Tumor flare after start of RAF inhibition in KRAS mutated NSCLC: a case report

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Abstract.
Here we describe a case of striking tumor flare after start of treatment with sorafenib and metformin as part of a phase II clinical trial. Previous reports have described a paradoxal activation of the MAPK pathway after treatment with a weak RAF inhibitor. This mechanism is based on inhibition of a negative feedback loop to upstream effectors of RAF and subsequently increased stimulation of the RAS-RAF-MEK-ERK (MAPK) pathway. We suggest that sorafenib may contribute to tumor progression through this mechanism and clinicians should be aware of this phenomenon when treating NSCLC patients with sorafenib.
Sorafenib, a multi-target tyrosine kinase inhibitor, has been intensively studied in non-small cell lung cancer (NSCLC). Sorafenib targets amongst others RAF kinases, downstream of RAS and is believed to be suitable for treatment in advanced NSCLC patients harboring a KRAS mutation. We performed 2 phase II clinical trials in advanced KRAS mutated NSCLC with single-agent sorafenib and sorafenib in combination with metformin, as treatment in second-line or beyond [1, 2].

Here, we describe a case of tumor “flare” immediately after start of treatment with sorafenib and metformin, which we believe may be the result of paradoxal activation of the RAS-MAPK pathway.

Figure 1. a. (left) A graph of tumor volume of the intrathoracic lesion followed in time (weeks). Black dots (•) represent tumor measurement assessed by CT scan. b. (below) CT scan images of the intrathoracic lesion followed in time.
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Case
A 43-year-old female with stage IV non-small cell lung cancer (NSCLC) of the right lower lobe and lymph node metastasis in the right upper neck was treated in first-line setting with carboplatin/paclitaxel/bevacizumab. Evaluation after 4 cycles showed a mixed response with regression of the intrathoracic lesion, but progression of the lymph node metastasis. Treatment was halted and the lymph node metastasis subsequently irradiated. The primary tumor was known to harbor a \textit{KRAS}’G12V’ mutation. She was enrolled in a phase II clinical trial with sorafenib 400 mg BID and metformin 1000 mg BID. Prior to start of treatment a thoracic CT scan was repeated showing no evident tumor growth (+9%) 8 weeks after end of first-line treatment. Tumor assessment after 3 weeks of treatment with sorafenib and metformin showed significant progression (+226%) of the intrathoracic lesion, lymphangitis carcinomatosa and a pleural effusion. Treatment was discontinued and third-line treatment with single-agent pemetrexed 500 mg/m^2 was initiated. CT evaluation after 2 cycles of pemetrexed showed a partial response (-66%; Fig. 1).

Discussion
Rapid progression of cancer has been described previously in studies with BRAF inhibitors. For example, in melanoma proliferative skin lesions are a well-known phenomenon in patients treated with BRAF inhibitors such as vemurafenib. It has been suggested that vemurafenib does not initiate these lesions, but accelerates growth by paradoxal activation of MAPK signalling[3]. An illustrative case report described a stage IV melanoma patient who was treated with vemurafenib[4]. During treatment a previously unrecognized \textit{NRAS} mutant chronic myelomonocytic leukemia (CMML) became clinically evident characterized by proliferation of a leukemic cell population with high ERK expression. Treatment with vemurafenib was interrupted showing decrease of leukemic cell count and a concomitant decrease of ERK expression. After restart of vemurafenib, the leukemic cell count rapidly increased. Figure 2 illustrates a possible mechanism by which sorafenib induces activation of the MAPK pathway. Under physiological conditions, wild-type RAF protein exists in an auto-inhibitory state[5]. Inhibition of RAF leads to its activation and can promote tumor progression in \textit{KRAS} mutated cells and models.
To our knowledge, we are the first to report possible tumor flare after treatment of \textit{KRAS} mutated NSCLC with sorafenib. We believe that paradoxal activation of a growth signaling pathway may drive this rapid progression based on previous reports in other malignancies.
Tumor flare after start sorafenib in KRAS mutated NSCLC treated with RAF inhibitors. Clinicians treating KRAS mutated (NSCLC) patients with RAF inhibitors should be aware of this phenomenon.

Figure 2. A model of paradoxal activation of the MAPK pathway. Sorafenib induces activation of RAF by inhibition of its auto-inhibitory state. This results in increased stimulation of the MAPK signaling pathway and induces accelerated tumor growth.
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References


