Neuro-Oncology
21(12), 1610–1611, 2019 | doi:10.1093/neuonc/noz157 | Advance Access date 24 August 2019

Letter to the Editor

Dabrafenib treatment in a patient with BRAF V600E ganglioglioma: circulating exosome-derived cancer RNA supports treatment choice and clinical monitoring

BRAF V600E mutation ($BRAF^{V600E}$) has been identified in a number of glioma subtypes, including ganglioglioma,[1] and the use of $BRAF^{V600E}$ inhibitors may significantly improve the clinical outcome of patients.[2,3] Here, we report a successful treatment with dabrafenib of a patient with $BRAF^{V600E}$ ganglioglioma, whose treatment has been monitored by MRI and by liquid biopsy to identify $BRAF^{V600E}$ in plasma.

In March 2015, a 31-year-old woman was referred to the University Hospital due to a motor aphasia of recent onset. The MRI displayed a fronto-parietal tumor with intense contrast enhancement. The patient underwent a subtotal tumor resection with a histologic diagnosis of World Health Organization grade III ganglioglioma. Immunohistochemistry documented focal expression of p53, CD34, and Ki-67 proliferation index of 3%; $BRAF^{V600E}$ was detected by pyrosequencing.

The patient received adjuvant radiotherapy with temozolomide. Ten months after the end of radiochemotherapy, progressive disease (PD) was documented by MRI. A second subtotal surgery was performed without any neurological impairment, and the pathology confirmed the original diagnosis. Based on the presence of the $BRAF^{V600E}$, dabrafenib (75 mg twice per day for the first 21 days, followed by 150 mg twice per day) was administered. During treatment, 6 mL of plasma were taken at each clinical evaluation, to assess $BRAF^{V600E}$ both in cell-free DNA (cfDNA) and in cancer mRNA from plasma-derived exosomes (exo-RNA), which were extracted with QIAamp circulating free nucleic acids and the exoRNeasy Maxi kit (Qiagen), respectively. The One-Step RT-ddPCR Advanced Kit for Probes (Bio-Rad) was used to obtain cDNA from exo-RNA, and both cfDNA and cDNA were analyzed by a digital droplet PCR (BioRad). The baseline (pretreatment) plasma

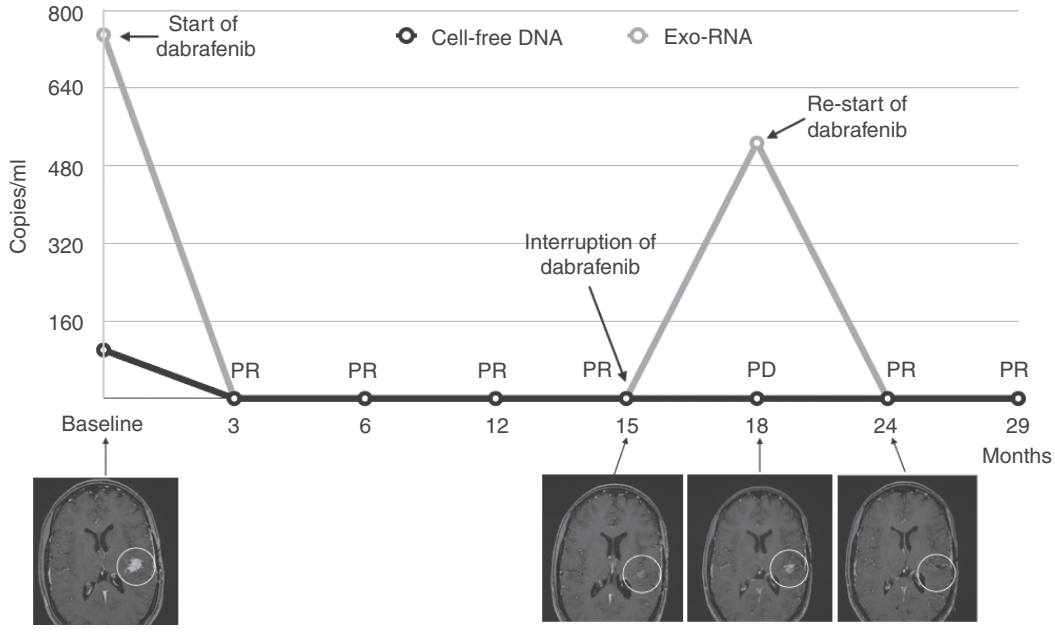

Fig. 1 Assessment of BRAF V600E mutation in cell-free DNA and exo-RNA during treatment with dabrafenib and its correlation with MRI and clinical response. White circles indicate the tumor in the MR images. PR: partial response; PD: progressive disease.

sample confirmed the presence of $BRAF^{V600E}$ at 100 copies/mL in cfDNA and at 750 copies/mL in exo-RNA. MRI, performed 2 months after the start of dabrafenib and then every 3 months, showed a major partial response (PR; Figure 1). After 15 months of treatment, due to the persistent PR, the administration of dabrafenib was discontinued. $BRAF^{V600E}$ in plasma rapidly declined from baseline to the the third month and remained negative until the fifteenth month, thus confirming the MRI finding. However, 3 months after the interruption of dabrafenib, PD was detected at MRI, although the patient was asymptomatic; for this reason, dabrafenib was restarted at the same schedule. Of note, the analysis of the cfDNA was negative for $BRAF^{V600E}$, while in the exo-RNA the $BRAF^{V600E}$ appeared again at PD (Figure 1). At data closure, after 11 months of dabrafenib rechallenge, the treatment is still ongoing and well tolerated and $BRAF^{V600E}$ is still undetectable in plasma.

While the administration of BRAF inhibitors, including dabrafenib and trametinib, is the treatment of choice for $BRAF^{V600E}$ melanoma, dabrafenib has been used in a limited series of patients with primary brain cancers.[2–5] At the best of our knowledge, this is the first case of a ganglioglioma in which changes in plasma levels of exo-RNA were able to document disease response to the rechallenge with dabrafenib, which was also documented by MRI. According to the data on the use of dabrafenib in $BRAF^{V600E}$ brain tumors,[3–5] this case provides evidence that this drug can be active in patients with $BRAF^{V600E}$ ganglioglioma. Moreover, the analysis of circulating tumor DNA/RNA demonstrated that exosomes may be a better vehicle of mutated allele in cerebral tumors compared with cfDNA, allowing the prediction of tumor progression and resistance to treatment.[6]

Additional prospective studies are needed to evaluate whether exo-RNA, integrated with sequential imaging analysis, may improve the management of patients with malignant brain tumors treated with drugs targeting actionable mutations, as in this case of $BRAF^{V600E}$ ganglioglioma.

Keywords

RAF | brain tumors | circulating free DNA | dabrafenib | exosome-derived cancer mRNA

Funding

This study was funded by research grants from the University of Pisa, Pisa, Italy, to Romano Danesi.

Conflict of interest statement. The authors declare no conflict of interest.

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