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Integrating Systemic Therapies into the Multimodality Therapy of Patients with Craniopharyngioma

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Opinion statement

The integration of targeted therapy into the multimodal management of craniopharyngiomas represents a significant advancement in the field of neuro-oncology. Historically, the management of these tumors has been challenging due to their proximity to vital brain structures, necessitating a delicate balance between tumor control and the preservation of neurological function. Traditional treatment modalities, such as surgical resection and radiation, while effective, carry their own set of risks, including potential damage to surrounding healthy tissues and the potential for long-term side effects. Recent insights into the molecular biology of craniopharyngiomas, particularly the discovery of the BRAF V600E mutation in nearly all papillary craniopharyngiomas, have paved the way for a targeted systemic treatment approach. However, advances have been limited for adamantinomatous craniopharyngiomas. The success of BRAF/MEK inhibitors in clinical trials underscores the potential of these targeted therapies not only to control tumor growth but also to reduce the need for more invasive treatments, potentially minimizing treatment-related complications. However, the introduction of these novel therapies also brings forth new challenges, such as determining the optimal timing, sequencing, and duration of targeted treatments. Furthermore, there are open questions regarding which specific BRAF/MEK inhibitors to use, the potential need for combination therapy, and the strategies for managing intolerable adverse events. Finally, ensuring equitable access to these therapies, especially in healthcare systems with limited resources, is crucial to prevent widening healthcare disparities. In conclusion, targeted therapy with BRAF/MEK inhibitors holds great promise for improving outcomes and quality of life for patients with BRAF-mutated craniopharyngiomas. However, additional research is needed to address the questions that remain about its optimal use and integration into comprehensive treatment plans.

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Author Contributions

Each author has substantially contributed to conducting the underlying literature review and drafting this manuscript. DG performed the primary literature review and drafted the manuscript for intellectual content. PB and SS have each contributed to the literature review and revised the manuscript for intellectual content.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Keywords

Craniopharyngioma; Systemic therapies; Multimodality therapy; Targeted molecular therapies

Introduction

Craniopharyngiomas are rare, mixed solid-cystic brain tumors that originate from the remnants of Rathke's pouch, an embryonic structure contributing to the development of the pituitary gland [1]. With an annual average of 617 cases in the USA, the incidence rate of craniopharyngiomas is approximately 0.18 per 100,000 [2]. Craniopharyngiomas can be categorized into two distinct histological subtypes, adamantinomatous and papillary, each with unique molecular and clinical characteristics [3–6]. Adamantinomatous craniopharyngioma follows a bimodal age distribution with peaks in the first and sixth decade of life while papillary craniopharyngioma rarely occurs during childhood [2, 7]. Recent molecular studies have identified BRAF mutations in over 90% of papillary craniopharyngiomas and CTNNB1 mutations linked to the Wnt pathway in adamantinomatous craniopharyngiomas in nearly all patients. These molecular alterations present potential opportunities for the use of targeted therapies [4, 6, 8–10]. While these tumors are histologically benign, their location near critical brain structures—such as the hypothalamus, internal carotid arteries, optic nerves, and pituitary gland—renders them clinically challenging to manage. As a result, complications including endocrine disturbances, visual impairment, and neurological and vascular abnormalities are common [11]. Given these challenges, a multidisciplinary approach involving specialists from fields such as neurosurgery, neurooncology, neuropathology, endocrinology, and radiation oncology is required in the care of these patients. Traditionally, treatment approaches have centered around surgical resection and radiation therapy [11, 12]. However, these conventional therapies pose their own challenges, as both surgery and radiotherapy are associated with a significant risk of complications [13–17]. In addition, the optimal treatment approach—e.g., extensive surgical removal or a more conservative surgical approach followed by radiation therapy—remains controversial. While intracavitary chemotherapy has been used in selected cases, the role of systemic therapy has traditionally been limited [18–20].

The recent advances in our understanding of the molecular biology of craniopharyngiomas have led to a paradigm shift in how we treat papillary craniopharyngiomas that harbor the BRAF V600E mutation [4]. In a recent biomarker-driven phase II trial for papillary craniopharyngiomas, targeted therapy with BRAF/MEK inhibitors resulted in durable responses in all patients who received at least one cycle of the treatment, highlighting the potential of this treatment approach [4, 21••]. Due to the remarkable success of BRAF/MEK inhibitors in the treatment of BRAF V600E mutated craniopharyngiomas, there is growing interest in integrating these novel targeted therapies into the established multimodal treatment regimens. Unfortunately, targeting the WNT/CTNNB1 pathway in adamantinomatous craniopharyngiomas, on the other hand, has proven challenging thus far, underscoring the need for further research into targeted treatment strategies for this histologic subtype [22, 23].

Traditional approaches to treatment

Historically, the optimal treatment for craniopharyngiomas has been controversial. The two primary strategies that have been used include aggressive surgery with the intent of achieving total tumor removal at diagnosis and a more conservative surgical approach, removing only a portion of the tumor followed by radiation therapy to target the residual disease [11, 12, 24, 25]. It is important to note that either approach is associated with potential risks and side effects. Aggressive surgical resection can lead to complications due to the tumor's proximity to vital brain structures, potentially resulting in neurological or endocrine dysfunctions [14, 16, 17]. On the other hand, a conservative surgical approach, although minimizing immediate surgical risks, necessitates radiation therapy for control of residual disease. Radiation, while effective, carries long-term side effects, including potential damage to surrounding healthy tissues, endocrine imbalances, and cognitive changes, as well as an increased risk of secondary malignancies and vascular complications [13, 15–17, 26, 27]. Balancing the immediate and long-term risks of these treatments therefore remains a significant challenge in the management of craniopharyngiomas.

Modern systemic therapies

Historically, systemic therapy has played a minor role in the treatment of craniopharyngioma. Intracavitary chemotherapy with bleomycin or interferon-α has been explored in selected cases, but its role has been limited due to modest evidence of benefit and potential toxic side effects [18–20]. However, recent advances in genomic research have shed light on the genetic underpinnings of craniopharyngiomas. The discovery of BRAF V600E mutations in papillary craniopharyngiomas and CTNNB1 mutations in adamantinomatous craniopharyngiomas has opened new avenues for targeted therapies [3–6]. Specifically, the identification of the BRAF V600E mutation suggested that patients with papillary craniopharyngiomas could potentially benefit from BRAF inhibitors, which have shown efficacy in other BRAF V600E mutant tumors [22, 28•, 29, 30]. This breakthrough highlighted the potential for a paradigm shift in the treatment approach for papillary craniopharyngiomas, moving to targeted, molecular-based therapies. A recent phase II study evaluated the efficacy of the BRAF–MEK inhibitor combination vemurafenib–cobimetinib for the treatment of craniopharyngiomas [21••]. The primary endpoint was objective response at 4 months, assessed using contrast-enhanced magnetic resonance imaging performed every 8 weeks. Patients were eligible for evaluation of the primary endpoint if they had received at least one dose of the study treatment [21••]. The study was designed such that patients were treated with targeted therapy for 4 cycles (defined as 28 days) and then received definitive surgery or radiation. In selected situations approved by the study chairs, patients were allowed to stay on vemurafenib–cobimetinib if they were responding to therapy and if definitive surgery or radiation was not recommended due to adverse events. Secondary endpoints included progression-free survival, overall survival, response as defined by enhancing volume, response as defined by non-enhancing volume, response duration, and adverse events. One patient received treatment for 8 days before stopping therapy due to toxic effects, including grade 3 anaphylaxis and grade 2 acute kidney injury. All patients who completed at least one cycle of therapy showed a response to BRAF–MEK inhibition within 4 months [21••]. The median reduction in tumor volume among patients

who had received vemurafenib–cobimetinib was 91%, ranging from 68 to 99% [21••]. The median reduction in enhancing tumor volume from baseline was 96%, ranging from 80 to 99% [21••]. The median reduction in cystic non-enhancing tumor volume from baseline was 82%, ranging from 41 to 93% [21••]. The estimated progression-free survival was 87% at 12 months and 58% at 24 months [21••]. Overall survival was 100% at both 12 months and 24 months [21••]. Furthermore, with a median follow-up duration of 22 months, 93% of patients maintained a volumetric response at the 12-month point [21••]. Of note, of the seven patients who did not receive surgery or radiation after stopping vemurafenib–cobimetinib, six showed no evidence of progression after stopping vemurafenib–cobimetinib at a median follow-up of 23 months. The results indicate that combined BRAF–MEK inhibitor treatment offers a promising strategy for treating papillary craniopharyngiomas harboring the BRAF V600E mutation. In addition, this approach has the potential of improving patient outcomes by reducing the risks and long-term adverse effects linked to current standard treatments.

On the other hand, targeting the WNT/CTNNB1 pathway in adamantinomatous craniopharyngiomas has proven to be challenging, partly due to significant off-target effects in critical tissues and the intricate cross-talk with other pathways [31]. Recent studies have also suggested a potential role for MAPK/ERK pathway activation in adamantinomatous craniopharyngiomas [32, 33]. MEK inhibitors, such as trametinib and binimetinib, have shown promise in reducing tumor growth in vitro and on a case report basis [32, 33]. These findings underscore the potential of targeting the MAPK/ERK pathway as a therapeutic approach for adamantinomatous craniopharyngiomas. Given these complexities and the relative lack of clinical experience with targeted therapies, further research is needed to ensure the safety and efficacy of targeted treatment strategies for adamantinomatous craniopharyngiomas. Recent work showing that several targets of antibody-drug conjugates (ADCs) are expressed in craniopharyngiomas raises the possibility of additional treatment strategies [23].

Integrated multimodal treatment

Surgical resection

Conventional treatment of craniopharyngiomas has primarily revolved around surgical resection [11, 12, 34]. The goal of surgery is to aid in achieving a histological diagnosis and removing as much tumor tissue as possible, while avoiding damage to nearby structures. Historically, an aggressive surgical approach has been favored [35, 36]. Recurrence rates following complete resection have been cited at roughly 20%, though there are reports indicating rates as low as 11.1% and as high as 90% [11]. Commonly applied surgical approaches include an open transcranial approach (TCA) and endonasal endoscopic approach (EEA) [37]. Other surgical techniques, including cyst decompression, ventriculoperitoneal shunt implantation, and Ommaya reservoir placement, may be employed in individual cases to relieve mass effect and associated symptoms [6]. Recent evidence suggests a higher likelihood of achieving gross total resection (GTR) and visual improvement with EEA when compared to TCA [38, 39]. However, ultimately the surgical approach should be tailored to the individual case and consider factors such as tumor size, location, and proximity to adjacent structures. While surgery can offer

immediate relief from mass effect of the tumor, complete resection is often challenging due to the tumor's proximity to vital structures such as the hypothalamus, optic nerves, and pituitary gland [11, 12, 34]. Subtotal resection followed by radiation therapy has since been shown to be associated with a reduced risk of endocrine, visual, and neurological deficits compared to aggressive gross total resection, while providing similar long-term disease control [11, 24, 25]. Given the inherent risks associated with surgical resection and the impressive results of BRAF-targeted therapy, a biopsy-first approach should be considered. This may be particularly true for patients with high suspicion for papillary craniopharyngioma based on clinical and neuroimaging characteristics. However, surgical resection will likely remain necessary in the upfront setting in cases where a BRAF mutation is not identified or where significant mass effect necessitates urgent intervention.

Radiation therapy

Radiation therapy serves as another cornerstone in the conventional treatment of craniopharyngiomas, especially when complete surgical resection is not achievable or in case of disease recurrence [11, 12, 24, 25]. Radiation therapy for craniopharyngioma has seen significant advances with the introduction of more precise and targeted techniques, including stereotactic and intensity-modulated approaches and proton beam therapy [11, 40–42]. High local control rates have been reported with modern radiation techniques [40–42]. Intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) are radiation techniques that are commonly used to reduce radiation exposure to adjacent brain tissue [11, 42]. Proton therapy has found increasing use, particularly in younger patients, due to its precision in targeting tumor tissue while minimizing damage to surrounding normal brain tissue, which is thought to reduce the potential for neurocognitive side effects [43]. Finally, stereotactic radiosurgery may be helpful in the treatment of small and solid tumors, with local control rates reported between 33.3 and 87% [11, 44–46]. Although radiation therapy can be effective in controlling tumor growth and preventing recurrence, it can also damage surrounding healthy tissue, leading to complications such as hypopituitarism, cognitive and visual changes, secondary malignancies, and an increased risk of vasculopathy [13, 15–17, 26, 27]. Notably, craniopharyngiomas, while predominantly benign, carry a risk of rare malignant transformation, often manifesting after multiple recurrences and, in some cases, following radiation therapy [47–49]. While traditionally radiotherapy has been suggested for most patients with subtotal resection, it may therefore be reasonable to delay radiation in favor of targeted therapy in selected cases with BRAF-mutated tumors.

Targeted molecular therapy

Due to the effectiveness of BRAF-targeted therapy in the treatment of papillary craniopharyngiomas, targeted molecular therapy should be considered as an alternative to surgery and radiation in the upfront setting. This approach has the potential to minimize adverse effects commonly associated with standard therapies and thereby improve the patient's overall quality of life. A histologic diagnosis and molecular testing for BRAF V600E mutation, if feasible, should be pursued in all cases, particularly when there is a high clinical suspicion for papillary craniopharyngioma [4]. Establishing a histological diagnosis allows clinicians to make an informed decision on the risks and benefits of surgical interventions and radiation versus targeted molecular therapies. While certain

imaging characteristics differentiating papillary and adamantinomatous craniopharyngiomas have been reported, these studies need to be validated in larger cohorts, and imaging should not be solely relied upon when making treatment decisions [50–52]. On the other hand, a recent study retrospectively evaluated MRI characteristics in 52 craniopharyngioma patients including 8 with BRAF V600E mutation and found that BRAF-mutated craniopharyngiomas were more likely to be suprasellar, spherical, predominantly solid, and homogeneously enhancing with a thickened pituitary stalk. The sensitivity and specificity for detecting a BRAF mutation when 3 out of these 5 criteria were met was 1.00 and 0.91, respectively, and the area under the ROC curve for all 5 diagnostic criteria was 0.989, suggesting that MRI characteristics could offer valuable guidance for preoperative BRAF/MEK inhibitor treatment decisions [53]. Further research is urgently needed to help establish more definitive imaging criteria that could allow for more accurate differentiation of histologic and molecular subtypes in the preoperative setting.

A trial of BRAF/MEK inhibitor therapy is reasonable for most patients with newly diagnosed BRAF-mutated craniopharyngiomas and may be considered in recurrent or progressive tumors that had originally been treated with surgery or radiation. This shift not only reflects the advances in our understanding of the molecular biology of craniopharyngiomas but also the evolving paradigm in neuro-oncology that seeks to balance therapeutic efficacy with quality-of-life considerations. Based on the results from the recent phase II trial in papillary craniopharyngiomas, treatment with a BRAF/MEK inhibitor combination should be pursued for at least 4 cycles before assessing treatment response and determining subsequent treatment steps [21••, 54, 55]. Notably, within this trial, a substantial reduction in tumor volume was observed, and a significant majority of patients exhibited a response to the BRAF–MEK inhibition within the initial 4 months of therapy [21••]. The significant reduction in tumor size also suggests a potential for improving outcomes of subsequent surgery or radiotherapy by allowing for smaller radiation fields or facilitating gross total resection of residual tumor. However, the precise role and optimal timing of additional therapies following targeted treatment remain currently unclear [21••, 54, 55]. It should be noted that, while definitive treatment with surgery or radiation was prespecified in the trial after four cycles of BRAF/MEK inhibitor therapy, treatment with vemurafenib/cobimetinib was continued in selected cases [21••]. Therefore, continuing BRAF/MEK inhibitor therapy, radiation, or surgery could all be reasonable options for patients who responded to initial targeted therapy. Overall, it appears reasonable to continue BRAF/MEK inhibitor therapy beyond 4 cycles in patients who derived clinical benefit and where definitive therapy with surgery or radiation is either contraindicated due to significant risk of side effects or declined by the patient. In these cases, it may be reasonable to continue targeted therapy until the maximal benefit of targeted therapy is achieved or tumor progression or unacceptable side effects occur.

Another area of uncertainty revolves around the necessity of dual BRAF–MEK inhibition for target treatment of craniopharyngiomas harboring the BRAF V600E mutation. Based on the current experience with other BRAF V600E-mutated tumors, the combination of BRAF-MEK inhibitor therapy appears at this point reasonable to mitigate the paradoxical activation of RAF protein that has been observed with first-generation RAF inhibitors such as vemurafenib [56, 57, 58•]. However, further research is necessary to determine the precise

role of combined BRAF-MEK inhibition, as well as the optimal duration and sequence of targeted therapy in the treatment of BRAF-mutated craniopharyngiomas. Moreover, it will be critical to establish clear strategies for handling adverse events, which can sometimes be intolerable, to ensure patient safety and treatment adherence.

Finally, the choice of the most effective BRAF/MEK inhibitors remains a topic of discussion. Currently, three BRAF/MEK inhibitor combinations are in clinical use: dabrafenib/trametinib, encorafenib/binimetinib, and vemurafenib/cobimetinib. In the absence of direct comparisons in randomized trials and based on their comparable efficacy in the treatment of BRAF V600E-mutated melanoma, each of these combinations can be considered viable. Overall, due to the current lack of definitive evidence favoring one approach over the other, the decision regarding the optimal treatment option should be made jointly with the patient, accounting for their unique circumstances and preferences.

Management of complications

Treatment of craniopharyngioma complications centers around management of symptoms and tumor-related organ dysfunction [11, 12, 37, 59]. Symptoms at the time of presentation are typically related to the local mass effect from the tumor resulting in damage to nearby structures and increase in intracranial pressure. Common presenting symptoms therefore include headaches, nausea, vomiting, visual changes, and cognitive dysfunction [12, 37]. Long-term complications on the other hand are often due to a combination of both direct effects from the tumor and tumor-directed therapies [13–16, 16, 17, 17, 26, 27]. Despite significant improvements in neurosurgical and radiation techniques, iatrogenic effects continue to pose a challenge and often significantly impact the quality of life of patients with craniopharyngiomas. Aggressive surgical approaches can result in an increased risk of hypothalamic and endocrine dysfunction and visual field deficits [14, 16, 17]. Radiotherapy can lead to optic neuropathies, especially when administered at high doses, and hypothalamic-pituitary dysfunction, which can take years to become evident [13, 15–17, 26, 27]. Distinguishing between effects from the initial tumor and side effects from treatments such as radiation or surgery is therefore often challenging. Given the tumor’s proximity to vital brain structures, patients often grapple with a multitude of chronic symptoms, including significant visual, hypothalamic, endocrine, and neurocognitive dysfunction [13–17]. The management of long-term complications in craniopharyngioma patients therefore requires a comprehensive multidisciplinary and individualized approach [11, 12, 34]. Endocrine dysfunction, such as diabetes insipidus or growth hormone deficiencies, often requires lifelong hormone replacement therapies and regular monitoring by endocrinologists [14, 17, 26]. Visual complications frequently arise, due to tumor proximity to the optic nerves [12, 35, 38, 46]. It is therefore essential for patients to undergo ophthalmologic evaluations at the time of diagnosis, with continued monitoring throughout their disease course. Neurological deficits, including cognitive and behavioral dysfunctions, can benefit from physical and occupational therapies. Psychological support, including counseling or therapy, is also important to address the emotional and cognitive challenges patients might face. Additionally, regular neuroimaging is crucial to monitor for potential tumor recurrence or progression of residual disease. Multidisciplinary care by an

experienced team of specialists is therefore essential to ensure optimal quality of life and address the diverse long-term complications associated with craniopharyngiomas.

Challenges and future prospects

The development of targeted therapies for BRAF-mutated craniopharyngiomas promises to revolutionize the management of these challenging tumors. However, the introduction of this new treatment modality brings about its own set of challenges and several questions remain. Traditional treatment modalities, such as surgical resection and radiation, have well-established protocols and known outcomes. However, the integration of targeted therapies necessitates a re-evaluation of these protocols. Determining the optimal timing and sequencing of targeted treatments in conjunction with, or in place of, conventional therapies remains a complex issue. Furthermore, the ideal length of treatment with BRAF-targeted therapy, required to maximize efficacy while minimizing potential side effects, is currently unknown. Prolonged treatment might improve tumor control but could also increase the risk of adverse reactions or lead to drug resistance. Conversely, shorter treatment durations might be insufficient to achieve desired outcomes or prevent recurrence. Cell-free DNA analysis, also known as liquid biopsy, holds promise for the diagnosis of BRAF-mutated craniopharyngiomas [21••, 60]. Initial exploratory studies found detectable BRAF V600E in the peripheral blood of a subset of patients with BRAF V600E-mutated craniopharyngiomas, an unexpected finding given that circulating tumor cells or cell-free DNA are felt to be uncommon in benign intracranial tumors [21••, 60]. Detecting BRAF V600E in peripheral blood prior to treatment could facilitate timely targeted therapy and help minimize risks associated with a surgical biopsy. However, several challenges remain, such as determining the sensitivity, specificity, and the influence of possible confounding factors such as prior surgical procedures on the results of cell-free DNA analysis in the diagnosis of BRAF-mutated craniopharyngiomas. Another challenge relates to ensuring that patients have access to molecular testing for potential therapeutic targets, such as the BRAF V600E mutation in papillary craniopharyngiomas. Additionally, the cost and availability of these new treatments, especially in healthcare systems with limited resources, can pose significant barriers. Therefore, the integration of these novel treatments may inadvertently widen healthcare disparities if historically marginalized and underserved populations lack equitable access. Given the complexities introduced by targeted therapies, further research is needed to adequately address these challenges and ensure the best possible outcome for patients.

Summary

Traditional treatments for craniopharyngiomas, such as surgical resection and radiation, pose significant risks due to the tumor’s proximity to vital brain structures, leading to potential neurological, endocrine, and visual complications. Moreover, radiation has been linked to long-term side effects like optic neuropathies and neurocognitive and hypothalamic-pituitary dysfunction. Recent genomic advances have identified the BRAF V600E mutation in nearly all papillary craniopharyngiomas. A phase II study on the BRAF–MEK inhibitor combination of vemurafenib–cobimetinib showed promising results, with significant tumor volume reductions and high response rates. Given these results, BRAF-targeted therapy

is emerging as a promising new treatment option in addition to traditional approaches for BRAF-mutated craniopharyngiomas. The complexities associated with integrating these novel treatments into the existing therapies for craniopharyngiomas underscore the need for further research to improve our understanding of these therapies and optimize and refine treatment protocols.

Conflict of Interest

DG and SS have no conflicts of interest or disclosures to report. PKB has consulted for Angiochem, Merck, Genentech-Roche, Lilly, Tesaro, ElevateBio, Dantari, Voyager Therapeutics, SK Life Sciences, Pfizer, ACI, Sintetica, Kazia, MPM, CraniUS, Axiom and InCephalo, serves on the Scientific Advisory Board for Kazia, has received grant/research support (to MGH) from Merck, Lilly, Mirati, BMS and Kinnate, and speaker's honoraria from Merck, Genentech-Roche, Lilly and Medscape.

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