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Arterial occlusion in patients with peripheral vascular disease treated with platinum-based regimens for lung cancer

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Abstract *Background*: Patients with cancer may be hypercoagulable, and smoking can cause both lung cancer and peripheral vascular disease. Cisplatin-based chemotherapy has been reported to cause a variety of vascular side effects. *Case reports*: Five patients with bronchogenic carcinoma and peripheral vascular disease developed acute arterial occlusion soon after receiving a combination of cisplatin or carboplatin plus etoposide. All these patients had risk factors for atherosclerosis and three of them had preexisting known peripheral vascular disease. *Conclusions*: The occurrence of acute arterial occlusion soon after initiation of chemotherapy suggests that it might have been a complication of this therapy. Hence, caution should be exercised when using platinum-based (and other?) chemotherapy in patients with known moderate or severe peripheral vascular disease.

Key words Arterial peripheral vascular disease · Platinum-based chemotherapy · Lung cancer

Introduction

Cisplatin is a drug widely used in the chemotherapy of bronchogenic carcinomas [1]. Vascular side effects of cisplatin combinations that have been noted recently include acute coronary events [2], cerebrovascular accidents [3], Raynaud's phenomenon [4], renovascular hypertension [5], and pulmonary emboli [6]. However, it has been questioned whether cisplatin therapy increases the incidence of cardiovascular adverse effects [7]. There have been reported cases of digital gangrene following therapy with vinca alkaloids and bleomycin for Kaposi's sarcoma associated with acquired immunodeficiency syndrome (AIDS) [8]. We describe here five patients with lung cancer and peripheral vascular disease who developed arterial occlusion shortly after chemotherapy with combinations containing cisplatin or carboplatin.

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Case reports

Case 1

A 54-year-old male with a 60 pack-year smoking history presented in January 1993 with hemoptysis. A chest radiograph showed a left upper lobe opacity. Bronchoscopy showed a tumor obstructing the left upper lobe bronchus. Mediastinoscopy showed the presence of mediastinal nodes positive for adenocarcinoma. The stage of his disease was T3, N3, MX at diagnosis. He had had a previous carotid endarterectomy for transient ischemic attacks (in 1985). He was treated with chemotherapy consisting of one cycle of cisplatin 80 mg/m^2 intravenously on day 1 and etoposide 100 mg/m^2 orally on day 1 to day 6 beginning 4 June 1993. A week after initiating chemotherapy, he developed cyanosis of his right great toe. He was evaluated and found on doppler study to have decreased circulation in his right leg below the knee. He was treated conservatively with pentoxifylline and analgesics. His symptoms worsened over the next week. On 15 June 1993, he was admitted to the hospital with worsening discomfort in his right leg. An angiogram showed that his descending aorta was blocked below the renal arteries. He developed gangrene of his right foot which required amputation below the knee. This was done on 30 June 1993. In the last part of June he developed hemoptysis and was given 2000 cGy of radiotherapy. He remained in hospital and subsequently expired on 6 July 1993.

Case 2

A 71-year-old male with a 40 pack-year history of smoking presented in April 1990 with hemoptysis, weight loss, and cough. He had

a previous history of atrial fibrillation, peripheral vascular disease, and an abdominal aortic aneurysm repair. A chest radiograph showed right upper lobe atelectasis. A bronchoscopy revealed a tumor in the right main stem bronchus. Biopsy showed the diagnosis to be small-cell lung cancer. He was felt to have limited stage disease at diagnosis. He received chemotherapy consisting of carboplatin 150 mg/m^2 intravenously on day 1 and etoposide 100 mg/m^2 orally on day 1 to day 7 for six cycles starting on 20 April 1990. He developed sudden weakness of his legs 10 days after beginning chemotherapy. He was found to have occlusive vascular disease of the aorta. He underwent axillary bifemoral grafting. After the planned six cycles of chemotherapy, he was given radiotherapy of 4500 cGy to the lung followed by prophylactic cranial irradiation. In January 1991, the lung tumor was noted to be progressing. As he then was asymptomatic he was initially observed without treatment. He was given further chemotherapy with 5-fluorouracil and folinic acid as in an investigational protocol. He was admitted on 29 July 1991 with acute pain in his left leg. No blood flow was demonstrable in his left leg on doppler study. He underwent exploration of the left groin and thrombectomy of the left axillofemoral graft. He had an episode of atrial fibrillation in the postoperative period. His disease was felt to be progressing and a decision was made to start him again on chemotherapy. He received cisplatin 75 mg/m^2 intravenously on day 1 and oral etoposide 100 mg/m^2 orally on days 1 to 7, beginning 12 August 1991, while he was in the hospital for worsening of his peripheral vascular disease. He then received the second cycle of carboplatin 150 mg/m^2 and etoposide 100 mg/M^2 orally for 7 days starting 21 October 1991. In November 1991 he was admitted with pain in his left foot with gangrenous toes. Amputation was suggested but his general condition was poor. Only pain control was attempted. He was subsequently transferred to a palliative care unit, where he died on 13 November 1991.

Case 3

A 54-year-old female was investigated for microscopic hematuria in September 1991. A chest radiograph showed a left upper lobe lesion. She did not have any respiratory symptoms at that time. She was a smoker of one pack of cigarettes per day. Her past history included hypothyroidism and transient ischemic attacks. Further investigations including needle biopsy led to a diagnosis of large-cell lung cancer metastatic to the mediastinal nodes. She was given radiotherapy of 6000 cGy over 6 weeks with concurrent chemotherapy with cisplatin and etoposide. Chemotherapy was begun on 19 September 1991 with cisplatin 75 mg/m^2 intravenously on day 1 and etoposide 70 mg/m^2 intravenously on day 1 and 140 mg/m^2 orally on the next 2 days. Half way through the second cycle of chemotherapy she developed leg paresthesias and low back pain. A myelogram was normal. Flow studies showed total lack of blood flow to the legs. A translumbar aortogram showed thrombosis of the aorta at the level of the renal arteries. On 25 February 1992, she had a thrombectomy of the aorta and aortobifemoral grafts. She was discharged home on 5 March 1992. She was last seen on 8 September 1994, at which time she was free of evidence of recurrence of her cancer or of her vascular disease.

Case 4

A 68-year-old male had an aortobifemoral bypass graft in 1984. He also had a past history of hypertension, angina and hypercholesterolemia. He was a smoker since childhood. He was admitted in November 1991 with a 2-cm supraclavicular lymph node. On biopsy, a diagnosis of small-cell cancer was made. He was started on chemotherapy on 31 December 1991. He received cisplatin 80 mg/m^2 intravenously on day 1 and etoposide 100 mg/m^2 intravenously on day 1 and 100 mg/m^2 orally on the next 4 days. He was given a second cycle of the same chemotherapy on 22 January 1992. In early February 1992, he was admitted with febrile neutropenia and then went on to develop a myocardial infarction. He received another cycle of chemotherapy with carboplatin 150 mg/m^2 intravenously on day 1 and etoposide 75 mg/m^2 orally for 7 days beginning 2 March 1992. In mid-March 1992, he developed pain in his right leg and went on to develop dry gangrene in the third, fourth and fifth toes. An angiogram showed complete occlusion of the left internal iliac artery and the right popliteal artery. On 10 April 1992 he underwent axillobifemoral grafting. In June 1992, he was admitted with increasing confusion and found to have several large metastatic lesions in his brain. He was given palliative radiotherapy, but did not improve. He was then transferred to a palliative care unit where he died on 6 August 1992.

Case 5

A 67-year-old female presented in February 1992 with a history of fatigue, weight loss, dysphagia, and hoarseness. She had a 25 pack-year history of smoking and a previous history of right carotid endarterectomy. A chest radiograph showed a left upper lobe lesion and postobstructive atelectasis. She had metastases to the liver and bone at the time of diagnosis. She was started on an investigational chemotherapy regimen consisting of gemcitabine. As her tumor progressed on this, she was then treated with cisplatin 80 mg/m^2 intravenously on day 1 and etoposide 100 mg/m^2 intravenously on day 1 and orally on the next 4 days. This chemotherapy was begun on 22 June 1992. On 6 July 1992, she was seen with a 5-day history of pain and numbness in her right foot. An angiogram showed complete occlusion of the right superficial femoral artery. On 24 July she underwent a femoropopliteal artery bypass using a vein graft. In October 1992, she developed a nonhealing ulcer on her right leg which required amputation. She also had ongoing pain in her left foot. In January 1993, she was readmitted when an aortogram showed occlusion of a previously stenosed area at the femoropopliteal junction on the left. A left femoropopliteal graft was done on 2 January 1993. She subsequently had increasing rib pain thought to be a result of tumor progression. She deteriorated and died on 21 April 1993.

Discussion

The association of Raynaud's phenomenon with chemotherapy was noted with bleomycin around 1977. Vogelzang et al. used a questionnaire to study the incidence of Raynaud's phenomenon in patients with testicular cancer undergoing combination chemotherapy. Digital ischemia occurred in 21% of patients treated with vinblastine and bleomycin, and the addition of cisplatin to the regimen doubled the incidence of Raynaud's phenomenon [9].

There are many reports, both of single cases and of series of cases, of cerebrovascular and cardiovascular arterial occlusion in patients treated with cisplatin-based chemotherapy [2, 3, 10, 11]. There are some reports of myocardial infarction and cerebrovascular accident in patients with no risk factors for atherosclerosis and normal angiography [3].

In our cases, all the patients had one or more risk factors for atherosclerosis. Three of the five had preexisting vascular disease. Hence, the development of arterial thrombi in these patients may have been solely

the result of the natural progression of their vascular disease or the known thrombogenic effects of their underlying malignancies. However, looking at the timing of events, we feel that combination chemotherapy including cisplatin or carboplatin plus etoposide may have played a role in the arterial occlusions suffered by these patients. The exact pathogenesis of these vascular events is not clear. One study has found a correlation between hypomagnesemia and Raynaud's phenomenon [12], and in that report it was sugested that hypomagnesemia potentiates spasm of arteries leading to occlusion. In a review of our patients, only one (case 3) had hypomagnesemia severe enough to receive supplements. Licciardello et al. have found an association between elevated plasma levels of von Willebrand factor antigen and arterial occlusive complications in patients on cisplatin-based chemotherapy [13]. They felt that a subgroup of patients susceptible to arterial occlusive complications could be identified based on elevated levels of von Willebrand factor antigen prior to chemotherapy. The exact pathophysiological basis for this association is unknown. They suggested that the mechanism is similar to thrombotic thrombocytopenia purpura and hemolytic uremic syndrome. In addition, patients receiving cisplatin undergo aggressive hydration and diuresis to reduce nephrotoxicity. If diuresis substantially exceeds hydration, such that dehydration ensues, this could also possibly increase the risk of thrombotic events. However, none of our five patients became clinically dehydrated.

In addition to cisplatin or carboplatin, all the above patients were also taking etoposide. In our review of the literature, we did not come across reports of etoposide causing vascular adverse effects. A report in 1992 has suggested an association of vascular adverse effects with ondansetron [14]. However, four out of five patients in that series received cisplatin as part of their combination chemotherapy. The manufacturer of ondansetron subsequently stated that there is no evidence that ondansetron contributed to those events [15]. In our patients, ondansetron was used as an antiemetic in patients 1, 4 and 5. We do not know if this added to the risk. In addition, it remains possible that some interaction between the various components of the treatment regimen may have been of more importance than the individual components themselves.

Nichols et al. evaluated patients entered on a testicular cancer intergroup study [7]. They did not find an increased risk of cardiovascular complications in the cisplatin-treated group when compared with the control group. The treated group consisted of patients receiving chemotherapy for adjuvant treatment and for recurrent disease. The control group were patients with early stage testicular cancer who were being closely observed. They suggested that sporadic cases of cardiovascular disease were coincidental.

In conclusion, all our patients discussed above had lung cancer and were smokers. They also had other risk factors for atherosclerosis. All of them had advanced malignancy, which itself could cause a hypercoagulable state. Hence, there are several possible explanations for the thrombotic events in these patients. However, because of the temporal relationships observed, we feel that their chemotherapy (cisplatin or carboplatin plus etoposide) may have played a role in precipitating their arterial thrombi. If the chemotherapy did indeed play a role in these events, it is unclear whether the major precipitating factor was the platinate drug, the etoposide, some other concurrent medication, or whether it was a nonspecific effect of chemotherapy in general. Of the agents used in these patients, cisplatin has most frequently been reported in the past to be associated with vascular events.

Patients developing arterial thrombi represent only about 2% of the estimated number of all lung cancer patients treated with chemotherapy at the Civic Division of the Ottawa Regional Cancer Centre between 1990 and 1993. Hence, for the average patient, the risk is not high. However, we would suggest caution and close observation for lung cancer patients with known moderate or severe peripheral vascular disease who are undergoing chemotherapy, particularly with platinum-based regimens. A recent multicentre placebo-controlled study has shown that very-low-dose warfarin is effective in preventing venous thromboembolism in patients with metastatic breast cancer receiving chemotherapy [16]. It is possible that such low-dose warfarin would also reduce the risk of arterial thromboembolic complications in lung cancer patients receiving platinum-based chemotherapy.

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