Dramatic Response Induced by Vemurafenib in a \textit{BRAF} V600E-Mutated Lung Adenocarcinoma

Case Report

A 66-year-old man, a never-smoker, was referred to our oncology department in April 2011 for stage IV non–small-cell lung cancer (NSCLC). The patient had developed progressive left thoracic pain followed by dyspnea and fatigue. A subsequent chest computed tomography (CT) scan showed massive left pleural effusion and pleural thickening, mainly involving the mediastinal pleura. Histologic examination of pleural biopsies revealed poorly differentiated adenocarcinoma that was positive for CK7 and thyroid transcription factor 1 and negative for Wilms tumor 1 and calretinin. \(^{18}\text{F}\)fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scanning additionally showed intense metabolic activity in the left pleura and celiac lymph nodes. Brain magnetic resonance imaging was negative.

Polymerase chain reaction (PCR) and pyrosequencing did not reveal any activating epidermal growth factor receptor (\textit{EGFR}) mutation. Reverse transcriptase PCR did not show any specific \textit{ALK} rearrangement. Given the patient’s never-smoker status, additional molecular analyses were performed and revealed a \textit{BRAF} V600E mutation.

The patient underwent left pleurodesis and subsequently completed four cycles of chemotherapy with cisplatin and pemetrexed, with a partial response. Eleven cycles of continuation maintenance chemotherapy with pemetrexed, with a nearly complete radiologic response, were delivered; however, PET/CT scanning in May 2012 showed progression in a single left pleural nodule and a left internal mammary lymph node, with high FDG uptake in both lesions. A left extrapleural pneumonectomy was discussed and performed in June 2012. Histologic examination showed a solid adenocarcinoma measuring 3 cm in largest diameter, with vascular invasion, positive resection margins in multiple pleural locations, and 14 metastatic lymph nodes, including six nonregional lymph nodes. The patient underwent hemithoracic external-beam radiotherapy with a total dose of 66 Gy encompassing all sites of incomplete tumor resection. After 10 sessions of radiotherapy at a dose of 2 Gy per day, and exactly 2 months after surgery, a follow-up CT scan revealed multiple new hepatic metastases involving both hepatic lobes (Fig 1). Off-label vemurafenib was started in September 2012 at a dose of 960 mg administered twice per day.

Concurrent radiotherapy that was restricted to the location of the positive resection margins was resumed, using a schedule of seven daily doses of 3 Gy, for a local total dose of 51 Gy, to prevent local symptomatic chest wall recurrence. Within 2 weeks, the patient developed a grade 3 rash covering the entire previously irradiated field that was consistent with a strong photosensitizing effect associated with a recall-like phenomenon; the rash persisted for more than 4 weeks (Figs 2A and 2B).

Follow-up CT scanning in September 2012 showed excellent partial response (Fig 3). PET/CT scanning in October 2012 after 6 weeks of treatment showed complete response, with no residual metabolic activity in the hepatic lesions (Fig 4). The patient is currently asymptomatic except for mild fatigue. During the third week of treatment, he developed common secondary skin lesions, such as keratoacanthoma, and treatment is ongoing under active surveillance.

Discussion

A growing number of distinct subtypes of NSCLC have been shown to be driven by a specific genetic alteration. So-called oncogene-addicted tumors are thus sensitive to inhibition of the corresponding activated oncogenic pathway. This new paradigm has substantially affected lung cancer treatment, shifting it from classical chemotherapy that is tailored according to the expected toxicity and histologic subtype to customized therapy for molecularly defined subsets of NSCLC, according to the specific oncogenic alteration.

Tumor genotype analysis has identified driver alterations in approximately 50% to 80% of patients with NSCLC. Sequist et al\textsuperscript{1} described a genetic driver change in 51% of more than 500 cases of NSCLC, mostly adenocarcinomas. The most common alterations identified were \textit{KRAS} or \textit{EGFR} mutations and \textit{ALK} rearrangements, as well as several rare alterations, including \textit{BRAF} mutations, in 1% of cases. Similarly, the National Cancer Institute’s Lung Cancer Mutation Consortium reported a prevalence of 54% of genetically defined, oncogene-addicted lung adenocarcinomas among 1,000 patients with NSCLC; \textit{BRAF} mutations were found in 3% of the samples.\textsuperscript{2}
**BRAF** mutations are found in approximately 1% to 5% of NSCLCs, almost exclusively in adenocarcinomas. BRAF functions as a kinase that links RAS guanosine triphosphatase to downstream proteins of the mitogen-activated protein kinase (MAPK) pathway by directly phosphorylating MEK. **BRAF** mutations have been shown to activate this proliferative pathway through a constitutive kinase activation and subsequently to activate MAPK2 and MAPK3, culminating in transcription of genes that favor proliferation and survival. The transforming ability was demonstrated in an inducible transgenic mouse model of **BRAF** V600E, in which mutant **BRAF** was sufficient for the development and necessary for the maintenance of lung adenocarcinoma.5

The mutations found in NSCLC are distinct from the melanoma setting: whereas **BRAF**-mutated melanoma harbors a V600E amino acid substitution in more than 80% of cases, NSCLC harbors non-V600E mutations in approximately 40% to 50% of cases; these mutations are located in exons 11 and 15. Remarkably, in recent reports, **BRAF** mutations were reported mainly in current or former smokers, and possibly predominantly in white patients.3,4,6 Screening 1,046 patients with NSCLC, Marchetti et al3 described **BRAF** mutations in 4.9% of adenocarcinomas and 0.3% of squamous NSCLCs. All non-V600E mutations (2%) that were detected in adenocarcinomas were found in smokers, and V600E mutations (2.8%) were substantially more frequent in women and in never-smokers. In this series, patients with **BRAF** V600E mutations had a more aggressive tumor histotype—characterized by micropapillary features—and phenotype, with shorter disease-free survival and overall survival. Interestingly, mutations in **BRAF** were mutually exclusive with **EGFR** and **KRAS** mutations and **ALK** rearrangements.
Current type I inhibitors that target BRAF, such as vemurafenib, have been designed to target the activated V600E mutant kinase, given that this specific mutation is largely predominant in metastatic melanoma, and vemurafenib has induced high response rates and prolonged survival. The activity of these type I inhibitors against other BRAF mutations found in NSCLC, such as G469A (39%) and D594G (11%), is unknown. Preclinical data suggest that non-V600E–mutated BRAF kinases are resistant to vemurafenib. In addition, there are preclinical data that suggest that BRAF mutations predict sensitivity of NSCLC cells to MEK inhibitors.

Clinical data on efficacy and resistance to BRAF pathway inhibitors in the lung cancer setting are scarce, and this subject is the focus of ongoing research. It has been observed that patients with colon cancer harboring BRAF V600E mutations show only a limited response to vemurafenib. In this setting, BRAF inhibition leads to rapid feedback activation of EGFR, and additional blockade of the EGFR pathway results in a strong synergy with BRAF V600E inhibition in vitro. The EGFR activation as an acquired mechanism of resistance has therefore been described in colorectal cancer and suggested in melanoma, in which vemurafenib inhibition of BRAF relieves an extracellular regulated kinase–dependent negative feedback loop that maintains EGFR in an inactive state. EGFR activation in turn activates the protein RAS, which promotes dimerization of BRAF. As RAF dimers are resistant to vemurafenib, activation of EGFR abrogates the drug’s inhibitory effect. Ubiquitous expression of EGFR in lung cancer cells might result in primary resistance to vemurafenib, as described with respect to colorectal cancer cells.

Response to vemurafenib in BRAF V600E–mutated lung adenocarcinoma has been reported in a single patient, who unfortunately experienced early death. In this article, we report a complete metabolic response in a patient with BRAF-mutated lung cancer.

The remarkable radiologic response of our patient argues against a similar pattern of EGFR feedbacks, at least in some BRAF V600E–mutated lung cancers, and suggests a potentially interesting activity of vemurafenib in this indication. Additional data are needed to prove this concept and describe tumor evolution and patient outcome under BRAF-targeted treatment. In addition to vemurafenib, other BRAF inhibitors are currently being tested. An ongoing phase II study is evaluating the selective BRAF kinase inhibitor dabrafenib (GSK2118436; GlaxoSmithKline, Philadelphia, PA) in patients with advanced NSCLC harboring BRAF mutations (A Phase II Study of the Selective BRAF Kinase Inhibitor GSK2118436 in Subjects With Advanced Non-Small Cell Lung Cancer and BRAF Mutations). A phase I study testing the multiple RAF kinase inhibitor (including CRAF, BRAF, and the activated mutant BRAF V600E) XL281 (BMS-908662; Bristol-Myers Squibb, Princeton, NJ) has also been completed (Safety and Efficacy Study of BMS-908662 Alone or in Combination With Cetuximab in Subjects With K-RAS or B-RAF Mutation Positive Advanced or Metastatic Colorectal Cancer), and results are awaited.

Targeting the MAPK pathway downstream of BRAF may abrogate signal transduction and inhibit tumor growth. MEK is such a target, and selumetinib (AZD6644; AstraZeneca, Wilmington, DE), a novel and highly selective MEK inhibitor, is being tested in an ongoing phase II clinical trial for patients with solid tumors harboring a BRAF mutation (AZD6244 in Cancers With BRAF Mutations).

Completion of radiotherapy concomitant with vemurafenib induced an impressive radiodermatitis that extended largely beyond the boundaries of the radiotherapy treatment field, and this hints at a radiation recall-like phenomenon. A high and frequent photosensitizing effect has been reported for vemurafenib that seems to be related to ultraviolet A. Our patient case suggests that x-ray toxicity could be based on a similar mechanism, and stresses the concept that vemurafenib should probably never be delivered concomitantly with radiotherapy.

In our patient, vemurafenib monotherapy induced rapid and complete metabolic and radiologic response. Close imaging follow-up with serial and multiple tumor biopsies on progression are planned and will be reported. Given that vemurafenib is already available on the market, such a case report is of importance to help guide innovative clinical research in a rapid and efficient manner, particularly in rare subsets of NSCLC. For the accumulating data to be applied to clinical practice, a continuous international collaborative effort is required to complete trials and provide a satisfactory level of evidence in terms of safety and outcome for our patients.

Solangé Peters, Olivier Michielin, and Stefan Zimmermann
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

ACKNOWLEDGMENT
S.P., O.M., and S.Z. contributed equally to this article.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None Consultant or Advisory Role: Olivier Michielin, Bristol-Myers Squibb (C), Roche (C) Stock Ownership: None Honoraria: None Research Funding: None Expert Testimony: None Patents: None Other Remuneration: None

REFERENCES


DOI: 10.1200/JCO.2012.47.6143; published online ahead of print at www.jco.org on June 3, 2013