Severe, but manageable hypoxia caused by bronchospasm induced by bevacizumab

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Abstract
Bevacizumab has a lower risk of treatment-related infusion reactions than other humanized monoclonal antibodies, and bronchospasm induced by bevacizumab has not been reported. We administered bevacizumab 15 mg/kg over 90 min infusion to a 34 year-old man with lung adenocarcinoma and childhood asthma. Then, grade 3 hypoxia developed and improved spontaneously. This reversible obstructive lung disorder was confirmed using a flow-volume loop, and the patient was diagnosed as having a bronchospasm due to infusion reaction of bevacizumab. This bronchospasm was easily manageable and preventable using an oral bronchodilator and an inhalant combination product, and the patient continued with bevacizumab therapy until the disease progression.

Introduction
Bevacizumab is a ≥90% human monoclonal antibody, with only the hyper-variable region remaining structurally murine, that binds vascular endothelial growth factor [1]. It improves response rates, progression-free survival and overall survival compared with chemotherapy alone in metastatic colorectal cancer, metastatic breast cancer, and advanced non-squamous and non-small cell lung cancer (NSCLC). The risk of treatment-related infusion reactions is far lower for bevacizumab than for other humanized monoclonal antibodies [2]. Especially, a bronchospasm induced by bevacizumab has never been reported. Here, we report a case of hypoxia and bronchospasm induced by bevacizumab as an infusion reaction in a patient with lung adenocarcinoma and childhood asthma.

Case Report
A 34-year-old man with childhood bronchial asthma that had improved during his late teens visited our hospital with dyspnea upon effort. A chest X-ray revealed a massive right pleural effusion. Cytology of the pleural fluid was positive for adenocarcinoma, and he was diagnosed with stage IV NSCLC. He underwent pleurodesis followed by first-line chemotherapy with four cycles of carboplatin and paclitaxel with bevacizumab in outpatient clinic. Bevacizumab maintenance was added until disease progression. The tumor progressed after two cycles of bevacizumab maintenance, although all toxicities during this period were mild and manageable. Second-, third-, and fourth-line therapies comprised crizotinib, pemetrexed and cisplatin plus docetaxel, respectively. Gemcitabine and bevacizumab were then administered under hospitalization as fifth-line therapy because the lung cancer had progressed and his physical status had deteriorated, despite having a performance status of 1. On day 1, gemcitabine was administered intravenously (i.v.) and bevacizumab (15 mg/kg) was infused over a period of 90 min. Five hours after the bevacizumab infusion, dyspnea developed upon moderate exertion and his blood oxygen saturation level (SpO2) decreased to 87% at rest without any physical signs. The dyspnea and SpO2 spontaneously resolved within 2 h. Gemcitabine alone was administered i.v. on day 8 and the
SpO₂ value did not decrease. On day 1 of the second and third cycles of this regimen, SpO₂ decreased about 5 h after the bevacizumab infusion, and a chest X-ray and computed tomography (CT) at this time did not detect any abnormal findings other than the lung cancer. We suspected that the hypoxia was associated with reversible bronchospasm induced by bevacizumab, and evaluated his pulmonary functions by spirometry before and after bevacizumab administration. On day 1 of the fourth cycle of this regimen, we repeated the pulmonary function test before and after bevacizumab administration. Figure 1A shows the flow-volume loop obtained before bevacizumab administration. The predictive vital capacity percentage (%VC) was slightly reduced by a pleural effusion, but a force expiratory volume in 1 sec (FEV₁.0) was 2.27 L and the ratio of FEV₁.0 over forced vital capacity 100 (FEV₁.0%) was 77%. The obstruction lung disorder was not observed. Figure 1B shows the flow-volume loop obtained after bevacizumab administration. Values for FEV₁.0, FEV₁.0% and SpO₂ were decreased (from 2.27 to 0.95 L; from 77% to 68% and <90% in room air, respectively). We administered procaterol 20 μg/body by inhalation and reevaluated the pulmonary functions. Figure 1C shows the flow-volume loop obtained after inhalation of procaterol. The obstructive lung disorder shown in Figure 1B was improved, and SpO₂ was recovered to >95%. We then had the patient inhale of fluticasone/salmeterol to prevent the bronchospasm. Figure 1D shows the flow-volume loop obtained at 11 h after the fifth cycle of bevacizumab. Dyspnea, decreased SpO₂, and the obstructive lung disorder were not evident during this cycle. We subsequently employed preventative fluticasone/salmeterol inhalation therapy prior to the administration of bevacizumab, which allowed a sixth cycle of therapy to be completed without bronchospasm. Subsequently, disease progression was detected on chest CT after the sixth cycle of chemotherapy, and bevacizumab therapy was discontinued. Regardless, fluticasone/salmeterol therapy was able to prevent bevacizumab-induced bronchospasm when administered for the last two cycles of therapy.

**Discussion**

Monoclonal antibodies have different toxicity profiles from cytotoxic drugs that are administered together with chemotherapy. They carry a risk for infusion reactions, which are caused by cytokine release from target and immune effector cells [3–5]. Most infusion reactions appear similar to a type I hypersensitivity reactions and range from mild allergic symptoms such as itching and flushing to severe responses resembling anaphylactic reactions, including bronchospasm [3–5]. Infusion reactions to bevacizumab have generally been mild and rare compared with other monoclonal antibodies [2], and bronchospasm has never been reported. Our spirometric findings proved that bevacizumab can induce bronchospasm.

This patient had grade 3 hypoxia in terms of the common terminology criteria for adverse events v4.0, although the bronchospasm and dyspnea were recognized as grade 1. These adverse events were undetectable during
first-line treatment with bevacizumab with carboplatin and paclitaxel. The first-line regimen also included premedication with a 16.5-mg bolus of dexamethasone, which might have masked the signs and symptoms of bronchospasm. Only 3 mg of dexamethasone premedication was administered in the regimen comprising bevacizumab with gemcitabine. In addition, physicians might have missed the initial symptoms of mild bronchospasm because they might have developed after the patient departed from the outpatient clinic where the first-line treatment was administered.

Bronchospasm caused severe hypoxia in this patient, but it was immediately improved by administering a beta2-agonist, and preventable by inhaling a corticosteroid and a long-acting beta2 agonist. Bevacizumab might be safe even in patients who develop bronchospasm as an infusion reaction if premedication is adequate.

In conclusion, we described a patient with advanced NSCLC and childhood asthma who developed bronchospasm and temporary, but severe hypoxia because of the treatment-related infusion reaction of bevacizumab. However, these adverse events were easily manageable and preventable using an oral bronchodilator and an inhaled combination product. To establish the adequate premedication preventing a bronchospasm, physicians should investigate the hypoxia induced by bevacizumab.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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