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Temozolomide on Aggressive Pituitary Adenomas: About 4 Cases and Review of the Literature

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Abstract

Introduction: Pituitary adenomas represent 15 to 20% of all brain tumors . They affect 1/1000 of the world population, some pituitary adenomas with high Ki-67 indexes exhibit aggressive behaviors, such as rapid growth, early and frequent recurrence, and resistance to conventional treatment, even in the absence of metastasis . Many trials have focused on the role of chemotherapy in the treatment of these aggressive and atypical adenomas

The objective: Monitoring of patients on temozolomide .

Material and methods: we report the follow-up of 4 patients (pts) of 10 pts treated in our department during the period (2012-2019), 2 women / 2 men presenting an aggressive pituitary macro-adenoma, having benefited from excision surgery, radiotherapy and received medical treatment with temozolomide initiated with clinical, biological and radiological evaluation of the therapeutic response and search for p53 and ki 67 in the diagnosis.

Results: A clinical improvement was noted in our 4 pts; Radiologically: a partial response was obtained in 1pts, two stabilities and one progression . The average duration of treatment is 26 months (12 - 40) with manageable side effects .

Conclusion: Temozolomide appears to be effective in the treatment of aggressive pituitary adenomas and may currently constitute a therapeutic alternative when all resources are exhausted, thus allowing control of the disease.

Keywords : Pituitary Adenomas, Agressive Tumors,Temozolomide

Introduction

Pituitary adenomas are rare tumors. They are divided into micro and macro adenomas depending on their size and may or may not be functional. Clinically, they manifest in three ways: tumor syndrome, hyper secretion syndrome or hormonal insufficiency which may or may not be associated. Considered benign, 40% of adenomas present characteristics of hormonal, radiological and histological aggressiveness (1). In 2004, the WHO defined adenomas showing signs of tumor proliferation as atypical: high mitotic activity, ki 67 > 3% and P53 positivity. aggressive forms combine radiological signs of invasion, rapid growth and

resistance to treatment causing a recurrence of around 10-35% between 4 and 20 years. Pituitary carcinoma is a rare entity responsible for cerebral and extracerebral metastases.
The management of hypopyseal adenomas must always be discussed in a Multi Disciplinary Team (MDT).
The therapeutic approach combining surgery, radiotherapy and medical treatment. . The combination of different therapeutics means available could improve the prognosis of these tumors, while awaiting the promising results of new therapies currently being evaluated.(2) . In recent years, numerous trials have focused on the place of temozolomide in hypopyseal adenomas

Materiel et Methods

We treated in medical oncology department in Pierre & Marie Curie center in Algiers 12 patient between 2013 and 2023 (n=12) Average age is 54 years, sex is 7M/5F .
The Time between diagnosis and medical treatment is 10 years.
We report four cases ,the first who were treated in our depatement

Case 1 Y.N. 34 years old , female with no particular history , in 2002 has presented headaches and visual impairment , a macroadenoma (12 × 15 × 13 mm) with an invasion of the suprasellar cistern was detected by MRI and complicated by blindness on the right and temporal hemianopia on the left and secondary amenorrhea without galactorrhea. The patient benefited from :

- -2002: partial excision because the tumor was very firm and fibrous, which improved the patient's headaches, but not her visual impairment. Pathological testing of the initial tumor tissue indicated a high Ki-67 index (20%), p53-positive immunostaining in some tumor cells (Figure 2).
- -Bromocriptine between 2002-2004;
- -2004: external radiotherapy;
- -December 2012: a second partial excision was performed

In May 2013, the patient experienced more severe visual impairment and headache accompanied by nausea and vomiting, and MRI revealed significant enlargement of the residual tumor (19 × 25 × 22 mm)
In june 2013 , the patient received TMZ treatment under the standard regimen of 200 mg/m2/d for 5 days of a 28-day cycle. The size of the tumor did not change but was stable for 36 months (Figure 1). Good clinical and biological tolerance observed in this patient.
However, TMZ treatment was discontinued at the patient's request, and she died of inflammation in july 2016, the duration of TMZ was 36 months .
Time between diagnosis and treatment with temozolomide: 11 years.

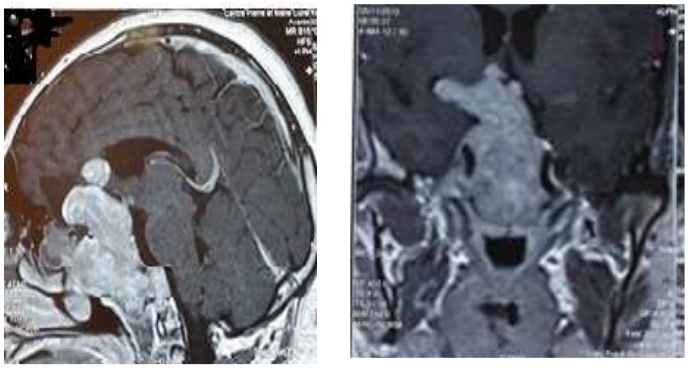


Figure 1. Adenome hypophysaire agressif avec atteinte multidirectionnelle

Case 2: C.H. 30 years old female with no previous history , has had a lactotropic pituitary macroadenoma since 2002 revealed by primary amenorrhea without galactorrhea. The patient was treated with bromocriptine between 2002-2010. she benefited from a partial excision in 2010 and 2011 but without success.

She received Cabergaline between 2010 and 2012.

When the tumor increase associated with high levels of prolactin and reduction in right visual acuity, temozolomide was started at a dose of 200mg/m^2 for 5 days every 28 days since 07/2012.

Time between diagnosis and treatment with temozolomide: 10 years.

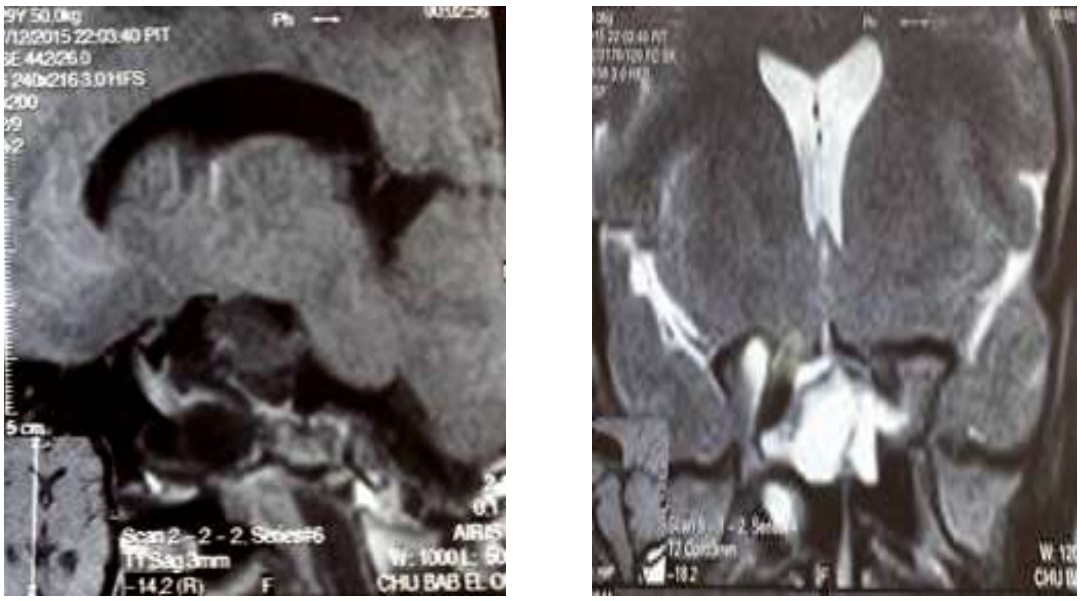
The patient was on temozolomide for 60 months.

Clinically, an improvement in vision on the right was noted and 30% reduction in tumor volume (Figure 2)

On a biological level, the evolution is as follows (Figure 3), it was excellent

Side effects are dominated by digestive toxicity: GII vomiting and GI constipation.

In August 2017 , the patient presented with, intracranial hypertension and dysphagia, and the MRI indicated that the tumor had enlarged rapidly and infiltrated the sphenoid and cavernous sinuses and the patient died .



Une réduction de 30% de la taille a été obtenue au bout de 6 mois de traitement puis une stabilité lésionnelle a été maintenue

Figure 2 : IRM After 6 months of temozolomide .30% Reduction

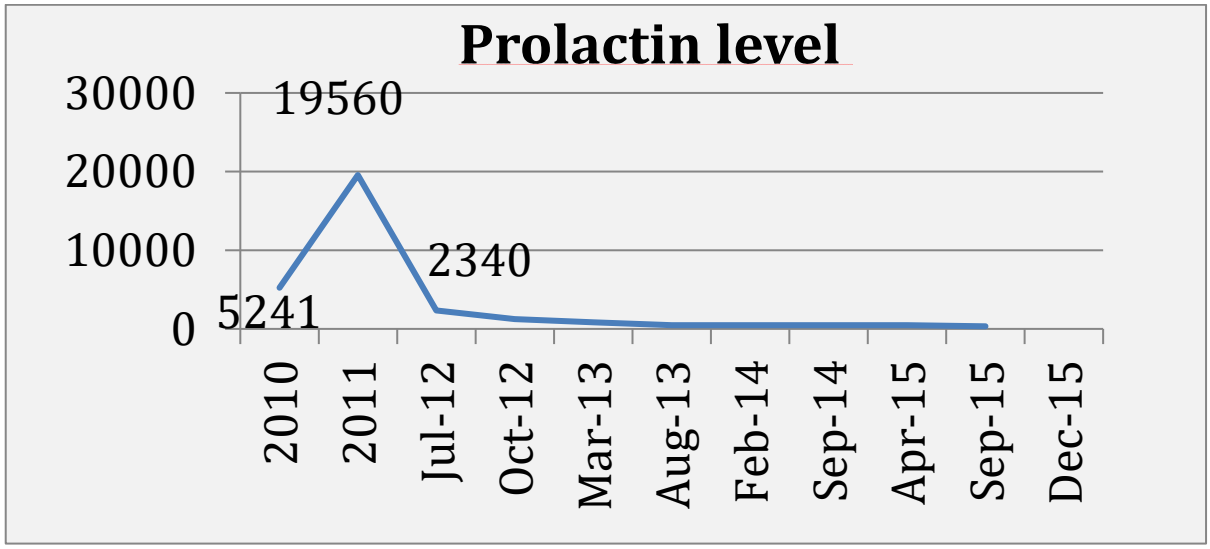


Figure 3 : Prolactin level with temozolomide

Case 3 : GA 54 years old, male , history of hypertension, followed since 2007 for non-secreting pituitary macroadenoma revealed by a reduction in visual acuity . He is Operated for four time :

- November 2007: partial resection Pathological test results indicated that the Ki-67 index was greater than 3% and P53 positive .
- December 2007: A second surgical intervention was performed to partially resect the tumor using a transcranial approach
- January 2008: surgical revision for splitting of the tumor volume going from 43/32mm in November to 86/31mm in January
- February 2008: transphenoidal approach repeated for persistence of visual disorders with MRI tumor process intra and supra sellar Pathological tests revealed that the Ki-67 index was greater than 10%. Patient received Cabergoline
- However, 96 months after the last surgery, MRI revealed regrowth of the residual tumor with invasion of the suprasellar cistern and left cavernous sinuses , the residue measuring
- 21/25 mm vs 16/19mm . Clinically reduction in visual acuity
- In July 2016: after MDT discussion ,we start treatment with temozolomide 200mg/m^2 for 5 days (d1=d28) . The patient received temozolomide for 3 years with a clinical and radiological stability and a good tolerance.

Case 4 : CC 75 years olde ,male followed since 2005 by a giant non-secreting pituitary macroadenoma revealed by a bilateral drop in visual acuity and headaches

MRI: multidirectional heterogeneous macro process measuring 50/43 /27mm .

- On March 2005: partial resection Pathological test results after immune histochemistry indicated that prolactinoma
- On July 2013: MRI finds a process of 51/50/30mm multidirectional .

The patient refuses any surgical revision ,we propose cabergoline .

In 2015 we noted the failure of medical treatment .

On June 2016: MRI finds a process of 51/51/10 mm with invasion of the 2 cavernous sinuses .

After MDT ,in july 2016 we start temozolomide 200 mg /m^2 For 5 days every 28 days

The time between diagnosis and starting temozolomide was 11 years , Thrombocytopenia grade 3 was the side effect .

In june 2017 MRI objective a progression disease (57/49/35mm) and patient died in september 2017.

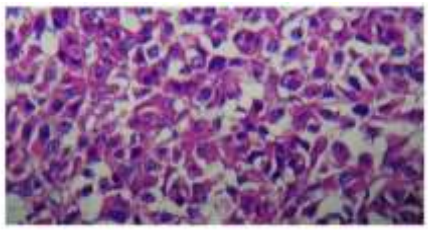


Figure 4 : Atypique Adenoma

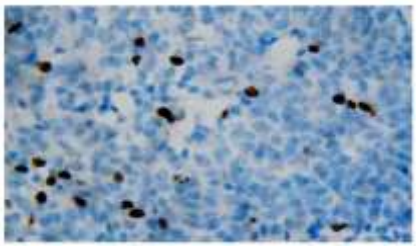


Figure 5 :Ki67 nuclear expression 10%

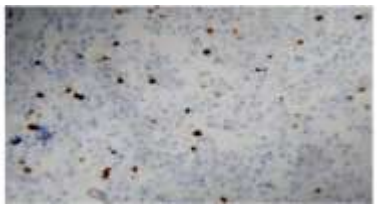


Figure 6 : Nuclear expression of P53

Discussion :

These cases illustrate the complexity of treating malignant pituitary adenomas. The pituitary tumors examined here are particularly aggressive with a rapid growth and ultimately resulted in death, despite multiple surgeries, radiotherapy, and/or salvage treatment with TMZ. The medical treatment of pituitary carcinoma is the same as that of large recurrent pituitary adenomas. Chemotherapy with cisplatin and etoposide gives very variable results (3), but are palliative.

In this moment , more 105 cases of pituitary adenoma or carcinoma have been reported in the literature. Temozolomide allowed disease control in 60% of cases (an objective response of 55% for adenomas and 58% for carcinomas).

These tumors also had very high Ki-67 proliferative indexes, which is a common histological feature of pituitary carcinoma ,It has also not yet been demonstrated that markers of tumor proliferation (Ki 67, mitotic index) and P53 (4)are predictive factors of response to TMZ (Figure 4 ,5 and 6) (5,6)

Is their an other therapies for agressive pituitary adenomas ?

Several targeted therapies for the Raf/MEK/ERK and PI3K/Akt/mTOR pathways have been tested (7,8,9). Bevacizumab (VEGF monoclonal antibody), an antiangiogenic, demonstrated its effectiveness after failure of temozolomide . Furthermore, several studies have reported that angiogenesis decreases tumor size in experimental animal models of pituitary tumors. VEGF expression is relatively high in pituitary adenomas; Therefore, anti-VEGF therapy has been used in some refractory pituitary adenomas and

pituitary carcinomas (10) The first case was published in 2012 (11).We need more trials to improve the prognosis (12)

Conclusion

Early diagnosis of these tumors is essential because this long evolution can be life-threatening even in the absence of metastases, which requires long-term monitoring of all patients.
The absence of data concerning the short and long term control of the disease does not make it possible to deduce the optimal duration of treatment, which constitutes one of the problems that must be addressed.

Références

1. McCormack A, Dekkers OM, Petersenn S, Popovic V, Trouillas J, Raverot G, et al . *Eur J Endocrinol* (2018) 178 (3):265–76. doi : 10.1530/eje-17-0933 [PubMed] [CrossRef] [Google Scholar
2. Yang Q, Li X. Base du réseau moléculaire de l'adénome hypophysaire invasif : un examen . *Endocrinol avant (Lausanne)* (2019) 10 :7. doi: 10.3389/fendo.2019.00007 [Article PMC gratuit] [PubMed] [CrossRef] [Google Scholar
3. Wang Y , Li J, Tohti M, Hu Y, Wang S, Li W, et al. pour la Thérapie Médicale . *J Exp Clin Cancer Res* (2014) 33 (1):56. doi : 10.1186/s13046-014-0056-y [Article PMC gratuit] [PubMed] [CrossRef] [Google Scholar]
4. Thapar K, Scheithauer BW, Kovacs K, Pernicone PJ and Laws EJ. p53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. Neurosurgery. 1996; 38:765-770, 770-771.
5. Yarman S, Kurtulmus N, Canbolat A, Bayindir C, Bilgic B, Ince N. Expression de Ki-67, P53 et du facteur de croissance endothélial vasculaire (VEGF) de manière concomitante dans les adénomes hypophysaires sécrétant l'hormone de croissance ; Lequel joue un rôle dans le comportement tumoral ? *Neuro Endocrinol Lett* (2010) 31 (6):823–8. [PubMed] [Google Scholar]
6. Choueiri TK, Kaelin WG, Jr. Cibler l'axe HIF2-VEGF dans le carcinome à cellules rénales . *Nat Med* (2020) 26 (10):1519–30. doi : 10.1038/s41591-020-1093-z [PubMed] [CrossRef] [Google Scholar]
7. Melnic E, Cimpean AM, Gaje PN, Raica M. Influence du profil hormonal sur l'expression du facteur de croissance endothélial vasculaire (VEGF a) dans les adénomes hypophysaires humains . *Anticancer Res* (2014) 34 (10):5867. [Google Scholar]
8. *8.Prolactinoma ErbB receptor expression and targeted therapy for aggressive tumors Endocrine 2013 DOI10.1007/s12020-013-0093-x*
9. 9.Cooper O et al. Prolactinoma ErbB receptor expression and targeted therapy for aggressive tumors. Endocrine 2014 : 46 318–327. (https://doi.org/10.1007/s12020-013-0093-x)
10. Lloyd RV, Scheithauer BW, Kuroki T, Vidal S, Kovacs K, Stefaneanu L. Expression du facteur de croissance endothélial vasculaire (VEGF) dans les adénomes et carcinomes hypophysaires humains . *Endocr Pathol* (1999) 10 (3):229–35. doi : 10.1007/BF02738884 [PubMed] [CrossRef] [Google Scholar]
11. *Anti-VEGF therapy in pituitary carcinoma Leon D. Ortiz et al.Pituitary (2012) 15:445–449 DOI 10.1007/s11102-011-0346-8*
12. Di Ieva A, Rotondo F, Syro LV, Cusimano MD and Kovacs K. Aggressive pituitary adenomas--diagnosis and emerging treatments. Nat Rev Endocrinol. 2014; 10:423-435.

13. Thapar K, Scheithauer BW, Kovacs K, Pernicone PJ and Laws EJ. p53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. Neurosurgery. 1996; 38:765-770, 770-771.
14. Kontogeorgos G. Predictive markers of pituitary adenoma behavior. Neuroendocrinology. 2006; 83:179-188.
15. Wierinckx A, Auger C, Devauchelle P, Reynaud A, Chevallier P, Jan M, Perrin G, Fevre-Montange M, Rey C, Figarella-Branger D, Raverot G, Belin MF, Lachuer J and Trouillas J. A diagnostic marker set for invasion, proliferation, and aggressiveness of prolactin pituitary tumors. Endocr Relat Cancer. 2007; 14:887-900.
16. Salehi F, Agur A, Scheithauer BW, Kovacs K, Lloyd RV and Cusimano M. Biomarkers of pituitary neoplasms: a review (Part II). Neurosurgery. 2010; 67:1790-1798, 1798.
17. Sav A, Rotondo F, Syro LV, Scheithauer BW and Kovacs K. Biomarkers of pituitary neoplasms. Anticancer Res. 2012; 32:4639-4654.
18. Lundin P and Pedersen F. Volume of pituitary macroadenomas: assessment by MRI. J Comput Assist Tomogr. 1992; 16:519-528.
19. Honegger J, Prettin C, Feuerhake F, Petrick M, Schulte-Monting J and Reincke M. Expression of Ki-67 antigen in nonfunctioning pituitary adenomas: correlation with growth velocity and invasiveness. J Neurosurg. 2003; 99:674-679.