ENDOCRINE TUMORS

BRAF V600E mutations in papillary craniopharyngiomaPriscilla K Brastianos¹ and Sandro Santagata^{2,3,4}

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Abstract

Papillary craniopharyngioma (PCP) is an intracranial tumor that results in high levels of morbidity. We recently demonstrated that the vast majority of these tumors harbor the oncogenic *BRAF* V600E mutation. The pathologic diagnosis of PCP can now be confirmed using mutation specific immunohistochemistry and targeted genetic testing. Treatment with targeted agents is now also a possibility in select situations. We recently reported a patient with a multiply recurrent PCP in whom targeting both *BRAF* and MEK resulted in a dramatic therapeutic response with a marked anti-tumor immune response. This work shows that activation of the MAPK pathway is the likely principal oncogenic driver of these tumors. We will now investigate the efficacy of this approach in a multicenter phase II clinical trial. Post-treatment resection samples will be monitored for the emergence of resistance mechanisms. Further advances in the non-invasive diagnosis of PCP by radiologic criteria and by cell-free DNA testing could someday allow neo-adjuvant therapy for this disease in select patient populations.

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Background

Craniopharyngiomas are uncommon epithelial neoplasms that arise above the sella turcica of the skull base, in the suprasellar, infundibulotuberal, and third ventricular areas of the brain (1, 2, 3). Despite their benign histologic appearance, these tumors pose many clinical challenges (4, 5, 6). The tumors arise in proximity to critical structures and can compress or infiltrate these vital neurological areas (4, 5, 6, 7). Visual defects, pan-hypopituitarism, cognitive deficits, personality changes, hyperphagia and morbid obesity are common

complications that result not only from the growth of the tumor but also often as a consequence of treatment with surgery, radiation, or both (4, 5, 6, 7, 8, 9, 10, 11). Moreover, scarring and reactive changes occur following surgical resection and radiation treatment. As a result, resecting recurrent tumors is fraught with difficulties. Patient management is further complicated by a lack of effective systemic chemotherapies (12) and by variations in clinical practice algorithms (13).

There are two histopathologic variants of craniopharyngioma. Adamantinomatous craniopharyngioma (ACP)

Invited Author's profile

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occurs in both children and adults, and papillary craniopharyngioma (PCP) occurs almost exclusively in adults. These variants have distinct histologic features (1, 14, 15).

When resection specimens are large and abundant, and well-preserved tumor epithelium is present, classification is routine on H&E stained sections (1, 14, 15). ACP has epithelium that grows in cords, lobules, and whorls, with palisading peripheral columnar epithelium and loosely arranged epithelium called stellate reticulum. 'Wet' keratin is a hallmark of this variant. PCP has well-differentiated monomorphic squamous epithelium covering fibrovascular cores with thin capillary blood vessels and scattered immune cells including macrophages and neutrophils. The epithelium lacks surface maturation and there is no 'wet' keratin (14, 15).

In some craniopharyngioma resection specimens, however, the epithelium is sparse or absent and establishing a definite diagnosis can be challenging (16). Some specimens for instance have prominent reactive changes with marked granulomatous inflammation, cholesterol clefts, and prominent lymphocytic inflammation. On small biopsies, some PCP can be difficult to distinguish from other suprasellar and infundibulotuberal masses such as non-neoplastic Rathke's cleft cysts (16, 17). These cysts are often lined by ciliated cuboidal or columnar epithelium, but prominent squamous metaplasia can also occur, resembling the epithelium of PCP (17).

Our recent genomic characterization of ACP and PCP revealed that each subtype of craniopharyngioma harbors highly recurrent activating mutations (18). We observed that over 90% of ACP have mutations in *CTNNB1* (18) consistent with other studies demonstrating that mutations in exon 3 of the gene encoding β -catenin and activation of the WNT pathway are important in the tumorigenesis of ACP (19, 20, 21, 22, 23). Unexpectedly, we found that over 90% of PCP have *BRAF* V600E mutations (18). *CTNNB1* and *BRAF* alterations were mutually exclusive, clonal, and specific to each subtype. This propitious finding has important implications for the diagnosis of PCP and the clinical management of some patients with this tumor.

Diagnostic evaluation of craniopharyngioma

The most immediate clinical impact of our findings is on everyday practical pathology diagnostics. Pathologists can now use immunohistochemistry (IHC) to guide diagnostic classification of suprasellar lesions. This is particularly helpful in specimens that are minute or have scant

epithelium. In cells that lack mutations in *CTNNB1* such as in PCP, the β -catenin protein is localized at the cell membrane. In ACP that harbors mutations in *CTNNB1*, β -catenin shifts into both the cytoplasm and nucleus of the neoplastic cells (19, 20, 21, 24). The development of a mutation-specific antibody (VE1) that recognizes *BRAF* V600E mutant protein but not WT *BRAF* protein provides pathologists with another IHC tool to discriminate PCP from ACP and from other entities that are in the differential diagnosis (25). Our study demonstrated a very high concordance between IHC results and genetic mutations in craniopharyngioma (18). Thus, IHC information can be used in diagnostic decision making when needed and when available as pathologists formulate their final diagnostic reports.

In addition to situations where specimens are minute, *BRAF* VE1 IHC may be useful in the routine evaluation of Rathke's cleft cysts (RCCs) (17, 26, 27). A recent re-evaluation of 33 suprasellar mass that were diagnosed as RCCs showed that three cases harbored *BRAF* V600E mutations (27). These cases had an atypical clinical presentation and two had squamous metaplasia. Upon re-evaluation of the pathology and clinical information, these three cases were re-classified as PCP. Hence, determining the *BRAF* status is likely of significant value when evaluating epithelial suprasellar lesions (17, 26, 27).

One caveat and challenge of using IHC to identify specimens harboring *BRAF* V600E mutations is that the VE1 antibody can cross-react with certain *BRAF* WT tissues. For example, endocrine tissues such as normal pituitary are immunoreactive with the VE1 antibody despite these tissues having WT *BRAF* (28). The VE1 antibody also cross-reacts with cilia (17, 26, 29) through recognition of epitopes in the axonemal dyneins of cilia that resemble the *BRAF* V600E peptide sequence used to generate the VE1 antibody (26). The cytosol of ciliated cells shows variable degrees of positivity (26). Thus, VE1 IHC of RCCs, which has ciliated epithelium, should be interpreted cautiously. In some cases where interpretation of the staining may be uncertain, allele-specific genetic testing for *BRAF* V600E mutation may be required to support the IHC results (17, 26, 27). In some institutions allele specific genetic testing may be the preferred diagnostic modality. Because over 90% of PCPs harbor *BRAF* V600E mutations, some institutions may find it sufficient to make diagnoses and guide therapy decisions based on review of H&E stained sections alone.

Currently, the WHO classification of craniopharyngioma does not require mutation assessment using surrogates like IHC or direct genetic testing (1). In time

though, the classification of craniopharyngioma could have at least four groups: ACP *CTNNB1* mutated, adamantinomatous craniopharyngioma *CTNNB1* WT, PCP *BRAF* V600E mutated, and PCP *BRAF* WT.

It is possible that the WT tumors may have different ways of activating *BRAF* or β -catenin that have not yet been identified. Uncovering the genetic drivers of the few *CTNNB1* and *BRAF* WT craniopharyngioma will allow for further refinement of these categories.

Interestingly, a study has suggested that *BRAF* V600E mutations and mutations in *CTNNB1* may co-exist in approximately 10% of ACP (30). While targeted sequencing from the validation set from our original genomic study did not detect ACP samples with *BRAF* V600E mutations (18), the possibility of co-occurring mutations is very intriguing and requires further exploration. If co-existence of mutations in craniopharyngioma is confirmed, it will be important to determine if either mutation is clonal or sub-clonal, the clinical course of such tumors as well as the optimal treatment.

Systemic treatment for *BRAF* V600E mutated PCP

While targeting and inhibiting β -catenin directly remains an unsolved challenge, considerable advances in the treatment of *BRAF* V600E mutant melanoma provide a paradigm for the targeted therapy of PCP (31, 32). Targeted therapy has been successful for treating patients with other *BRAF* V600E mutated tumors (33) including hairy cell leukemia (33, 34, 35, 36, 37, 38, 39), Erdheim Chester Disease (33, 40), ameloblastoma (41, 42, 43), and pleomorphic xanthoastrocytoma (33, 44, 45, 46, 47).

Using targeted agents that inhibit *BRAF* and MEK, we recently achieved a dramatic response in a patient with a multiply recurrent *BRAF* V600E mutated PCP (48). Prior to therapy with *BRAF* and MEK inhibitors, the patient required several urgent neurosurgical decompressions for a rapidly growing tumor, which had a very large cystic component. The patient suffered from panhypopituitarism and chronic bilateral optic neuropathy. We first treated the patient with the *BRAF* inhibitor dabrafenib alone. In 17 days, the solid part of the tumor decreased by 50% and the cystic portion by 70%. Because concomitant inhibition of *BRAF* and MEK has been shown to reduce the emergence of resistance in melanoma (31), we added trametinib for an additional 14 days. During the treatment the solid part of the tumor decreased by 85% and the cystic portion by 81%. The size of the cyst may have decreased as the treatment compromised the tumor epithelium and presumably diminished cyst fluid secretion. The residual

tumor was resected and then 3 weeks later the patient was administered radiation therapy. Eight months following the radiation therapy, the patient remains without new symptoms (48).

Review of the histology of the specimens that were resected before and after dabrafenib/trametinib treatment revealed a remarkable effect (Fig. 1). The Ki67 proliferation index decreased from over 20% in the pre-treatment tumor to <0.5% in the on-treatment tumor. Radiation therapy was administered 3 weeks after this final on-treatment tumor resection. The combined dabrafenib and trametinib treatment led to a prominent immune response with foamy macrophages engorging the fibro-vascular cores and CD8-positive T cells infiltrating throughout the tumor. This suggests that targeted therapy unleashes a strong anti-tumor immune response in PCP, a phenomenon that also appears to be elicited by *BRAF* inhibition in melanoma (49, 50, 51).

Figure 1

H&E stained sections of pre- and post-treatment PCP from case reported in Brastianos et al., JNCI 2015 (48). Top panel shows the recurrent tumor. The lower panel shows the tumor following treatment with dabrafenib and trametinib.

Development of resistance to *BRAF* and MEK inhibitors is common in patients with melanoma. Whole exome sequencing data from the pre- and on-treatment tumors from our patient did not identify the emergence of any known genetic drivers of *BRAF* resistance (18). The low frequency of mutations and limited genomic complexity of these tumors suggest that combined therapy may effectively limit the emergence of resistance but high vigilance for the emergence of treatment resistance mechanisms will be required.

The rationale of concomitantly targeting *BRAF* and MEK for PCP treatment is supported by a recently published report using single agent vemurafenib treatment in a patient with a *BRAF* V600E mutant PCP (52). Similar to the response observed in our patient, that tumor was also exceptionally responsive to targeted treatment, with a near complete radiological response after 3 months. When vemurafenib was held, however, the tumor re-grew in 6 weeks. Tumor growth was stabilized when vemurafenib was re-administered but tumor progression subsequently ensued. The tumor progression seen in that patient treated with single agent vemurafenib suggests combining *BRAF* and MEK inhibition will be preferable for prolonged and durable control of tumor growth.

Phase II clinical trial study evaluating the combination of *BRAF* and MEK inhibition in patients with PCP

Given these exceptional tumor responses and the consistent occurrence of the *BRAF* V600E mutation in the vast majority of PCPs, we are now designing a multicenter phase II study evaluating the combination of *BRAF* and MEK inhibition in patients with PCPs. We will study the effect of dual inhibition because of the improved efficacy of the combination over single agent *BRAF* inhibitors in other *BRAF*-mutant tumors. As most resistance to single-agent *BRAF* inhibitors occurs because of reactivation of the RAF-MEK-ERK (MAPK) pathway, the addition of MEK inhibition delays the emergence of resistant clones. Furthermore, the major complication of RAF inhibitor treatment is the development of cutaneous squamous-cell carcinoma. This complication is significantly reduced in patients receiving the combination of dabrafenib and trametinib compared with those receiving single agent treatment alone (31). Systemic treatment will be administered until definitive therapy with surgery or radiation therapy is indicated. Correlative studies will be performed with a focus on obtaining pre- and post-treatment tissue which will be characterized with whole exome sequencing and RNA-sequencing in an attempt to identify potential

mutations, genomic aberrations, or transcriptional mechanisms that might render PCP tumors either refractory or resistant to treatment.

Future outlook

The current standard of care for treating PCP involves surgery and radiation and can lead to substantial morbidity. Therefore, a neo-adjuvant approach for treating these tumors could be of use in selected patient populations. Such strategies are commonly used for prolactin producing pituitary adenomas which are treated with bromocriptine as well as for germ cell tumors. Of note, we were able to detect mutant *BRAF* V600E DNA circulating in the blood of our exceptional responder patient (48). This finding is encouraging and suggests that confirming the presence of PCP may be achievable through non-invasive “liquid biopsy” methods such as cell-free DNA (cfDNA) detection testing. Our trial will include explorative objectives designed to carefully assess such capabilities. Moreover, the development of validated radiological criteria for discriminating PCP and ACP from one another and from other tumors will be important for evaluating patients with suprasellar masses (3, 53, 54, 55, 56). A combination of improved non-invasive diagnostics coupled with effective targeted therapy could provide a new treatment paradigm that in molecularly selected patient populations reduces the morbidities associated with surgery and radiation and improves the outcomes of patients with PCP and other rare brain tumors (57).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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