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Review

Targeted Therapy in the Management of Modern Craniopharyngiomas

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Abstract

Background: The proximity of craniopharyngiomas (CPs) to critical neurovascular structures can lead to a host of neurologic and endocrine complications that lead to difficulty with surgical management. In this review, we examine the molecular and genetic markers implicated in CP, their involvement in tumorigenic pathways, and their impact on CP prognosis and treatment. **Methods**: We undertook a focused review of relevant articles, clinical trials, and molecular summaries regarding CP. **Results**: Genetic and immunological markers show variable expression in different types of CP. *BRAF* is implicated in tumorigenesis in papillary CP (pCP), whereas *CTNNB1* and *EGFR* are often overexpressed in adamantinomatous CP (aCP) and *VEGF* is overexpressed in aCP and recurrent CP. Targeted treatment modalities inhibiting these pathways can shrink or halt progression of CP. In addition, *EGFR* inhibitors may sensitize tumors to radiation therapy. These drugs show promise in medical management and neoadjuvant therapy for CP. Immunotherapy, including anti-interleukin-6 (IL-6) drugs and interferon treatment, are also effective in managing tumor growth. Ongoing clinical trials in CP are limited but are testing BRAF/MET inhibitors and IL-6 monoclonal antibodies. **Conclusions**: Genetic and immunological markers show variable expression in different subtypes of CP. Several current molecular treatments have shown some success in the management of this disease. Additional clinical trials and targeted therapies will be important to improve CP patient outcomes.

Keywords: craniopharyngioma; adamantinomatous; papillary; BRAF; beta-catenin; CTNNB1; immunotherapy; molecular biology; EGFR

1. Introduction

Craniopharyngiomas (CPs) can result in high levels of morbidity and mortality because of their involvement of critical neurovascular structures. Available treatment strategies, including surgery and radiotherapy, have limitations and known complication profiles. Thus, novel therapies are needed to improve long-term outcomes postoperatively. Currently, no medical therapies are widely established to treat CPs, but recent advances in molecular biology have revealed potential molecular pathways that could be exploited to develop new therapeutics. Targeted molecular therapy has the potential to minimize the adverse outcomes currently associated with medical management of CPs. Here, we performed a scoping review of known molecular pathways and markers identified in the pathogenesis of CP and evaluate studies/case reports and current clinical trials evaluating the use of targeted treatments. Search terms for "targeted treatment", "craniopharyngioma", and repeat searches for key identified genes was performed.

2. Epidemiology and Clinical Features

CPs are benign epithelial tumors that originate from the sellar region, specifically the craniopharyngeal duct. They are classified as World Health Organization grade I lesions [1] and show a bimodal age distribution, with peak incidence rates observed in children aged 5–14 and adults aged 50–74 years [2]. These tumors are quite rare, with incidences ranging from 0.17 to 0.2 cases per 100,000 people in the U.S [3].

CPs may present with focal neurological deficits, ophthalmologic disturbances, endocrinopathies, and evidence of intracranial hypertension [4,5]. Ophthalmologic disturbances, seen in 62–84% of patients, may manifest as bitemporal hemianopsia due to compression of the optic chiasm or visual disturbance secondary to intracranial hypertension. Endocrinopathies occur because of damage to the hypothalamic–pituitary axis and can be present at time of diagnosis [6]. Endocrinopathies are seen in 52–87% of patients and include one or more hormonal deficiencies and panhypopituitarism. Patients may also present with diabetes insipidus or develop it along the course of treatment. Focal neurological deficits may include seizures, headaches, nausea, vomiting, and hydrocephalus [7].

Clinical manifestations are heavily dependent on the anatomic location of the CP, specifically whether the tumor is in a prechiasmal, retrochiasmal, or intrasellar location [4]. Tumors in prechiasmal locations are more likely to manifest with visual disturbances and optic atrophy, whereas those in retrochiasmal locations present with increased intracranial

pressure and hydrocephalus and intrasellar tumors typically manifest with headache and endocrinopathies. Diagnosis of childhood CP is usually made late, often years after the initial symptoms manifest [8]. In children, any combination of headache, visual deficits, regressed development or reduced growth rate, and/or polydipsia should include CP as a differential diagnosis.

3. Current Management

Craniopharyngiomas pose a significant challenge in medical management because of their proximity to neurovascular elements, the hypothalamus, subcortical structures, and the cerebral cortex [9]. An infiltrative and unpredictable growth pattern is often seen, making safe resection difficult. Despite advances in surgical management and radiation, the morbidity and mortality of patients with CP remains high, highlighting a need for the development of novel treatment approaches. CPs have the highest mortality rate of sellar tumors, even after adjusting for other clinical factors [10]. Overall mortality may be 3–5 times higher than the baseline population risk [5,11]. Morbidity and mortality for CPs are influenced by tumor location, tumor size, and treatment strategy. Overall survival in mixed pediatric and adult populations has been reported to be between 54–96% at 5 years, 40–93% at 10 years, and 66–85% at 20 years, indicating that conventional surgical care is not sufficient for improved survival [5]. Complications of CP treatment can include visual loss, panhypopituitarism, diabetes insipidus, obesity, cardiovascular disease, stroke, sleep disturbances, dysfunctional thermoregulation and thirst, and lower bone density [12].

Current treatment options rely on maximal safe resection; the choice of gross-total resection (GTR) or subtotal resection (STR) depends on the extent of encasement or invasion of critical neurovascular structures. Regardless of the extent of resection, multidisciplinary treatment at experienced centers for management of CPs is favored to improve extent-of-resection and reduce neurological morbidity [13]. Radiotherapy, although beneficial in reducing tumor recurrence, is controversial due to the potential neurovascular morbidity. Post-operative conventional radiotherapy (CRT) for CP is associated with new pituitary deficits, including worsening of partial hypopituitarism, observed in 20–60% of irradiated patients studied in the literature, and radiation induced optic neuropathy [14,15]. In contrast, fractionated stereotactic radiation therapy (FSRT) and stereotactic radiosurgery (SRS) have lower toxicity rates and greater safety and efficacy in terms of hypothalamic and visual function. As a result, SRS and FSRT have largely replaced CRT methods for post-operative treatment of CP. In addition, optimal timing after tumor resection, whether immediately after surgery or after tumor progression, is undetermined. In a study of adults with CP undergoing GTR, STR + adjuvant radiotherapy, or STR alone, the rates of recurrence were similar between GTR and STR + adjuvant radiotherapy [16]. Furthermore, a meta-analysis of 744 CP patients undergoing GTR vs. STR + adjuvant radiotherapy showed no difference in overall survival and progression-free survival between groups [17]. However, a retrospective review of a pediatric cohort with primary and recurrent CP showed that patients with upfront GTR had significantly longer progression-free survival, supporting the notion that GTR offers a better chance of disease control and cure [18].

On the other hand, several studies have shown that GTR is associated with a higher risk of neurologic, ophthalmic, and endocrinological deficits. In the pediatric population GTR has higher morbidity and mortality related to hypothalamic dysfunction including hyperphagia, hypothalamic obesity, thermal dysregulation, diabetes insipidus, and cognitive deficits [19]. A retrospective, single-center analysis of 178 pediatric patients treated between 1960 and 2017 showed that radical resection was associated with higher risks of worsening visual acuity, panhypopituitarism, diabetes insipidus, psychosocial impairment, and new-onset obesity [20]. Importantly, while conservative management showed a higher risk of multiple recurrences and radiation induced vasculopathy, this was balanced by similar rates of tumor control and a lower risk of long-term morbidities in comparison to GTR. Another retrospective analysis of 30 pediatric patients found that GTR resulted in an average loss of 9.8 points of IQ while a combined surgical/radiotherapy group lost an average of only 1.25 points [21]. Long-term adverse effects of radiotherapy include hormone deficiencies, hearing loss, vision loss, and cognitive worsening [5]. Similarly, a study on the extent of resection and long-term functional outcome in adults with craniopharyngioma found that conservative management led to equal long term visual, endocrinological, and hypothalamic outcomes in comparison to GTR [22]. Additionally, the addition of adjuvant radiotherapy with STR led to better local control of the tumor, and none of the patients that received this intervention had recurrence for more than five years in the follow up period.

Overall, studies have shown that radical resection has similar benefit but an increased risk of deficits compared with STR + adjuvant radiotherapy, which has resulted in a practice shift over time to maximize function and quality of life. These studies remain difficult to compare over time because of variations in treatments strategies. Nonetheless, the refinement of less invasive surgical approaches has helped foster a need to better understand CPs and derive new treatment options.

4. Papillary and Adamantinomatous CPs

CPs can occur as either of two primary histologic subtypes, namely adamantinomatous (aCP) and papillary (pCP) (Table 1, Fig. 1). The aCP subtype is more prevalent overall, more common in children and is characterized by cystic and/or solid components, calcifications, necrotic

Table 1. Differential characteristics between aCP and pCP.

Characteristic	Adamantinomatous CP	Papillary CP
Age	More common in children	More common in adults
Tumor type	Cystic and/or solid components	Solid and/or cystic components
Calcifications and necrosis debris	Frequent	Uncommon
Histologic hallmarks	Peripheral basal cell layer of palisading epithelium and nodules of wet keratin and anucleated cells	Squamous epithelium creating papillae of different sizes and lack of a basal cell layer of palisading cells
Surgical margins	Frequently irregular	Well demarcated
Invasion	More aggressive	Less aggressive
Mutation	CTNNB1	$BRAF^{V600E}$

debris, and fibrous tissue [23]. Surgical margins in aCP are more frequently irregular, making resection difficult. Histologic hallmarks include a peripheral basal cell layer of palisading epithelium, loosely aggregated stellate cells, and nodules of wet keratin and anucleated cells [23,24]. Wet keratin is highly calcified and grossly appears as white flecks.

In contrast, pCPs are more common in adults, are usually well demarcated, and do not tend to invade nearby critical structures. Macroscopically, pCPs are solid or mixed with cystic and solid components. Calcifications are uncommon in pCPs. Histologically, they show growing cells with squamous epithelium creating papillae of different sizes and lack a basal cell layer of palisading cells.

Furthermore, histologic subtyping to determine risk factors for CP recurrence has yielded conflicting evidence. In some studies, pCPs have shown higher 5-year survival rates, less aggressive disease progression, and less risk of recurrence in comparison to aCPs [25]. However, other studies have not found significant differences [6,26]. Although aCPs are more likely to be invasive and make GTR more challenging, no differences in recurrence have been found between aCPs and pCPs independent of resection status [25]. GTR seems to be the most important factor influencing risk of recurrence.

Not only are their histological features distinct, but aCPs and pCPs demonstrate differing gene and methylation patterns [27]. DNA methylation profiling after analysis of the most variably methylated CpG sites has shown that aCPs and pCPs are characterized by two unique methylation clusters [27]. Therefore, histologic subtypes also differ on an epigenetic and transcriptional level. Furthermore, whole-exome sequencing has revealed that aCPs and pCPs consist of mutations that are mutually exclusive and clonal, specifically catenin beta 1 (*CTNNB1*) and B-Raf ($BRAF^{V600E}$) mutations, respectively [28]. *CTNNB1* was the most commonly mutated gene in aCPs, present in 11 of the 12 tumor specimens, and exclusive to exon 3. In contrast, pCPs had mutations in the $BRAF^{V600E}$ gene and no mutations for *CTNNB1*. Similarly, mutational analysis of a larger number of CP tumor samples showed activating mutations and deletions in exon 3 of the *CTNNB1* gene exclusive to aCP tumors [27]. In contrast, *BRAF* mutations were only found in pCP tumors, with subsequent Sanger sequencing confirming the $BRAF^{V600E}$ mutation. It is likely that these and other mutational pathways account for the clinical variation seen in CP subtypes and play a role in patient outcomes.

5. BRAF mutations in pCPs

BRAF mutations are implicated in the tumorigenesis of pCPs. Whole-exome sequencing, next-generation panel sequencing, pyrosequencing, and Sanger sequencing revealed the prevalence of *BRAF* mutations in pCPs in 81–100% of tumors [3,28–30]. The $BRAF^{V600E}$ mutation leads to glutamic acid in place of valine and uncontrolled activation of this serine threonine kinase that normally regulates the mitogen-activated protein kinase/extracellular signal–related kinase (MAPK/ERK) signaling pathway. The MAP/ERK pathway is well known for its role in cell proliferation and differentiation. The existence of a $BRAF^{V600E}$ mutation–specific antibody (VE1) can be diagnostic, especially in cases where diagnosis of pCPs is challenging, but its specificity is still unclear and the use of sequencing is often required.

Recent studies have shown the possibility of targeted therapy with $BRAF^{V600E}$ inhibitors, which have demonstrated success in treatment of other malignancies harboring this mutation [29,31–40]. Some recent studies have also shown that magnetic resonance imaging features have been used to successfully predict the presence of $BRAF^{V600E}$ mutations in patients with CPs with high sensitivity and specificity [41]. These features include suprasellar tumor location, spherical shape, solid component predominance, homogeneous enhancement, and thickened pituitary stalk. Improved preoperative determination of genetic drivers in CP may aid in designing neoadjuvant targeted therapy. Preoperative genetic status may alter surgical decision-making, which can potentially better justify an STR in a situation where good postoperative adjuvant treatments are available.

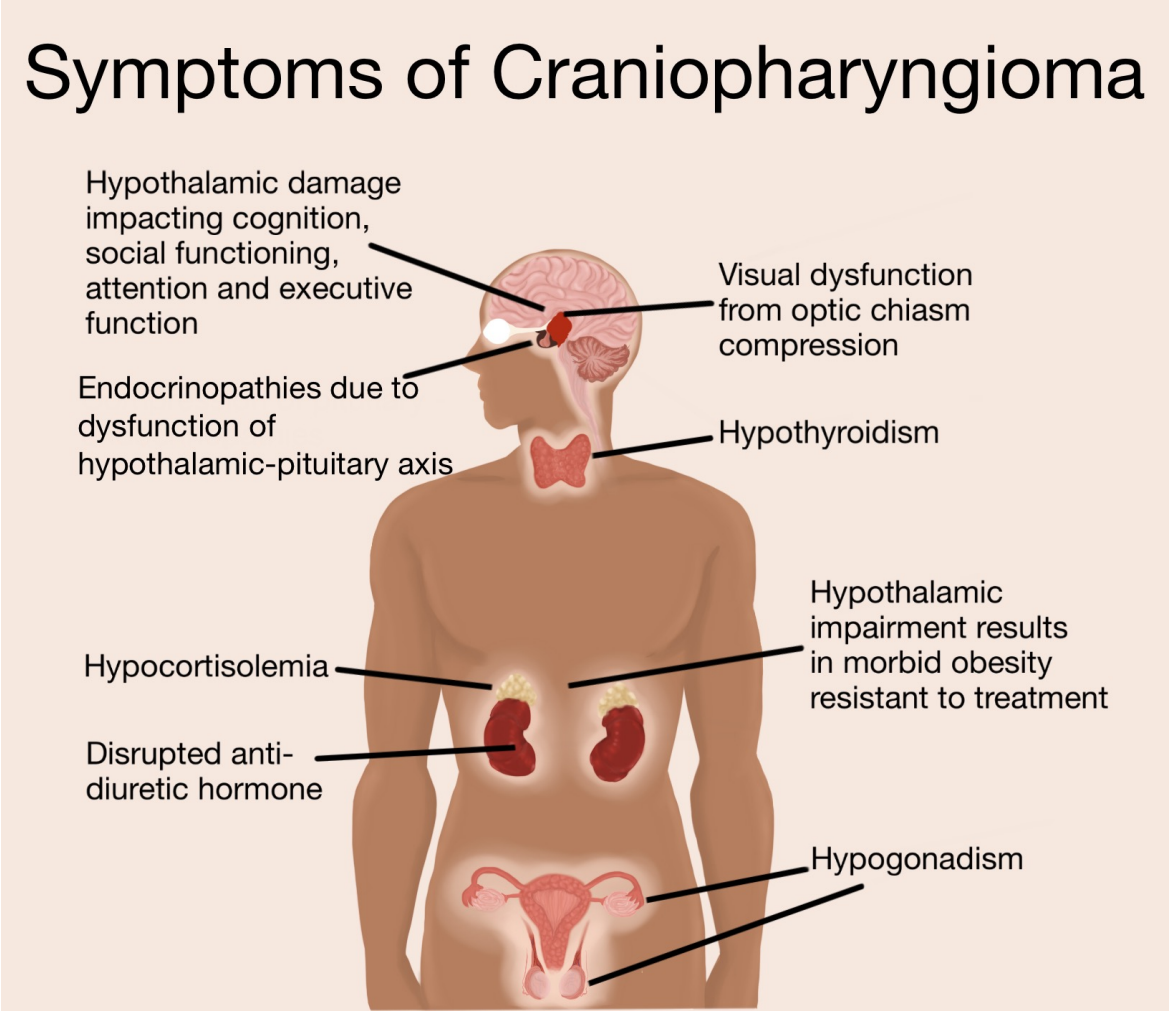

Fig. 1. Overview of symptoms and clinical changes from craniopharyngioma.

6. CTNNB1 Mutations and Pathogenesis in aCPs

Disruption of the catenin β-1 (*CTNNB1)* and the corresponding Wnt pathway are implicated in the tumorigenesis of aCPs (Fig. 2). β-catenin is found either in the cell membrane or the cytoplasm, where it is to be degraded by proteasomes [24]. aCPs show upregulation of the β-catenin/Wnt (LEF1 and AXIN2) and sonic hedgehog (SHH) signaling (GLI2, PTCH1, and SHH) pathways in comparison with pCPs. β-catenin is regulated by a destruction complex consisting of tumor suppressor adenomatous polyposis coli (APC), scaffolding proteins Axin1/Axin2, and phosphokinases GSK3B and CK1. Once bound to the complex, β-catenin is phosphorylated on its N-terminal region encoded by exon 3. Mutations in exon 3 in the *CTNNB1* gene lead to constitutive β-catenin activity by inhibiting its phosphorylation and degradation [42]. The Wnt pathway becomes activated upon Wnt ligand binding to receptors, which leads to inhibited degradation of β-catenin and GSK3B, allowing relocation of the ligand-binding complex to the nucleus where β-catenin leads to activation of lymphoid enhancer factor and T-cell factor transcription factors. *CTNNB1* mutations can impact a wide array of pathways involved in cell proliferation, differentiation, and cell migration [42].

Genetically engineered mouse models expressing oncogenic β-catenin have shown that overactivation of the Wnt pathway is sufficient to lead to formation of tumors that parallel human aCPs and consist of cell clusters accumulating β-catenin [3]. However, it is vital to note that mouse aCPs can lack wet keratin and calcifications and thus do not completely parallel human aCPs. Although mouse models, primary cell cultures, and xenografts are clinically useful in the study of aCPs, they do not recapitulate all the characteristics of human aCPs, highlighting a need for more comparable human models [3]. A xenotransplant mouse model has been proposed to better study potential novel therapies [43].

The β-catenin/Wnt pathway has proven to be an essential potential target of novel therapies for CP. To our knowledge, there are no ongoing clinical trials targeting the β-catenin/Wnt pathway in CP tumors, although Wnt pathway inhibition is currently being investigated for non–central

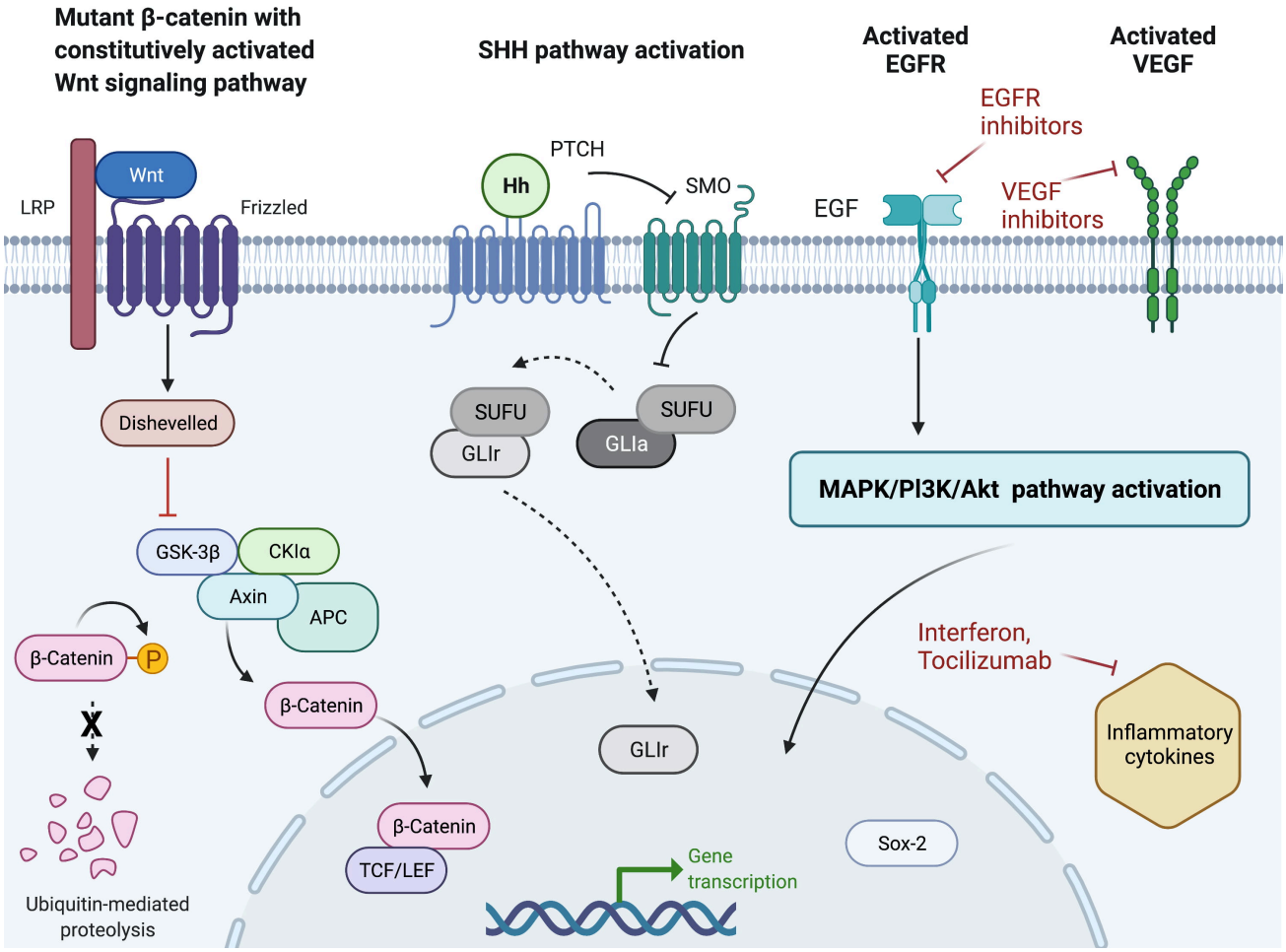

Fig. 2. Signaling pathway and targeting of adamantinomatous craniopharyngioma. Upregulation of the β-catenin signaling pathway is governed by mutant β-catenin, which resists ubiquitin-mediated proteolysis. Upregulation of sonic hedgehog (SHH) signaling is seen along with the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) signaling pathways. Only targeted therapy of EGFR, VEGF, and inflammatory cytokines has been described with adamantinomatous craniopharyngioma. APC, adenomatous polyposis coli; CKIα, casein kinase 1 alpha; GLI1, glioma-associated oncogene; Hh, sonic hedgehog; LRP, low-density lipoprotein receptor-related protein; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinases; PTCH, patched; SMO, smoothened; SUFU, suppressor of fused homolog; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; VEGF, vascular endothelial growth factor.

nervous system tumors in various clinical trials (clinicaltrials.gov identifiers NCT03901950, NCT02675946, and NCT03447470) [44]. NCT03901950 is a phase 1 trial investigating study drug XNW7201, a Wnt protein blocker in patients with advanced solid tumors. NCT02675946 is investigating study drug CGX1321, a Wnt pathway inhibitor in patients with advanced solid tumors and in combination with Pembrolizumab in patients with advanced gastrointestinal tumors. Finally, NCT03447470 is a phase 1 trial investigating Wnt inhibitor RXC004 as monotherapy or in combination with Nivolumab in patients with advanced malignancies. Despite its promising potential, it is vital to note that β-catenin/Wnt targeting is possibly associated with significant off-target effects [44].

aCPs also show upregulation of SHH signaling (GLI2, PTCH1, and SHH) pathways in comparison with pCPs. The SHH signaling pathway, essential to organ development and maintenance of stem cell niches, is also upregulated in both mouse and human aCPs [24]. SHH binds to the receptor Patched 1 (PTCH1), resulting in disinhibition of Smoothened (SMO), a transducer. Once active, SMO induces a signaling cascade and activates target genes. In gene expression studies of aCP mouse models, SHH was overexpressed in β-catenin cell clusters. In humans, expression of SHH mRNA and receptor PTCH1 have also been found in β-catenin cell clusters. Therefore, SMO inhibitors are another potential therapy in CP management and have demonstrated success in treating advanced human cancer [45].

7. Epidermal Growth Factor Receptor Signaling in CP

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that has also been found to be overexpressed in both human and mouse aCPs [32]. Similarly to β-catenin, EGFR activation is associated with cellular proliferation, differentiation, motility, and apoptosis. In cell clusters of aCPs, EGFR has demonstrated high rates of expression. *In vitro* and animal studies have demonstrated the correlation of EGFR pathway activation with enhanced fascin-1 expression, cell growth, and migration in aCP cells [46–48]. Fascin is a cytoskeletal actin-binding protein that manages cell motility and invasiveness [49]. Furthermore, the presence of an activated EGFR pathway in β-catenin–accumulating cells at the infiltrating borders of the tumor supports the role of EGFR in brain invasion [46,50–52]. Stache *et al*. [53] demonstrated the impact of EGFR signaling on promoting aCP resistance to radiation through enhancing survivin (an antiapoptotic protein) gene expression. They have also reported that inhibition of EGFR activity leads to increasing cell death in response to radiotherapy [53].

8. Other Signaling Pathways

Different cell populations are implicated in the pathogenesis of aCPs. Cell clusters, characterized by whorl-like patterns near the infiltrative regions of the tumor, have an unknown function but represent a different cell population from other tumor cells [3]. Cell clusters in aCPs have demonstrated differential increased expression of Axin2 and BMP4 RNA as well as increased protein translation in comparison with surrounding tumor cells. In addition, increased cellular migratory potential is seen, indicating that other mechanisms determine which cells form clusters [24,46].

Sox2+ stem cells represent another distinct population of cells that have been shown to stimulate tumorigenesis via a paracrine mechanism [3]. Embryonic induced mice expressing degradation-resistant β-catenin in Sox2+ cells have been shown to develop tumors with β-catenin–accumulating cluster cells similar to those of human aCPs [54]. Interestingly, genetic tracing and molecular analyses have shown that pituitary tumors do not originate from Sox2+ stem cells, but the stem cell clusters do release factors that impact the surrounding tissue and may induce cell transformation and tumor growth [24,55]. It is proposed that Sox2+ cells form quiescent β-catenin–accumulating clusters of daughter cells that are secretory and quiescent and signal via members of fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), epithelial growth factor, SHH pathways, cytokines, and chemokines [3].

9. aCP Cystic Tumor Pathogenesis

The cystic component of CP is responsible for significant symptoms due to mass effect and is associated with a risk of recurrence [56]. Management of cystic CPs may involve intracavitary delivery of radioisotopes or drugs which allows for local treatment to the cyst lining leading to elimination of the secretory epithelial lining and ultimately deficient fluid production and cyst shrinkage [7]. Nonetheless, targeted therapies targeting the cystic component of CPs represent an intriguing potential option for treatment. Several agents have been studied in cystic areas of CP, including P32, interferon (IFN), and bleomycin [57,58]. However, improved understanding of the cystic components of CP has opened the possibility of more targeted treatment options.

Human aCPs are characterized by a combination of both solid and cystic components within the tumor, and molecular studies have characterized important inflammatory mediators in the solid and cystic components. Cystic fluid in human aCPs has been found to contain elevated levels of cytokines and chemokines, specifically interleukin (IL)-6, IL-8, IL-10, CXCL1, indoleamine 2, 3-dioxygenase (IDO)-1, and defensin 1-3 [59,60]. Similarly, in solid components, transcript levels of IL-6, CXCL, IL-6, and CXCR2 were elevated. *In vitro* studies have identified the role of IL-6 in mitogenesis, growth, and migration of aCP cells [30,60]. aCPs were also found to have higher transcript levels of immunosuppressive factors IL-10 and IDO-1. These findings are relevant given that they represent the role of immune system modulators in tumor behavior. For instance, IL-6 is an important activator of the STAT3 pathway, which leads to chronic inflammation and suppression of antitumor activity when dysregulated [61]. Similarly, IL-10 has been observed to have an immunosuppressive role in the brain and in tumor models [62,63]. Alpha defensins 1–3 and antimicrobial peptides involved in the innate immune system have been identified in the cystic component of CPs [59]. Importantly, alpha defensin expression decreases after treatment of CPs with IFN-α and correlates with the effectiveness of this treatment, highlighting the role of immune mediators in tumorigenesis. The entire role of immune system modulators in aCP tumorigenesis has yet to be described, but these findings point to the potential role of targeted therapy toward immune system modulators. To our knowledge, no studies have investigated the cystic and solid components of pCPs.

10. Molecular and Immune Mediators of CP Recurrence and Tumor Growth

Recurrence of CPs represents a formidable challenge because of the unpredictable behavior, morbidity, and potential mortality. CPs have a recurrence rate of approximately 65%, with most occurring within the first 10 years after surgery [64]. Given that the histologic subtype is not likely to provide prognostic value, other molecular markers

may have higher relevance. In terms of histologic features, the presence of cystic lesions or whorl-like arrays in aCPs has been associated with higher risks of recurrence [25]. Reactive gliosis, a response consisting of proliferation and hypertrophy of glial cells after damage, has also been associated with increased rates of recurrence, although only one study has provided supportive evidence [25].

Molecular markers can be significant predictors of CP recurrence. According to Coury *et al*. [25], molecular markers that have consistently yielded convincing evidence regarding expression and increased risk of recurrence include Ki-67, epithelial cell adhesion molecule (Ep-CAM), pituitary tumor transforming gene (PTTG-1), survivin, specific retinoic acid receptor (RAR) subtypes, osteonectin, and the chemokines CXCL12 and CXCR4. Increased expression of Ki-67, a marker of proliferation in tumors, has been found in aggressive CPs and predicts a higher risk of recurrence and faster tumor growth. Similarly, the antiapoptotic protein survivin is upregulated in the brains of CP patients compared with healthy brains [65]. Interestingly, survivin had higher expression in aCPs compared with pCPs or recurrent tumors. Furthermore, EpCAM, a cell adhesion molecule associated with several cancers, and PTTG-1, an oncogene, show increased expression in recurrent aCPs compared with primary CPs [66]. The presence of osteonectin, a glycoprotein with a role in tumor angiogenesis and proliferation, in the stroma surrounding the CP has also shown a positive correlation with CP recurrence rate [67]. The expression and lack of expression of certain retinoic acid receptor (RAR) subtypes is also associated with recurrence. RARs have a role in cell maturation and differentiation. Low RAR-B and high RAR-y expression in CPs was associated with a higher risk of recurrence within two years of surgery [68]. Finally, expression of chemokines CXCL12/CXCR4 has been associated with worse progression-free survival in pediatric CPs [69].

Moreover, recurrent tumors are characterized by upregulation of angiogenesis, as driven by vascular endothelial growth factor (VEGF). Indeed, recurrent CPs have higher expression of VEGF, and aCPs have been shown to have higher VEGF expression in comparison with pCPs [70,71]. The latter finding supports previous descriptions of aCP as more invasive and difficult to resect. More recently, molecular profiling has revealed the presence of senescent cells in mouse and human aCPs [72]. Senescent cells secrete senescence associated secretory phenotype (SASP), proinflammatory cytokines, chemokines, growth factors, and proteases. SASP is responsible for the recruitment of immune cells for elimination and promotes the progression of tumor cells via promotion of angiogenesis, extracellular matrix remodeling, or epithelial mesenchymal transition. In fact, it has been shown that targeting the SASP response in β-catenin cluster cells leads to a reduction in tumor inducing potential and highlights a need for further investigation into the role of senescent cells in aCPs.

Immune checkpoint inhibitors have been used and approved for treatment of a variety of cancers, and their role in CP management remains to be explored. pCPs have shown expression of programmed-death ligand 1 (PD-L1) in some tumor cells [73], and Lin *et al*. [74] reported that recurrent CPs have more PD-L1–expressing cells than primary CPs. Another study of PD-L1 expression showed that it was predominant in the cyst lining of aCP and colocalized with β-catenin in the nucleus [73]. In comparison, PD-L1 was primarily within the tumor stromal fibrovascular cores in pCP. These studies indicated that immune checkpoint inhibitors may have a role in management of CPs.

11. Usage of BRAF inhibitors for pCP

Various cancers with positive BRAF mutations have been treated with BRAF inhibitors, including melanomas and thyroid and colorectal cancers [75–77]. The identification of $BRAF^{V600E}$ mutations in pCP has unleashed a new perspective on the pharmacological treatment of CP [29,31–39]. A total of 11 reported cases of pCP have been treated with a BRAF inhibitor, either dabrafenib or vemurafenib, and with or without a mitogen-activated protein kinase (MEK) inhibitor, trametinib (Table 2, Fig. 3). MEK inhibitors could be effective by blocking the downstream MAPK/ERK pathway, which has been shown to be downstream of EGFR signaling in CP [78,79]. The combination of a MEK inhibitor with BRAF inhibitor in the treatment of melanomas has been shown to reduce development of tumor resistance to BRAF inhibitors and improves patient survival [76,80,81].

Single-agent therapy with the BRAF inhibitor dabrafenib (150 mg by mouth twice daily) or vemurafenib (960 mg by mouth twice daily) was used in 4 cases [32,34,36,40]. Dual targeted therapy using trametinib (2 mg by mouth daily), in combination with BRAF inhibitor, was prescribed in 7 patients [29,31,33,35,37–39]. Regardless of treatment regimen, all case reports demonstrated favorable clinical response. Tumor volume reduction—ranging from 55% to 100%—was seen in all cases, and both solid and cystic portions of tumor were responsive to treatment. These reports mostly included patients with progressive or recurrent pCP that had failed primary treatment. The interruption of treatment because of side effects resulted in tumor regrowth in 2 cases; however, the tumors shrank again after readministration of agents in both cases [29,32–40]. In another case, Himes *et al*. [34] reported stable disease over 1 year after discontinuation of dabrafenib therapy.

Combined BRAF and MEK inhibitors have been well tolerated in all reported patients. One patient with recurrent $BRAF^{V600E}$-mutated tumor treated with dabrafenib and trametinib had reduced tumor volume within a month of treatment [31]. The most common adverse effect for combined inhibitors has been fever (Table 2, Ref. [29,31–40]. Other side effects include rash, arthralgia, myalgia, cough,

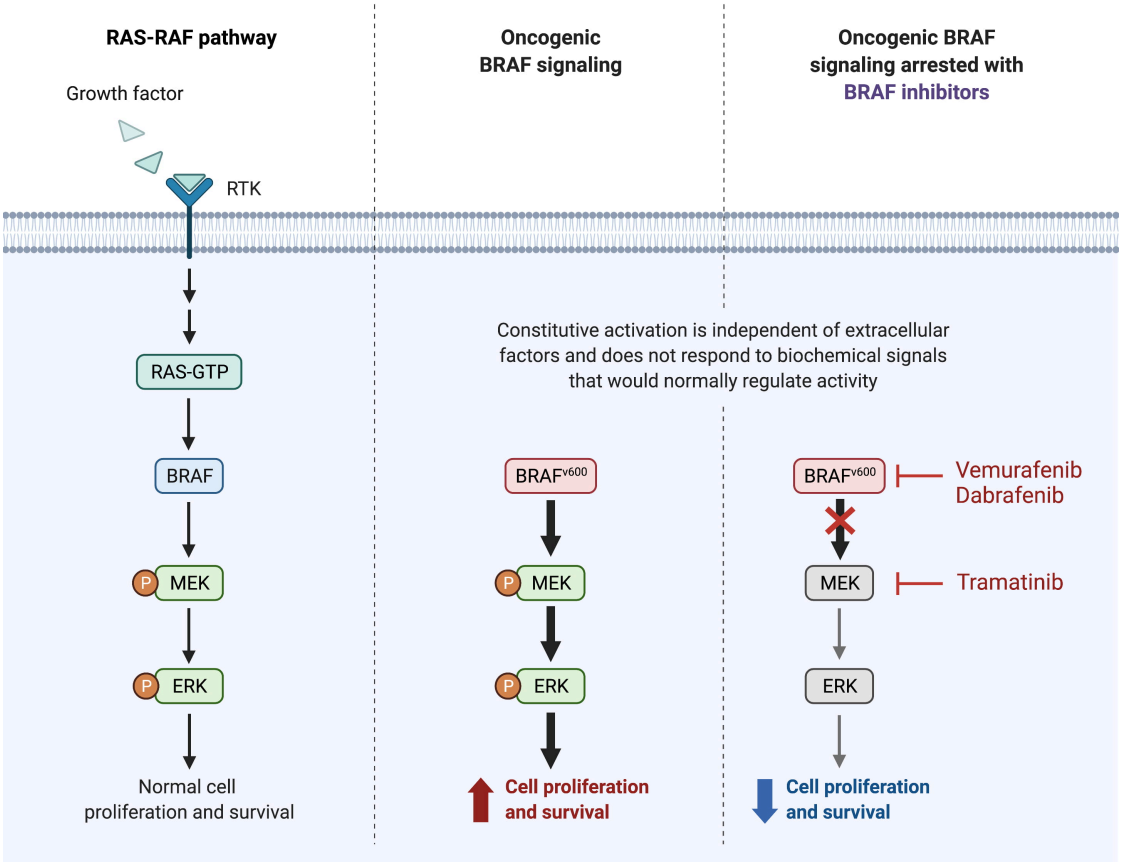

Fig. 3. Signaling pathway and targeting of papillary craniopharyngioma. Constitutive activation of the BRAF signaling pathway occurs with the V600E mutation in papillary craniopharyngioma. Inhibition of $BRAF^{V600E}$ with vemurafenib or dabrafenib along with inhibition of MEK with tramatinib has shown efficacy. ERK, extracellular signal-related kinase; MEK, Mitogen-activated protein kinase kinase; RTK, receptor tyrosine kinase; RAS-GTP, Ras-guanosine triphosphate.

and elevated liver enzymes. These symptoms also have been reported in patients treated with BRAF inhibitor for other type of diseases [82–84].

Preoperative treatment with BRAF/MEK inhibitors may be helpful as a neoadjuvant treatment by reducing tumor volume. Juratli *et al.* [37] reported a patient with $BRAF^{V600E}$-mutated pCP who received dual-agent targeted therapy after biopsy of lesion. A significant reduction in the tumor size (>80%) and improvement of the patient's symptoms was observed after 6 months of treatment [37]. This report for the first time suggested the potential use of targeted therapy as a neoadjuvant treatment. Further investigations, particularly clinical trials, are needed to determine the optimal drug combination, dose, and duration, as well as to evaluate the safety and efficacy of treatment.

Recently, minimally invasive and noninvasive methods for preoperative tumor diagnosis including the use of magnetic resonance imaging characteristics that predict BRAF-mutated pCP [41,85] and detection of circulating $BRAF^{V600E}$ mutations in peripheral blood have been described [31]. These proposed diagnostic approaches need to be validated in prospective studies; however, if a BRAF-mutated pCP could be identified preoperatively through reliable noninvasive techniques or a routine tissue biopsy (using image-guided transcranial or transsphenoidal techniques), neoadjuvant targeted therapy with these agents could reduce tumor burden and facilitate surgical intervention or radiation therapy and potentially reduce associated morbidities.

12. Potential Use of EGFR Inhibitors

EGFR inhibitors, as either monoclonal antibodies or tyrosine kinase inhibitors, represent a potential therapeutic in the management of CPs and have been efficacious for the treatment of non–small-cell lung cancer (NSLC), breast, and colorectal cancer [86]. Indeed, *in vitro* experiments have demonstrated that gefitinib (a selective EGFR inhibitor) treatment prevents migration and motility of tumor cells and significantly reduces fascin mRNA expression in aCP cells [78]. In addition, EGFR inhibitors could provide another therapeutic benefit by increasing tumor cell sensitivity to radiation [53]. Further animal models and preclinical studies will be needed to investigate the benefit of EGFR inhibitors in the treatment of aCPs.

Table 2. Studies describing the use of targeted therapy in *BRAF*^{V600}-mutated papillary craniopharyngiomas.

Paper	Age/Sex	Prior treatment	Targeted treatment agent(s)	Duration	Treatment after targeted therapy	Response to treatment	Final outcome	Complication(s)
Brastianos *et al*. 2016 [31]	39/M	5 surgeries	dabrafenib 150 mg bid + trametinib 2 mg bid (after 21 days)	52 days	TSS + RT	85% and 81% reduction in solid and cystic components at 35 days	stable disease after 18 mo	Low-grade fever
Aylwin *et al*. 2016 [32]	57/F (27 at diagnosis)	3 surgeries + RT	vemurafenib 960 mg bid	10 mo (3 mo interruption after 3 mo)	surgery for CSF leak	near-complete resolution after 3 mo	Progression after 7 mo	CSF leak with meningitis due to tumor shrinkage
Rostami *et al*. 2017 [29]	65/M	1 surgery	dabrafenib 150 mg bid + trametinib 2 mg daily (after 21 days)	7 weeks	RT	91% reduction of the tumor at 15 weeks		fever
Roque *et al*. 2017 [33]	47/F	1 surgery + Ommaya cyst aspiration + RT	dabrafenib 150 mg bid + trametinib 2 mg daily	7 mo	none	near disappearance of tumor at 7 mo		intermittent fever
Himes *et al*. 2018 [34]	52/M (47 at diagnosis)	1 surgery + RT	dabrafenib 150 mg bid (dose reduction after several weeks then dose was increased to 225 mg daily)	12 mo	none	significant decrease in tumor size at 6 mo	stable disease 1 year off therapy	joint pain
Bernstein *et al*. 2019 [35]	60/M	4 surgeries + RT	dabrafenib 150 mg bid + trametinib 2 mg daily (after 14 days)	28 mo	none	100% tumor reduction at 2 mo	complete response at 28 mo	verrucal keratosis
Rao *et al*. 2019 [36]	35/M	1 surgery + shunt	dabrafenib 150 mg bid	24 mo	none	Complete response of solid component at 24 mo		none
Juratli *et al*. 2019 [37]	21/M	biopsy	dabrafenib 150 mg bid + trametinib 2 mg daily	6 mo	none	80% response at 6 mo		none
Khaddour *et al*. 2020 [38]	39/M	1 surgery	dabrafenib 150 mg bid + trametinib 2 mg daily	9 mo	gamma knife radiosurgery	>70% tumor reduction at 9 mo	in remission for 2 years	mild fever
Di Stefano *et al*. 2020 [39]	55/F	1 surgery	dabrafenib 150 mg bid + trametinib 2 mg daily	12 mo	RT	94.5% tumor shrinkage after 72 days	stable at 385 days	fatigue, coughing, peripheral edema
Chik *et al*. 2021 [40]	37/M (10 at diagnosis)	4 surgeries	vemurafenib 960 mg bid	40 mo	2 surgeries followed by RT and gamma knife	55% tumor reduction at 15 mo		arthralgia, myalgia, elevated liver enzymes, severe sun sensitivity

RT, radiotherapy; bid, twice daily; TSS, transsphenoidal surgery; CSF, cerebrospinal fluid.

13. Tyrosine Kinase Inhibitors of VEGF Receptors

VEGF regulates angiogenesis and promotes tumor growth, metastasis, and recurrence [86,87]. One downstream pathway in aCP of Wnt/β-catenin signaling is expression of VEGF [9,79,87]. Studies demonstrated that recurrent aCPs show higher levels of VEGF expression than primary tumors, suggesting that VEGF expression may have an important role in growth and invasiveness of aCP [88–91]. Furthermore, Hu *et al*. [92] showed the association of VEGF expression with CP radiosensitivity. Tumors with a higher level of VEGF receptor-2 expression are insensitive to ^{32}P-colloid interstitial radiotherapy. These findings suggest that the VEGF pathway could be a potential target in medical therapy of aCP. New treatment modalities with VEGF inhibitors, such as bevacizumab, could have a therapeutic benefit in the management of CP. Higher VEGF expression in recurrent and aCP tumors suggest that tyrosine kinase inhibitors of VEGF receptor may have a therapeutic role in preventing or delaying CP recurrence [92]. No trials have evaluated the use of VEGF inhibitors alone in aCP patients. Grab *et al*. [93] reported a significant decrease in tumor cyst size after treatment with combination of systemic tocilizumab (a monoclonal antibody against IL-6 receptor) and bevacizumab in a case of recurrent aCP.

14. Role of Directed Therapies against Inflammatory Mediators in aCP

The role of the immune microenvironment in CP pathogenesis is increasingly recognized in recent years [94], and several studies have attempted to evaluate the use of selective inflammatory blockade as a potential therapeutic target for treatment of aCP [44]. IFN has antitumor activity through inhibition of cell proliferation and modulation of the host's immune response [95,96]. Several studies have investigated the efficacy of intracystic and systemic administration of IFN with promising results. Cystic treatment can delay surgery or radiotherapy through cyst shrinkage, which can reduce the patient's risk profile for treatment, especially in children [97–100]. Jakacki *et al*. [101] reported the result of systemic IFN-α2a administration in patients with progressive or recurrent CP. Among 12 patients at the end of study, a radiologic response was demonstrated in 3 patients with predominantly cystic tumors (one patient with complete response). In patients without progressive disease that completed one year of therapy, progression was seen in 3 and 6 patients after discontinuation of IFN, respectively. The median time to progression was 25 months. Yeung *et al*. [102] explored the efficacy of pegylated IFN in treatment of 5 patients with recurrent CP. Pegylated IFN-α2b was shown to be more effective because of longer plasma half-life compared with non-pegylated IFN [103]. All patients treated with pegylated IFN-α2b experienced stable disease or better in response to treatment (2 complete responses, 2 partial responses, 1 stable disease) [102]. No evidence of disease progression was observed during the follow-up period. Like the previous study, all patients had predominantly cystic tumors in this series [102]. The Pediatric Brain Tumor Consortium conducted a multicenter phase 2 study of using pegylated IFN-α2b in children and young adults with unresectable or recurrent CP [104]. Among 7 patients who did not have previous radiotherapy, 2 had a partial response and 1 had a durable response $>$3 months. No patient who failed radiotherapy had a response with pegulated IFN-α2b, but treatment was well tolerated. While promising, the role of IFN as an alternative treatment for patients with recurrent or progressive CP remains unclear given that these studies had small sample sizes, short follow-up periods, and did not include solid CPs. Still, the use of IFN in the future, particularly in tumors with a predominantly cystic component warrants further investigation given that it has been shown to delay disease progression and may defer the need for radiation therapy in children with CP.

Targeting of IL-6 has been evaluated as a method to modulate inflammatory signaling in CPs. Grob *et al*. [93] reported the first systemic use of tocilizumab, a monoclonal antibody against IL6-R, in the management of two patients with cystic aCP that was refractory to intracystic therapy. They administered tocilizumab alone in one patient and tocilizumab in combination with bevacizumab (VEGF inhibitor) in another. A partial tumor response and significant decrease in cyst volume were seen in both patients. Grob *et al*. [93] proposed tocilizumab as a new potential agent for the treatment of cystic aCP. Currently, a Phase 0 clinical trial (NCT03970226) is investigating the efficacy of tocilizumab in the management of aCP.

15. Current Clinical Trials in CP

Only a handful of clinical trials are currently evaluating targeted agents in CP (Table 3). A Phase 2 clinical trial (NCT03224767) is investigating the combined use of BRAF and MEK inhibitors (vemurafenib and cobimetinib) for the treatment of $BRAF^{V600E}$ mutant pCPs in adults 18 years or older. Patients are given vemurafenib for 28 days combined with cobimetinib for 21 days with up to 5 repeated cycles. Outcome measures include response rate, progression-free survival, and overall survival.

NCT03970226 is a phase 0 study examining the role of tocilizumab, a monoclonal IL-6 antibody, in the treatment of newly diagnosed and progressed aCPs in children and adolescents 2 to 21 years of age. In this study, patients are given systemic tocilizumab, and the presence of drug metabolites, IL-6 levels, and other inflammatory markers are measured within tumor tissue, tumor cyst, or CSF fluid. If drug metabolites are detected, patients are eligible for concurrent enrollment to evaluate the efficacy of tocilizumab by measuring progression-free survival, overall response rate, 1-year disease stabilization, and tissue analysis using various biomarkers. Lastly, NCT03610906

Table 3. Current clinical trials in molecular targeted therapy of CP.

Clinical trial	Phase	Molecular target	Objective
NCT03224767	II	BRAF Pathway	To study the combined used of BRAF and MEK inhibitors (vemurafenib and cobimetinib) for the treatment of $BRAF^{V600E}$ mutant papillary craniopharyngiomas in adults 18 years or older
NCT03970226	Zero	IL-6	To study the role of tocilizumab, a monoclonal IL-6 antibody, in treatment of newly diagnosed/progressed aCp in children and adolescents ages 2–21 years
NCT03610906	I/II		To identify new potential areas of target in pediatric patients

is a phase 1/2 study that aims to identify new potential areas of target in pediatric patients but is not examining any targeted treatment.

16. Conclusions

There are multiple promising genetic and molecular biomarkers being explored for prognostic and therapeutic purposes in CP. Differences in histology, namely between aCP and pCP, do not necessarily correlate with prognosis and outcomes; however, different mechanisms for pathogenesis of these subtypes have aided in understanding the disease and targeting therapeutics. Overexpressed oncogenes in CP include genes controlling cell growth, proliferation, and angiogenesis among other pathways. These mutations can serve as both therapeutic targets and biomarkers of prognosis. Furthermore, variations in molecular markers can be seen in recurrent versus primary CP, indicating that differences in mutational signatures could potentially help understand and predict recurrence. Inhibition of some genes overexpressed in recurrent CP may be able to reduce recurrence rates overall. Currently, the primary treatment for recurrent CPs should include repeat surgery or radiosurgery given that current investigative targeted therapies are emerging.

Oncogenic gene mutations in CP are also implicated in other forms of cancer and have been targeted for therapy with molecular inhibitors. Drugs targeting these pathways have been tested with reasonable success on medically managed CPs. Apart from pure medical treatment, a promising application for such drugs is for neoadjuvant therapy to be followed by radiation or resection. EGFR inhibitors could both prevent tumor growth and sensitize the tumor to subsequent radiation therapy. Inhibitors of the BRAF/MEK pathway in pCP have proven to be effective in shrinking tumors and may facilitate resection. VEGF inhibitors, in combination with IL-6 inhibitors, have also been shown to reduce tumor size, although no studies have been done with VEGF inhibitors alone. Further studies and clinical trials are needed to examine these applications for their therapeutic potential. Immunotherapy may also have potential for combating CP growth and spread. Current clinical trials are examining the use of IL-6 inhibition in CP treatment. The expression by pCP tumors of PD-L1, especially in recurrent tumors, also suggests anti-PD-1/PD-L1 immunotherapy as a potential route for CP therapy.

Challenges remain in applying our knowledge of molecular drivers towards clinical treatment in CP. Only a handful of clinical trials are currently evaluating the role of molecular treatments, with reports of successful agents only being found in rare case reports. Driver mutations and their associated signaling pathways should be further explored within *in vitro* and animal models; however, clinical studies are also required to translate the therapeutic value in CP management and establish the efficacy of these agents.

Author Contributions

MR, MT, SY, AS, SC, and GNP researched and wrote the paper. JJE and MK edited the paper. All authors contributed to editorial changes in the paper. All authors read and approved the final paper.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. JJE (Mizuho–royalties), MK (Thieme–royalties).

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