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BRAF/MEK DOUBLE BLOCKADE IN REFRACTORY ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA

OPEN

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,¹ is an interesting target for tyrosine kinase inhibition,²

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,^{3,4} partly due to paradoxical reactivation of the mitogen-activated protein kinase (MAPK) pathway by various molecular mechanisms, notably ERK reactivation.⁵ 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.⁶ 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.⁷ 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.⁸ 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 models⁹ and human tumor samples before and after therapy from patients with metastatic melanoma^{10,11} have shown that BRAF inhibition increases the expression of major histocompatibility complex molecules/tumor antigens and recruits CD8+ T cells

Figure Pathologic characterization of anaplastic pleomorphic xanthoastrocytoma (PXA) and radiologic response to BRAF/MEK double blockade therapy

(A) Border zone of anaplastic PXA with tumor at the bottom sharply delineated from the normal brain at the top (hematoxylin & eosin, $\times 10$). The tumor forms large solid sheets composed of highly pleomorphic tumor cells. Cells have an epithelioid pattern, presenting abundant cytoplasm. Nuclei are irregularly bordered, eccentric, and nucleated with frequent nuclear inclusions. More than 5 mitoses per 10 high power field were identified. Neither microvascular proliferation nor necrosis was present. Inset shows higher magnification of the tumor, highlighting large pleomorphic cells (hematoxylin & eosin, $\times 40$). (B) Anaplastic PXA is seen at the right of the image, with strong granular cytoplasmic immunostaining for V600E-mutant BRAF in tumor cells (V600E-mutant BRAF immunohistochemistry, DAB, $\times 10$). Control brain with no immunostain is seen in the left part of the image. Inset shows higher magnification of immunostained tumor cells (V600E-mutant BRAF immunohistochemistry, DAB, $\times 40$). Serial axial T2-weighted imaging (C) and axial and coronal planes T1-weighted imaging with gadolinium (D, E) MRI show radiologic response to BRAF/MEK double blockade (from left to right: December 2015 [prior to BRAF/MEK double blockade], February 2016, April 2016, June 2016). Note the anomalies in high signal on T2-weighted imaging in the temporal lobe (dashed arrows in C) and enhancing lesions located in the temporal lobe and pons that gradually disappear (dashed arrows and white arrows in C-E).

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.

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1. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol* 2011;121:397–405.

2. Lee EQ, Ruland S, LeBoeuf NR, Wen PY, Santagata S. Successful treatment of a progressive BRAF V600E mutated anaplastic pleomorphic xanthoastrocytoma with vemurafenib monotherapy. *J Clin Oncol* 2016;34:e87–e89.
3. Usualieva A, Pierson CR, Kavan CA, et al. Primary meningeal pleomorphic xanthoastrocytoma with anaplastic features: a report of 2 cases, one with BRAF (V600E) mutation and clinical response to the BRAF inhibitor dabrafenib. *J Neuropathol Exp Neurol* 2015;74:960–969.
4. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012;366:707–714.
5. Jha S, Morris EJ, Hruza A, et al. Dissecting therapeutic resistance to ERK inhibition. *Mol Cancer Ther* 2016;15: 548–559.
6. Long GV, Weber JS, Infante JR, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol* 2016;34:871–878.
7. Johnson DB, Flaherty KT, Weber JS, et al. Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. *J Clin Oncol* 2014;32:3697–3704.
8. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature* 2010;464:431–435.
9. Boni A, Cogdill AP, Dang P. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res* 2010;70: 5213–5219.
10. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res* 2013;19: 1225–1231.
11. Cooper ZA, Frederick DT, Juneja VR, et al. BRAF inhibition is associated with increased clonality in tumor-infiltrating lymphocytes. *Oncoimmunology* 2013;2:e26615.

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