Cerebrovascular accident during cisplatin-based combination chemotherapy of testicular germ cell tumor: an unusual case report

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Even though testicular nonseminomatous germ cell tumors (NSGCTs) usually have a good prognosis and high curability rates, unpredicted complications owing to chemotherapy regimens might complicate the course. Modalities that are commonly used to cure NSGCTs have well-known side effects. Thromboembolism, which is infrequently associated with germ cell tumors and the vascular toxicity of chemotherapeutics, causes morbidity and mortality. We report a young testicular NSGCT patient, without any known underlying risk factor, who experienced an unpredicted cerebrovascular accident after he received cisplatin-based combination chemotherapy. *Anti-Cancer Drugs* 19:97–98 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Clinical correlation between cancer and venous thromboembolism (VTE) is well established and cancer patients have a higher risk of developing VTE when compared with healthy controls [1,2].

As the prognosis for most testicular cancer patients is good with high rates of curability, acute and long-term complications owing to chemotherapy should be determined accurately and prevented, if possible. Although thromboembolism is known to occur with germ cell tumors, venous vascular toxicities like VTE constitute the highest proportion of toxicities. Arterial thromboembolism, including cerebrovascular accidents or myocardial infarction during chemotherapy of testicular cancer, is rare but possible [3]. Herein, we report a patient with NSGCT, who received cisplatin-based chemotherapy, and in whom a cerebrovascular accident occurred soon after treatment.

Case report

A 17-year-old boy was admitted to the medical oncology clinics 1 week after high inguinal orchidectomy with the pathological diagnosis of testicular NSGCT. On the pathological evaluation, vascular invasion was noted, and the spermatic cord, tunica albuginea and the adjacent connective tissue were also seen to be affected. On thoracoabdominal computed tomography (CT), bilateral lung parenchymal metastasis and thoracic and retroperitoneal lymphadenopathies were reported. He was a nonsmoker. Neither was any sign of coagulation disorder seen in his past medical history nor was any liver metastasis reported by the imaging studies. Postoperative serum level of β-human chorionic gonadotropin was 8.00 mIU/ml (0–3 mIU/ml); of α-fetoprotein, 17 337 ng/ml (0–13.6 ng/ml) and of lactate dehydrogenase, 346 IU/l (100–190 IU/l). Complete blood count, liver and renal function tests were within normal limits. The coagulation tests, namely, prothrombin time, activated partial thromboplastin time and fibrinogen were also within normal limits. He was administered four cycles of BEP chemotherapy including 30 mg/day (20 mg/m^2/day) of cisplatin for 5 days, 180 mg/day (120 mg/m^2/day) of etoposide for 3 days and 30 mg/day of bleomycin at the 1st, 8th and 15th days in 21-day cycles. At the seventh day of the fourth cycle of BEP therapy, the patient was admitted to the emergency department with complaints of left hemiplegia and facial paralysis. Cranial CT of the patient demonstrated multiple hemorrhagic infarcts that included the right frontotemporoparietal location. At 2 and 9 days later, control cranial CT, and 21 days later, cranial magnetic resonance imaging also demonstrated the lesions as being hemorrhagic infarcts rather than metastases. The repeated prothrombin time, activated partial thromboplastin time and fibrinogen levels were within normal limits. The serum levels of antithrombin III, protein-C and protein-S were also within normal limits. Transthoracic and transesophageal echocardiograms demonstrated neither thrombus in the heart and

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aorta nor atrial and/or ventricular septal defects. Steroid treatment against edema was started. A rehabilitation program was afterwards initiated. Although there was clinical response and regression of the tumor markers, the chemotherapy was postponed because of the poor performance status of the patient. After completing the physical rehabilitation program, combination chemotherapy including paclitaxel and gemcitabine was initiated, but he could not have optimal dosing owing to complications including neutropenic fever. Although partial responses were observed during chemotherapy, complete remission was never accomplished and he died 26 months after the diagnosis of testicular cancer with progressive disease.

Discussion

Patients with NSGCT are highly curable especially if the disease is in the early stages. Three or four courses of platinum-based combination chemotherapy regimens such as cisplatin and etoposide, with (BEP) or without (EP) bleomycin is the standard of care. VTE seen during the treatment of germ cell tumors is more common than the arterial type [3]. Antineoplastic agents including cisplatin might be associated with vascular complications that include not only venous (deep vein thrombosis, pulmonary embolism) but also arterial thrombosis and/or hemorrhages (cerebrovascular accidents, myocardial infarction, and thrombosis of femoral, iliac, renal and popliteal arteries) [3–7].

Cerebrovascular complications are common in patients with malignancy and arise from a variety of mechanisms, including tumor embolization, vasculitis, nonbacterial thrombotic endocarditis, consumption coagulopathy, impaired clearance of activated coagulation factors or complications directly related to antineoplastic therapy [8,9]. The major risk factors for developing thromboembolic events in germ cell tumors are liver metastases and the administration of high doses of dexamethasone [3]. Although smoking is a risk factor in terms of endothelial damage, cerebrovascular accidents may develop after cisplatin-based regimens even in the nonsmoker group [10].

The pathogenesis of thromboembolic phenomena in cancer patients is probably multifactorial, involving both local factors (endothelial lesions) and systemic factors (coagulation abnormalities). The mechanism of endothelial toxicity is uncertain; however, arterial thrombosis usually results from vascular endothelial injury leading to the secretion of proinflammatory cytokines and, less frequently, to altered hemostatic balance. Many of these disorders reflect the direct effects of antineoplastic drugs or their metabolites on the endothelium [7,11,12]. Local factors like retroperitoneal lymph node metastasis might cause vascular compression and stasis that can contribute to thromboembolism [3]. Chemotherapy-induced alterations of the clotting cascade or platelet activation are other possible mechanisms.

To conclude, even though the treatment choices of the malignancies are highly improved, some unexpected rare side effects can complicate the course. Complications during the treatment of malignancies decrease the quality of life, and should be accurately foreseen and discussed. Further evaluation with prospective studies might be needed to identify the risk factors for thrombosis and to determine the strategies that should be used to prevent and treat such complications in patients treated with cisplatin-based chemotherapy.

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