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EDITORIAL

Is MGMT the best marker to predict response of temozolomide in aggressive pituitary tumors? Alternative markers and prospective treatment modalities

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Introduction

The majority of pituitary tumors have a benign clinical course. However, a subset exhibits aggressive behavior, with early recurrence, rapid progression, and resistance to conventional therapies. Approximately, 0.2% are carcinomas showing frank malignancy and cause central nervous system and/or distant systemic metastases [1]. Currently, most pituitary adenomas can be successfully managed with modern surgical techniques and advanced medical treatment modalities, although the abovementioned subset may need adjuvant radiotherapy [1, 2]. Clinically aggressive refractory tumors nevertheless remain challenging to treat. Temozolomide (TMZ), which is an alkylating chemotherapeutic agent that inhibits tumor progression by blocking DNA replication, has today become a rational therapeutic option for aggressive/malignant pituitary tumors resistant to conventional therapeutic modalities [3–7]. Patients treated with TMZ show a remarkable improvement rate, with 5-year overall survival [6, 8]. The cytotoxicity of TMZ depends on the expression of O-6 methylguanine DNA transferase (MGMT), a DNA repair enzyme. Since the presence of MGMT in tumor cells inactivates TMZ effectiveness, negative MGMT expression predicts responsiveness to therapy [5, 7, 9], with several studies reporting a good correlation between the absence of MGMT expression and effectiveness of TMZ to refractory aggressive adenomas. TMZ is also capable of absorbing low MGMT stores, this being evident in tumors that showed negative or low MGMT expression which were removed from the responding patients [10, 11]. However, given that some patients with MGMT-negative tumors do not respond [7, 9, 12], it is questionable whether immunohistochemistry for detection of MGMT yielded false-positive or false-negative results. The existence of such diagnostic dilemmas means that it is uncertain whether MGMT is the best predictive biomarker to select patients for treatment with TMZ. Currently, other markers are available which could be potential substitutes for MGMT.

This work attempts to shed light on the immunohistochemical detection of MGMT while seeking to illuminate the existing clinical controversies. In addition, it presents alternative biomarkers and also novel and emerging therapeutic interventions beyond TMZ for the treatment of refractory aggressive pituitary tumors.

Controversial issues

MGMT is currently considered as the gold standard to select candidate patients with carcinomas and aggressive adenomas for administration of TMZ. As a rule, absence of low MGMT expression predicts response to TMZ treatment [5, 6, 8]. However, in some patients with apparently negative MGMT, adenomas do not respond [2, 12]. This lack of concordance of MGMT expression and response to TMZ treatment has not been fully elucidated. In a recent study where we described in detail the technical problems that may lead to false-low or false-negative MGMT expression, after direct application of the monoclonal antibody for immunohistochemical detection of MGMT, all but one adenomas (96%) were negative. Surprisingly, after application of antigen retrieval protocols using either proteolytic enzymatic digestion with pronase or with pretreatment of Tris-EDTA buffer, another three of the

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adenomas that were initially negative changed to positive, while the remaining 21 (84%) continued to yield negative results. This 3-fold increase in MGMT expression may explain the lack of effectiveness of TMZ therapy in patients with adenomas that are false-negative for MGMT [13].

Given the inconsistency of MGMT immunohistochemistry, some clinicians rely on elevated Ki-67 LI or strong expression of p53 to start administration of TMZ, without asking a pathologist to evaluate MGMT status [2, 14]. However, these markers cannot predict the effectiveness of treatment with TMZ [11, 15], several reports having shown no significant correlation between MGMT expression and Ki-67 LI with respect to the efficacy of TMZ treatment [15–17]. In addition, the assumption that atypical adenomas might have more aggressive clinical behavior has never been proven. For this reason, in the recent WHO edition of the classification of pituitary adenomas, the use of Ki-67 and p53 is not recommended for routine diagnosis [18]. As a result, the category *"atypical adenomas"* has been eliminated [19].

Implication of technical issues

Although specific monoclonal antibodies against MGMT are available, several parameters interfere with the immunohistochemical procedure, creating technical problems [3, 20]. These parameters involve pre- and post-analytical conditions. Pre-analytical issues include delayed or prolonged formalin fixation of adenoma samples. Formaldehyde, although currently used as a standard method for tissue fixation, requires special attention so that problems in immunohistochemistry may be overcome. Moreover, the duration of storage of paraffin tissue blocks may be crucial. Post-analytical conditions include establishment of optimal working dilution of the antibody, which should be determined by the end user. In addition, low sensitivity of the antibody or the detection system may result in false immunoreactivity [13, 20]. Unmasking of hidden antigen sites in the tissue specimens requires pretreatment with antigen retrieval protocols [21]. The optimum protocol should be carefully evaluated and standardized in each pathology laboratory. It should be stressed that application of the appropriate antigen retrieval immunohistochemical protocol is crucial to obtain consistent results for patients who are candidates to receive TMZ therapy [13].

In general, negative or low MGMT expression is suggested as a predictive criterion to initiate treatment with TMZ. However, no consensus regarding the best system to evaluate MGMT expression at present exists [16, 20]. Furthermore, there is no agreement as to what should be the cut-off percentage of positive nuclei [5, 6, 15]. Other problems relate to the discrepancies in interobserver and intraobserver variations, which are difficult to eliminate.

Advanced predictive biomarkers

The precise mechanisms underlying MGMT expression remain to date largely unresolved. MGMT promoter methylation (MGMT-PM) represents as one of the proposed mechanisms responsible for suppression of MGMT expression, which results in reduced MGMT protein levels [22]. MGMT-PM tends to be common in aggressive pituitary tumors. The presence of MGMT-PM was investigated in a study including ten primary pituitary carcinomas, four disseminated metastases, and 12 silent type 3 pituitary adenomas. According to the recent WHO classification, the latter have been renamed *"plurihormonal PIT-1 positive adenomas"* and belong to the newly introduced *"high risk adenomas"* category [23]. Overall, 33% of carcinomas exhibited homogenous MGMT-PM in both tumor and metastatic specimens, while low immunohistochemical MGMT expression was noted in 50% of them. Regarding the silent subtype 3 pituitary adenomas, 42% of them showed MGMT-PM, while MGMT immunostaining was predominately negative (92%) [24]. Although an inverse correlation between MGMT-PM and MGMT immunohistochemistry was observed in some studies, the role of regulation of MGMT expression in pituitary tumors remains controversial [12, 24, 25]. In contrast to MGMT expression, the technical problems related to MGMT immunohistochemistry mentioned above have no effect on the evaluation of MGMT-PM status. Thus, the method is considered to be a more reliable option than immunohistochemistry for MGMT [20]. However, the complexity of MGMT regulatory mechanisms underlines the need for more in-depth research into the relationship between MGMT changes and patient response to TMZ [24].

The DNA mismatch repair (MMR) proteins, MLH1, MSH2, and MSH6 (MutS homolog 2 and MutS homolog 6, respectively), serve as alternative markers to MGMT to predict response to TMZ therapy. In the MMR pathway, heterodimers of MSH2 and MSH6 detect DNA base mismatches due either to errors in DNA replication or to DNA damage. During DNA synthesis, this pathway activates the G2-M DNA damage checkpoint and stimulates apoptotic mechanisms [20, 26]. Expression of MMR proteins in aggressive pituitary tumors is linked to the effectiveness of TMZ treatment [15]. Nuclear immunoexpression of MSH6 correlates with a significant response to treatment with TMZ [17]. Patients with MSH6 positive tumors are responders to TMZ, whereas others with immunonegative tumors do not respond [11]. Unfortunately, many patients eventually develop resistance to treatment with TMZ. It is notable that adenomas removed from patients who responded to treatment show depletion of MSH6 immunoreactivity [16]. However, a recent study reports no differences in MSH6 immunoreactivity between adenomas from recurrent cases and from patients in remission [12]. In addition to MSH6, loss of MSH2 was

observed in a patient who developed rapid resistance to TMZ [27]. Conceivably, loss of MSH2 and MSH6 expression occurring during tumor progression may explain the development of resistance to TMZ treatment.

Novel and emerging treatment modalities

A novel therapy that has recently emerged to manage patients with aggressive tumors who developed resistance to TMZ is currently the recommended first-line chemotherapy. Bevacizumab is an antiangiogenic drug targeting the vascular endothelial factor (VEGF). Bevacizumab inhibits angiogenesis, resulting in the suppression of tumor growth. The drug was recently applied either as monotherapy or in combination with TMZ in two patients, one of them with a clinically aggressive silent corticotroph adenoma subtype 2, the other with a functioning corticotroph carcinoma immunoreactive for VEGF. Bevacizumab stopped tumor progression for 26 months and 5 years of follow-up, respectively [28, 29]. It should be noted that VEGF expression predicts a favorable outcome of treatment. Therefore, immunohistochemical evaluation of VEGF should be applied before embarking on anti-VEGF treatment [28].

Tyrosine kinase inhibitors (TKI) belong to the ErbB family, which includes epidermal growth factor receptor (EGFR). Acting through the ErbB signaling pathway, TKI lead to reduced TK phosphorylation of targeted proteins. Up to two-thirds of patients with Cushing's disease show ubiquitin-specific protease 8 mutations that may underlie the increase in EGFR signaling in corticotroph tumors [30]. Gefitinib, an EGFR-targeting tyrosine TKI, has therapeutic efficacy in corticotroph adenomas, which predominately show nuclear expression of EGFR. Gefitinib blocks EGFR activity, inhibits tumor cell proliferation, and induces apoptosis. Treatment of corticotroph adenomas with gefitinib leads to decreased tumor volume and corticosterone levels [31]. Lapatinib, an oral drug which is a EGFR/ErbB2 tyrosine kinase inhibitor, has been administrated to six patients with aggressive lactotroph adenomas who have been treated with the maximally tolerated dopamine agonist therapy. After 6 months, tumor size was decreased in one patient and prolactin (PRL) levels were reduced up to 42% in three other subjects. EGFR and ErbB2 immunohistochemical expression was not detectable in three tumors and did not correlate with treatment response. The results suggest that EGFR/ErbB2-targeted therapy with lapatinib may control continued tumor growth of aggressive lactotroph adenomas [32].

Immune checkpoint inhibitors (ICPIs) may be another option for the treatment of aggressive pituitary tumors. Only a single case of a patient with corticotroph carcinoma treated consecutively with nivolumab and ipilimumab (anti-CTLA-4 and anti-PD-L1 monoclonal antibodies, respectively) has been reported. After the treatment, a 59% decrease of primary tumor volume and 92% of the main liver metastasis volume was noted, while the levels of plasma ACTH were decreased. The tumor samples retained immunohistochemical expression for MSH6 and PD-L1 staining in < 1% of tumor cells. After 6 months' therapy, the patient continued to respond [33]. Therefore, ICPIs constitute a potential alternative for the treatment of aggressive pituitary tumors, particularly in patients resistant to TMZ.

Everolimus (EVE) is an oral mTOR inhibitor. After binding to a FKBP12, the drug inhibits mTOR and its downstream signaling cascade resulting in decreased protein synthesis, reduced cell growth, and cell cycle arrest. To date, EVE has been tested in six patients with aggressive pituitary tumors. Three patients, one with a lactotroph adenoma and two with a corticotroph adenoma, who were treated with EVE in combination with other treatment modalities, showed transient stability for 5 to 12 months [34–37]. Given that the number of cases is very low, it remains to be clarified whether mTOR inhibitors could be useful to treat patients with highly aggressive, refractory pituitary tumors who failed to respond to other treatment modalities, including TMZ.

In conclusion, significant progress has been made over the past decade in the treatment of aggressive pituitary tumors. Considering the importance of immunohistochemistry in the detection of predictive markers, knowledge concerning the technical drawbacks leading to false-negative results may explain the current clinicopathological controversies. Other markers, such as MSH6, might be better alternatives to MGMT. Emerging treatment modalities beyond TMZ, such as anti-VEGF therapy and other novel and apparently promising therapeutic options, are opening up new horizons for the future management of aggressive pituitary tumors.

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