

# Aortic Occlusion in Patients Treated with Cisplatin-Based Chemotherapy

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## Abstract

Cisplatin-based chemotherapy is one of the most common chemotherapy regimens that is complicated by thromboembolic events. A wide spectrum of vascular events exists, including venous and arterial thromboses of varying severity and location. However, total occlusion of the aorta is very unusual. We describe two patients with atherosclerotic vascular disease who developed occlusion of the abdominal aorta after cisplatin-based chemotherapy.

**Key Words:** Cisplatin-based chemotherapy, thrombosis, aorta, peripheral vascular disease.

## Introduction

PATIENTS WITH CANCER have a highly increased risk of thrombotic events, with venous thrombosis far more common than arterial thrombosis. However, compared to venous thrombosis, arterial vascular events are more likely to be life or limb threatening. A number of chemotherapeutic medicines have been associated with an increased rate of thromboembolism. Anti-cancer drugs known to cause vascular events include platinum-based compounds, vinca alkaloids, bleomycin, dacarbazine, L-asparaginase, tamoxifen, and diethylstilbestrol. The wide spectrum of arterial and venous thromboembolic events are well-known complications of cisplatin-based chemotherapy, but total aortic occlusion is very uncommon. We present two patients with known atherosclerotic disease who developed total occlusion of the abdominal aorta following cisplatin-based chemotherapy.

## Case 1

A 52-year-old female presented with poorly differentiated gastric adenocarcinoma with liver metastases. Her history was remarkable for insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, smoking and ischemic heart disease. Her chronic medications were aspirin, atenolol, slow-released nifedipine, simvastatin and valsartan. The patient received chemotherapy consisting of cisplatin 75 mg/m<sup>2</sup> intravenously on day 1; 5-fluorouracil 1200 mg/m<sup>2</sup> as continuous intravenous infusion; and 5-fluorouracil 400 mg/m<sup>2</sup> as intravenous bolus and leucovorin 200 mg/m<sup>2</sup> on days 1, 2, 15, and 16. On day 18 of the chemotherapy cycle, the patient developed paresthesias of both legs and buttock pain. After a few hours her legs were cold, painful, pale and weak. No femoral, popliteal or distal foot pulses were detected. Doppler study showed occlusion of the aorto-iliac segment with total lack of blood flow to the legs. A clinical diagnosis of aortic occlusion with bilateral leg ischemia was made, and subcutaneous low-molecular-weight heparin (LMWH), enoxaparin, was started. A computed tomography (CT) scan showed thrombosis of the aorta immediately below the level of the renal arteries, and thrombosis of both common and external iliac ar-

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teries with open femoral arteries. The patient's poor general condition, due to extensive metastatic disease, precluded surgical intervention and thrombectomy. She remained in the hospital and subsequently expired.

### Case 2

A 57-year-old female was investigated for chest pain and hyponatremia. She had a history of smoking, hyperlipidemia and ischemic heart disease, with myocardial infarction two years earlier. She was being treated with simvastatin and aspirin. A CT scan revealed a left lower lobe mass and multiple liver lesions. A transbronchial biopsy identified the mass as small-cell lung cancer. The patient received four cycles of chemotherapy using cisplatin 80 mg/m<sup>2</sup> intravenously on day 1 of the cycle and etoposide 100 mg/m<sup>2</sup> intravenously on days 1–3; this was repeated every 21 days. Three days after completion of the fourth cycle of chemotherapy, the patient developed numbness in her left hand and left foot. The next day she was admitted to the hospital with severe pain in her back and both legs. The neurological examination was normal. Spinal cord compression was suspected, but a CT scan of the head and spine was normal. During the next 24 hours the patient developed cyanosis of both feet. Doppler study showed occlusion of the aorto-iliac segment and stenosis of calf arteries bilateral with ankle-brachial indexes of 0.32 and 0.11 in the right and left sides, respectively. A CT scan showed saddle thrombus beginning 3 cm above the aortic bifurcation (see Figure). Subcutaneous enoxaparin (LMWH) was started, and the patient underwent bilateral transfemoral thrombectomy. A repeat Doppler study, performed 5 days after the operation, revealed stenosis of the right calf arteries with ankle-brachial indexes of 0.76 and 1.2 in the right and left sides, respectively. Enoxaparin was continued. The chemotherapy regimen was changed to carboplatin and etoposide. Two months after surgery the patient was free from peripheral vascular disease symptoms, and the ankle-brachial index was 0.75 in each leg.

### Discussion

Cisplatin-induced thromboembolic events are well-known and widely described complications of cisplatin-based chemotherapy. Several hypotheses have been proposed to explain the occurrence of venous and arterial complications in patients treated by cisplatin-based chemotherapy, including hypomagnesemia, damage of the vascular endothe-



**Figure.** A contrast enhanced coronal CT section shows saddle thrombus beginning 3 cm above the aortic bifurcation.

lium, and elevated von Willebrand factor plasma levels (1). A wide spectrum of vascular events exists, including venous and arterial thrombosis of various severities and locations. However, total occlusion of the aorta is very unusual, and only two cases have been described previously (2) Our patients had multiple risk factors for cisplatin-induced complications, including evidence of widespread atherosclerotic disease, liver metastases, hypomagnesemia and antiemetic therapy with dexamethasone. Both patients developed total occlusion of the abdominal aorta and were treated with low-molecular-weight heparin (enoxaparin), and one of them underwent surgical revascularization.

There are a few published studies concerning the incidence of vascular complications of platinum-based chemotherapy.

Weijl et al. (1) performed a retrospective study of 179 patients who received a cisplatin-containing regimen for germ-cell cancer. Eighteen vascular events occurred in 15 patients (8.4%), including three arterial events. Liver metastases and the administration of  $\geq 80$  mg dexamethasone per cycle as antiemetic therapy were risk factors for the development of major thromboembolic complications.

Numico et al. (3) recently evaluated major vascular events in 108 patients with non-small-cell lung carcinoma treated with cisplatin and gemcitabine chemotherapy. Overall, 22 vascular episodes occurred in 19 patients (17.6%), including 10 arterial events (2 myocardial infarctions, 7 lower limb arterial thromboses, 1 ischemic stroke) and 12 venous thromboemboli. Four patients died

due to the vascular events and 3 patients required surgical revascularization.

In a retrospective study of 263 patients who received cisplatin as part of chemotherapy for urothelial cancer, Czaykowski et al. found a 12.9% incidence of vascular events with a 4.1% incidence of arterial thrombosis (4).

Mathews et al. (2) described 5 patients who received chemotherapy with combinations containing cisplatin or carboplatin for lung cancer, and developed arterial thrombosis soon after initiation of treatment. Cardiovascular risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, smoking and preexisting arterial disease, were detected as important risk factors for the development of arterial thrombosis. In this study, two cases of aortic occlusion were described. One patient underwent thrombectomy of the aorta with aortobifemoral grafts and was free from vascular symptoms three years after the operation. A second patient underwent axillary bifemoral grafting and developed a recurrence of leg ischemia after cisplatin with etoposide chemotherapy one year later. He underwent thrombectomy of one of the axillofemoral grafts.

Since cisplatin-induced thromboembolic events are not rare, we suggest that preventive anticoagulation during and a few days following the administration of cisplatin-based chemotherapy may be effective in patients with multiple risk factors for vascular events.

Use of preventive anticoagulation in cancer patients at high risk of thrombosis is not new in oncology. Very-low-dose warfarin has proven to be effective in patients with metastatic breast cancer receiving chemotherapy (5). LMWH (nadroparin) at a fixed, prophylactic dose and warfarin at a fixed, very low dose had a similar benefit-to-risk ratio and lowered the risk of adverse events in the prevention of thrombosis associated with central venous catheters in cancer patients (6). Although interaction between warfarin and cisplatin has not

been reported in the literature, use of warfarin with other chemotherapeutic drugs (5-fluorouracil or etoposide) commonly given in combination with cisplatin may alter the metabolism and anticoagulant effect of warfarin (7, 8). We suggest that preventive anticoagulation by LMWHs may be more effective and safer.

However, further prospective studies are needed to confirm the possible effectiveness of LMWH in preventing vascular events in cancer patients receiving platinum-based therapy.

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