

Case Report

Rapid Improvement of the Performance Status and Reduction of the Tumor Size in KRAS-Mutated Colorectal Cancer Patient Receiving Binimetinib, Hydroxychloroquine, and Bevacizumab

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Keywords

Colorectal cancer · KRAS mutation · Binimetinib · Hydroxychloroquine · Bevacizumab

Abstract

Activating RAS mutations occur in more than a half of colorectal cancers (CRCs). RAS-mutated CRCs are notoriously difficult to treat given that they are characterized by the aggressive disease course and the lack of appropriate targeted therapies. Recent preclinical studies demonstrated that RAS-mutated cells escape from therapeutic MEK inhibition by the development of autophagy, and this escape may be prevented by the administration of an antimalarial drug, hydroxychloroquine. The available clinical data are limited to a single case observation involving a patient with KRAS-mutated pancreatic cancer. Here, we report a woman with KRAS G12D-mutated CRC, whose tumor did not respond to conventional therapy. The combination of binimetinib, hydroxychloroquine, and bevacizumab was administered as a last-hope option. The patient experienced rapid improvement of the performance status. The tumor lumps demonstrated 17% reduction in the size within the first 6 weeks of the therapy. This report calls for evaluation of the efficacy of a combination of MEK inhibitors and hydroxychloroquine, possibly with the addition of bevacizumab, in chemotherapy-resistant patients with RAS-mutated cancers.

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Published by S. Karger AG, Basel

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Introduction

RAS mutations occur in approximately 80–90% of pancreatic carcinomas, 60% of colorectal cancers (CRCs), 30% of lung malignancies, and in many other tumor types. There is a huge diversity of RAS-activating nucleotide substitutions, with most of the alterations located within codons 12, 13, 59, and 61. Recent development of KRAS G12C-specific drugs led to a breakthrough in the treatment of lung cancers carrying this mutation. The design of inhibitors of RAS proteins carrying other amino acid changes turned out to be highly complicated, given that the conformation of mutated RAS enzymes is generally considered “non-druggable.” Consequently, there are attempts to develop “universal” drugs for RAS-driven pathways, which either interfere with the upstream regulation of RAS or counterbalance the consequences of RAS activation [1–3].

Cancers carrying KRAS, NRAS, HRAS, or BRAF mutations are characterized by the upregulation of MEK kinase. Accordingly, pharmacological MEK inhibition demonstrated promising results in preclinical models of RAS/RAF-driven cancers. However, clinical trials involving single-agent MEK inhibitors in patients with RAS and BRAF mutations produced largely disappointing results [2, 3]. It was recently shown that the escape of RAS/RAF-mutated tumors from MEK inhibition is mediated by autophagy. Furthermore, the use of the antimalarial drug hydroxychloroquine, which is a known pharmacological downregulator of autophagy, potentiated antitumor activity of MEK inhibitors in preclinical experiments and in a single observation involving a patient with KRAS-mutated pancreatic cancer [4, 5].

Colon cancer accounts for more than a million cases worldwide, with about a half of CRC patients dying from this disease [6]. Molecular characteristics of CRC directly influence treatment plans for this cancer. Approximately 30% of CRCs do not carry mutations in KRAS, NRAS, and BRAF genes. These patients are eligible for the use of EGFR-targeted antibodies, cetuximab and panitumumab. BRAF-driven cancers account for 5–10% of CRCs and can be managed by a combination of BRAF V600E-specific drugs with EGFR and/or MEK inhibitors. Microsatellite instability is characteristic for 2–4% of CRCs and is associated with tumor responsiveness to the inhibitors of immune checkpoints. Approximately 2% of CRCs are driven by activation of HER2 oncogene and, therefore, sensitive to HER2 inhibition [7]. RAS-mutated tumors are obviously the most prevalent and the most troublesome category of CRCs, given their association with an aggressive disease course and the lack of appropriate targeted therapy. The development of new approaches for the treatment of RAS-mutated CRCs is of utmost importance [3].

Case Report

The patient was a 41-year-old female who was diagnosed with sigmoid adenocarcinoma in January 2018. The patient was considered potentially eligible for surgery. Surgical intervention revealed stage T4N2M1 tumor, which involved all layers of the colorectum, showed peritoneal dissemination, and metastasized to the ovaries. Complete cytoreduction was achieved by sigmoid resection, extended lymph node dissection, hysterectomy with adnexectomy, and parietal subtotal peritoneumectomy. The molecular analysis revealed that the tumor contained KRAS G12D mutation. The anatomic involvement of the ovaries suggested that the patient may have a concurrent ovarian cancer. However, the pathological report and the KRAS mutation analysis confirmed the gastrointestinal origin and the identical KRAS status for all tumor lumps. Therefore, the diagnosis of multiple primary carcinoma (i.e., the combination of CRC and ovarian cancer) was considered highly unlikely and the woman was managed as a CRC patient. The FOLFOX adjuvant therapy was given for 6 cycles. Starting from

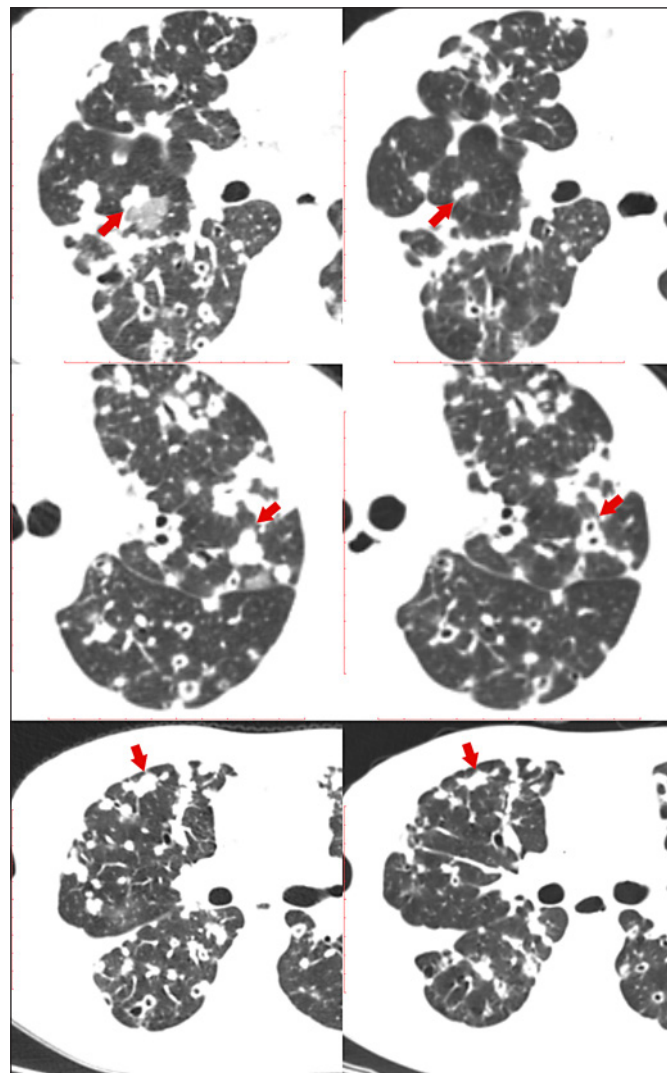


Fig. 1. Reduction of the size of lung metastases in a patient with KRAS-mutated CRC, who received combination of binimetinib, hydroxychloroquine, and bevacizumab. The results of the initial examination are given on the left, and the images obtained after 6 weeks of the therapy are presented on the right. Measurable metastatic lumps demonstrate a reduction of the size (top: from 15 × 9 mm to 12 × 6 mm, –25%; middle: from 14 × 13 mm to 13 × 11 mm, –11%; bottom: from 16 × 11 mm to 13 × 8 mm, –22%).

June 2018, the patient went on to observation. The disease relapse was revealed in November 2018: there was a metastatic spread in the lungs and peritoneum accompanied by ascites. The patient received XELOX plus bevacizumab from November 2018 to May 2019, then capecitabine plus bevacizumab from July 2019 to January 2020. This resulted in disease stabilization lasting until March 2020, when computed tomography revealed progression of lung metastases, involvement of the lung lymph nodes and bilateral pleuritis. The performance status deteriorated to ECOG 2.

The reintroduction of chemotherapy, for example, the use of irinotecan-containing schemes, did not look feasible due to apparent chemoresistance of the tumor and poor condition of the patient. The option of a compassionate experimental therapy was discussed with this woman, and she provided an informed consent to receive binimetinib 30 mg twice per day, hydroxychloroquine 400 mg twice per day, and bevacizumab 7.5 mg/m² every 3 weeks. The treatment started in the beginning of April and led to the relief from dyspnea within the first days of the therapy. Twelve days of the treatment resulted in a decline of the serum level of the CA 19-9 marker from 118 to 69 U/mL and of CEA protein from 430 to 251 U/mL, while there was a rise of the CA-125 marker from 164 to 340 U/mL. The performance

status improved to ECOG 1. The control computed tomography was carried out 6 weeks after the treatment start and revealed evidence for a 17% reduction in the size of lung metastases (stable disease by RECIST 1.1, shown in Fig. 1).

Discussion

Great caution has to be taken while discussing this single case observation. The inability to discern the contribution of each single drug is an intrinsic limitation of antitumor combination therapies. In particular, single-agent MEK inhibitors occasionally demonstrated tumor responses in patients with various RAS/RAF-mutated cancers [2, 3], so it is not self-explanatory whether the same effect could be achieved with binimetinib alone, or, alternatively, the addition of hydroxychloroquine was critical for the improvement of the health status in this otherwise incurable patient. Bevacizumab was added to binimetinib plus hydroxychloroquine combination purely due to empirical assumptions, given that this drug improves the delivery of various therapies to tumor lumps and based on the extensive experience of using bevacizumab in CRC patients [8]. The patient is currently on observation, therefore, the degree of the maximal response and the duration of the disease control remain to be seen.

The therapeutic interference with the RAS/RAF pathway may significantly depend on the organ and tissue context. For example, single-agent BRAF V600E inhibition may induce tumor responses in patients with BRAF-mutated melanoma; however, it shows limited if any efficacy in CRC patients. This difference is attributed to the feedback activation of EGFR signaling in gastrointestinal tumors, while melanoma cells lack functional EGFR and, therefore, rapidly adapt to BRAF downregulation [9]. Use of the KRAS G12C inhibitor AMG 510 in lung cancer patients produced highly encouraging results, while the administration of the same drug in patients with KRAS G12C-mutated CRC did not result in the same level of efficacy in the early stages of a CRC trial [10]. Therefore, it is not immediately clear if the therapeutic data obtained on KRAS-driven CRCs are applicable to other cancer types carrying activating genetic alterations in the RAS/RAF signaling cascade. There is also a growing appreciation of the fact that distinct RAS genes and distinct RAS-activating amino acid substitutions are not entirely equivalent in their biological function, hence one could expect unequal efficacy of RAS-specific therapies in tumors with various mutation types [11].

KRAS-mutated CRC is apparently the most common RAS-mutated tumor in the world, considering the annual incidence of CRC and the proportion of KRAS-driven cases within this disease entity [1, 6]. There are limited options for the long-term management of these patients. We believe that this case report calls for a pilot trial on the efficacy of the combination of binimetinib and hydroxychloroquine, possibly with the addition of bevacizumab, in subjects with chemotherapy-resistant RAS-mutated CRC.

Statement of Ethics

The patient has given a written informed consent to publish her case (including publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work has been supported by the Russian Science Foundation (grant 17-75-30027). Funding sources did not influence the conduction of the study or description of its results.

Author Contributions

S.V. Orlov and E.N. Imyanitov designed the study. M.A. Urtenova and M.A. Sviridenko treated the patient. D.V. Nesterov analyzed the results of the computed tomography. T.N. Sokolova performed laboratory analysis and contributed to the manuscript preparation. E.N. Imyanitov wrote the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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