

Myocardial infarction and other major vascular events during chemotherapy for testicular cancer

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Background: Chronic vascular morbidity resulting from chemotherapy for testicular germ-cell cancer (TGCC) is recognized. Cardiovascular events (CVEs) occurring early during chemotherapy are less understood. We evaluated the incidence and clinical features of CVEs associated with chemotherapy of TGCC.

Patients and methods: A questionnaire was sent to 355 institutions in Germany to explore for early CVEs occurring during 1996–2008. To assess the relative incidence of CVEs, the number of events was put into relation to the total number of patients treated during the time span ($n = 8233$, calculated from national database). The response rate was 79%.

Results: Twenty cases with myocardial infarction (MI), 3 with cerebral stroke, and 2 with arterial thrombosis were recorded. The estimated incidence of MI and of all CVEs during chemotherapy is 0.24% [95% confidence intervals (CIs) 0.137% to 0.349%] and 0.30% (95% CI 0.188% to 0.423%), respectively. This estimate represents a minimum figure because the calculation is on the basis of simplifications. Six MI patients had no risk factors. Coronary angiography was indicative of thromboembolic rather than atherosclerotic origin of MI.

Conclusions: There is a small but definite risk of major early CVE associated with chemotherapy of TGCC. Physicians caring for TGCC patients must be aware of this hazard.

Key words: chemotherapy, cisplatin, myocardial infarction, testicular cancer, thromboembolism, vascular complication

introduction

Testicular germ-cell cancer (TGCC) is a paradigm of a curable cancer [1]. In light of the substantial efficacy of modern management of TGCC, the disadvantages of treatment become a growing issue. Cisplatin, the most efficacious drug to treat TGCC, is associated with numerous untoward effects [2–4]. Particular concerns have been raised by late cardiovascular events (CVEs) [5–7], which are caused by long-lasting degenerative processes initiated by chemotherapy or promoted indirectly by metabolic changes following systemic therapy [8, 9]. Yet, there is also increasing awareness of early vascular toxicity, e.g. arterial thromboembolism, myocardial infarction (MI), and cerebral stroke occurring right at the time of chemotherapy [10]. Pathogenetically, early events must be different from chronic vascular disease since degenerative processes would require long exposure times to cause damage. Current experience with acute vascular toxicity is on the basis of anecdotal reports and few case series [11–15]. Thus, we carried out a survey to assess clinical features and the

incidence of early major CVEs associated with chemotherapy of TGCC.

patients and methods

A nationwide survey was conducted during 2006–2008, to ascertain CVEs occurring in TGCC patients during chemotherapy or within 6 weeks [12]. A total of 355 institutions were surveyed using a questionnaire inquiring for MIs and other major CVEs encountered during the last decade. Clinical details were ascertained regarding patients with events.

To obtain a rough estimate of the overall incidence of CVE during chemotherapy, the number of events was related to the total number of TGCC patients receiving chemotherapy in Germany during the time span explored (1996–2008). According to the national database of the Robert Koch Institut, Berlin, the total number of testis cancer cases is $n = 47\,651$ (www.rki.de). A reduction of 10% was made to obtain the number of germ-cell tumors, only. The relative proportion of cases requiring chemotherapy was assumed to be ~40% and 10% for nonseminoma and seminoma, respectively [16]. A further correction was done with respect to the response rate of the survey (79%). A proportion of 2% was added to account for relapses requiring chemotherapy. Thus, the total number of TGCC cases undergoing chemotherapy in the participating institutions amounts to $n = 8233$.

Results of the survey were tabulated and evaluated descriptively. The age of TGCC patients with MI was compared with the age of MI patients

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Table 1. Synopsis of MIs during chemotherapy of testicular germ-cell cancer—results of a nationwide survey in Germany

Patient number	Age (years)	Histology	Clinical stage	Number of cycles of chemotherapy before MI	Risk factors	ECG: ST elevation	Coronary angiography	Type of coronary occlusion	Additional events	Treatment	Outcome
1	36	S	Good risk	3	–	+	LAD	TE	–	Attempted PTCA, thrombolytic therapy	Alive
2	36	NS	Good risk	3	Dm, sm	+	LAD/RCX	TE	Cerebral stroke	PTCA	Dead of stroke
3	39	S	Good risk	4	Sm, fh	+	LAD	TE	–	Thrombolytic therapy	Alive
4	48	NS	High risk	4 + HD	BMI 27.4	+	RCA, RCX	Vasospasms	–	Conservative	Dead of MI
5	44	S	Good risk	3	BMI 27.8, sm	+	LAD/D1	TE	–	Attempted PTCA	Alive
6	45	NS	Good risk	1	Sm, Kawasaki syndrome, previous MI	n/i	RCA	TE	n/i	PTCA + stent	Dead of MI
7	44	S	Good risk	2	Dm, sm	+	RCA	Intima dissection	Cerebral stroke	PTCA + stent	Alive
8	24	NS	Intermediate risk	2	–	+	LAD	TE	–	PTCA + stent	DOD
9	46	S	Good risk	4	BMI 26.9	n/i	n/i	n/i	n/i	n/i	Alive
10	43	NS	Good risk	1	BMI 32.1, sm, ah, fh	+	LAD/RCX	TE	–	Attempted PTCA, thrombolytic therapy	Alive
11	31	NS	Good risk	4	sm	n/i	LAD	Circumscript stenosis	–	Conservative	Alive
12	44	S	Good risk	3	–	+	LAD	Circumscript stenosis	–	PTCA + stent	Alive
13	44	NS	Good risk	2	–	n/i	LAD	TE	–	PTCA + stent	Alive
14	42	NS	High risk	4 + HD	Sm, ah	n/i	LAD/RCX	Coronary atherosclerosis	–	Conservative	Dead of MI
15	39	NS	Intermediate risk	4	–	+	No angiography	–	–	Conservative	Dead of neutropenic sepsis
16	40	S	Good risk	3	Sm	+	RCX	TE	–	PTCA, thrombolytic therapy	Alive
17	33	NS	CS I	2	Sm	n/i	LAD	Circumscript stenosis	Thrombosis of femoral artery	Coronary bypass surgery	Alive
18	34	NS	Good risk	3	–	+	RCA	TE	–	PTCA + stent	Alive
19	42	S	Good risk	2	Sm, hyperlipidemia, drug addiction	n/i	RCA	TE	–	PTCA	Alive
20	55	S	Good risk	3	Sm, hyperlipidemia	+	LAD	TE	–	PTCA + stent	Alive

MI, myocardial infarction; ECG, electrocardiogram; S, seminoma; LAD, left anterior descending artery; TE, thromboembolic event; NS, nonseminoma; Dm, diabetes mellitus; sm, smoker; fh, familial history; HD, high dose; BMI, body mass index; RCA, right coronary artery; RCX, ramus circumflexus; D1, diagonal branch; n/i, no information; DOD, dead of disease; ah, arterial hypertension; CS, clinical stage; PTCA, percutaneous transluminal coronary angioplasty.

Table 2. Other acute vascular events during chemotherapy for TGCC

Event	Age (years)	Cycle of Cx	TGCC histology	Additional events	Outcome	Remarks
Cerebral stroke	52	3	NS	PE	Alive	
Cerebral stroke	47	2	S	–	Alive	Stenosis left carotid artery
Cerebral stroke	40	8 (HD)	S	Intermittent atrial fibrillation	DOD	
Thrombosis popliteal artery	44	2	S	PE	Alive	
Thrombosis popliteal artery	49	2	S	Re-embolism after surgical embolectomy	Alive	

TGCC, testicular germ-cell cancer; Cx, circumflexus; NS, nonseminoma; PE, pulmonary embolism; S, seminoma; HD, high dose; DOD, dead of disease.

admitted to a community hospital (Albertinen-Krankenhaus) in Hamburg, Germany, during 2006–2008.

results

Twenty-five patients with CVE were reported, 20 with MI (Table 1), 3 with cerebral ischemic infarction, and 2 with peripheral arterial thromboembolism (Table 2). One case had been documented earlier [17]. The estimated rate of major CVEs and MIs occurring during chemotherapy is 0.30% [95% confidence intervals (CIs) 0.188% to 0.423%] and 0.24% (95% CI 0.137% to 0.349%), respectively.

Median age of the patients with MI is 42 years (range 24–55 years), which compares with a median age of 71 years (range 35–98 years) found in 1205 patients admitted for acute MI to Albertinen-Krankenhaus. Except for one patient with clinical stage I, all the MI patients had metastatic disease. Chemotherapy consisted of conventional PEB (cisplatin, etoposide, bleomycin) or PEI (ifosfamide instead of bleomycin) regimens. A median number of three cycles had been applied before MI. Two MI patients had only one course (Table 1). With respect to risk factors regarding cardiovascular disease, 12 MI patients were smokers, 1 nonsmoker, while smoking status is unknown in the remainder. One patient (Table 1, patient 5) had a history of Kawasaki syndrome and a previous MI at the age of 25 years. Diabetes mellitus type I, arterial hypertension, and familial history of MI, respectively, were reported in two of the patients, each. Six patients had no risk factor. With respect to cardiological findings, 14 patients had typical electrocardiogram (ECG) changes with ST elevation. Upon coronary angiographic examination, occlusion of the left anterior descending artery was found in 12 of 18 patients, while the right coronary artery was involved in 5 cases. Five patients had multiple occlusions (Figure 1). In 12 cases, coronary angiographic features were strongly indicative of thromboembolic origin of MI because no atherosclerotic signs were detectable (Figure 1). One case was indicative of coronary vasospasm and one had intima dissection.

Three patients developed additional vascular events concomitantly, two cerebral strokes and one femoral arterial occlusion. Six MI patients died, three of whom secondary to MI. Other reasons for death were cerebral stroke developing in addition to MI, neutropenic sepsis, and progressive TGCC, respectively.

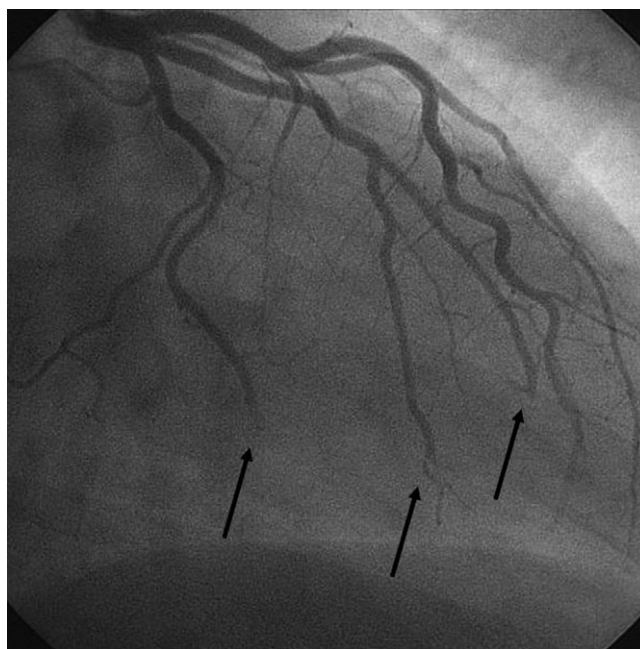


Figure 1. Coronary angiography (patient 16, Table 1) showing multiple thromboembolic occlusions (arrows) of distant branches of ramus circumflexus. Except for the sites of occlusive accidents, there are no atherosclerotic lesions in the coronary vessels discernible.

discussion

incidence of major vascular complications

The central result of this study is the documentation of a small but definite risk of major acute cardiovascular complications occurring during chemotherapy of TGCC. The overall rate of major CVE is ~0.30%. Clearly, this figure bears the risk of underestimation since our methodology relies on the cooperation of many individual institutions and the calculation critically rests on a number of simplifications. The rate of acute thromboembolic events including venous thromboses and pulmonary embolisms occurring during TGCC chemotherapy has been found to be in the range of 7.4% to 19% [11, 18]. Gerl [19] noted 3 strokes and 3 MIs among 485 chemotherapy patients corresponding to a CVE rate of 0.5%. That figure is in accordance with the rate reported in this article.

The potential of immediate cardiovascular toxicity resulting from chemotherapy is substantiated by ~28 cases of MIs occurring in TGCC patients reported to date [10, 13–15, 20].

We identified five cases with cerebral stroke (Tables 1 and 2). Only 20 such cases have been documented to date [11, 13, 15, 20–22]. Noteworthy, two of our cases were afflicted with both, MI and stroke, one had MI and femoral arterial occlusion (Table 1). Multiple major CVEs in the same TGCC patient have been observed previously [20, 23, 24]. Thrombosis of large arteries is very rarely encountered in TGCC patients [11, 18, 24, 25].

clinical features

The most striking clinical feature associated with MI in TGCC patients is the median age of 42 years, which is much younger than the median age of MI patients (71 years) of the general population. Prognostic outcome of MI appears to be superior in TGCC compared with cases of the general population, which may be related to low comorbidity of the young individuals. Whether the cumulative dose of chemotherapy is of significance remains unclear as yet. A median number of three cycles had been applied before the event. But, CVE has occurred even after only one cycle.

The majority of our MI cases presented with ST elevations in the ECG, which is the typical finding in MI of the general population. Also, the topographic anatomical pattern of coronary arterial occlusions in TGCC patients is not different from findings in the general type of MI.

pathogenetic considerations

One-third of our cases did not have any significant CVE risk factor. Accordingly, the majority of the MI patients did not show atherosclerotic changes upon coronary angiography or post-mortem autopsy, respectively. Also, multivessel infarction was observed in five patients. These observations in conjunction with previous reports [15] indicate that MIs occurring in chemotherapy patients are probably caused by thromboembolic events rather than by atherosclerotic stenosis. Cerebral strokes and peripheral arterial occlusions are probably induced by the same mechanism. Vasospasms secondary to chemotherapy could be another mechanism, which may be concluded from one autopsy case of our series that revealed the absence of both atherosclerotic changes and clots.

The Institut Gustave Roussy Group demonstrated body surface area and elevated serum levels of lactate dehydrogenase (LDH) to be associated with thromboembolic events [11]. These parameters appear to be meaningful indeed because they may point to conditions possibly relevant to the pathogenesis of thromboembolism in TGCC patients, i.e. tumor burden (LDH) and dosage of chemotherapy (body surface area). Our study could not evaluate this intriguing concept because the relevant data were not available due to the retrospective and multiinstitutional way of patient accrual.

TGCC patients appear to be more prone to CVE than other cancer patients [11]. Accordingly, Starling et al. [26] found a significantly higher rate of CVEs in gastric cancer patients receiving cisplatin compared with those receiving other regimens. Cisplatin evidently induces endothelial cell damage as

revealed by the increase of plasma levels of von Willebrand factor during chemotherapy [10]. Also, an increased clotting activity of erythrocytes has been observed in the presence of cisplatin [27]. In all, early vascular complications during TGCC chemotherapy do probably result from the combined effects of first, the basic thrombophilic predisposition of cancer patients; secondly, endothelial cell damage; and thirdly, excess coagulability triggered by chemotherapeutic drugs.

Conceivably, chemotherapy-associated clinical measures may further advance the coagulation cascade.

Support for this view comes first, from the young age of the TGCC patients; secondly, the absence of risk factors in many of the patients; thirdly, the occurrence of multiple vascular events; and fourthly, the absence of atherosclerotic features in the majority of MI cases.

conclusion

There is a small but definite risk of MIs, cerebral strokes, and peripheral arterial occlusions occurring during chemotherapy of TGCC. Patients having risk factors for cardiovascular disease beforehand appear to be at greater risk. Physicians applying chemotherapy for TGCC should be aware of this hazard. It appears rational to consider prophylactic anticoagulant medication, e.g. acetylsalicylic acid at least in high-risk patients.

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disclosure

None of the authors declares a conflict of interest.

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