Neoadjuvant B-RAF and MEK inhibitor targeted therapy for Adult Papillary Craniopharyngiomas: A new treatment paradigm

E JOUANNEAU[1,2], F CALVANESE[1], R MANET[1], A VASILJEVIC[3], H PARIS-REFAHI[4], F DUCRAY[5], G RAVEROT[4,2]

1. *Pituitary and Skull Base Neurosurgical Department, Reference Center for Rare Pituitary Diseases HYPO, "Groupement Hospitalier Est" Hospices Civils de Lyon, "Claude Bernard" Lyon 1 University, Hôpital Pierre Wertheimer, 59 Pinel Boulevard, Lyon, Bron 69677, France*

2. *Lyon University, Université Claude Bernard Lyon 1, 69007 Lyon, France*

3. *Department of Pathology, Groupement Hospitalier Est, 59 Boulevard Pinel, Bron F-69677, France*

4. *Endocrinology Department, Reference Center for Rare Pituitary Diseases HYPO, "Groupement Hospitalier Est" Hospices Civils de Lyon, "Claude Bernard" Lyon 1 University, Hôpital Louis Pradel, 59 Pinel Boulevard, Lyon, Bron 69677, France*

5. *Department of Neuro-Oncology, Hospices Civils de Lyon, Groupement Hospitalier Est, Neurology Hospital, 69007 Lyon, France*

Background: The management of craniopharyngiomas is associated with high long-term morbidity especially in the case of hypothalamic involvement. Over the past decade, it has been established that the BRAF V600E mutation plays a central role in the oncogenesis of Papillary Craniopharyngioma leading to the use of targeted therapy with encouraging preliminary results. However, there are few reported cases in English medical literature. We report the result of our experience in the Department of Pituitary and Skull Base surgery in Lyon that has led to a change in management of these challenging tumors.

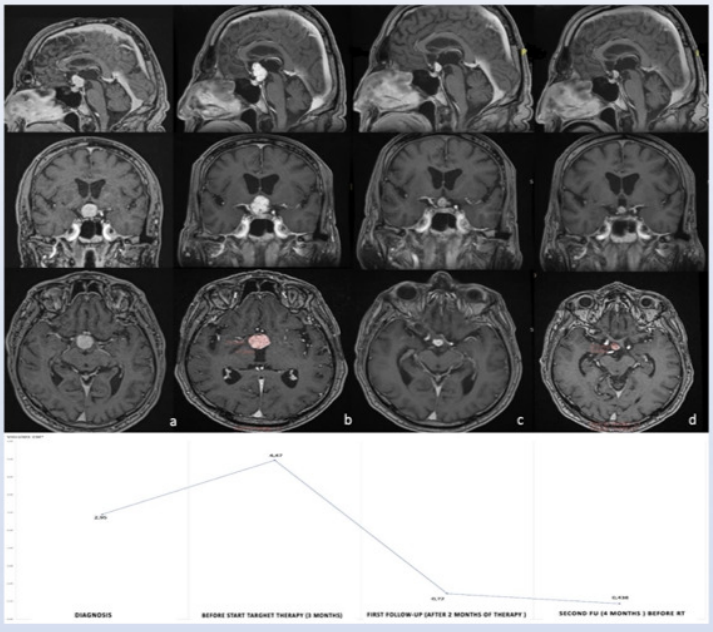


FIGURE 2. Post-gadolinium axial, coronal and sagittal T1WI MRI images showing result after Neoadjuvant treatement in 69 years-old man affected by newly diagnosed PCP. (A) Postcontrast T1-weighted image shows large homogeneously enhanced intraventricular mass measuring 19 x 18.5 mm maximal axis and 2.945 cm3 volume. (B) Shows progression of the intraventricular tumor portion after trans-ventricular endoscopic biopsy (18% of tumor volume). Panels c and d show a dramatic reduction in volume at 2 months (C) and 4 months (D) after commencing combined BRAF/ MEK inhibitor treatment. Note complete resolution of the mass effect on suprasellar neurovascular structures and on Monro's foramen. Volume curve has been reported in the inferior part of figure. RT, radiotherapy.

Material and Method: In the last 2 years, four cases of tuberoinfundibular and ventricular Papillary Craniopharyngiomas have been treated with combined BRAF/MEK inhibitor therapy at our Institute. In three cases target therapy has administered as adjuvant treatment (i.e before radiotherapy) or in case of recurrence (one case with solid tumor, one cystic and one with mixed morphology)(FIG.1). In one case of solid tumor, the BRAF/MEK inhibition therapy was used as neoadjuvant treatment before radiotherapy and/or resection surgery (FIG.2).

Results: The efficacy of combined BRAF/MEK inhibitor therapy find confirmation in the review of the 11 previously published cases. A drastic and rapid tumour volume reduction has been reported in case of solid papillary craniopharyngiomas (i.e. 60% after 2 months and 90% after 5 months of treatment) whereas , in cystic form ,the rate and magnitude of response is much slower and modest. In our neo-adjuvant case, only a tumor biopsy has been performed by neuroendoscopic tras-ventricualr approach and the combined targeted therapy was administered in order to minimize the target before using radiotherapy. In all cases of solid lesions, the radiological improvement allowed clinical improvement without significant side effects.

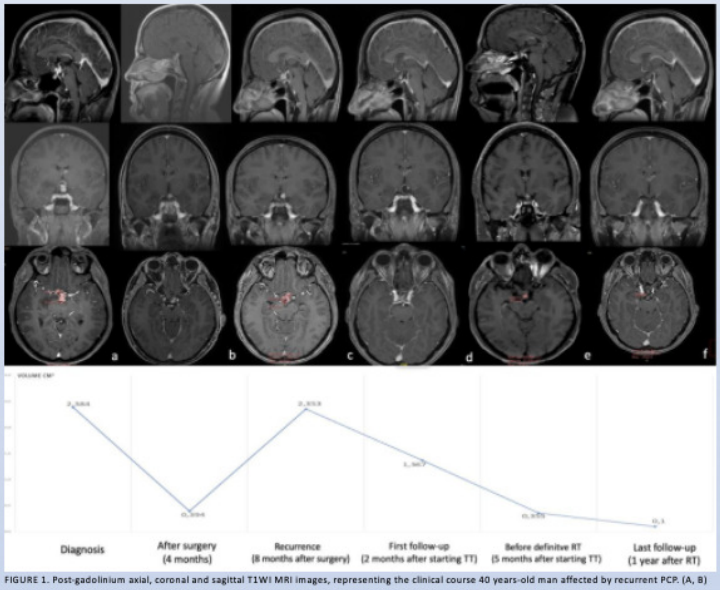
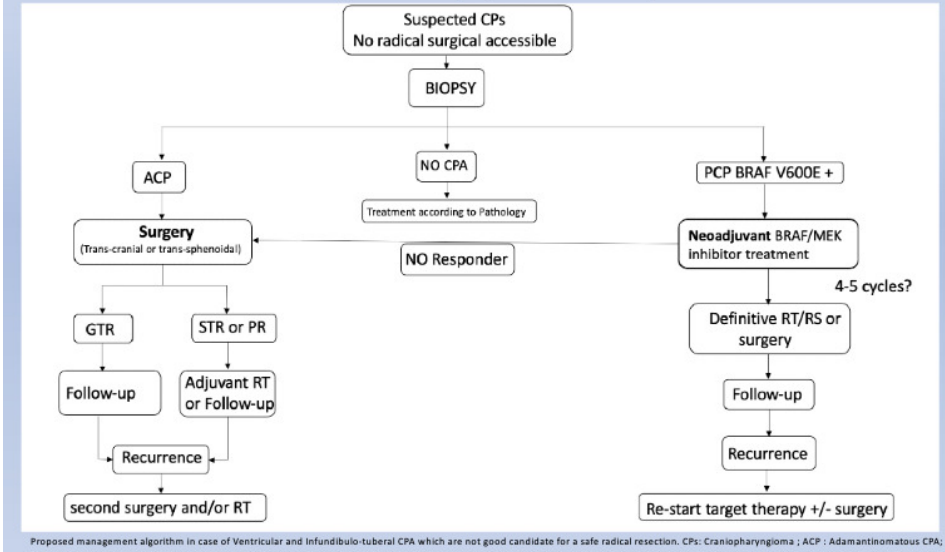


FIGURE 1. Post-gadolinium axial, coronal and sagittal T1WI MRI images, representing the clinical course 40 years-old man affected by recurrent PCP. (A, B) Shows the tumor volume and presentation at time of diagnosis (25.4 x 15.0 mm maximal axis and 2.384 cm3 volume) and after surgery (maximal axis: 7.5 x 11.5 mm, volume: 0.394 cm3). (C) Shows tumor recurrence/regrowth at 12 months postoperatively (13 x 24 mm and a volume of 2.353 cm3). (D, E) Show dramatic and rapid reduction in tumor volume at 2 months (80 %) and 4 months (90%) after starting combined anti-BRAF/MEK therapy. (F) Shows results at 1 year after final radiotherapy (near complete response). Volume curve has been reported in the inferior part of figure. TT: B-RAF and MEK inhibitor targeted therapy; RT: radiotherapy.

Conclusion: Based on our experience and a systematic review of the pertinent medical literature, we confirm the efficacy and good tolerance of BRAF/MEK inhibitor targeted therapy for papillary craniopharyngiomas. The effect seems less encouraging on the cystic component. A change in the current Craniopharyngioma treatment paradigm should be considered to avoid high-risk procedures. ***In cases of giant or invasive tumors, a simple tumor biopsy*** could be considered as the first step to select a subset of patients with Papillary craniopharyngiomas harboring BRAF V600E mutation . In such tumors, ***neoadjuvant combined therapy should be applied for a few months in order to shrink the tumor before considering a curative approach*** (surgery or radiotherapy/radiosurgery) on smaller target with reduction in long-term morbidity.

The authors report no financial and/or non-financial conflicts of interest concerning the materials or methods used in this study or the findings specified in this study.



Proposed management algorithm in case of Ventricular and Infundibulo-tuberal CPA which are not good candidate for a safe radical resection. CPs: Craniopharyngioma ; ACP : Adamantinomatous CPA; PCP : Papillary CPs ; RT : radiotherapy ; RS : radiosurgery .

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