Temozolomide therapy: Focus on patients with pituitary carcinoma

Pituitary carcinomas are extremely rare, representing no more than 0.1–0.2% of all pituitary tumors. They are characterized by invasion of adjacent structures and rapid proliferation and defined by the presence of distant metastases to intra-or extra-cranial sites.[1] In many cases, they are the result of the progressive transformation of an apparently benign, invasive macroadenoma. According to the latest classification of endocrine organ tumors, from the World Health Organization, a Ki-67 labeling index >3%, as well as extensive nuclear staining for p53 and increased mitotic activity could be suggestive of more aggressive behaviour, but the diagnosis of pituitary carcinoma is still based on the presence of cerebrospinal or systemic metastases.[2] Pituitary carcinomas with metastatic intraspinal involvement are an even more rarely reported clinical event. Indeed, up to this time, only 17 cases of pituitary carcinoma with intraspinal metastasis have been reported in literature.[3]

Owing to the low incidence of pituitary carcinomas, there is not much experience regarding treatment. Surgery, fractionated or nonstereotactic radiosurgery (gamma-knife, linear accelerator, or cyberknife), peptide receptor radionucleotide therapy, and medical therapy with dopamine agonists, long-acting somatostatin analogs (lanreotide and octreotide), tamoxifen, cyproheptadine, OP'DDD (mitotane) or systemic cytotoxic chemotherapy protocols (procarbazine-etoposide-lomustine, lomustine-doxorubicin, and lomustine-5-fluorouracil) have been proposed, but effects are most often inconstant or palliative, and a prolongation of patient's long-term survival has not been reported,[1,4] while surgical excision of metastases seems, in some cases, to have improved chances of survival.[5]

Temozolomide (TMZ), a second-generation alkylating cytostatic drug, introduced in the management of refractory glioblastoma multiforme, but effective in other central nervous system neoplasms as well as in neuroendocrine tumors, is currently considered the gold standard therapy for treatment of gliomas.[6,7] This chemotherapeutic agent acts by alkylating and methylating specific guanine residues, thus damaging DNA and triggering the death of tumor cells (apoptosis).

Response to TMZ is related to the down-expression of O(6)-methylguanine methyltransferase (MGMT), an enzyme which can repair this type of DNA damage, removing alkylating adducts from DNA.[8,9] Despite an inverse correlation being found between MGMT expression and response to TMZ, this observation has not been definitively confirmed given that the absence of MGMT expression does not always predict tumor response.[9] For this reason, MGMT status should be considered a poor predictor of treatment outcome and should not be used to select patients potentially candidate to TMZ therapy. The specificity of TMZ, administered orally, for the management of brain tumors is due to its ability to quickly cross the blood–brain barrier, and to good liposolubility in brain tissue. Moreover, it is not cell-cycle specific, thus making it more advantageous in the treatment of relatively slow-growing tumors, such as pituitary tumors.[10]

More recently, TMZ has been proposed and since 2006, also used in the treatment of patients with pituitary carcinomas and aggressive pituitary adenomas resistant to conventional management.[11,12]

In a review of literature based on published case reports from 2006 to 2013, Chatzellis *et al.* reported 29 cases of pituitary carcinomas and 32 cases of aggressive pituitary adenomas receiving TMZ therapy, in literature, with an overall clinical and radiological response rate of approximately 69% in carcinomas and 60% in aggressive adenomas while data from 4 studies of small cohorts showed an average partial tumor response in 55% of patients with carcinomas and 41% of those with aggressive pituitary adenomas.[1] On the contrary, considering tumor stabilization as a positive outcome, TMZ effectiveness increased up to 72% in carcinomas and 70.5% in aggressive adenomas.[1] In a recently published cohort study of 31 Italian patients receiving TMZ for aggressive pituitary adenomas (25 cases) or carcinomas (6 cases) resistant to standard therapies, the 2-year progression-free survival was 47.7%, and the 2-year disease control duration was 59%.[13] The 2-year and 4-year overall survival rates were 84.0% and 59.6%, respectively, thus confirming that this drug can be

considered an additional effective therapeutic option for the treatment of this type of tumor. TMZ was well tolerated demonstrating a tolerable safety profile, with severe side effects occurring during treatment in only two patients. In conclusion, TMZ can be considered an effective and safe option for carcinomas and aggressive pituitary adenomas but MGMT status is not useful in predicting treatment outcome. For the future, considering as a possible stratification factor the MGMT methylation status, it could be interesting design adequately clinical trial to identify whether TMZ, alone or in association with other chemotherapeutic agents, is superior than the standard treatment.

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Website: www.ruralneuropractice.com

DOI: 10.4103/0976-3147.181478

How to cite this article: Curtò L. Temozolomide therapy: Focus on patients with pituitary carcinoma. J Neurosci Rural Pract 2016;7:335-6.