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Review Article

Recent Therapeutic Advances in Pituitary Carcinoma

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ABSTRACT

Pituitary carcinoma (PC) is a rare, aggressive malignancy that comprises 0.1–0.2% of all pituitary tumors. PC is defined anatomically as a pituitary tumor that metastasizes outside the primary intrasellar location as noncontiguous lesions in the central nervous system or as metastases to other organs. Similar to pituitary adenoma, PC originates from various cell types of the pituitary gland and can be functioning or nonfunctioning, with the former constituting the majority of the cases. Compression of intricate skull-based structures, excessive hormonal secretion, impaired pituitary function from therapy, and systemic metastases lead to debilitating symptoms and a poor survival outcome in most cases. PC frequently recurs despite multimodality treatments, including surgical resection, radiotherapy, and biochemical and cytotoxic treatments. There is an unmet need to better understand the pathogenesis and molecular characterization of PC to improve therapeutic strategies. As our understanding of the role of signaling pathways in the tumorigenesis of and malignant transformation of PC evolves, efforts have focused on targeted therapy. In addition, recent advances in the use of immune checkpoint inhibitors to treat various solid cancers have led to an interest in exploring the role of immunotherapy for the treatment of aggressive refractory pituitary tumors. Here, we review our current understanding of the pathogenesis, molecular characterization, and treatment of PC. Particular attention is given to emerging treatment options, including targeted therapy, immunotherapy, and peptide receptor radionuclide therapy.

Keywords: pituitary carcinoma, immunotherapy, aggressive pituitary tumors, PRRT

INTRODUCTION

The majority of pituitary neoplasms are pituitary adenomas (PAs), which are common, benign glandular tumors that are derived from the adenohypophysis and classified by their endocrinologic cell lineage.[1] These tumors are also broadly differentiated by size as either macroadenomas ($\geq$ 1 cm) or microadenomas ($<$ 1 cm). Treatment of PA is indicated when patients become symptomatic, either from mass effect or from the excess production of hormones such as prolactin, adrenocorticotropic hormone (ACTH), growth hormone (GH), and thyroid-stimulating hormone (TSH).[2] Most symptomatic PAs have a favorable response to the combination of surgical resection and hormonally targeted therapies, with a 5-year survival rate of $>$ 90%.[3] Less commonly, these tumors are locally destructive, treatment resistant, and have high recurrence rates, which are defining features of what the World Health Organization (WHO) now recognizes as aggressive pituitary tumors (APTs).[4] In the most extreme cases, 0.1–0.2% of tumors metastasize outside of their primary intrasellar location as noncontiguous foci within the central nervous system or systemically, becoming pituitary carcinomas (PCs).[5–7] While no well-established histopathologic, molecular, or genetic distinctions exist between PA and APT and PC,[8] the metastatic nature of PC establishes it as a clinically distinct entity.[9] To avoid the need to reclassify PAs as PCs upon the identification of metastases, the WHO proposed that pituitary tumors be classified as pituitary neuroendocrine tumors to encompass both entities.[10,11]

An adenoma-to-carcinoma progression model of PC has been hypothesized,[12] with limited evidence suggesting rare cases of de novo tumor origination.[13] Studies have reported a highly variable latency period between the diagnosis of adenoma to the first metastatic lesion, with a mean of approximately 5–6 years and

occurrence as late as 29 years after the initial diagnosis.[14,15] Efforts to identify morphologic, immunohistochemical, or molecular markers to predict metastatic potential are still ongoing.[16] Greater than 70% of PCs are functional, with corticotroph (ACTH-producing) and lactotroph (prolactin-producing) tumors being the most common, followed by less frequently reported cases of luteinizing hormone, GH- or follicle-stimulating hormone, and TSH-producing tumors.[17]

The initial clinical presentation of PC mirrors that of invasive PA; most clinical manifestations result from local sellar and cavernous sinus impingement, including headaches, visual disturbances, cranial nerve palsy, and hormonal imbalances, such as Cushing disease (hypercortisolism).[18] A diagnosis cannot be made until metastatic disease is identified,[19] at which point management is increasingly difficult. Treatment strategies include surgical resection, radiotherapy, and biochemical and cytotoxic treatments. Temozolomide (TMZ), an alkylating chemotherapy agent, has shown efficacy in the treatment of PC,[20] but sustained treatment responses are uncommon, with frequent disease progression and a 2-year survival rate not exceeding 50%.[21–23]

Because of the diagnostic and therapeutic challenges that arise in managing this rare entity, in this review paper we summarize our current understanding of PC by reviewing recent advances in its diagnosis, molecular characterization, and treatment, with particular attention to the emerging role of immunotherapy for patients with this rare, aggressive malignancy.

Pathogenesis and Molecular Characterization

The pathogenesis of PA and its transition to APT and PC is complex and poorly understood; elucidating a unifying paradigm has been difficult because of inherent differences among pituitary cell subtypes. Given the trophic influence of hypothalamic hormones on stimulation of the anterior pituitary gland, hypothalamic dysregulation may provide the initial proliferative stimulus that triggers pituitary cell growth. However, it seems more likely that intrapituitary factors, namely the activation of selective oncoproteins or loss of suppressor factors, are the primary drivers of tumorigenesis.[24]

In one study, deregulation in the Rb/p16/cyclin D1/cyclin–dependent kinase 4 pathway was found in up to 80% of PAs.[25] The pituitary tumor–transforming gene, a regulator of anaphase and activator of growth signals that include vascular endothelial growth factor (VEGF)/fibroblast growth factor,[26] was found to be overexpressed in 90% of adenomas, with little or no expression in healthy pituitary tissue.[27,28] It has also been theorized that the benign nature of most PAs may result partially from oncogene-induced senescence,[29,30] a mechanism in which early genomic aberrations, including alterations in the pituitary tumor–transforming gene, trigger powerful intrinsic tumor-suppressive activities, mainly through the p53/p21 and p16/Rb inhibitory pathways.[31] Experimental pituitary tumor models in rats have demonstrated increasing levels of nuclear p21 over time after an initial proliferative phase in somatolactotroph cell lines.[32] An immunohistochemical study also showed lower nuclear staining of p16 in all pituitary tumors than that in normal pituitary tissue, with the decrease most pronounced in six cases of PC.[33 The loss of oncogene-induced senescence mechanisms seems to be a recurrent factor in the malignant transformation observed in PCs.[34] These findings are accompanied by the caveat that these and other senescence patterns are not consistent across pituitary cell subtypes.[35]

In addition, the upregulation of proangiogenic factors, most notably including epidermal growth factor, VEGF, and matrix metalloproteinase-9, have been implicated in PC pathogenesis.[36] Numerous other mediators, such as the upregulation of cyclin-dependent kinases and downregulation of apoptotic proteins such as Bcl-2, have also been implicated as potential contributors to aggressive behavior and recurrence.[33] It remains challenging to identify key molecular patterns within the malignant transformation of these heterogeneous tumors because the evolution from adenoma to carcinoma is typically gradual, with an extended clinical latency.

Currently, pituitary tumors are characterized mainly by proliferative markers, with the WHO recommending the use of Ki-67 index $> 3\%$, p53 immunoreactivity, and an elevated mitotic count as potential markers of clinical aggressiveness.[37] The validity of Ki-67 as a prognostic marker is recognized in many tumors,[38] but its use remains unclear in pituitary tumors.[39] Multiple studies refute its prognostic value,[40] while others demonstrate a significant inverse relationship between the Ki-67 index and the risk of recurrence,[41] as well as the ability to stratify among noninvasive adenomas, APTs, and PCs on the basis of the degree of Ki-67 index elevation.[42] Ultimately, while the established cutoff of 3% is controversial, Ki-67 seems to have high sensitivity but low specificity for predicting tumor recurrence and invasive potential.[43] Thus, other immunohistochemical markers, such as p53, and other clinical characteristics, such as resistance to conventional treatment regimens and regrowth after repeat resections, should also be used to prompt more aggressive early management and more frequent interval imaging and endocrine evaluations.[44]

TREATMENT

PAs become clinically significant and prompt treatment as a result of excess hormone production or mass effect and impingement on surrounding cranial structures.[45] The initial course may involve medical therapy, as is the case with prolactinomas, for which dopamine agonists such as bromocriptine or cabergoline are often sufficient to reduce tumor size and achieve biochemical remission, or primary surgical resection in the case of ACTH-, GH-, or TSH-producing adenomas.[46] Surgical approaches emphasize maximal resection, with a pre-

ferred transsphenoidal approach, to alleviate mass effect and facilitate biochemical remission.[47] Radiotherapy is generally used when surgery is inadequate to control the tumor or in the setting of inoperable recurrence.[48] Stereotactic radiosurgery is generally preferred,[49] although when targeting lesions near or within the optic chiasm, fractionated radiotherapy is often used to reduce the risk of developing an optic neuropathy.[50]

Medical therapy for PA and APT involves reducing excess hormone secretion from functional pituitary tumors using medications such as somatostatin analogs (octreotide, lanreotide, and pasireotide) and dopamine agonists (bromocriptine and cabergoline). Somatostatin analogs exert counterregulatory effects on the release of a variety of hormones, including GH, TSH, and ACTH. Bromocriptine and cabergoline act as agonists at pituitary D2 receptors, inhibiting the release of GH, prolactin, and ACTH by increasing dopamine antagonism.

The initial treatment of PCs involves multidisciplinary assessment for re-resection, reirradiation, hormonal therapies, and cytotoxic chemotherapies. Of note, reirradiation has been shown to be helpful in controlling tumor mass but not necessarily in limiting excess humoral secretion from these tumors.[51] Thus far, TMZ, an alkylating agent that is used as the standard of care for high-grade gliomas, has shown the most promise and is now established as a first-line chemotherapy option for the treatment of PCs.[52] In 2018, the European Society of Endocrinology published clinical practice guidelines that included a recommendation for TMZ monotherapy after the failure of standard therapies, using standard 150–200 mg/m^2 dosing for 5 days every 28 days, treatment evaluation after three cycles, and the continuation of therapy for at least 6 months in patients who experienced a response to this initial three-cycle regimen.[44] Several recent larger-scale retrospective studies have noted median progression-free survival (mPFS) durations ranging from 23 to 40 months with TMZ monotherapy.[53,54] In a recent large-scale meta-analysis of 21 studies involving 421 patients with either APTs or PCs, an mPFS duration of 20 months was noted with a 40% radiologic response rate in the patient cohort, which improved to 60% with chemoradiotherapy.[55] While there are cases that demonstrate more durable, sustained treatment responses,[56,57] a substantial proportion of patients with PC do not experience a response to TMZ or experience recurrence after an initial response.

Given these findings, further research has sought to understand the potential predictors of response to TMZ therapy in APTs and PCs. Previous studies have established that low expression of O^6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that mechanistically counteracts the alkylating effects of TMZ, is associated with chemoresistance in various gliomas.[58] In one study of 24 patients with PCs, the tumor cell nuclei of nonresponders had median MGMT staining of 93% compared with 9% in responders.[59] An independent research group also reported an association between low MGMT expression and positive treatment response in PCs.[60] However, other studies have suggested a more equivocal relationship, which is likely complicated by conflicting interstudy reliability and inconsistent immunohistochemistry staining methods.[61] Overall, the evidence is not robust enough to exclude from therapy patients who have high MGMT expression; however, the previously mentioned European Society of Endocrinology clinical guidelines still recommend determining MGMT status via immunohistochemistry as a tool to guide therapy (low-evidence recommendation).[44] Another DNA repair gene that is implicated in the prediction of response to TMZ is *MSH6*, a gene that codes for a DNA mismatch repair protein for which mutations are associated with an increased risk of malignancy, such as that seen in Lynch syndrome. One case reported the evolution of TMZ resistance in a patient with PC and an *MSH6* mutation from immunopositive to immunonegative in the setting of an otherwise MGMT-negative, p53-mutated lactotroph carcinoma, suggesting that loss of MSH6 was the driver of resistance to TMZ.[62] A small-scale retrospective analysis of 13 patients, 10 of whom were noted to have PC, demonstrated that immunopositivity of MSH6, but not Ki-67, p53, or MGMT, was correlated with an improved response to TMZ, with a lower likelihood of progressive disease.[63]

Given the high rates of relapse after TMZ monotherapy, there have been efforts to use combinatorial approaches to treat PC. In one case series, the use of concurrent radiotherapy and TMZ resulted in the sustained control of treatment-resistant extraneural metastases in two patients with PC.[64] The addition of capecitabine to TMZ (CAPTEM) is another regimen that has been shown to be effective. Capecitabine is a prodrug of 5-FU, an antimetabolite agent that has been shown to be synergistic with TMZ in vivo in the treatment of neuroendocrine neoplasms.[65] In a large clinical trial of 144 patients with advanced pancreatic neuroendocrine tumors, the mPFS duration was 22.7 months in patients receiving CAPTEM compared to 14.4 months in patients receiving TMZ alone.[66] In one case series of four patients with corticotroph PCs, two patients experienced complete disease regression, and one had stable disease for $>$ 4.5 years after CAPTEM.[67] However, other available case reports have demonstrated more variable responses[68,69]; ultimately, prospective trials will be needed to elucidate whether CAPTEM is superior to TMZ monotherapy in patients with PC. In cases of TMZ nonresponse, case reports have demonstrated varying degrees of success for salvage regimens, including etoposide with cisplatin/carboplatin.[70–72] In one case of a patient diagnosed with a corticotroph carcinoma at age 14, treatment with carboplatin and 5-fluorouracil resulted in prolonged survival; the patient is noted to still be in disease remission over a decade after her initial diagnosis.[73]

Targeted Therapies

As our understanding of the role of angiogenic growth factors and the PI3KAkt//mTOR pathway on the tumorigenesis of malignant endocrine tumors evolves,[74] efforts have focused on targeted therapy as an alternative strategy to improve clinical outcomes in APT and PC.

The expression of VEGF is upregulated in both invasive adenoma and PC compared to noninvasive adenoma,[75,76] suggesting a role for targeting VEGF with bevacizumab or the VEGF receptor with sunitinib or sorafenib.[77] One case report demonstrated a lack of disease progression on bevacizumab for 26 months after TMZ failure,[78] and another demonstrated 5 years of stability when bevacizumab was combined with TMZ.[79] A case treated with bevacizumab following disease progression on checkpoint inhibitor (CPI) therapy resulted in an 8-month progression-free (PFS) survival.[80] Lapatinib, a tyrosine kinase inhibitor that targets epidermal growth factor has been approved for use in metastatic HER2 breast cancer; it was also tested in a recent phase 2 prospective trial of treatment-resistant prolactinoma and was effective in three cases of locally invasive APT, but not in a patient with prolactinoma with craniospinal metastasis.[81] In contrast to anti-VEGF and epidermal growth factor therapies, targeting mTOR through the use of everolimus has thus far not been effective in PC when used as monotherapy[82] or in combination with hormonal therapies.[83] It seems plausible that these and other targeted therapies are more effective in carefully selected patients with more activating mutations, although currently there is no specific evidence to validate this hypothesis. While current evidence regarding targeted therapy use in patients with PC and APTs is limited, there is some preliminary evidence that combinatorial approaches using targeted and cytotoxic therapies can be effective in a subset of patients.

Immunotherapy

The immune tumor microenvironment involves a complex interplay among many different tissue components, including infiltrating immune cells, tumor cells, resident tissue cells, such as fibroblasts and endothelial cells, and the extracellular matrix.[84] Through these complex interactions, tumor cells evade immune responses through several mechanisms, including the upregulation of coinhibitory cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and the programmed death ligand 1 and 2 (PD-L1 and PD-L2, respectively) pathways,[85] which have been shown to be present to variable degrees across pituitary tumor subtypes.[86] A recent analysis of 60 pituitary tumor samples demonstrated increased expression of PD-L2 and CD80/CD86, coreceptors that are able to interact with CTLA-4, in more APTs.[87] Furthermore, hypophysitis and hypopituitarism are well-established adverse events seen primarily in patients receiving CTLA-4 blockade.[88] Given these findings, there is a mechanistic basis for the use of immunotherapy in APT and PC.[89]

A recent phase 2 trial of pembrolizumab, a PD-L1 receptor blocker, in rare tumors included four patients with PC.[90] One patient with a corticotroph carcinoma experienced disease progression after TMZ, CAPTEM, and multiple rounds of targeted radiotherapy. However, after treatment with pembrolizumab, the patient had regression of intracranial and metastatic disease that was sustained for 42 months after treatment initiation. Interestingly, this patient was noted to have a hypermutator phenotype that included both *MSH2* and *MSH6* mutations. Another patient with a corticotroph carcinoma, who experienced disease progression after stereotactic radiosurgery and TMZ, also demonstrated a partial response, with a progression-free survival duration of 12 months at the time of study conclusion. The other two patients, one with silent corticotroph carcinoma and one with lactotroph carcinoma, did not experience a response to pembrolizumab.[91]

In addition to pembrolizumab monotherapy, five individual case reports have noted success with dual immune-checkpoint blockade in the treatment of PC. In one patient with functional corticotroph carcinoma with hepatic metastases who received therapy with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4), five cycles of therapy resulted in a 92% reduction in dominant hepatic metastasis and a 59% reduction in the recurrent intracranial component, along with stable disease 6 months after study conclusion on nivolumab maintenance.[92] In one case of corticotroph carcinoma, stable disease was observed 1 year after ipilimumab and nivolumab therapy,[93] while two other cases reported 8 months of stable disease on this regimen.[80,94] Recently, a patient with lactotroph carcinoma treated with ipilimumab and nivolumab had complete, sustained remission 24 months after the initiation of therapy. To date and to our knowledge, this is the only reported case with complete radiologic and endocrinologic response.[95] Evidently, although a subset of patients responded to CPI therapy, larger-scale prospective trials are needed to further clarify the role of these agents. Ongoing studies (ClinicalTrials.gov Identifiers: NCT02834013 and NCT04042753) are testing the efficacy of ipilimumab and nivolumab in APT and PC patients.[89] A summary of the results of key immunotherapy trials conducted in patients with pituitary carcinoma can be referenced in Table 1.

A recent systematic review of the use of immunotherapy specifically in APTs and PCs noted several important trends in the observed cases, including the slightly more favorable therapeutic response in corticotroph than in lactotroph carcinoma.[96] This may be the result of an increased number of infiltrating CD8+ T cells in functional corticotroph tumors compared with lactotroph and other tumor subtypes.[97] While such a proposed mechanism is plausible, there remains a need to determine whether the biomarkers used to predict

Table 1. Immunotherapy Studies in Patients with Pituitary Carcinomas

Tumor Subtype and Metastases	Time from PA to PC Diagnosis (months)	Prior Treatments			Immune CPIs	Outcomes	Reference
		Prior Surgeries	Radiation Therapy	Medical Treatments			
Corticotroph carcinoma with cerebrospinal and liver metastases	54	TSS (×3) Blt adrenalectomy	RT (×5) 1. Cavernous sinus 2. Sellar region (×2) 3. RT orbit 4. LT optic nerve	1. TMZ (16 cycles) 2. CAPTEM (2 cycles) 3. FGFR inhibitor (2 cycles) 4. CCNU + bevacizumab (1 cycle)	1. Pembrolizumab (29 cycles)	-PFS 69 months after pembrolizumab initiation -PR radiologic (60%) -CR of ACTH levels -Alive 146 months after PC diagnosis	Majd et al (2020)[90]
Corticotroph carcinoma with craniospinal, bone, liver, and pleural metastases	45	-Stereotactic radiosurgery (×2) -Blt adrenalectomy	RT (×1) 1. Pituitary fossa	1. Pasireotide 2. TMZ (7 cycles) 3. CAPTEM (7 cycles)	1. Pembrolizumab (34 cycles) -Ongoing treatment	-PFS 32 months after pembrolizumab initiation -PR radiologically (32% reduction in liver lesions) -PR of ACTH levels (2,000 → 628) -Alive 56 months after PC diagnosis	Majd et al (2020)[90]
Corticotroph carcinoma with cranial and bone metastases	131	-CNS surgery (×3) -Vertebroplasty/ vertebral body biopsy	RT (×4) 1. Sellar region 2. Spine 3. Skull base 4. RT frontal dural-lesion	1. TMZ (12, 7, and 2 cycles) 2. IDO1 pathway inhibitors (11 cycles) 3. CAPTEM (6 cycles) 4. CDK pathway inhibitor (3 cycles)	1. Pembrolizumab (6 cycles)	-PFS 4 months after pembrolizumab initiation, discontinued therapy because of subsequent progressive disease -Alive 138 months after PC diagnosis	Majd et al (2020)[90]
Lactotroph carcinoma with craniospinal and liver metastases	81	-CNS surgery (×1) -Sacral mass biopsy	RT (×2) 1. Sellar region 2. Spine	1. Cisplatin/etoposide (1 cycle) 2. TMZ (12 and 2 cycles) 3. CAPTEM (2 cycles) 4. Bevacizumab, temsirolimus, valproate (2 cycles) 5. PRRT therapy with Lu-177 (1 treated)	1. Pembrolizumab (6 cycles) 2. Other PD-1/PD-L1 pathway inhibitors (2 cycles)	-Progressive disease with increase in PRL levels after starting pembrolizumab -Deceased 46 months after PC diagnosis	Majd et al (2020)[90]
Corticotroph carcinoma with liver metastases	68	-TSS ×4 -Blt adrenalectomy	-RT (×2) 1. Sellar region (×2)	1. Pasireotide, ketoconazole + cabergoline 2. CAPTEM (4 cycles) 3. Etoposide/ carboplatin (2 cycles)	1. Ipilimumab/ nivolumab (5 cycles) 2. Maintenance nivolumab (ongoing at study conclusion)	-PFS 8 months after immune CPI initiation -PR radiologic (92% reduction in dominant hepatic metastases, 59% decrease in recurrent intracranial metastases) -CR tumor marker from 45,000 → 66) -Alive ∼30 months after PC diagnosis	Lin et al (2018)[92]

Table 1 continues on next page

Table 1. Continued

Tumor Subtype and Metastases	Time from PA to PC Diagnosis (months)	Prior Treatments			Immune CPIs	Outcomes	Reference
		Prior Surgeries	Radiation Therapy	Medical Treatments			
Corticotroph carcinoma with cerebrospinal and liver metastases	204	-TSS (×3)	-RT (×3)	1. TMZ (10 or 3 cycles) 2. Pasireotide, cabergoline, hydroxyurea	1. Ipilimumab/ nivolumab (5 cycles) 2. Nivolumab (4 cycles)	-PFS ~4 months after immune CPI initiation prior to progressive disease -PR radiologic (> 50% reduction in liver metastases, resolution of T2 lesion) -PR tumor marker (ACTH 13,813 → 549) -Deceased 22 months after PC diagnosis	Duhamel et al (2020)[94]
Lactotroph carcinoma with cerebrospinal metastases	48	-TSS (×3) -Debulking of spinal metastatic disease	-RT (×1) 1. Sellar region	1. TMZ (~3 cycles) 2. Bevacizumab (3 cycles)	1. Ipilimumab/ nivolumab (2 cycles) -Pause because of autoimmune nephritis 2. Nivolumab (17 cycles) 3. Rechallenge with ipilimumab/ nivolumab (4 cycles)	-PFS 8 months after bevacizumab initiation -PR radiologic (> 50% of primary intracranial and metastatic lesions) -Alive 24 months after PC diagnosis	Lamb et al (2020)[80]
Corticotroph carcinoma with cerebrospinal metastases	72	-Stereotactic radiosurgery (×2) -Blt adrenalectomy	None	1. Ketoconazole, pasireotide, cabergoline 2. TMZ (9 cycles)	1. Ipilimumab/ nivolumab (4 cycles) 2. Nivolumab/ ketoconazole maintenance	-PFS 12 months after ipilimumab/nivolumab initiation at the study conclusion, on nivolumab/ ketoconazole maintenance -SD radiologic (no interval change) -PR tumor marker (ACTH 419 → 268) -Alive 21 months after PC diagnosis	Sol et al (2021)[93]
Lactotroph carcinoma with brain, lung, and pancreatic metastases	72	-LT lobectomy, LT splenopancreatectomy -CNS surgery (×1) -TSS (×2)	RT (×4) 1. Sellar region (×2) 2. Cavernous sinus (×1) 3. Cerebellar and posterior cavernous sinus lesion (×1)	1. TMZ (43 cycles)	1. Ipilimumab/ Nivolumab (4 cycles) 2. Nivolumab maintenance therapy	-Sustained remission 24 months after ipilimumab/ nivolumab initiation, on nivolumab maintenance therapy -CR radiologic (no evidence of lesions intracranially or at other metastatic sites) -CR tumor marker (prolactin > 10,000 → undetectable) -Alive 96 months after PC diagnosis	Goichot et al (2021)[95]

ACTH: adrenocorticotropic hormone; Blt: bilateral; CAPTEM: capecitabine + temozolomide; CCNU: lomustine; CDK: cyclin-dependent kinase pathway; CNS: central nervous system; CPI: checkpoint inhibitor; CR: complete response; FGFR: fibroblast growth factor receptor; IDO1: indoleamine 2,3-dioxygenase 1; LT: lactotroph carcinoma; PA: pituitary; PC: pituitary carcinoma; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; PFS: progression-free survival; PR: partial response; PRL: prolactin; PRRT: peptide radionucleotide receptor therapy; RT: radiotherapy; SD: stable disease; TMZ: temozolomide; TSS: transsphenoidal surgery.

treatment response of CPI in other solid tumor malignancies (such as tumor-mutational burden [TMB], microsatellite instability, PD-L1, and increased tumor-infiltrating T cells) are also predictive of treatment response in APTs and PCs.[98]

In particular, TMB, defined as the number of somatic mutations per coding area of a tumor's genome, has been an emerging clinical biomarker[99]; hypothetically, tumors with high TMB have an increased number of neoantigens, which can help native immune cells to recognize and kill tumor cells.[100] TMB could be of particular relevance to PC because of the high rate of hypermutation that occurs commonly after TMZ use, and the poor prognosis, such hypermutation, typically portends.[101] However, the correlation of high TMB with response to immunotherapy has been demonstrated to be tumor specific, showing favorable prognostic value in melanoma and lung but not in gliomas, for example.[102] Given demonstrated tumor-specific correlation, future studies must ascertain whether high TMB could be useful as a predictor of response to immune checkpoint inhibitor (ICI) therapy. Based on a recent retrospective, observational cohort study that included 15 PCs and APTs treated with ICIs in France, four corticotroph carcinomas with negative PDL-1 staining and $< 1\%$ CD8+ T cell infiltration demonstrated partial response. This result suggests that the lack of presence of these typically favorable prognostic markers does not preclude immunotherapy response[103]; however, neither high TMB nor microsatellite instability have been specifically studied yet.

Peptide Receptor Radionuclide Therapy

Pituitary tumor histotypes have been shown to express, widely and heterogeneously, the various somatostatin receptor (SSTR) subtypes, with somatotrophs, for example, mainly expressing SSTR2 and SSTR5 and lactotrophs expressing SST1 and SST5.[104] Peptide receptor radionuclide therapy (PRRT) technology uses radiolabeled peptides, including somatostatin analogues such as ^{177}Lu DOTA-TATE, to target SSTR receptors and selectively deliver cytotoxic doses of radiation.[105]

PRRT has been evaluated to a limited extent in APTs and PCs. Of 13 total published cases of PRRT in patients with APT in the medical literature, four experienced a clinical response, defined by either growth arrest or shrinkage of the tumor bulk, improvement in clinical signs and symptoms, or biochemical improvement.[106] In our experience, one patient with a metastatic prolactinoma progressed after a single course of PRRT. To date, there have been three reported cases of success with PRRT in PC. One patient demonstrated stable disease for over 4 years after the initiation of treatment,[107] and another remained radiologically stable, with a complete response in some leptomeningeal nodules 40 months after treatment induction.[108] A more recent case report of a patient with highly resistant corticotroph PC demonstrated sustained clinical stability of over a year after four doses of Lu DOTA-TATE were given following ipilumumab and nivolumab, suggesting a synergistic response between PRRT and CPI.[109] A notable potential advantage of PRRT is its eventual ability to effectively differentiate between clinical responders and nonresponders through the use of quantitative positron emission tomography (PET)-derived parameters on SSTR imaging.[110] The use of pretherapeutic maximum standardized uptake values (SUVmax) of various radiolabeled somatostatin analogs on PET/CT scans have been demonstrated to both be correlated strongly with PRRT response[111] and be predictive of PRRT, with greater than 95% sensitivity or specificity in some studies.[112]

Conversely, a limitation of PRRT is its toxicity, with marrow suppression and nephrotoxicity being major dose-limiting side effects,[113] a particular concern for PC patients who have already received cytotoxic chemotherapy. In one larger-scale retrospective analysis of 807 patients who underwent PRRT for neuroendocrine tumors, 2.5% of patients developed myelodysplastic syndrome; 33% of patients also experienced some degree of nephrotoxicity, although it was severe (grade 3–4) in only 1%.[105]

Of note, there is currently a phase 2 clinical trial for PRRT use in patients with SSTR+ neuroendocrine tumors for which patients with PC would be eligible, and the trial will help clinicians to further determine the efficacy for PRRT use in patients with PC.

CONCLUSION

PC is a rare neuroendocrine malignancy that remains challenging to treat given that no well-defined standard therapy exists. Treatment recommendations are largely driven by small prospective and retrospective case series. Most patients undergo resection, focal radiotherapy, and medical therapy that is directed at reducing hormone hypersecretion and its clinical manifestations (biochemical therapy), decreasing tumor size to improve mass effect and related neurologic symptoms (chemotherapy), and correcting hormone deficiencies. TMZ remains the first-line chemotherapy to treat PC, which is refractory to the above standard therapies. Other combinatorial approaches, such as CAPTEM and therapies targeting VEGF and CPI, seem to offer the greatest potential to improve outcomes. Conducting clinical trials in PC is exceedingly difficult because of the rarity of the disease and the lack of access to specialized centers by all patients. Therefore, large multicenter clinical trial efforts are needed to be able to conduct meaningful research in this orphan disease. Importantly, future research should focus on establishing a national tumor bank and databases for APTs and PCs to expand our understanding of their molecular pathogenesis and resistance to different treatment modalities.

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