Vemurafenib-Induced Pulmonary Injury

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To the Editor:

For patients with malignant melanoma, in non-resectable stage III or stage IV and showing evidence of oncogenetic BRAF mutation, therapy with the selective tyrosine kinase inhibitor vemurafenib is the state of the art. In phase 1, 2, and 3 clinical trials vemurafenib was associated with consistent efficacy and improved survival [1–3]. Multiple cutaneous side effects like rash, arthralgia, photosensitivity, and keratoacanthoma-like lesions have been reported [4].

We report the case of a 48-year-old woman with metastatic melanoma under therapy with vemurafenib, who presented with bipulmonary infiltrates mimicking atypical pneumonia (fig. 1A). Pulmonary symptoms with sporadic dry coughing and an elevated temperature of 37.5°C developed at week 10 after initiation of treatment with a standard dose of vemurafenib, 960 mg twice daily. C-reactive protein was initially elevated at 4.6 mg/dl (normal < 0.5) up to a peak value of 7.0 mg/dl after 3 days; procalcitonin levels remained at 0.1 ng/ml (< 0.1) and leukocyte count at 9,900/nl (4,500–11,000); and oxygen saturation was 98% spontaneously. Bronchoalveolar lavage (BAL) was conducted twice, but indicated no signs for a viral, bacterial or fungal origin of the infiltrates. Serum antibodies were negative for relevant pathogens (*Aspergillus*, *Candida*, *Chlamydia*, *Legionella*, cytomegalovirus and *Mycoplasma*). No additional medication was administered.

Due to the tentative diagnosis of an atypical bacterial pneumonia, oral treatment with levofloxacin 500 mg once daily and clarithromycin 250 mg twice daily was initiated over a course of 3 weeks, while treatment with vemurafenib was discontinued. Follow-up computed tomography scans showed

a nearly complete remission of the infiltrations 6 days after discontinuation of vemurafenib therapy (fig. 1B). Vemurafenib was administered again at the standard dose (960 mg twice daily) for 2 weeks after withdrawal. 3 weeks after re-initiation of vemurafenib the lung infiltrations worsened again. Because of 2 surgical interventions (uterine metastatic bleeding and non-responding axillar lymph node metastasis) administration of vemurafenib had to be stopped, twice for 3 days in each case. During these, albeit short, treatment pauses the lung infiltrates regressed once again, confirming a causative correlation to vemurafenib treatment. Because of the good response of the target lesions, we decided to continue vemurafenib treatment but at a reduced dose of 720 mg twice daily. Under this regimen, pulmonary infiltrates were no longer observed (fig. 2).

Fig. 1. **A** Thoracic chest CT scan with multiple bipulmonary infiltrates 10 weeks after begin of a therapy with vemurafenib. **B** Follow-up CT scan of the chest 6 days after discontinuation of vemurafenib, showing a regression of infiltrates. **C** Worsening of the pulmonary infiltrates 3 weeks after continuation of vemurafenib at a dose of 960 mg twice daily. **D** Follow-up CT scan 3 days after discontinuation of vemurafenib.

Fig. 2. Time course of the appearance of pulmonary infiltrates with vemurafenib treatment.

Chemotherapy-induced lung injury has been described previously. Multi-tyrosine kinase inhibitors like gefitinib and imatinib, given to patients for different oncological diseases such as advanced liver cancer, chronic myelogenous leukemia and gastrointestinal tumors, have been identified as risk factors for interstitial pneumonia [5, 6]. The large variety of tumors with proven selective BRAF mutations, such as anaplastic thyroid cancer or adenocarcinoma of the lung, indicate that treatment with selective BRAF inhibitors like vemurafenib may well play an increasing role in the treatment of these diseases in future [7, 8]. Programmed death-1 (PD-1) receptor antibodies have also recently been shown to be

associated with pulmonary toxicity [9, 10]. To our knowledge this is the first report of pulmonary injury associated with vemurafenib treatment. Since this problem is just emerging, and may even vary based upon nature of the underlying malignancy, we recommend that patients receiving vemurafenib should be monitored closely for lung toxicity.

Disclosure Statement

The authors declare no conflict of interests.

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