Cisplatin-associated thrombosis

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The discovery of cisplatin has made arguably the biggest contribution to cancer medicine, providing the basis for the chemotherapy treatment of many malignancies. In addition to well-documented toxicities such as neurotoxicity, cisplatin-induced vascular toxicity is becoming an increasing concern, with some authors describing it in up to 12% of patients. Given the efficacy of cisplatin, vascular toxicity represents a significant survivorship issue. We describe different manifestations of cisplatin-associated thrombosis and its putative pathophysiology. *Anti-Cancer Drugs* 19:927–929 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Case studies

Case report 1

A 27-year-old man was diagnosed with metastatic non-seminomatous germ cell tumour. He had bulky disease with elevated β-human chorionic gonadotropin (51 451) and α-fetoprotein and a performance status of zero. The prognosis was poor necessitating four cycles of bleomycin, etoposide and cisplatin (BEP). After two cycles, the patient achieved an excellent serological and clinical response, but developed chest pain. Angiography revealed coronary artery thrombosis necessitating stent insertion. In the absence of cardiac risk factors and in view of the temporal relationship with chemotherapy, cardiologists ascribed chemotherapy to be a significant contributory factor to the patient's myocardial infarction.

Case report 2

A 37-year-old man was diagnosed with a retroperitoneal anaplastic tumour consistent with a primary retroperitoneal seminoma. His medical history revealed only varicose vein repair and a 10 pack year history of smoking. The patient was treated with BEP. His first cycle was complicated by numbness in his right foot attributed to neurotoxicity and a rash on his legs attributed to bleomycin. After the second cycle of BEP, the patient was admitted with a pyrexia of 39°C, delirium and painful right foot and left hand. Physical examination revealed absent right dorsalis pedis and posterior tibial pulses as well as a weak left radial pulse. The patient was treated for neutropenic sepsis and a diagnosis of acute ischaemic foot was made. Vasculitis and thrombophilia screen were negative. Further opinions were sought from the vascular surgeons, haematologists and plastic surgeons. The aetiology of the ischaemia was believed to be an arterial thrombus rather than an embolism. The patient was therefore treated with intravenous heparin. As the patient had a good response after two cycles of chemotherapy, he was treated with two further cycles of EP (bleomycin was omitted because of rash). After completing chemotherapy, the patient underwent an emergency thrombectomy and below knee amputation for progression of the ischaemia. The patient was anticoagulated with warfarin and remains in remission.

Case report 3

A 22-year-old man was diagnosed with metastatic non-seminomatous germ cell tumour and commenced on BEP chemotherapy. His first two cycles were well tolerated except an episode of neutropenia requiring granulocyte colony-stimulating factor. After his third cycle, he was admitted with presyncope. His ECG showed widespread ST elevation. His initial troponin was negative but subsequently began to rise. A diagnosis of pericarditis was made. The following day, the patient developed profound weakness in his right arm, loss of power in his right leg, nominal aphasia and anterior neck pain. Echocardiography was normal on two occasions, as was a vasculitis screen. An MRI scan of the brain showed a left temporoparietal infarct. A carotid Doppler scan showed a mobile blood clot in his left internal carotid artery that was removed by embolectomy. Haematological opinion was of chemotherapy and cancer leading to a hypercoaguable state producing carotid thrombosis. The patient was anticoagulated with warfarin. A restaging computed tomography scan after completion of chemotherapy confirmed complete remission. The patient recovered with specialist rehabilitation.

Discussion

Different clinical manifestations of cisplatin-associated thrombosis can cause significant morbidity and mortality. Cisplatin-associated vascular toxicity comprises (i) venoocclusive disease, (ii) venous or arterial thrombosis, and (iii) vascular ischaemia [1]. Researchers have

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attempted to identify those at risk of cisplatin-associated thrombosis. In a prospective study of gemcitabine-associated and cisplatin-associated vascular events, 22 events occurred in 108 lung cancer patients. No risk factors were statistically significant, but there was a nonsignificant trend towards presence of liver and brain metastases [2]. Similarly, no difference was found between cervical cancer patients receiving chemo-radiotherapy who had thromboembolism compared with those who did not [3]. Among 184 germ cell patients, 8.4% of patients developed thromboembolic disease. Liver metastases and use of high-dose dexamethasone were predictive factors for developing vascular toxicity [4]. In a case–control study of germ cell patients (controls were individuals without germ cell tumours receiving cisplatin), high lactate dehydrogenase and body surface area greater than 1.9 increased the risk of thromboembolic disease [5]. Potentially, these factors could be used to identify patients at high risk so that thromboprophylaxis can be instigated.

Raynaud's phenomenon is the most common vascular effect of cisplatin occurring in up to 37% of patients. Raynaud's is caused by vasospasm and can persist up to 20 years after completion of chemotherapy in 25% of patients [6]. Cisplatin-treated patients have an exaggerated cold response and an increased vasoconstrictor reflex in a cold provocation test. Thus, cisplatin may impair autoregulation particularly in the terminal arterioles by altering the sympathetic nervous system [7].

Cardiac events are more frequent among patients with germ cell tumour, with 14 extra cases of coronary artery disease per 10 000 person years occurring [8]. Mediastinal irradiation, cisplatin, vinblastine and bleomycin chemotherapy, but not BEP, were associated with increased risk of myocardial infarction. Cardiac events occurring many years after treatment may relate to increased total and low-density lipoprotein cholesterol with decreased high-density lipoprotein. Some patients develop elevated luteinizing hormone and follicle-stimulating hormone and lower testosterone suggestive of gonadal damage. This may lead to metabolic abnormalities increasing cardiovascular risk [6].

Cisplatin also alters the balance between thrombosis and dissolution of blood clots. Putative mechanisms of action include: decreased protein C activity and elevated von Willebrand factor levels [9]. Protein C inhibits coagulation: its levels maybe decreased by proteolytic enzymes released after cisplatin-induced vascular injury. Von Willebrand factor levels may be increased by stimulation of the endothelium by cisplatin thus promoting platelet aggregation. This can lead to a thrombotic thrombocytopenic purpura-like picture [9]. Measuring von Willebrand factor levels before chemotherapy may identify those at risk of thromboembolic complications [10]. Cisplatin can also alter cytokine profiles; for example, increasing tumour necrosis factor (procoagulant for endothelial cells) and decreasing prostacyclin synthesis causing intravascular platelet aggregation. Thrombocytosis itself may influence thrombosis [11].

Biochemical imbalances such as hypomagnesaemia may contribute to cisplatin-associated thrombosis [9]. Hypomagnesaemia causes hypertension and increases intracellular calcium-causing vasoconstriction. Hypomagnesaemia potentiates vasoconstrictor actions of renin, angiotensin, serotonin and noradrenaline. This can cause vasospasm and thus ischaemia or thrombosis. Hypomagnesaemia may play a key role in acute vascular events associated with cisplatin.

Cisplatin can cause direct endovascular damage by free-radical-induced lipid peroxidation in endothelial cells [12]. This can cause intimal thickening and platelet aggregation. Light microscopy studies have demonstrated cisplatin-induced bulging and swelling of endothelial cells. Electron microscopy has demonstrated lesions in endothelial cells, the basement membrane and damage to pericytes after cisplatin treatment [13]. In-vitro studies have shown that cisplatin leads to activation of caspase 3-like activity causing necrosis rather than the usual apoptosis. Subsequent inflammation may facilitate thrombosis [14]. Another in-vitro study showed cisplatin induces platelet reactivity via direct or indirect activation of platelet phospholipase A2 [15], which increases platelet aggregation and thromboxane production. Cisplatin may also impair fibrinolysis thus promoting thrombosis [13].

Conclusion

Cisplatin-associated thrombosis is an increasingly recognized complication causing morbidity and even mortality. Cisplatin-associated thrombosis is multifactorial with different mechanisms influencing acute and chronic presentations. For acute thrombosis, cisplatin has a direct effect on the endovascular milieu; for example, neurological, biochemical, cytokine and prostaglandin changes. In the longer term, thrombosis is a result of chronic endothelial, endocrine and autonomic perturbations. Further data are required to help predict those at risk and also to prevent thrombotic outcomes. Furthermore, particularly in individuals with a good life expectancy, risk factors for thrombosis should be aggressively determined, monitored and treated.

References

1 Barcelo R, Lopez-Vivanco G, Mane JM, Rubio I, Munoz A, Fernandez R. Distal ischaemic changes related to combination chemotherapy with gemcitabine and cisplatin: description of four cases. *Ann Oncol* 2000; **11**:1191–1194.

2 Barcelo R, Munoz A, Lopez-Vivanco G. Prospective evaluation of major vascular events in patients with non-small cell lung cancer treated with cisplatin and gemcitabine. *Cancer* 2005; **104**:1110–1111.
3 Jacobson GM, Kamath RS, Smith BJ, Goodheart MJ. Thromboembolic events in patients treated with definitive chemotherapy and radiation therapy for invasive cervical cancer. *Gynaecol Oncol* 2005; **96**:470–474.
4 Weijl NI, Rutten MFL, Zwinderman AH, Jan Keizer J, Nooy MA, Rosendaal FR, *et al*. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Onc* 2000; **18**: 2169–2178.
5 Piketty AC, Flechon A, Laplanche A, Nouyrigat E, Droz JP, Theodore C, Fizazi K. The risk of thromboembolic events is increased in patients with germ cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. *Br J Cancer* 2005; **93**:909–914.
6 Meinardi MT, van der Graff WTA, van Veldhuisen DJ, Runne WJ, Sluiter WJ, de Vries EGE, *et al*. Cardiovascular morbidity in long term survivors of metastatic testicular cancer. *J Clin Oncol* 2000; **18**:1725–1732.
7 Hansen SW, Olsen N, Rossing N, Rerth M. Vascular toxicity and the mechanism underlying Raynaud's phenomenon in patients treated with cisplatin, vinblastine and bleomycin. *Ann Oncol* 1990; **1**:289–292.
8 Van den Belt-Dusebout AW, Nuver J, de Wit R, Gietema JA, ten Bokkel Huinink WW, Rodrigus PT, *et al*. Long term risk of cardiovascular disease in 5 year survivors of testicular cancer. *J Clin Oncol* 2006; **24**:467–475.
9 Anders JC, Grigsby PW, Singh AK. Cisplatin chemotherapy (without erythropoietin) and risk of life threatening thromboembolic events in carcinoma of the uterine cervix: the tip of the iceberg? *Rev Lit Radiat Oncol* 2006; **1**:14.
10 Matthews J, Goel R, Evans WK, Shamji F, Stewart DJ. Arterial occlusion in patients with peripheral vascular disease treated with platinum-based regimens for lung cancer. *Cancer Chemother Pharmacol* 1997; **40**: 19–22.
11 Zecchina G, Ghio P, Bosio S, Cravino M, Camaschella C, Scagliotti GV. Reactive thrombocytosis might contribute to chemotherapy-related thrombophilia in patients with lung cancer. *Clin Lung Cancer* 2007; **8**: 264–267.
12 Ohashi S, Yazumi S, Nishio A, Fukui T, Asada M, Chiba T. Acute cerebral infarction during combination chemotherapy with S1 and cisplatin for a young patient with a mucin producing adenocarcinoma of the stomach. *Intern Med* 2006; **45**:1049–1053.
13 Gerl A. Vascular toxicity associated with chemotherapy for testicular cancer. *Anticancer Drugs* 1994; **5**:607–614.
14 Dursun B, He Z, Somerset H, Oh D-J, Faubel S, Edelstein CL. Caspases and calpain are independent mediators of cisplatin-induced endothelial cell necrosis. *Am J Physiol Renal Physiol* 2006; **291**:f578–f587.
15 Togna GI, Togna AR, Franconi M, Caprino L. Cisplatin triggers platelet activation. *Thromb Res* 2000; **99**:503–509.