BRAF/MEK double blockade in refractory anaplastic pleomorphic xanthoastrocytoma

MIGLORINI, Denis, et al.
A 32-year-old woman was diagnosed in February 2012 with a grade II pleomorphic xanthoastrocytoma (PXA) of the right parietal lobe. A complete excision was performed, followed by tumor bed irradiation (66 Gy). A local relapse occurred in September 2013, for which a partial resection was performed, confirming a grade II PXA. Immunohistochemical analysis indicated the presence of a BRAFV600E mutated protein, and combined treatment with vemurafenib and bevacizumab was initiated. A partial response was rapidly obtained, sustained for 12 months. In June 2015, a third surgery was performed for an extended relapse invading the right cerebral hemisphere. Histopathologic examination revealed anaplastic (grade III) PXA and confirmed the presence of the BRAFV600E mutation (figure, A and B). After unsuccessful treatment with bevacizumab and lomustine, tumor treating fields therapy was applied between August and December 2015. Treatment was complicated by severe skin toxicity, with progressive appearance of a 4-cm scalp wound. Concurrently, the patient developed a severe left hemiparesis with ataxia, hemispatial neglect, and central facial palsy. MRI revealed major disease progression. The patient was subsequently referred to our institution.

We initiated combination therapy with dabrafenib 300 mg/d (BRAF inhibitor) and trametinib 2 mg/d (MEK inhibitor) in January 2016. Tolerance was poor, with noninfectious fever, grade III neutropenia, and vomiting. Following reduction of the dabrafenib dose to 150 mg/d, all side effects gradually resolved within 3 weeks. An impressive clinical and radiologic response was observed, with improvement in general condition and regaining of autonomy, partial recovery of the motor deficit, and disappearance of headaches. The response and clinical benefit is ongoing at 11 months of treatment. The figure, C, illustrates the major radiologic changes during this treatment.

Discussion. This case confirms that BRAFV600E mutation, harbored by two-thirds of PXAs, is an interesting target for tyrosine kinase inhibition, incites major questions on the escape mechanisms observed after BRAF-targeted therapy, which may differ in PXA and other tumor types, and provides a proof of principle for the double BRAF/MEK blockade as a therapeutic potential for PXA.

Indeed, the duration of the clinical benefit after BRAF inhibition is often limited to a few months, partly due to paradoxical reactivation of the mitogen-activated protein kinase (MAPK) pathway by various molecular mechanisms, notably ERK reactivation. Laboratory and clinical data suggest that this resistance could be partially reversed with combined BRAF/MEK inhibition, the latter being a downstream molecule in the MAPK pathway. However, in the context of melanoma, it has been shown that the double blockade has to be initiated at the beginning of treatment, whereas it is ineffective in patients progressing after single-agent BRAF inhibition. In contrast, we demonstrate here that a BRAF/MEK double blockade provided a major clinical benefit for a patient with refractory anaplastic PXA previously treated with single-agent BRAF inhibitor. The molecular mechanisms underlying such behavioral differences need to be explored, so as to fully exploit the synergistic potential of dual or multiple inhibitions. A molecular hypothesis to be considered could be the intratumoral ratio of wild-type (wt) BRAF vs mutated BRAFV600E. Indeed, in melanomas with a wt BRAF component, the BRAF inhibition is ultimately inducing a MAPK pathway reactivation, leading to resistance and rapid tumor growth. It is noteworthy that the clinical case reported here is characterized by a fairly homogeneous expression of the mutated BRAFV600E protein (figure, B), which may explain the long duration of response.

Despite the present outcome of this case, current experiences with TKI indicate that progression will eventually occur. This is warranting the introduction of or combination with other treatment strategies, such as the combined or sequential use of MAPK inhibitors with immune checkpoint inhibitors. Indeed, murine models and human tumor samples before and after therapy from patients with metastatic melanoma have shown that BRAF inhibition increases the expression of major histocompatibility complex molecules/tumor antigens and recruits CD8+ T cells.
but maintains them in a suppressed state by a concomitant increase in the expression of programmed cell death 1 (PD-1) molecule. Thus, future studies should investigate the combined use of BRAF/MEK inhibition—to attract T cells—with an anti-PD-1 monoclonal antibody aiming to upregulate their function.
Finally, considering the impressive radiologic response (figure, C), an important lesson that could be derived from this case report is the possibility to use a double BRAF/MEK inhibition as a neoadjuvant approach before surgery. Indeed, PXAs are often extended to several anatomical regions, rendering challenging a complete resection. Neoadjuvant cytoreductive therapy could potentially facilitate the surgical step and help maintain the functional integrity of the patient.

From Geneva University Hospital, Switzerland.

Author contributions: D. Migliorini, P.-Y. Dietrich: study conceptualization, drafting and revising the manuscript for intellectual content. D. Aguiar, A. Lobrinus, M.I. Vargas: drafting the figure and revising the manuscript for intellectual content.

Acknowledgment: The authors thank the patient and her family for consent to publish this report and Simon Rhoad and Anna Patrikidou for English editing.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures. The Article Processing Charge was paid by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Received August 26, 2016. Accepted in final form December 29, 2016.

Correspondence to Dr. Migliorini: denis.migliorini@hcuge.ch


Registration Now Open for 2017 AAN Annual Meeting in Boston

Discover the Annual Meeting everyone’s talking about. We changed the entire format and feel of the AAN Annual Meeting for 2016—and people took notice! We’re doing it again in 2017, and adding even more changes to the docket. Register today to experience the value, choice, customization, and innovation that only an AAN Annual Meeting can offer. We look forward to seeing you April 22-28 in Boston. Register today at AAN.com/view/AM17.
BRAF/MEK double blockade in refractory anaplastic pleomorphic xanthoastrocytoma
Denis Migliorini, Diego Aguiar, Maria-Isabel Vargas, et al.

*Neurology* 2017;88;1291-1293 Published Online before print February 24, 2017
DOI 10.1212/WNL.0000000000003767

This information is current as of February 24, 2017

### Updated Information & Services
including high resolution figures, can be found at:
http://www.neurology.org/content/88/13/1291.full.html

### References
This article cites 11 articles, 6 of which you can access for free at:
http://www.neurology.org/content/88/13/1291.full.html#ref-list-1

### Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
**Primary brain tumor**
http://www.neurology.org/cgi/collection/primary_brain_tumor

### Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/about.xhtml#permissions

### Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/addir.xhtml#reprintsus