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## PITUITARY NEUROENDOCRINE TUMORS: FROM OLD TREATMENTS TO INNOVATIONS, FROM EFFICACY TO TOLERANCE, FROM BENIGNITY TO CARCINOMAS, WHERE DO WE STAND NOW?

Frederic CASTINETTI, Gerald RAVEROT

Pituitary neuroendocrine tumors are usually slow-growing lesions, raising 3 potential issues: the risk of local compression, especially the optic chiasm; the risk of hypersecretion and its consequences; the risk of pituitary deficiencies and its consequences. They are considered as rare diseases, which also means that Transsphenoidal surgery remains the first line treatment of such tumors, no matter the phenotype, except for prolactinomas, a disease in which the medical treatment is usually preferred. However, transsphenoidal surgery can fail leading to prolonged medical treatments. Over the last 20 years, major advances have been made on the medical approach of such tumors after failed surgery with prospective trials describing new drugs (such as pasireotide, pegvisomant, osilodrostat, levoketoconazole, mifepristone...) or large exhaustive retrospective studies re-designing the efficacy and tolerance of well-known drugs (such as ketoconazole, metyrapone or cabergoline). The classical approach of pituitary tumors based on the assumption that they are benign have been counterbalanced by studies on the aggressiveness of some of these tumors and the risks of recurrence or even metastases (for the ones which will become pituitary carcinomas), leading to new therapeutic challenges. Despite all these improvements, our knowledge of the behavior of pituitary neuroendocrine tumors and the reasons why they would or not respond to a given treatment remains incompletely understood.

As we approach the year 2023, we felt it was important to provide an update on the therapeutic management of pituitary neuroendocrine tumors. Rather than reviewing the anti-secretory efficacy of the various drugs available, a topic that has been the subject of numerous consensus and reviews in recent years, we have preferred to opt for original reviews dealing with challenging practical questions which might be considered by any endocrinologist interested in pituitary diseases such as: what second-line treatment should be considered in acromegaly resistant to first-generation somatostatinergic receptor ligands (by S. Choloiro et al.)? How best to monitor the side effects of medical treatments of Cushing's disease (by F. Castinetti)? What are the risks of treating a prolactinoma with dopamine agonists in a patient with a history of psychiatric disturbance (by P. Chanson)?

But what would an update be without a section on therapeutic innovation? Next years' management, or at least what we might imagine, will also be detailed in original reviews on therapeutic innovations to be expected in acromegaly (by L. Kasuki and M. Gadelha), Cushing's disease (by V. vonSelzam and M. Theodoropoulou) and gonadotropic tumours (by N. Even-Zohar and Y. Greenman), the latter also including a discussion of the use of domain agonists in this indication. All these reviews will discuss the possible new drugs available in an individualized medical perspective, as it is likely that the future will allow us to choose the most optimal treatment for the phenotypic profile of the patient and/or the molecular profile of the tumor (especially by targeting specific signaling pathways).

Finally, we could not propose an update issue without mentioning the major topic of the last ten years, which is the management of aggressive tumors and pituitary carcinomas. Thanks to international collaborative work, promoted in particular by the European Society of Endocrinology, detailed efficacy data of the first-line molecule, temozolomide, are available and are the subject of the review by A. McCormack presented in this thematic issue, fifteen years after its first description in this indication. As temozolomide is not always effective, other options can be discussed: immunotherapy is one of the most promising ones, and this is what G. Raverot will try to show in an original review summarizing the mechanisms of action, the efficacy and the potential place of these new treatments in pituitary carcinomas.

The strength of this special issue on pituitary neuroendocrine tumors lies in the originality of the approach described in its reviews. We therefore hope that this special issue will provide you with insights for your daily practice, but also encourage you to carry out collaborative work, which is more necessary than ever to advance in the understanding and management of rare pituitary tumors.