Annals of Oncology **11**: 1191–1194, 2000.

Clinical case

Distal ischemic changes related to combination chemotherapy with cisplatin and gemcitabine: Description of four cases

R. Barceló, G. López-Vivanco, J. M. Mañé, I. Rubio, A. Muñoz & R. Fernández

Medical Oncology, Hospital de Cruces, Osakidetza/Servicio Vasco de Salud, Barakaldo, Spain

Key words: cisplatin, drug-induced toxicity, gemcitabine, lung cancer, vascular damage

Introduction

Cancer chemotherapeutic agents have been related to three main forms of vascular toxicity: 1) Veno-occlusive disease of hepatic vessels or in rare instances, of pulmonary vessels [1]. 2) Venous or arterial thrombosis [2]. 3) Vascular ischemia involving cerebral, myocardial, or extremity arterial vessels [3]. The number of agents implicated in these toxicities is increasing (Table 1), although the precise pathogenesis of these toxic effects has not been elucidated. Vascular changes may also be related to the underlying neoplasms or to unrecognized previous vascular disease, e.g., tobacco-related. Distal arterial ischemia is a rare complication induced by chemotherapy, and may be associated with preexistent organic changes.

In the present article we report four cases of lung cancer and peripheral ischemia during chemotherapy with cisplatin and gemcitabine.

Case report 1

A 51-year-old white male, single, presented with a diagnosis of squamous-cell lung cancer. He had been smoking 30 packs/year, had had traumatic fracture of ribs two years before, had been exposed at work to asbesto for two years 20 years ago, and had no other relevant medical history.

One month before diagnosis he developed a cough with blood stained sputum, 14 kg weight loss, dyspnoea, hoarseness, and chest pain. A CT scan showed a large central mass, infiltrating mediastinal structures (left pulmonary artery, left atrium, right pulmonary artery), with atelectasis of left lung, and pleural effusion. Flexible fiberoptic bronchoscopy showed tracheal compression and diffuse infiltrative tissue in the left main bronchial tree with obstruction at the division to the upper lobe. Biopsy showed squamous-cell carcinoma with keratin pearls. Days later, the patient developed acute symptoms of fever, dyspnea and left thoracic pain, and a left empyema was evacuated.

When first seen at our Department, the patient had ECOG performance status of 1. On physical examination he had clubbing and hypoventilation at the base of the left lung. Pulses were normal and there was no peripheral edema. White-cell count was 24,700 per mm^3, platelet count 613,000 per mm^3. Blood chemical and enzyme values included calcium 10.9 mg/dl, albumin 3.1 g/dl, sodium 131 mmol/l, lactate dehydrogenase 660 U/l. FEV1 was 1.4 l (44.8% of predicted).

Staged as IIIB, combination chemotherapy was started with cisplatin and gemcitabine. The treatment schedule consisted of intravenous cisplatin (100 mg/m^2), with hydratation, serotonin blockade, corticosteroids, every three weeks and intravenous gemcitabine (1,200 mg/m^2) on days 1 and 8 every three weeks.

After two cycles, toxicity was mild and well tolerated. On day 8 of the second cycle, he complained of pain and erythema on dorsum and sole of left foot that had began

Table 1. Some anticancer agents with vascular toxicity.

Hepatic veno-occlusive disease
BCNU, cisplatin, busulfan, cyclophosphamide, cytarabine, dacarbazine, urethane, azathioprine, etoposide, mitomycin, 6-thioguanine, gemcitabine, high-dose therapy
Pulmonary veno-occlusive disease
Bleomycin, mitomycin, BCNU
Budd–Chiari syndrome
Dacarbazine, 6-thioguanine, cytarabine, methotrexate
Raynaud's phenomenon
Cisplatin based polichemotherapy, bleomycin combinations, vinca alkaloid combinations, doxorubicin
Myocardial infarction and ischemia
Vinca alkaloids, bleomycin, cisplatin–bleomycin–vinblastine combinations, 5-fluorouracil
Thrombotic microangiopathy
Mitomycin, cisplatin, carboplatin, bleomycin, gemcitabine
Thrombosis and thromboembolic events
Cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone, doxorubicin, tamoxifen, cisplatin-gemcitabine combination?

after day one of the second cycle. Examination revealed erythema and pain on palpation of distal area of left foot. Pulses were felt. NSAIDs were given, with relief of pain. When third cycle started, he was well, with a good response on chest radiography. Persistent pain in left foot was still a problem, and the Vascular Department was consulted. When he came to fourth cycle, he complained of intense pain in his left foot that was worse at night, with coldness. Urgent evaluation with arteriography revealed a normal abdominal aorta, a 50% stenosis of left common iliac artery, normal femoral vessels (common and superficial), popliteal artery stenosis but permeable and sural vessels were not refilled. Right common and superficial femoral arteries were permeable, as two sural vessels, but with severe stenosis of the right tibio-peroneal tree.

Five months after the diagnosis of his cancer, a left infracondileal amputation was performed due to severe distal obliterans arteriopathy. Reevaluated with CT scan, two mediastinal subcarinal nodes of 1.5 cm and 2 cm diameter and a linear slight collapse of lingula were seen. He has adapted well to his leg prothesis and has started radical radiation therapy.

Case report 2

A 46-year-old male was diagnosed of squamous carcinoma of the upper lobe of the right lung. He had been smoking 60 packs/year and drinking 40 grams of ethanol/day, had hypercholesterolemia for five years with no treatment. He also had arterial hypertension treated medically for two years, one episode of renal colic ten years before and a sacro-coxygeal fistula. Two years before presentation, a left submandibular pleomorphic adenoma was resected. He also had suffered a traumatic fracture of his right hip and a pneumonic illness.

Four weeks before the diagnosis of cancer he developed acute right chest pain, which responded well to NSAIDs. Later, haemoptysis was seen, and after chest radiography and CT scan, bronchoscopy and biopsy, an upper right lobe squamous-cell lung cancer was diagnosed, stage $T_2N_3M_0$–IIIB. Physical examination and blood tests were normal. He had an ECOG performance status of 0, and combination chemotherapy was started with cisplatin and gemcitabine, with schedule identical to case 1. On the second week after the initial cycle, the patient consulted due to pain in his feet after chemotherapy (days one and eight), more intense in the right foot, with colour changes. Interpreted as basal arterial problem, with vasospastic phenomena, a doppler echography only showed a slight deficit in arterial supply. Treated with triflusal an antiplatelet agent and buflomedil a vasoactive drug, his pain resolved. Chemotherapy was continued with good tolerance, and when evaluated after third cycle, progressive disease was seen, with an upper right lobe mass of 4 cm, mediastinal nodes of 5 cm and superior vena cava compression. Treatment was switched to paclitaxel monotherapy (200 mg/m^2). He had progressive disease after three cycles with brain metastases and no response to palliative radiation therapy. He died five months after the cancer diagnosis. Necropsy was not allowed.

Case report 3

A 67-year-old male was diagnosed of poorly differentiated non-small-cell carcinoma of the right lung. He had been smoking 50 packs/year until 14 years before, and had no other relevant medical history. Five months before diagnosis, chest pain followed by cough and dyspnea developed. CT scan and bronchoscopy showed right lung atelectasis, pleural effussion and multiple mediastinal adenopathies. There was an endobronchial mass in the intermediary bronchus, biopsy of which showed poorly differentiated non-small-cell carcinoma. Repeated cytology of the pleural effussion did not show malignant cells. Mediastinoscopy showed multiple adenopathies with poorly differentiated non-small-cell carcinoma.

Physical examination and blood tests were normal. He had an ECOG performance status of 1, and combination chemotherapy was started with the regime described above. After three cycles dyspnea and cough resolved, and a partial response was seen with CT scan. After the third cycle the patient complained of pain and coldness in the left foot, with functional claudication at 20 metres. This improved with triflusal and buflomedil. Reevaluated with CT scan after six cycles, there was only a small nodule in the lower right lobe, 3 × 2 × 1.5 cm, and no adenopathy were seen. After the sixth cycle, his left foot pain worsened, with absence of pedial and popliteal pulses. Fifteen days after, a thrombus was removed from the left popliteal artery, and three days later, a new thrombus was removed and a venous patch inserted, and his symptoms resolved.

Case report 4

A 62-year-old male was diagnosed as having a squamous carcinoma of the left lung. He had smoked 50 packs/year and drunk 60 grams of ethanol/day. He had a history of peptic dyspepsia treated with anti-H2 medication, chronic bronchitis with dyspnea, inguinal surgery for a hernia, appendicectomy and a benign prostatic hypertrophy not requiring treatment.

One month before diagnosis, he developed malaise with 10 kg weight loss. He then developed cough, fever and purulent sputum. On CT scan and chest X-ray, atelectasis of the left lung due to a left hilar mass was seen. Bronchoscopy and biopsy was diagnostic of squamous-cell carcinoma, stage $T_4N_1M_0$. Chemotherapy with cisplatin and gemcitabine, as described above, was begun. After three cycles, clinical and radiologic stabilization was seen.

He complained of distal claudication at 200 metres.

Pedial pulses were palpable, with distal coldness. Acute distal arterial ischemia was diagnosed. His popliteal pulses were palpable, but distal pulses in the right leg and foot were not felt. Triflusal and buflomedil were given. After five cycles of chemotherapy, his subacute ischemia worsened, with arterial thrombosis. Popliteal thrombectomy and patch repair was performed twice without success. Clinical and radiological local cancer progression was also evident. A week after his second thrombectomy, a right infracondileal amputation was needed. One day after amputation, abdominal pain began, urgent laparotomy showed intestinal ischemia, and he died the next day.

Discussion

Distal ischemic changes in cancer patients are rare. They may be related to organic vascular disease due to hypercholesterolemia, arterial hypertension, or exposure to tobacco. They may also be related to mucin and non-mucin-producing tumours or to cancer treatment. All these factors may combine and it may be difficult to attribute an exact role in their genesis to one or another [4, 5].

Breast cancer chemotherapy has been related to arterial thrombosis during treatment, with an incidence of 1.3%. The mechanism is not well understood, but statistically significant decreases in protein C and protein S levels were noted. Tamoxifen has also been implicated in thrombosis, procoagulant effect and modest reductions in antithrombin III and protein C [6].

Some cisplatin combinations have been related to cerebral vascular strokes or to myocardial infarction, sometimes preceded by Raynaud's phenomenon [7]. In our experience, cisplatin use does not seem to have been followed by any vascular event in an heterogeneous population of more than 700 patients (4–6 cycles/patient), treated with diferent combinations in the four years period 1994–1998 (lung cancer, testicular cancer, head and neck and esophageal carcinoma, ovarian carcinoma, nasopharyngeal cancer, bladder carcinoma…).

Dacarbazine has been related to Budd–Chiari syndrome. Veno-occlusive disease of the liver has been reported in patients treated with high-dose chemotherapy and also in patients with acute myelocytic leukemia who were treated with thioguanine and daunomycin with or without cytarabine. Asparaginase inhibites synthesis of many plasma proteins including prothrombin, factors V, VII, VIII, IX, X, and XI, fibrinogen, antithrombin III, protein C, protein S, and plasminogen, and has been related with thrombotic complications [6].

Treatment with 5-fluorouracil, an antitumoral antimetabolite, has been related to myocardial ischemia and infarction, sometimes in patients without previous coronary disease. Pathogenesis is not completely understood, although it may be related to coronary spasm. Treatment with nitrates and prevention with calcium antagonists have been advocated [8, 9].

A difluorated analogue of ara-C, gemcitabine, also an antimetabolite, has not been related to arterial ischemia, thrombosis or vascular spasm. It is a drug with a few major side effects, both hematologic and non-hematologic [10]. Seldom, cases of edema due to capillary leak syndrome, fatal lung toxicity with alveolar damage or veno-occlusive disease with liver failure have been described [11–13]. Changes in glomerular filtration do not seem to be relevant [14]. A case of hemolytic-uremic syndrome has been described [15].

Cisplatin plus gemcitabine combination chemotherapy for lung cancer patients has been evaluated in phase I, II and III trials [16–18]. The main toxicities have been mild neutropenia and thrombocytopenia, with no toxic deaths. No peripheral vascular events have been reported in hundreds of lung cancer patients treated with different schedules of cisplatin and gemcitabine.

In the first case described, an asymptomatic previous organic lesion was aggravated while on cisplatin–gemcitabine chemotherapy, with irreversible ischemia and unavoidable amputation. In the second case, cancer treatment was followed by pain and colour changes in feet, with no relevant basal arterial flow obstruction seen in doppler echography. His symptoms disappeared with medical treatment. In the third and fourth cases, ischemic symptoms appeared during chemotherapy, arterial thrombosis developed, thrombectomy and a vascular patch were required, and in one case, amputation was mandatory. Basic coagulation studies were normal, but deficiences of antithrombin III, protein C, protein S or other alterations were not studied.

In our experience of 33 lung cancer patients, treated with a mean of 4.8 cycles of cisplatin plus gemcitabine, we have seen these four cases of distal ischaemia. Clinical evaluation for distal ischaemia in the other patients, discovered no other cases with subtle changes. These findings point to an unusual phenomenon, perhaps related to a specific predisposition.

To our knowledge, no cases of vascular toxicity related to this combination have been published. The sequence of events related to treatment and the time of onset of symptoms point to some effect of the chemotherapeutic agents, but more data are needed to conclude whether cisplatin and gemcitabine were causally related to these events. Putative mechanisms are not known.

Physiology of arterial spasms is being studied and chemical mediators of platelet or endothelial origin are being characterized [19]. In cancer patients, tumor factors and anticancer agents may also be implicated. Some cytotoxic agents, like vinblastine, can have a direct endothelial effect which may lead to vascular collapse and tumor necrosis. Drugs with new mechanisms against tumoral vessels are being explored [20].

Peripheral ischemia is a rare event in cancer patients. Unusual symptoms, especially when new agents are being used, should be followed up by appropiate studies. As more patients are treated with this combination, cases of Raynaud's phenomenon, distal ischemia or

arterial thrombosis should be sought. In the presence of arterial spasms, anticoagulant and vasodilatator therapy may be useful. More severe organic vascular disease may require more agresive approaches.

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Received 28 April 1999; accepted 7 July 1999.

Correspondence to:
R. Barceló, MD
Medical Oncology
Hospital de Cruces
Plaza de Cruces s/n
48903 Barakaldo
Bizkaia
Spain