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Treatment Options for Optic Pathway Gliomas

Reena P. Thomas, MD, PhD
Iris C. Gibbs, MD, FACR
Linda Wei Xu, MD
Lawrence Recht, MD[*]

Address
[*]Stanford University Hospital, 875 Blake Wilbur Drive, Stanford, CA 94305, USA
Email: lrecht@stanford.edu

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Opinion statement

Gliomas that affect the optic pathways are for the most part low-grade neoplasms that often, but not always, have good prognoses. Optimal treatment and management of optic pathway gliomas remains unclear and the decision hinges upon several factors including patient age, tumor location, and visual symptoms. We favor a treatment approach that is dependent on the location of tumor within anterior, chiasmal or posterior/hypothalamic visual pathways. In children who are minimally or not symptomatic, we recommend observation rather than early treatment intervention. Most of these patients will have neurofibromatosis type 1 (NF1) based on the natural history and their pilocytic astrocytoma histology. Serial magnetic resonance imaging studies and formal neuro-ophthalmology testing should enable close observation of these patients, with intervention being reserved for when tumor progression results in significant visual loss or proptosis. Chemotherapy is an accepted first line treatment, and a number of effective medications are available, although no agent has proven clearly superior. If progression is accompanied by the complete loss of vision, surgery can be utilized to help alleviate structural issues (ie, proptosis). Minimally symptomatic chiasmal or hypothalamic tumors that arise in the setting of NF1 can also be observed initially because of their favorable prognosis. Children with NF1 and chiasmal or posterior visual tumors who progress either on imaging or clinical grounds (ie, development of significant visual deficits) should be treated first with chemotherapy rather than radiation therapy to minimize the effects on the developing central nervous system. Individuals without NF1 presenting with a chiasmal or hypothalamic mass are candidates for biopsy to determine the underlying pathology of the lesion. Symptomatic patients with pilocytic astrocytoma should first receive chemotherapy. In contrast, other histologies including malignant optic pathway gliomas should be treated similar to other gliomas that occur in other locations with appropriate doses of radiation and chemotherapy.

Introduction

Optic pathway gliomas (OPGs) are astrocytic neoplasms that are typically low-grade tumors arising from the optic nerve, chiasm or posterior tract [1••]. They account for approximately 2 % of gliomas in the central nervous system and 3 % 5 % of childhood intracranial tumors. OPGs commonly present in childhood with 75 % of patients being diagnosed prior to the age of 10 and 90 % by the age of 20 [2]. Classification is based on anatomic location and concomitant diagnosis of neurofibromatosis type 1 (NF1) [3]. The pathogenesis of OPGs may be related to allelic chromosomal loss such as loss of chromosome 17q that can occur in pilocytic astrocytomas or loss of neurofibromin in patients with NF1 [4].

Tumors arise in the anterior visual pathway in 25 % 30 % and can be further subdivided into orbital, intracanalicular, or intracranial prechiasmal lesions. These tumors are almost exclusively pilocytic astrocytomas, and growth is almost universally slow. Tumors may be infiltrative or demarcated from the normal optic nerve and invasion of the leptomeninges can often be seen. Compression of the optic nerve may occur as the tumor enlarges, resulting in demyelination and atrophy of the nerve. In contrast, posterior visual pathway tumors arising in the optic chiasm, hypothalamus, or anterior third ventricle, are a more heterogeneous group of tumors and are more often nonpilocytic astrocytomas. Therefore, their behavior is also more heterogeneous and their prognosis is significantly poorer [5, 6].

Presenting symptoms depend upon the location in which the tumor arises. Patients with orbital lesions most commonly present with proptosis and less likely with strabismus or spasmus nutans. Because of the young age at diagnosis, visual impairment is a relatively uncommon presenting symptom although fundoscopic examination may exhibit edema or pallor of the optic disc. Chiasmal lesions most often present with visual symptoms but can also present with symptoms arising from obstructive hydrocephalus. Hypothalamic gliomas may present as diencephalic syndrome such as failure to thrive in an alert and cheerful child. Children may present with endocrinopathies leading to precocious puberty or accelerated linear growth. Patients with NF1 should have annual ophthalmologic screening for identification of optic pathway gliomas until age 10 [1••, 7].

The diagnosis of OPG should be considered in situations of unexplained visual loss, monocular or asymmetric nystagmus, diencephalic syndrome, or optic nerve atrophy. Brain magnetic resonance imaging (MRI) including fine cuts through the orbit and optic pathway is the diagnostic imaging of choice. Findings may include tubular thickening of the optic nerve and chiasm, a suprasellar lesion, or optic nerve/tract involvement. Differential diagnoses include suprasellar germinoma, craniopharyngioma, glioma, sarcoidosis, lymphoma, or Langerhans histiocytosis [8]. The natural history of OPGs varies dependent on the histologic findings, location, and the genetic background of NF1 [9, 10].

Overall, OPGs are associated with an indolent clinical course and long-term survival, underscoring the need for addressing long-term treatment complications in treatment decisions [11]. Patients with NF1 and a more anterior location of the tumor are associated with the most favorable outcomes. Visual acuity loss is the most significant morbidity associated with OPGs, with blindness developing in almost 20 % of affected individuals. For this reason, treatment should be based on patient's age, genetic predisposition (NF1), location of the lesion, and growth rate and is best rendered by a multidisciplinary team including ophthalmology, radiation oncology, neuro-oncology, neuroradiology, and neurosurgery (Table 1) [12–15].

Treatment

Diet and lifestyle

Although no specific studies have looked at OPGs and diet, there have been some studies looking at the use of ketogenic diets and gliomas in general. The use of the ketogenic diet derives from the Warburg hypothesis that tumor tissue relies mostly on glycolysis rather than oxidative phosphorylation for metabolism. In using the ketogenic diet, which provides low carbohydrates, high fat, and moderate protein, glucose levels in the blood are decreased and ketone

Table 1. Presentation, pathology, and treatment options based on anatomic location

Location	Presentation	Pathology	Treatment Options
Anterior	• Proptosis • Strabismus • Spasmus nutans • Visual Impairment	Pilocytic astrocytomas	• Surgery considered for proptosis, blindness, significant mass effect, gross total resection possible • Chemotherapy • Radiation
Chiasmal	• Visual impairment • Obstructive hydrocephalus	More heterogeneous tumor types	• Surgery considered for significant mass effect, hydrocephalus, gross total resection not typically possible • Chemotherapy • Radiation
Posterior/ hypothalamic	• Diencephalic syndrome • Failure to thrive • Precocious Puberty • Accelerated linear growth	More heterogeneous tumor types	• Surgery only considered for significant mass effect, no gross total resection possible • Chemotherapy • Radiation

bodies that bypass glycolysis are funneled directly into oxidative phosphorylation for metabolism. Mouse studies have shown that a ketogenic diet led to smaller tumor size, increased survival, and alterations in gene expression and reactive oxygen species [16]. Anecdotally, there have been some case reports on patients who have had success with tumor control on a ketogenic diet, but one clinical trial in patients with glioblastoma multiforme on ketogenic diets showed some difficulty with diet tolerability and minor differences in overall progression free survival [17].

Pharmacologic treatment

There have been no definitive studies establishing the superiority of one specific chemotherapeutic agent over others for OPGs. At our institution, we prefer starting with temozolomide given its favorable side effect profile, but all other chemotherapy options listed have been used for OPG treatment both alone and in conjunction.

Standard dosage 150 mg/m^2 once daily for 5 days of a 28 day cycle.

Contraindications Hypersensitivity to temozolomide or any component of the formulation; hypersensitivity to dacarbazine; myelosuppression.

Main drug interactions Valproic acid.

Main side effects Myelosuppression, moderate emetic potential, Pneumocystis jirovecii pneumonia, constipation.

Special points Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents. At our institution, this is our first line agent due to tolerability of side effect profile.

Cost/cost effectiveness 100 mg (5) capsules, $1261.45

Standard dosage 450 mg/m^2 in 1 h infusion on day 1 in a 3-week cycle.

Contraindications	Allergic reaction to carboplatin, cisplatin, or other platinum-containing formulations, mannitol, or any component of the formulation; myelosuppression or bleeding.
Main drug interactions	May enhance effect of immunosuppressant drugs, ototoxic effects of aminoglycosides, and neurotoxic effects of cisplatin (ie, peripheral neuropathy).
Main side effects	Myelosuppression, electrolyte abnormalities, renal impairment, hepatic impairment, ototoxicity.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	450 mg/45 mL (45 mL) intravenous solution, $120.
Standard dosage	30 mg/m^2/d in a 3-h infusion with mannitol and saline on day 1 and 2 out of 3-week cycle.
Contraindications	Hypersensitivity to cisplatin, other platinum-containing compounds, or component of the formulation; pre-existing renal impairment; myelosuppression; hearing impairment.
Main drug interactions	Aminoglycosides, immunosuppressants, myelosuppressive agents. Main side effects: nausea, vomiting, hypersensitivity/anaphylactoid reactions, hyperuricemia, infusion site reactions, neurotoxicity, ototoxicity, renal toxicity.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	200 mg/200 mL (200 mL) $86.64.
Standard dosage	1500 mg/m^2 in a 1-h infusion on day 1 out of 3-week cycle
Contraindications	Hypersensitivity to cyclophosphamide or any component of the formulation
Main drug interactions	Vitamin K antagonists, immunosuppressants, CYP3A4 inhibitors, CYP2B6 substrates, cardiac glycosides.
Main side effects	Myelosuppression, cardiotoxicity, fertility, nausea, vomiting, hemorrhagic cystitis, hypersensitivity, immunosuppression, pneumonitis, secondary malignancies, wound healing impairment.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	1 g (1) cyclophosphamide reconstituted solution $879.00.
Standard dosage	150 mg/m^2/d in 1-h infusion on day 1 and 2 out of 3-week cycle.
Contraindications	Hypersensitivity to etoposide or any component of the formulation.
Main drug interactions	May decrease the metabolism of CYP3A4 substrates and enhance the anticoagulant effect of vitamin K antagonists (ie, warfarin).
Main side effects	Myelosuppression, hypersensitivity reaction (anaphylactic-like reactions), hypotension with rapid administration, secondary malignancies.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	1 gm/50 mL (50 mL) intravenous solution, $105.60.
Standard dosage	120 mg/m^2/d, days 1 7 in a 3-week cycle.
Contraindications	Hypersensitivity to procarbazine or any component of the formulation; myelosuppression.

Main drug interactions	Inhibits monoamine oxidase thus enhancing the effects of multiple classes of medications that are metabolized by these enzymes. Patients should be placed on a diet that minimizes exposure to tyramine.
Main side effects	High emetic potential, myelosuppression, CNS toxicity (paresthesia, neuropathy), hypersensitivity.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	100 capsules (matulane oral) 50 mg, $6434.81.
Standard dosage	1.5 mg/m^2 in a 1-h infusion on day 1 out of 3-week cycle.
Contraindications	Patients with the demyelinating form of Charcot-Marie-Tooth syndrome, preexisting neuropathy.
Main drug interactions	May decrease the metabolism of CYP3A4 substrates.
Main side effects	Constipation, infusion site reactions from extravasation, neurotoxicity, respiratory distress or bronchospasm, uric acid nephropathy.
Special points	Unlabeled use; Dosage varies depending on its use with other chemotherapeutic agents.
Cost/cost effectiveness	Vincasar PFS intravenous 1 mg/mL (1 mL) $18.06.

Interventional procedures

Ophthalmological screening [20–23]

Patients with known OPGs and those diagnosed with NF1 should be serially screened for progressive visual loss. Although visual acuity is the primary screening test, it is difficult to perform in younger children. Visual evoked potentials and optical coherence tomography (OCT) are tools that can be helpful in the screening visit.

Contraindications	None.
Complications	None.
Special points	More thorough testing may be necessary in younger children given inconsistencies in their acuity exam.
Cost/cost effectiveness	High

MRI brain [24]

Cases with characteristic imaging findings on MRI can obviate biopsy of suspected lesions for diagnosis. MRI is the preferred method of imaging although head CT can be used as an initial screening tool at the time of presentation or when MRI is contraindicated. Lesions are often isodense to brain and contrast enhancement may be variable.

Contraindications	Renal impairment may preclude contrast use.
Complications	None.
Special points	Sedation is often necessary for children to complete MRI.
Cost/cost effectiveness	High.

Surgery

Surgery is typically considered only in the event of single nerve involvement, progressive and disfiguring proptosis, blindness, and significant mass effect or hydrocephalus. Complete resection of a tumor would only be considered and possible if the lesion is limited to one optic nerve because the procedure may cause blindness. Tumor resection or ventricular shunting may be needed in the setting of obstructive hydrocephalus.

Contraindications Diffuse or bilateral optic nerve involvement.

Complications Blindness.

Special points Patients with NF1 often have diffuse disease burden with increased failure rate after surgical intervention.

Cost/cost effectiveness Variable.

Assistive devices

Dependent on degree of vision loss and best evaluated by blind rehabilitation service experts.

Therapy and exercise

Blind rehabilitation services and vision therapy.

Usage Indicated when visual loss may be impairing independent functioning.

Special points Consider school for the blind for implementation of multidisciplinary approach to therapy.

Cost/cost effectiveness High.

Other treatments [25–28].

Radiation

Once utilized as the primary treatment modality, radiotherapy is typically deferred until at least age 5 7 because of the potential for late risks including endocrinopathy, vasculopathy, and cognitive decline. Radiotherapy is considered a viable option in children older than age 5 7 whose tumors are not amenable to surgery and/or tumors that have progressed despite other treatments. Conventionally, external-beam fractionated radiation therapy has been the treatment of choice. Radiotherapy is associated with 10-year relapse-free survival rates of 71 % 90 % and stabilization of vision of 69 % 81 % [29–32]. Indeed with regard to tumor stabilization and visual outcomes, radiotherapy is the modality with which other options are compared and remains the fall-back option when others fail. The results of a number of studies have suggested that using early introduction of radiotherapy rather than after visual decline or chemotherapy progression is associated with better visual outcomes [29–32]. For example, in a study of 27 patients with OPG treated at St. Jude Children's Cancer Hospital on a prospective trial of conformal radiotherapy as the first treatment, patients were more likely to have useful vision before and after radiotherapy. [25] Although radiotherapy is effective, given the long-term survival for these patients, early radiotherapy has to be counterbalanced with

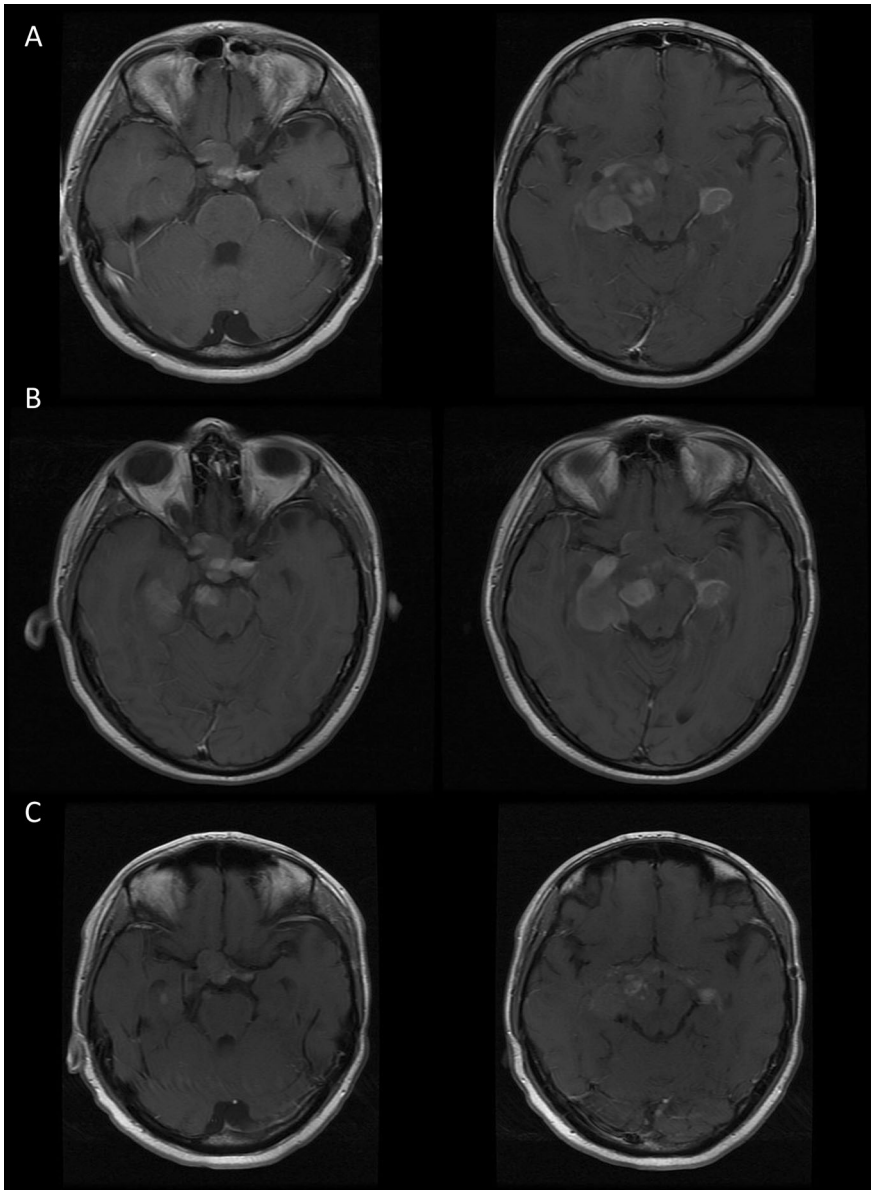

Fig. 1. Tumor control following bevacizumab. **A,** Contrast enhancing MRI axial slices from a patient with an optic tract glioma previously treated with surgical debulking, carboplatin, vincristine, etoposide, vinblastine with progression noted at next scan 3 months later. **B,** Patient was started on bevacizumab with continued tumor stabilization over 4 years later (**C**).

development of complications later in life. Highly conformal techniques of radiation including proton beam radiotherapy and fractionated stereotactic radiotherapy have shown promise to limit the radiation exposure to surrounding brain tissue and minimize associated late risks [29, 30, 33, 34].

Contraindications Relative contraindication in age less than 5 years.

Complications Visual loss, edema, cognitive dysfunction, endocrine abnormalities, vasculopathy.

Special points	Maximal effect of radiation may take years to be observed. Irradiation is associated with an increased incidence of secondary tumor development occurring years later and can result in the development of secondary Moyamoya disease, especially in NF1 patients.
Cost/cost effectiveness	Variable.

Emerging therapies

Standard procedure	Chemotherapy.
Contraindications	Hemorrhage, wound healing difficulty, recent surgery.
Complications	Hemorrhage, gastrointestinal perforation, hypertension, wound dehiscence.
Special points	Most effective if edema associated with lesion contributing to symptoms or clinical presentation. Figure 1 demonstrates an example of OPG treated with bevacizumab at our institution with prolonged tumor control.
Cost/cost effectiveness	400 mg/16 mL (16 mL), $3115.87.

Pediatric considerations

The information provided in this manuscript applies mostly to children given the fact that the mean age of patients at diagnosis is 8.8 years.

Compliance with Ethics Guidelines

Conflict of Interest
Reena Parada Thomas, Iris C. Gibbs, Linda Wei Xu, and Lawrence Recht declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Highlights the use of bevacizumab as a new treatment optic pathway gliomas.