Intersticial pneumonitis after oxaliplatin treatment in colorectal cancer

Xavier Hernández Yagüe, Ester Soy, Bernardo Queralt Merino, Josep Puig, Miguel Beltrán Fabregat and Ramón Colomer

Oncología Médica. Institut Català d'Oncologia. Girona. Spain.

Progressive respiratory failure developed in a 68 year-old female who was treated with single-agent oxaliplatin for colorectal cancer. Only one cycle of 5-fluorouracil had been previously administered. Computed tomography of the chest showed lesions that suggested pulmonary fibrosis. There was an unfavourable response to treatment with corticosteroids, antimicrobial and antifungical agents. Lung biopsy findings were compatible with interstitial pneumonitis. The patient died 20 days after admission due to irreversible respiratory failure. This is the first case reported in the literature of interstitial pneumonitis related to single-agent oxaliplatin administration.

Key words: oxaliplatin, pulmonary fibrosis, colorectal cancer, interstitial pneumonitis.

Hernández Yagüe X, Soy E, Queralt Merino B, Puig J, Beltrán Fabregat M, Colomer R. Intersticial pneumonitis after oxaliplatin treatment in colorectal cancer. Clin Transl Oncol. 2005;7(11):515-7.

INTRODUCTION

Lung toxicity associated with anticancer drugs is usual. Some clinical syndromes include pneumonitis/fibrosis, noncardiogenic pulmonary edema or hypersensitivity lung disease. Pulmonary toxicity associated to bleomycin or nitrosoureas has been extensively studied. There are additional reports of lung injury after cytarabine, gemcitabine, docetaxel, vinblastine, methotrexate, liposomal doxorubicin and trastuzumab use[1,2]. Some of the more recent anticancer drugs, such as oxaliplatin, still have not been avaluated in this setting. A literature review shows two reports of 5-fluorouracil (5-FU) plus oxaliplatin associated with pulmonary toxicity[3,4]. There are, however, no reports that conclusively link oxaliplatin to pulmonary toxicity.

CASE REPORT

A 68-year-old women, with a previous histoy of allergy to penicilin and acarus underwent a right hemicolectomy for colon cancer in May 2003. Pathology showed a moderately differenciated adenocarcinoma, 5 centimeters in its largest diameter, that infiltrated the pericolonic fat and the serosa. There was also perineural and vascular invasion. Involvement was observed in one of fourteen regional lymph nodes. Staging did not show distant disease. She was diagnosed of a colon cancer stage IIIB, pT4 pN1 M0 (TNM classification), Dukes C; with a high relapse risk. The patient had a good performance status and she was indicated adjuvant chemotherapy with 5-FU and folinic acid using the Mayo Clinic schedule. The chest X-ray pre-chemotherapy was normal. The first cycle was administered on 30th June 2003. On the ninth day of the cycle she had grade III stomatitis, pharyngitis, vomiting and severe diarrhea (more than 7 stools/day). She was changed to oxaliplatin (85 mg/m^2 D1 intravenous in a two hours infusion every 3 weeks). Six cycles were administered from 27th August 2003 to 19th January 2004. She had only grade II thrombopenia as chemotherapy related toxicity. On 9th February 2004, however, she was admitted because of progressive dyspnea with haemoptoic sputum ocasionally. During the last two weeks she had cough. She did not take any drugs at home in the last weeks. She was afebrile. On physical examination dry velcro crackles were audible in both lung bases. A high-resolution computed tomography (HR-CT) of the chest showed bilateral interstitial infiltrates on peripheric parenchyma and thickened septal lines (fig. 1). Respiratory functional tests demonstrated a moderately-severe restrictive pulmonary disease. The bronchoscopy found chronic bronquitis and the bronchial biopsy showed squamous methaplasia. Bronchoalveolar lavage fluid showed mild inflammation, with 90% macrophages and 10% lymphocytes. Cultures were non-significant. CEA, Ca 19.9, citomegalovirus serologies and blood cultures for aerobic and anaerobic

Correspondence: Javier Hernández Yagüe.
Oncología Médica.
Institut Català d'Oncologia.
Ctra. França, s/n.
17001 Girona. España.
E-mail: xhernandez@icogirona.scs.es

Received 7 April 2005; Revised 8 June 2005; Accepted 11 July 2005.

Fig. 1. High resolution computed tomography of the chest with bilateral intersticial infiltrates on peripheric parenchyma and thickened septal lines.

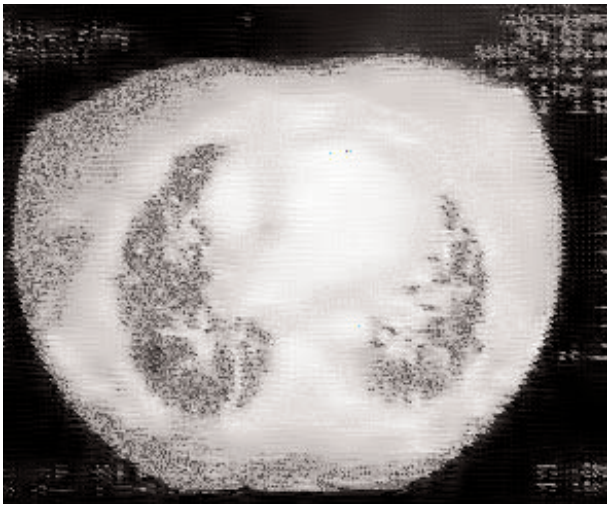

Fig. 2. Computed tomography with massive bilateral interstitial infiltrates, thickened interlobulillar septal lines and massive alveolar ocupation in both lung.

bacteria were negative. It was indicated to begin oral treatment with prednisone with the presumptive diagnosis of idiophatic pulmonary fibrosis. At the begining of the treatment the patient felt better in terms of dyspnea and clinical status. Four weeks later, however, the patient presented progressive respiratory failure. A computed tomography (CT) showed massive bilateral interstitial infiltrates, thickened interlobulillar septal lines and massive alveolar ocupation in both lungs (fig. 2). After an unsuccessful attemp of medical treatment and noninvasive ventilation, she was intubated and mechanically ventilated. Serum studies showed CEA 13.2 ng/ml (0.01 – 5 ng/ml), Ca 19.9, and serologies for hepatitis virus types B and C were negative. Bronchioalveolar lavage did not show malignant cells or oportunistic infection. A wide spectrum antibacterial and antifungical treatment was used, with vasoactive drugs (because of haemodynamic inestability), sulphametoxazol/trimetoprim and high doses of intravenous prednisone. Her pulmonary function did not improve after four days of treatment. A lung biopsy was performed by thoracostomy. The anatomopathological findings were interstitial pneumonitis with associated diffuse alveolar abnormalities in exudative phase. Microscopical description showed interalveolar septi with lymphoplasmocytic infiltrate, fibroblastic proliferation foci and normal lung areas with hyperplasia of alveolar cells type II. Squamous methaplastic foci and hyalinic membrane draped the alveolar walls. Twenty-one days after admission the patient died due to irreversible respiratory failure.

DISCUSSION

We report the first clinical case of lung toxicity after oxaliplatin use. Oxaliplatin is a diaminocyclohexano platinum with activity reported in advanced colorectal cancer[5]. In clinical and preclinical studies it has been established the toxicity in relation to its use. The major toxicity is a peripheal sensory neuropathy; renal, haematological and gastointestinal are less frequent[6,7]. Although two reports have suggested an association of oxaliplatin and pulmonary toxicity, in these cases 5-FU was also used[3,4]; and it is difficult to establish the individual contribution of oxaliplatin to the pulmonary damage. In our case report we can exclude other concurrent drugs, as well as infectious causes, because the patient was afebrile, she did not respond to antibacterial and antifungical therapy, there were negative results in blood cultures and absence of opportunist infections signs in bronchioalveolar lavage. In addition, the pathological findings exclude lymphangitic carcinomatosis, histiocytosis X, sarcoidosis, alveolar proteinosis, alveolar haemorrhage, bronchiolitis obliterans organizing pneumonia and lymphangiomatosis. The patient has not been exposed to thoracic ionizing radiation. Therefore, we believe that the cumulative use of oxaliplatin was the responsible of pulmonary damage in front of the idiophatic aetiology[8]. Interstitial pneumonitis can be a type of idiophatic pulmonary fibrosis in which lesions in different evolutive phase coexist in the Katzenstein pathological classification. There is a theory that attemps to relate the anatomopathological findings and a possible aetiology in repeated injury over the alveolar epithelial cell[9], such as the administration of a drug. In our report, the patient has received repeated doses of oxaliplatin as single agent, until a few weeks before the start of respiratory symptoms. It is mandatory to remember the patient received one cycle of 5-FU (425 $mg/m^2 \times 5$ days) that was stopped because severe gastrointestinal toxicity. Taking into account the data we suggest that oxaliplatin can be responsible of the interstitial pneumonitis and, as the reports published

before, it could be related to the previous 5-FU exposition too. There is reported a case of acute interstitial pneumonia and extremely rapid unfavourable course[10] as the patient in our report.

References

1. Briasoulis E, Pavlidis N. Noncardiogenic pulmonary edema: an unusual and serious complication of anticancer therapy. The Oncologist. 2001;6:153-61.
2. Radzikowska E, Szczepulska E, Chabowski M et al. Organizing pneumonia caused by trastuzumab (Herceptin) therapy for breast cancer. Eur Respir J. 2003;21(3):552-5.
3. Gagnadoux F, Roiron C, Carrie E, et al. Eosinophilic lung disease under chemotherapy with oxaliplatin for colorectal cancer. Am J Clin Oncol. 2002;25(4):388-90.
4. Trisolini R, Lazzari Agli L, Tassinari D, et al. Acute lung injury associated with 5-fluorouracil and oxaliplatinum combined chemotherapy. Eur Respir J. 2001;18(1):243-5.
5. Becouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol. 1998;16(8):2739-44.
6. Ramanathan RK, Clark JW, Kemeny NE, et al. Safety and toxicity analysis of oxaliplatin combined with fluorouracil or as a single agent in patients with previously treated advanced colorectal cancer. J Clin Oncol. 2003;21(15): 2904-11.
7. Raymond E, Chaney SG, Taamma A, et al. Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol. 1998;9(10):1053-71.
8. Selman M, Thannickal VJ, Pardo A, et al. Idiopathic pulmonary fibrosis: pathogenesis ang therapeutic approaches. Drugs. 2004;64(4):405-30.
9. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157:1031-315.
10. Kaido M, Koide O, Obata H, et al. An autopsy case of acute interstitial pneumonia. J UOEH. 1990;12(3):361-7.