the 3 patients. In summary, the sensitivity and specificity of DF measurements were 87% and 92%, respectively. These results are summarised in Table 2.

Raynaud's phenomenon (RP) and prior treatment

Due to the long observation period, different chemotherapy regimens with different doses of cytotoxic agents and different modes of application were used. Treatment regimens were classified into five groups (Table 3). 17 of 30 patients (57%) with RP, transitory or permanent, belonged to the PVB group compared to 9 of 36 cases (25%) in the PEB ± Vincristine (Vcr) group ($P < 0.01$). No significant correlation between the frequency of RP and the number of chemotherapy cycles applied was found, however, the small numbers in each comparable subgroup may be responsible for this result. The total cumulative doses of P, E and vinblastine (Vbl) applied showed no influence on the frequency of development of RP, whereas a significant correlation between the cumulative dose of B and the frequency of RP was observed (Table 3). This trend was observed for each comparable subgroup, but statistically significant results were only gained for the group of patients treated with PVB-chemotherapy, either with bolus (mean cumulative B-dose: 146 mg/m^2 versus 120 mg/m^2) or as continuous infusion of B (mean cumulative B-dose: 298 mg/m^2 versus 226 mg/m^2) (U-test, $P < 0.5$). In all regimens, B and Vbl were given at doses of 15 and 6 mg/m^2 per day, respectively, with a varying number of days per cycle, depending on the treatment regimen. P was given at different single doses ranging from 20 to 40 mg/m^2 per day, and E with single doses between 100 and 170 mg/m^2 per day. No correlation between vascular toxicity and the single doses of E or P was found. Furthermore, the mode of B application seemed to have an influence on the occurrence of RP as shown in Table 4. Patients receiving B as continuous infusion (12–24 h) had an RP incidence of 43% (6/14 patients) in comparison to 69% (11/16 patients) receiving B-bolus therapy (not significant). The incidence of RP in the continuous infusion group was lower despite a considerably higher cumulative dose of B applied to these patients compared to patients from the bolus group (255 mg/m^2 versus 150 mg/m^2, respectively).

A slight protective effect against RP of high dose steroids, applied as part of the anti-emetic therapy, was seen (33% RP with steroids versus 44% RP without, not significant). No influence on vascular toxicity was observed in relation to the type of electrolyte supplementation during chemotherapy, to renal function, to magnesium loss, serum cholesterol levels or obesity of the patients (Table 5). Vascular toxicity was also not correlated to the development of other possibly chemotherapy-related late toxicities, such as oto- or neurotoxicity. Fifty-one per cent of patients without RP showed some degree of persistent neurotoxicity and 27% symptoms of ototoxicity, compared to 45% neuro- and 21% ototoxicity in patients with RP [16, 17]. Smoking was not a significant risk factor for development of RP (42% patients with RP among current smokers versus 32% pts with RP among non-smokers). The two patients with diabetes

Table 5. Development of secondary Raynaud's phenomenon in relation to additional risk factors

		Raynaud's phenomenon*		
		Persistent	Transient	None
All eligible patients	90	27 (30%)	6 (7%)	50 (56%)
Smoking habits (No. of patients)				
smoker (at least 5 years >10 cigarettes/day)	38	13 (34%)	3 (8%)	19 (50%)
former smoker (at least >4 years non-smoker)	15	3 (20%)	2 (13%)	9 (60%)
non-smoker	37	11 (30%)	1 (3%)	22 (60%)
Mean serum magnesium level (mmol/l)				
prior to chemotherapy	0.81	0.81	0.77	0.81
lowest level documented during chemotherapy follow-up	0.69	0.71	0.75	0.67
at time of study	0.81	0.80	0.82	0.80
Mean serum creatinine level (μmol/l)				
prior to chemotherapy	88	88	83	85
highest documented value after chemotherapy	92	89	85	93
at time of study	97	99	93	100
Mean serum cholesterol level (mmol/l)				
at time of study	6.09	5.67	7.03	6.31
Blood pressure (mmHg) (systolic/diastolic)				
before chemotherapy	128/79	129/81	141/88	125/76
at time of study	129/87	131/92	137/87	126/86
Steroids given during chemotherapy (No. of patients)†				
none	16	4 (25%)	3 (19%)	8 (50%)
moderate dose	25	8 (32%)	0 (0%)	16 (64%)
high dose	21	7 (33%)	0 (0%)	14 (67%)

* Note that 7 patients were not classified due to non-specific symptoms; † Data not available for some patients.

Table 6. Chemotherapy-related Raynaud's phenomenon and other vascular toxicities in patients with testicular cancer

Author [Ref.]	No. patients	Chemotherapy regimen	Frequency of vascular toxicity	Comments
Vogelzang (1981) [25]	60	VblB PVB	RP: 21% RP: 41%	clinical examination RP: correlation to smoking
Scheulen (1982) [36]	271	VblB +/− PDox (B-continuous infusion)	RP: 2.6%	clinical examination all patients received steroids correlation to cumulative B-dose
Garnick (1983) [38]	57	PVB	RP: 13%	clinical observation RP completely reversible
Vogelzang (1985) [35]	31	PVB (B-i.v. bolus)	RP: 43% fatal heart attack: 3%	clinical examination RP: correlation to prior hypomagnesaemia no correlation to P dose, or smoking
Fossa (1986) [7]	43	PVB + other	RP: not analysed BP elevated: 2% cardiovascular dis.: 5%	retrospective chart review
Creutzig (1987) [43]	99	PVB + other	RP: 39%	clinical examination RP: correlation to cumulative B-dose
Hansen (1988) [9]	34	PVB	BP elevated: 18%	clinical examination
Roth (1988) [12]	229	PVB +/− Dox	"digital cold sensit.": 50% cardiovascular dis.: 3% (of 147 patients alive)	retrospective chart review RP: no correlation to Vbl-dose or number of chemotherapy courses
Stefenelli (1988) [44]	21	PVB	RP: 33% cardiovascular dis.: 38% (only acute toxicity)	chart review, mail-questionnaire no correlation to smoking or chemotherapy
Hansen (1989) [10]	32	PVB	RP: 44% plus 6% transitory	clinical examination no correlation to mg level, smoking or cumulative B/Vb dose
Moul (1989) [37]	244	not stated	RP: 1% cardiovascular dis.: 1%	retrospective chart review
Aass (1990) [4]	149	PVB +/− (CCNU)	RP: 25%	mail-questionnaire RP: no correlation to smoking
Bissett (1990) [5]	74	PB + Vinca alkaloids	RP: 45% BP elevated: 24% ECG changes: none cardiovascular dis.: 5%	clinical examination RP: no correlation to smoking, cumulative chemotherapy dose or magnesium level after chemotherapy
Boyer (1990) [6]	30	PVB 7 patients other	RP: 27% BP elevated: 13% ECG changes: 10% cardiovascular dis.: 3% ser.chol. elevated: 67%	clinical examination RP: in 3 patients only transitory symptoms
Gietema (1992) [8]	57	P + other	RP: 23% BP elevated: 28% cardiovascular dis.: 2% ser. chol. elevated: 100%	clinical examination
Nichols (1992) [39]	180	P + other	cardiovascular dis: 0%	mail-questionnaire
Schwabe (1992) [13]	21	P + other	RP: 10% BP elevated: 24% ECG changes: 10% ser. chol. elevated: 62%	clinical examination

B, bleomycin; BP, blood pressure; ctx, chemotherapy; dis, disorders; Dox, doxorubicin; P, cisplatin; RP, Raynaud's phenomenon; ser chol, serum cholesterol level; Vbl, vinblastine.

mellitus prior to chemotherapy did not develop RP. Interestingly, all 7 patients with hypertensive blood pressure prior to chemotherapy developed persisting RP.

Other major vascular toxicities

Apart from RP as a manifestation of chemotherapy-induced vascular toxicity, the possibility of cardiovascular toxicity should be mentioned. 2 of 90 patients developed a myocardial infarction: a 45-year-old, heavy smoker without a history of RP or high blood pressure at 4 years after chemotherapy; and a 40-year-old former smoker with symptoms of a typical RP and elevated blood pressure prior to chemotherapy at 5 years after chemotherapy.

Transient ischaemic ECG changes were noticed in 9 patients (10%) during chemotherapy. 7 of these (78%) later developed RP. All patients apart from the two with myocardial infarction remained without clinical episodes of angina, and none received regular cardiac medication. There were no cerebrovascular incidents in our study group.

The mean diastolic arterial blood pressure for all patients significantly increased after chemotherapy (79 versus 87 mmHg), while the systolic pressure was not altered compared to pre-chemotherapy values (128 versus 129 mmHg). The increase of diastolic pressure was equally found in patients from all different chemotherapy treatment groups, but a statistically significant (U-test, $P < 0.05$) higher mean cumulative dose of P was found in the group with increased blood pressure (585 mg/m^2) compared to patients with normal blood pressure (442 mg/m^2).

DISCUSSION

Raynaud first described the typical symptoms now referred to as Raynaud's phenomenon (RP) in 1862 [18]: intermittent spasm of the digital arteries, precipitated by cold or stress, presenting with pallor due to ischaemia, followed by cyanosis and then redness and pain caused by hyperaemia as the circulation restores itself. The pathomechanisms behind the clinical symptoms are still not fully understood. Two entities of RP can be differentiated, either primary (idiopathic) RP, a purely transient cold- or stress-induced constriction of the smooth muscle cells in an otherwise normal artery [19], or secondary RP-like symptoms, associated with systemic disease of various aetiologies, caused by impairment of the digital circulation through additional factors, such as vascular stenoses or altered blood viscosity.

Since first described in 1977 [14], RP is a well recognised complication after chemotherapy for testicular cancer. Although it is considered as a form of secondary RP, reports on morphological changes in the vessel wall remain controversial [20, 21]. Despite clinical evidence supporting bleomycin as the causative agent for this form of vascular toxicity [22, 23], the synergistic action of vinblastine and of other potentiating factors for the development of RP remain controversial [24]. Following the introduction of cisplatin as part of combination chemotherapy for testicular cancer [2], the first large studies of vascular toxicity were reported by Vogelzang in 1981 [25]. He found 37% of 60 patients with a minimum follow-up of 12 months after chemotherapy developed RP. The incidence of RP was higher in patients who had received PVB-therapy (41%), compared to those with vinblastine and bleomycin alone (21%). Symptoms had started at a median of 10 months after chemotherapy. Approximately half of the patients noticed a gradual resolution of their symptoms over time after a median follow-up of 18 months.

In our cohort of 90 patients, 37% had developed RP, which was transient in only 6 patients (7%) and remained persistent in 27 patients (30%) with constant severity; 56% were without any evidence of RP. Although only few patients in our study group reported the classical triad of symptoms, the histories and clinical observations we acknowledged as RP were typical in their relationship to cold and were supported by the pathological results of digital PP and DF measurements after cold exposure. Our results demonstrate high sensitivity (95%) and specificity (100%) for the detection of RP achieved by light plethysmographical registration of digital blood flow before and after a 10 min cold provocation test. The sensitivity of PP was slightly higher than that of DF. The onset of clinical symptoms ranged from during chemotherapy up to 36 months later. All patients had bilateral symptoms and none developed digital ulcerations. The incidence of RP was significantly higher in patients treated with PVB-chemotherapy (57%) compared to those treated with PEB (25%) ($P < 0.01$) Although 63% (17/27 patients) found the RP attacks "annoying" and 11% (3/27 patients) considered them as "severe", most patients were able to change their lifestyle to avoid cold exposure and therefore decrease the frequency of attacks. None of the patients were receiving treatment specifically for RP, although calcium-channel blockers may be of therapeutic value in the amelioration of RP attacks [26].

In 1982, Scheulen and Schmidt reported a considerably lower incidence of 3% RP [27] in a cohort of 271 testicular cancer patients treated with vinblastine and bleomycin (B). Simultaneous application of anti-emetic steroids as a protective factor against vascular toxicity were discussed in this study. In our study, only a slight protective effect of steroids was found with 33% of RP in the high-dose steroid group compared to 44% in patients not receiving steroids. The low incidence reported by Scheulen and associates may, therefore, be related to the use of B as a continuous infusion. Our results demonstrated a lower frequency of RP in patients receiving PVB-chemotherapy with 5–6 days of continuous infusion B (43% with RP) compared to patients treated with B given on three separate days as a bolus injection (69% with RP), despite a higher median cumulative dose of B in the continuous infusion group (255 mg/m^2 versus 150 mg/m^2, respectively). Continuous infusion of B has also been reported to result in less pulmonary toxicity [28, 29], while the antitumour activity of B in testicular cancer, as demonstrated in a xenograft animal model, does not seem to depend on the mode of application [30]. Irrespective of the mode of B administration, the incidence of RP increased significantly with the cumulative dose of B given. The higher incidence of RP in PVB compared to PEB patients argues for an additional toxic effect of vinblastine, but not etoposide. However, this effect was not related to the doses of vinblastine applied.

The pathophysiology of chemotherapy-induced RP still remains unsolved. A relationship between RP and polyneuropathy has been suggested in a Norwegian study [31]. Among 17 PVB-treated patients with RP in our cohort, 8 (47%) showed clinical signs of neuropathy, comparable to the 12 patients (40%) with neuropathy among 30 PVB-treated patients. These findings do not support the hypothesis that nerve damage may result in changes in the arterial vasoconstrictor response [9].

Magnesium wasting, particularly related to subclinical renal damage following cisplatin [32], has also been associated with neurotoxicity [33] or vasospastic disease [34] in some studies. In 1985, Vogelzang [35] showed that the severity of hypomagnesaemia during chemotherapy predisposes to an increased risk of RP, while Hansen [9] found no correlation between RP and hypomagnesaemia. Although most of our patients had transient

hypomagnesaemia during chemotherapy (all had returned to normal levels at our evaluation 5 years after therapy), there was no correlation between the degree of transient hypomagnesaemia and the development of RP, excluding a major influence of magnesium levels on the development of vascular toxicity [5].

Another factor related to vascular disease is smoking, but none of the large studies reviewed in Table 6, except the one by Vogelzang and colleagues [25], have been able to show convincing results regarding the risk of smoking for development of RP. The frequency of smokers with RP in our patients was 48% (16/33) compared to 38% (19/50) in patients without RP. Smokers seemed to be at a slightly higher risk of developing RP than the non-smokers (42% versus 32%). Our cohort may still be too small to demonstrate a significant influence of smoking when taking the large individual differences of sensitivity to nicotine-associated damage into account.

It appears to be an important finding that the mean diastolic arterial blood pressure in our patients increased by 10% after chemotherapy when compared to the baseline level prior to treatment. This elevation is probably not explained by the physiological increase with age since the systolic pressure level remained almost constant. Hansen and associates [9] also reported a significant increase in the diastolic, but not the systolic blood pressure, with 6 patients (18%) developing arterial hypertension after chemotherapy. In our study, the diastolic blood pressure of 8 patients (9%) (age: 36 years (21–51)), with a diastolic blood pressure <80 mmHg prior to chemotherapy, was increased by at least 20 mmHg to >95 mmHg. Other investigators have reported between 13–25% of patients with newly developed hypertension after chemotherapy for testicular cancer among a total of 182 patients in four different studies [5, 6, 8, 13]. None of these investigators found a significant correlation with reduced renal functions or alterations of the renin–angiotensin–aldosterone axis. Bosl [40] showed a significant increase of plasma renin activity and aldosterone after chemotherapy in 79% of patients with testicular cancer, none of these developed hypertension or RP, making this finding difficult to interpret. Following PVB-therapy at Indiana University, U.S.A. [40], treatment-related hypertension was not reported.

In our patients, a connection between RP and hypertension seems to exist. All 7 patients with hypertension prior to chemotherapy experienced transient or persisting RP, and 5 of 8 patients with newly developed arterial hypertension after chemotherapy also developed RP. The pathophysiological explanation may be a similar regulatory mechanism for the different capillary vessels [41, 42], which might also explain the possible association between RP and a decreased pulmonary function after chemotherapy for testicular cancer [27, 43].

Several authors have also compared the frequency of coronary heart disease with secondary RP [44, 45]. In our study group, 7 of 9 (78%) patients with ischaemic ECG alterations during chemotherapy later developed RP. Secondary RP preceding a myocardial infarction has been reported after platinum-based chemotherapy [46]. Among our 90 patients, two men in their 40s developed myocardial infarctions at 4 and 5 years after chemotherapy, respectively. One of these patients presented with RP-like-symptoms before the infarction. However, both patients had additional risk factors for coronary artery disease, such as elevated cholesterol levels, one was a heavy smoker and the other had arterial hypertension. There has been no major cerebral vascular accident in our patients so far. Doll [46] reported 2 young patients with cerebrovascular accidents despite a normal four-vessel cerebral angiography.

Table 6 provides a summary of possible chemotherapy-related vascular toxicities observed in other major studies. In 1992, Gietema [8] and Raghavan [47] reported on risk factors for coronary artery disease, such as hypercholesterolaemia and obesity, in patients treated for testicular cancer. Elevated levels of cholesterol may be explained by endocrinological disturbances resulting from both orchidectomy and chemotherapy. The mean serum cholesterol level in our patients prior to chemotherapy was 4.7 mmol/l compared to 6.1 mmol/l after chemotherapy, with one third of patients presenting clearly abnormal values, only half of which had been elevated prior to chemotherapy. However, there was no correlation between hypercholesterolaemia and the development of RP or the elevation of blood pressure.

In conclusion, RP is the most common vascular toxicity after chemotherapy for testicular cancer, affecting one third of patients. No other risk factors for RP apart from combination chemotherapy of bleomycin with vinblastine, the cumulative dose of bleomycin and possibly the mode of bleomycin application as bolus therapy were identified. PP represents an easily available non-invasive procedure that should be used in combination with a thorough history and clinical examination to confirm the suspected diagnosis of RP during follow-up of testicular cancer patients. The correlation observed between the appearance of RP and hypertension may be based on a similar pathomechanism. Fortunately, major vascular events appear to be rare after chemotherapy for testicular cancer. Due to new developments in chemotherapy and supportive treatment, the problems in determining risk factors for chemotherapy-related late vascular toxicities will continue and the prospective evaluation of therapy-related toxicity needs to become standard in the care of patients with testicular cancer during the next decade. Besides modifying therapy schedules in order to improve the results of cancer treatment, the effort to identify factors responsible for the development and intensity of late toxicities should not cease, considering the important subjective impact of late side-effects which might be avoided.

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APPENDIX

Questionnaire concerning vascular toxicity

Have you ever experienced one of the following symptoms in your extremities—continuously or sporadically—over a longer period of time:

—pain
—needles and pins, tingling
—pallor, numbness
—burning, cramps

Where exactly are the symptoms located, and can you explain them in your own words?
Please describe the circumstances of the first episode.
Do you see a possible connection with your malignancy or its therapy?
How did these symptoms develop over time?
Was there anything you could do to produce or ameliorate the symptoms?
Is there a connection to cold temperature?
How often did/do you experience the symptoms?
How would you best describe the severity, do they affect your daily life?

Do you feel any of the following symptoms at any time:

—chestpain
—heartburn
—shortness of breath

(Description and explanation as above)

Do you feel as strong on exercising as before the disease?
When do you notice differences?

—slow walking
—climbing stairs (how many flights?)
—running/jogging
—doing heavy work or sports (please characterise)

Please characterise the symptoms.

Have you ever experienced any of the following:

—swollen legs or ankles
—heart attack

Did your doctor ever mention that you have a heart or lung problem? Did you experience any heart or lung problem during chemotherapy? Please describe in your own words.

Do you know of any problems with your vascular system? Has your doctor ever mentioned hypertension or atherosclerosis? Please explain. Do you ever experience limping (claudication) on exercise?

Have you ever experienced any of the following?

—cerebral seizure/fit
—cerebral stroke
—loss of sensation
—paralysis, facial palsy
—disturbance of speech

Please explain the details.

Do you take a medication for any of the above mentioned symptoms or illnesses?