Letter to the Editor

Chemotherapy

Chemotherapy 2010;56:69–70
DOI: 10.1159/000282286

Received: March 5, 2009
Accepted after revision: June 30, 2009
Published online: February 8, 2010

Interstitial Pneumonitis after Treatment with Bevacizumab and Pegylated Liposomal Doxorubicin in a Patient with Metastatic Breast Cancer

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We report on a patient with metastatic breast cancer in whom interstitial pneumonitis developed after treatment with bevacizumab in combination with pegylated liposomal doxorubicin (PLD). Re-exposure to PLD after recovery was without any pulmonary side effects.

A 53-year-old woman presented with symptomatic histologically proven diffuse metastatic infiltration of the stomach as the only site of disease 5 years after primary diagnosis of lobular breast cancer. Treatment with PLD (Caelyx®) 20 mg/m^2 in combination with bevacizumab (Avastin®) 10 mg/kg every 2 weeks was started in a study protocol.

Treatment was initially well tolerated and abdominal symptoms disappeared completely. After 3 courses of treatment, the patient developed persistent cough and shortness of breath. High-resolution CT scan showed ground glass opacities compatible with interstitial pneumonitis. Analysis of arterial blood gases confirmed the presence of hypoxemia. As history and diagnostic work-up could rule out other causes of interstitial pneumonitis (infections, tumor progression and autoimmune disorders), drug-induced interstitial pneumonitis was regarded the most likely cause of respiratory symptoms. All antineoplastic drugs were discontinued. With prednisone 50 mg daily, tapered off over 6 weeks, symptoms resolved promptly, and lung function tests and CT scan after 6 weeks documented improvement (table 1). We assumed bevacizumab more likely causative for drug-induced pneumonitis than PLD as there are much more safety data available for PLD without clear evidence of interstitial pneumonitis related to PLD [1]. Thus, we decided to reinitiate PLD alone after a 3-month treatment holiday. No pulmonary side effects were noted, suggesting bevacizumab being the cause of interstitial pneumonitis. Pulmonary complications observed so far with bevacizumab are hemorrhage and hemoptysis, mainly observed in lung cancer patients and more commonly seen in patients with squamous cell carcinoma of the lung than in those with nonsquamous histology [2]. Only lately, a first description of interstitial pneumonitis in a patient treated with the combination of bevacizumab and docetaxel has been reported [3].

The pathogenesis of antineoplastic drug-induced lung injury is poorly understood. Direct injury to pneumocytes or the alveolar capillary endothelium (chemical alveolitis) may contribute to chemotherapy-induced lung injury. Monoclonal antibodies like rituximab and trastuzumab have also been associated with interstitial pneumonitis. Cytokine release and inability of pneumocytes to respond to lung injury through HER2 inhibition have been postulated as mechanisms in these cases [4]. Recently, abnormal vascular endothelial growth factor expression has been shown in patients with interstitial pneumonitis [5]. We hypothesize that by impairing the alveolar repair mechanism through antiangiogenic mechanisms, lung injury may be potentiated by bevacizumab and may facilitate the development of pneumonitis as observed in our patient.

Here, we report a case of interstitial pneumonitis most likely associated with the drug bevacizumab. As bevacizumab was given in combination with chemotherapy, the causative role of bevacizumab is not definitely proven. However, since the patient's re-exposure to PLD was without any pulmonary symptoms, pneumonitis was most likely caused or potentiated by bevacizumab. Physicians should thus be aware of this rare but serious side effect when prescribing this drug.

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0009–3157/10/0561–0069$26.00/0

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Table 1. Symptoms, diagnostic procedures and results

	At diagnosis	At follow-up
Clinical signs and symptoms	cough and dyspnea CTC grade III	resolved
CT of the chest	ground glass opacities in several areas of the lung (high-resolution CT)	normal
Bronchoscopy with bronchoalveolar lavage	total cell count 119 × 10^6 lymphocytes 49% macrophages 48% neutrophilic granulocytes 1% eosinophilic granulocytes 2% no malignant cells no growth of fungi, bacteriae including acid-fast bacilli	
Blood gas analysis on room air at rest	pH 7.44 pCO_2 35.6 mm Hg pO_2 50.1 mm Hg alveolo-arterial oxygen gradient 48.4 mm Hg oxygen saturation 85%	
Oxygen saturation by pulse oximetry at rest	oxygen saturation 89%	oxygen saturation 95%
Lung function tests		
Forced vital capacity	3.00 liters (95% predicted)	3.50 liters (111% predicted)
Forced expiratory volume	2.56 liters (95% predicted)	2.74 liters (102% predicted)
Diffusing capacity for carbon monoxide	4.5 mmol/min/kPa (54% predicted)	6.9 mmol/min/kPa (82% predicted)

CTC = Common terminology criteria for adverse events, version 3.0.

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