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Review paper

Vascular toxicity associated with chemotherapy for testicular cancer

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Cisplatin-based chemotherapy considerably improved the outcome of patients with metastatic germ cell tumors. Apart from Raynaud's phenomenon, a frequent side effect, vascular toxicity associated with chemotherapy for testicular cancer, has not been described precisely. Although major vascular complications such as myocardial infarction, stroke and pulmonary embolism seem to occur infrequently, they raise concern with regard to the safety of chemotherapy. Also, potential late vascular toxicity has to be taken into account. Whereas a cause and effect relationship is probable for some vascular events following chemotherapy, some cases may represent coincidence or may be disease related. Presently, the very low incidence of major vascular events should not enter into therapeutic decisions.

Key words: Chemotherapy, myocardial infarction, pulmonary embolism, Raynaud's phenomenon, stroke, testicular cancer.

Introduction

The introduction of cisplatin by Einhorn and Donohue considerably improved the clinical outcome of patients with metastatic testicular cancer.[1] Agents frequently used in cisplatin-based combination chemotherapy protocols are etoposide, bleomycin, vinblastine and ifosfamide. Side effects of these drugs include gastrointestinal toxicity, myelosuppression and alopecia. Moreover, bleomycin has a dose-limiting pulmonary toxicity, and the administration of cisplatin is associated with nephro-, neuro- and ototoxicity. These side effects are common and more or less dose-dependent. Although they are tolerable in the majority of patients treated with standard protocols, treatment-related mortality is around 5% in large clinical trials.[2]

Apart from the above-mentioned side effects, vascular toxicity associated with chemotherapy for germ cell tumors has been described by several investigators. Whereas Raynaud's phenomenon is observed in a considerable proportion of patients, major vascular events seem to occur infrequently. However, several reports about myocardial infarction, stroke and pulmonary embolism raise concern, as these complications are invaliding and life threatening in young patients with a high chance of being cured from malignancy. Single cases of fatal small bowel necrosis[2] and rectal infarction[3] have also been reported. This review summarizes the data in the literature, and attempts to distinguish between disease- and chemotherapy-related factors leading to vascular complications. Moreover, attention is focused on potential long-term vascular toxicity.

Mechanisms of vascular toxicity

The occurrence of thromboembolic events in patients with malignant diseases is a well recognized phenomenon which is due to complex alterations of the clotting system and an impaired fibrinolysis. Cytotoxic chemotherapy may enhance prothrombotic hemostatic abnormalities. Another mechanism leading to thromboembolic events may be endothelial cell damage, as antineoplastic agents reach their highest concentrations at the blood–endothelial interface. In this context, vascular damage has been discussed to be an important anti-tumor mechanism of antineoplastic agents.[4]

Of the antineoplastic agents used in the treatment of testicular cancer, bleomycin has been most frequently incriminated to cause vascular damage, as it can lead to Raynaud's phenomenon alone[5] or in combination with vinblastine and cisplatin.[6] A preclinical experimental study showed multifocal vasculitis with venous occlusion in rhesus monkeys after the administration of bleomycin;[7] this study, however, provided no data on potential long-term vascular alterations. Furthermore, bleomycin has been shown to stimulate collagen production in cultural fibroblasts.[8] Light and electron microscopic

studies demonstrated that bleomycin causes characteristic endothelial changes in capillaries and small arterioles with cumulative administration. Endothelial lesions ranged from vacuolization to detachment and necrosis.[7]

Recently, morphological studies on blood vessels in rats provided evidence that cisplatin, the most active agent against testicular cancer, also can cause endothelial injury.[9] The authors of this paper studied vascular damage of the common carotid artery in cross-sections by light microscopy and methacrylate casts by scanning electron microscopy; capillary lesions in the area of the sternocleidomastoid muscle were examined by transmission electron microscopy. The light microscopic studies demonstrated that cisplatin induced damage like swelling and bulging of endothelial cells from the basement membrane. The scanning electron micrographs showed a marked reduction of the tiny vascular network. Moreover, the transmission electron studies disclosed severe lesions of the endothelial cells, the basement membrane and the pericytes of the capillaries.[9]

Presently, it is not clear whether the direct cytotoxic effect is the only mechanism by which antineoplastic agents can lead to endothelial injury. Several chemotherapeutic agents including cisplatin and bleomycin have been shown to amplify the production of tumor necrosis factor and other cytokines.[10,11] As tumor necrosis factor-α induces procoagulant activity on endothelial cells *in vitro*,[12] such an indirect mechanism may play an additional role in the development of vascular injury.

An important vascular-mediated component in anti-tumor action has also been postulated for vinblastine, a commonly used agent in former chemotherapy protocols against testicular cancer. It was discussed that vinblastine acts on solid tumors by a host-mediated mechanism which induces vascular damage and loss of blood flow within the tumor.[13] During the last years, etoposide was frequently substituted for vinblastine in chemotherapy protocols for testicular cancer because of diminished neuromuscular toxicity.[2,14,15] Althouth early reports suggested some vascular toxicity associated with the administration of etoposide,[16,17] presently there is little evidence that this kind of toxicity plays an important role in conventional doses as used in protocols for testicular cancer. However, high-dose etoposide as used in bone marrow transplantation conditioning regimens can lead to hepatic venoocclusive disease.[18]

A further putative factor leading to vascular toxicity in association with cisplatin-based chemotherapy is hypomagnesemia due to renal dysfunction.[19] Cisplatin-induced tubular injury leads to hypomagnesemia by causing a decrease in the maximal rate of reabsorption of the divalent cation. In two series, 76 and 87% of patients treated with cisplatin developed hypomagnesemia; median time to onset of hypomagnesemia was 63 days.[19,20] In the series by Schilsky *et al.*,[20] 38% of patients still showed hypomagnesemia 3 years after cisplatin-containing chemotherapy. Although the majority of patients with hypomagnesemia in the series by Vogelzang *et al.*[19] were asymptomatic, experimental data demonstrated that magnesium deficiency in the media potentiates the contractile responses of the arteries to norepinephrine, acetylcholine, serotonin, angiotensin and potassium.[21] Therefore, hypomagnesemia may be a cause of arterial spasms. An association between magnesium deficiency and hypertension was also described.[22] However, the biological significance of these findings remains to be defined in chemotherapy-treated patients with testicular cancer. Furthermore, renal tubular function recovers with time leading to normalization of serum magnesium levels.[19,23] Therefore, magnesium deficiency probably is not responsible for late vascular effects.

Recently, the antiemetic agent ondansetron was suspected to contribute to acute vascular complications following chemotherapy.[24] However, despite the frequent use of ondansetron, so far only one group of investigators has reported a potential vascular toxicity[24] and a putative mechanism involved has not been discussed.

During recent years, attention was focused on potential long-term vascular toxicity following cisplatin-based chemotherapy. While some authors found an increased prevalence of hypercholesterolemia after cisplatin-containing chemotherapy,[25–27] which may lead to an increase of cardiovascular risk, other investigators were not able to confirm this finding.[28]

In the following sections, Raynaud's phenomenon, myocardial infarction and coronary artery disease, stroke and pulmonary embolism, and the pathogenetic mechanisms potentially involved are described separately.

Raynaud's phenomenon

Raynaud's phenomenon is characterized by transient episodes of vasoconstriction accompanied by changes in color of the affected digits (white pallor, cyanotic blue and deep red); attacks are

precipitated by exposure to cold and may be bilateral or unilateral. Raynaud's phenomenon was described after single-agent treatment with bleomycin.[5] Vogelzang *et al.* observed Raynaud's phenomenon in 21% of patients treated with bleomycin and vinblastine, but the addition of cisplatin increased the frequency up to 41%.[6] A similar incidence of Raynaud's phenomenon after cisplatin-based combination chemotherapy was described by several investigators.[29,30] In contrast, Scheulen and Schmidt observed Raynaud's phenomenon in only 2.6% of patients treated with vinblastine and bleomycin, with or without cisplatin. The authors attributed this considerably lower incidence to their routine use of corticosteroids.[31]

Raynaud's phenomenon usually appears about 3–6 months after discontinuation of chemotherapy;[32] Vogelzang *et al.* described a median interval of 10 months from the start of chemotherapy.[6] Trophic changes of the fingertips were observed in some patients by the above-mentioned investigators, but other authors could not confirm this finding. Digital ischemia led to life-style alterations in 12 of 20 patients of the above-mentioned report.[6] Gangrene of the fingers or deterioration with time have not been reported. Therapeutic trials with topic nitroglycerine did not prove to be beneficial.[6] A gradual resolution of symptoms with time was observed in around 50% of patients.[6] In long-term follow-up studies persistent Raynaud's phenomenon was found in 10–49% of patients, whereby the varying frequency may be partly explained by different methods of evaluation (questionnaire, telephone interview or physical examination at a visit to the hospital).[29,30,33–35]

Raynaud's phenomenon is divided into two pathophysiological groups. Obstructive Raynaud's phenomeon is characterized by structural abnormalities of the vessel walls and reduced lumen, which is occluded by a normal vasoconstrictor response to cold. In vasospastic Raynaud's phenomenon, the calibers of the vessels are normal but there is an exaggerated vasoconstrictor response to cold. As in a study by Hansen and Olsen[23] none of the patients showed an increased systolic pressure gradient from arm to finger, it seemed unlikely that significant hemodynamic organic obstructions of the arteries led to chemotherapy-induced Raynaud's phenomenon. However, since bleomycin is known to cause structural alterations in small blood vessels, a minor contribution of anatomical changes cannot be excluded. An exaggerated and prolonged vasoconstrictor response to cold, with a mean flux reduction of 61%, was found in a study using laser Doppler flowmetry.[32] Moreover, the mean restitution time exceeded 7 min. Both findings were regarded as consistent with vasospastic-type Raynaud's phenomenon. An increased sympathetic vessel tone was discussed to be attributable to vinblastine. However, Roth *et al.* were not able to find a correlation between "digital cold sensitivity" and the number of courses of induction therapy administered, the dosage of vinblastine used during induction or the administration of vinblastine as maintenance therapy.[33] In the study by Vogelzang *et al.*[6] the development of Raynaud's phenomenon was unrelated to total doses of vinblastine, bleomycin and cisplatin. Presently, no conclusive data are available as to whether the substitution of etoposide for vinblastine reduces the incidence of Raynaud's phenomenon. Cisplatin alone was not reported to cause Raynaud's phenomenon, but the addition of cisplatin to bleomycin and vinblastine was shown to increase the frequency. The potential mechanism by which cisplatin contributes to Raynaud's phenomenon is hypomagnesemia due to renal magnesium wasting. Vogelzang *et al.*[19] found that the severity of prior hypomagnesemia predicted an increased risk of Raynaud's phenomenon. As all patients in the study by Hansen and Olsen[23] had normal serum magnesium levels after a median of 78 months after chemotherapy, the presence of Raynaud's phenomenon does not seem to be correlated with hypomagnesemia. However, hypomagnesemia may play a role in the development of Raynaud's phenomenon. While in one study Raynaud's phenomenon was significantly more common in cigarette smokers,[6] other investigators were not able to confirm this association.[30] Two reports could not ascertain any correlation between cisplatin–vinblastine-induced neurotoxicity and Raynaud's phenomenon,[6,30] while Bissett *et al.*[29] suspected some degree of cross-correlation of toxicity

Myocardial infarction and coronary artery disease

Twenty three cases of myocardial infarction in male patients receiving combination chemotherapy for germ cell tumors have been documented in the literature.[3,28,33,34,36–45] The majority of these patients were treated according to the PVB protocol including cisplatin, vinblastine and bleomycin, while a few patients received etoposide-containing regimens. A few patients were given maintenance therapy. Two patients underwent an additional

mediastinal irradiation, a known risk factor for the development of coronary artery disease.[33] The patients' ages ranged from 19 to 55 years (median 38 years). It is of interest that of the eight patients whose myocardial infarctions were documented in reports on large clinical trials, only one was younger than 35 years. In contrast, of the remaining 15 patients, whose myocardial infarctions were published as case reports, 10 patients were younger than 35 years. The latency between the last administration of chemotherapy and myocardial infarction ranged from a few hours to 8 years (median 1.5 years). Seventeen patients developed myocardial infarction during complete remission, three patients had active disease and in three further cases the response was not yet evaluable at the time of infarction. The fact that the majority of patients were in complete remission argues against a predominant role of disease-related factors contributing to vascular events. Myocardial infarction was fatal in 10 of the 23 patients. Six of these deaths occurred in patients younger than 35 years. Anatomical changes were found in some[3,28,38–40] but not all[34,36,45] patients by coronary angiography or autopsy. Some patients were reported to have cardiovascular risk factors, but the authors did not provide data on potential risk factors consistently. However, some authors[40,44,45] emphasized that patients younger than 30 years who developed myocardial infarction had no risk factors.

In a retrospective analysis, Stefenelli *et al.*[46] detected angina pectoris in eight of 21 patients (38%) with a mean age of 30 years who received chemotherapy for testicular cancer consisting of cisplatin, vinblastine and bleomycin. Angina pectoris began a median of 5.6 weeks after initiation of chemotherapy and persisted for 2–7 days. As nine of 10 patients with episodes of acute vascular toxicity had metastatic disease and only one received adjuvant therapy, the authors discussed an activation of clotting factors by the release of toxic substances from necrotic tumor tissue as a possible pathogenic factor. A weakness of this study was that the authors evaluated only typical subjective symptoms using a standardized questionnaire and interview, but technical examinations (electrocardiography) were not performed routinely. Thus the frequency of acute vascular toxicity may be overestimated by this study. Furthermore, the observations by Stefenelli *et al.*[46] do not provide an explanation for most cases of myocardial infarction described in the literature, as the majority of events arose during complete remission.

Nichols *et al.*[43] investigated the incidence of coronary artery disease and myocardial infarction among 459 eligible patients on the Testicular Cancer Intergroup study. Ninety patients (20%) received two courses of adjuvant chemotherapy, 83 patients (18%) received full-chemotherapy for metastatic disease and 286 patients (62%) never receiving chemotherapy constituted the control group. This study provided no evidence of an increased incidence of heart disease among patients treated with either adjuvant or curative chemotherapy. Moreover, hypertension, one of the known risk factors for coronary artery disease, was found in equal frequencies among chemotherapy-treated and untreated patients. A relative weakness of this study is that approximately 40% of the patients did not answer to the questionnaire. Furthermore, the study had limited power to detect significant differences in low-frequency toxic events. Nevertheless the authors drew the conclusion that cardiovascular events in association with chemotherapy for germ cell tumors may represent coincidence. The authors based their hypothesis on data of the Framingham study which demonstrated a substantial incidence of coronary artery disease in the young male population.[47]

However, due to the very young age of some patients and a lack of coronary risk factors, some authors suspected a cause and effect relationship between chemotherapy for testicular cancer and myocardial infarction. A further argument was the relatively close temporal association between administration of chemotherapy and myocardial infarction in some of the reported cases. Of interest is the report by Bodensteiner who described a 24 year old patient with fatal myocardial infarction 7 months after completing one cycle of cisplatin, vinblastine and bleomycin.[39] Coronary angiography had been normal 8 months before infarction. Although some case reports suggested a potential causative role of chemotherapy, large clinical trials presently do not provide evidence of an increased risk of coronary artery disease after chemotherapy for testicular cancer.[43] However, published studies cannot rule out a moderate increase of incidence. Longer follow-up and data on considerably larger numbers of patients will be necessary to draw definitive conclusions.

Recently, attention was drawn to studies investigating changes of plasma lipids after chemotherapy for testicular cancer. Hypercholesterolemia was first described by Boyer *et al.*[25] in 20 of 30 patients (67%) with a median follow-up of 75 months (range 48–126) after commencement of chemotherapy. In this retrospective study,[25] elevation of cholesterol was

significant when compared with a control population. The same group later confirmed the initial findings in a prospective study, which, however, included only 17 patients.[27] Moreover, maximum duration of follow-up was only 24 months. In the same year, Gietema *et al.*[26] reported on a cohort study including 57 patients with a median follow-up of 88 months (range 56–143). These authors[26] found that patients treated with chemotherapy for testicular cancer, when compared with a sample of healthy Dutch men, had an elevated serum cholesterol level and a higher body mass index 4–6 years after treatment ($p < 0.05$). Moreover, the HDL cholesterol level was lower in the chemotherapy group compared with that of healthy men ($p < 0.05$). A significant elevation of serum cholesterol was not observed in patients treated with orchiectomy only, who constituted a further control group. Comparing the chemotherapy-treated and stage I patients, a significant difference in cholesterol levels was only observed in the group aged 20–29 years ($p < 0.001$). The latter finding is of special interest, as the effect of an elevated serum cholesterol level on the risk for cardiovascular disease might be more pronounced in young adults than in elder patients.[48] Ellis *et al.*[28] published a retrospective study including 47 patients which was contradictory to the three above-mentioned reports. The authors did not find a significant difference with regard to the plasma cholesterol concentrations between patients with testicular cancer treated with chemotherapy and patients with germ cell tumors receiving no chemotherapy. However, patients in the control group tended to be somewhat older, but if comparison was restricted to patients 25–44 years of age no significant difference was found. Moreover, a comparison of the chemotherapy-treated patients with the New Zealand male population did not show a significant difference of cholesterol levels. Combining the data of the four above-mentioned studies[25–28] no definite conclusions can be drawn. Even if further studies confirm an increase of cholesterol after cisplatin-based chemotherapy, the biological relevance of such a finding remains to be determined. Moreover, the importance of other risk factors for coronary artery disease should be also examined. Of special interest would be a study on the smoking cessation habits among survivors of testicular cancer.

Cerebrovascular accident

Cerebrovascular complications are not uncommon in patients with malignant diseases, and may arise from various mechanisms including tumor embolization, vasculitis, non-bacterial thrombotic endocarditis and consumptive coagulopathy.[49] Moreover, cerebrovascular events may be related to antineoplastic therapy. Since the beginning of the last decade cerebrovascular insults associated with cisplatin-containing chemotherapy have been reported by several authors.[50–54] Kukla *et al.*[50] described five patients with head and neck cancer developing cerebrovascular accidents after chemotherapy with cisplatin, bleomycin and vincristine. Each of the patients was over 50 years of age and three had a previous history of heart disease or stroke. However, a close temporal relationship between the administration of chemotherapy and the vascular complications suggested a causal association. Other investigators also described cerebrovascular accidents after cisplatin-containing chemotherapy in patients with known risk factors for arteriosclerosis.[52–54] Licciardello *et al.*[52] recognized an elevated von Willebrand factor antigen as a potential risk factor for chemotherapy-related acute vascular events. The authors assumed that endothelial damage may be a major pathogenetic factor.

Although large numbers of patients with testicular cancer have been treated since the introduction of cisplatin in 1977, the first report on cerebrovascular events in association with cisplatin-based chemotherapy for testicular cancer appeared in 1986.[36] Eight cases of cerebrovascular accidents following cisplatin-based chemotherapy of testicular cancer have so far been documented in the literature.[3,24,36,37,45,55,56] The ages of the patients ranged from 19 to 58 years (four patients were younger than 30 years). Four patients had active disease at the time of the cerebrovascular event, while two patients were in complete remission and one had a partial response with tumor marker normalization; a further patient developed the insult during adjuvant chemotherapy for resected stage II testicular cancer. In two of the eight cases the cerebrovascular accident occurred 1 week after initiation of chemotherapy.[3,37] A further patient developed a stroke 2 days after completion of the second chemotherapy course.[56] In patients neurologic deficits began at the end of the third chemotherapy cycle,[36,55] in two other patients during the sixth and eighth cycle,[24,45] respectively. In one case the interval from discontinuation of chemotherapy was 4 months.[36] Angiographic studies were reported from five patients. In two cases no endovascular abnormalities were identified,[36] whereas in two other patients an occlusion of the middle cerebral artery was documented.[55,56] In a further patient cerebral

angiography was consistent with occlusive arteritis in the right frontal and left temporoparietal regions.[3] No tumor cells were identified in the surgically removed thrombus of one of the latter cases.[55] Three patients died from cerebrovascular accident, one in complete remission,[56] one with favorable response[55] and the third with refractory disease.[3] Two patients showed a resolution of neurologic symptoms and were alive with testicular cancer at the time of the reports.[24,45] Three patients were alive with no evidence of cancer at the time of the reports, one with complete neurologic recovery and two with persistence of neurologic deficits.[36,37] A close temporal association between the administration of chemotherapy and the cerebrovascular event in the majority of reported cases suggests a causal relationship. Moreover, the young age of the patients and the lack of vascular risk factors in most of the reported cases argue against coincidence. Considering the above-reported experimental findings,[9] drug-induced endothelial damage might be the most important pathogenetic factor. A cumulative vascular damage due to the administration of sequential chemotherapy cycles may play a role, since in the majority of reported cases patients had received more than one cycle prior to the vascular event. In cerebrovascular events occurring more than 2 months after commencement of chemotherapy, vascular spasms due to hypomagnesemia may be an additional pathogenetic factor.[45] Moreover, in patients with active disease, a contribution of malignancy-related factors has to be considered. Although cisplatin-containing chemotherapy apparently plays a role in the development of cerebrovascular accidents in young patients with testicular cancer, it must be emphasized that the incidence of such complications is very low. In a recent review by Nichols *et al.*,[43] no cases of cerebrovascular event were identified among 2047 patients treated with chemotherapy for testicular cancer.

Pulmonary embolism

The incidence of pulmonary emboli in patients treated with chemotherapy for testicular cancer is also very low, since only four cases of this complication were reported in the above-mentioned review.[43] Ten further cases of pulmonary embolism in patients receiving chemotherapy for testicular cancer have been documented in the literature.[37,57–61] Lederman and Garnick[61] reported on three (26, 30 and 31 years old) men, two of whom had only elevated serum tumor markers and the third had metastatic pulmonary disease. In one patient a deep venous thrombosis of a leg was found, whereas in the other cases no sources of emboli were identified. The authors[61] assumed that similar mechanisms as discussed for myocardial infarction and cerebrovascular accident may lead to pulmonary emboli. Bleomycin-induced endovascular damage was considered to be the most important pathogenetic factor.

Cantwell *et al.*,[37] however, demonstrated that deep venous thrombosis and pulmonary embolism in patients receiving chemotherapy for germ cell cancer were significantly associated with the presence of retroperitoneal metastases with at least one node of more than 5 cm in maximum diameter. In a review of the literature, Stockler and Raghavan[57] found that pulmonary embolism in patients with testicular cancer was closely related to neoplastic venous involvement. Pulmonary embolism frequently occurred prior to the initiation of chemotherapy and tumor thrombi were found at surgery or post-mortem examination in the majority of cases.

In conclusion, the majority of cases of pulmonary emboli in patients with metastasized testicular cancer may ensue from tumor embolism, while in a few cases a pathogenic role of drug-induced endovascular damage cannot be excluded.

Conclusions

A wide spectrum of antineoplastic agents has been recognized to cause vascular damage. Whereas it is generally assumed that the primary mechanism by which chemotherapy brings about tumor regression is the direct cytolysis of tumor cells, the blood vessels of tumor tissue may be an important target of antineoplastic agents, as most drugs achieve the highest concentrations at the blood–endothelial interface. However, the cytotoxic drug effect apparently is not strictly confined to the more rapidly proliferating endothelial cells in tumor vessels. Therefore, vascular damage of normal vessels may occur frequently but may be subclinical in the vast majority of treated patients with the exception of Raynaud's phenomenon. However, in a small subset of patients major vascular complications arise.

Vascular events such as myocardial infarction, stroke and pulmonary embolism in patients receiving chemotherapy for testicular cancer raise concern, as they are invaliding and life threatening in young patients with a high chance of being cured from malignancy. It is justified to assume a patho-

genic role of chemotherapy in the development of cerebrovascular events, but the incidence of these complications seems to be very low. A cause and effect relationship is defined less distinctly for cases of myocardial infarction following chemotherapy; some of the reported cases may simply represent coincidence. Long-term follow-up data on very large numbers of patients will be necessary to clarify whether chemotherapy significantly increases cardiovascular risk. Pulmonary emboli predominantly are a result of tumor embolism but a minor contribution of drug-induced endovascular damage seems possible. In conclusion, the very low incidence of major vascular complications following cisplatin-based chemotherapy for testicular cancer should not enter into therapeutic decisions.

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