Case Report/Case Series

Marked Recovery of Vision in Children With Optic Pathway Gliomas Treated With Bevacizumab

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IMPORTANCE Children with optic pathway gliomas (OPGs) frequently experience vision loss from their tumors. Standard front-line treatment using carboplatin-based chemotherapy typically produces only a modest benefit (eg, stabilization or 0.2 logMAR improvement) in visual acuity (VA). Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and acts primarily as an anti-angiogenic agent. Recent reports suggest a qualitative improvement in vision after bevacizumab-based treatment in children with OPGs.

OBSERVATIONS We report 4 cases of pediatric OPGs (2 neurofibromatosis type 1–related and 2 sporadic cases) that received treatment with bevacizumab due to progressive VA or visual field (VF) loss despite prior treatment with chemotherapy or proton-beam radiation. All 4 subjects demonstrated a marked improvement in their VA, VF, or both while receiving bevacizumab-based therapy. Three patients had complete resolution of their VA or VF loss in at least 1 eye—2 of whom had previously received bevacizumab therapy.

CONCLUSIONS AND RELEVANCE Given that most patients with OPG-related visual impairment will show modest or no visual improvement with standard treatment, the incorporation of bevacizumab in these cases may greatly improve visual outcomes and should be considered in appropriate clinical situations.

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Children may experience vision loss from optic pathway gliomas (OPGs), which are low-grade gliomas of the proximal afferent visual pathway. Treatment using standard front-line therapy with carboplatin and vincristine produces mild improvement (ie, 0.2 logMAR) in visual acuity (VA) in approximately one-third of children with neurofibromatosis type 1 (NF1)–related or sporadic (non-NF1) OPGs.[1,2] There have also been recent reports of qualitative visual improvement after bevacizumab-based treatment.[3]

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and acts primarily as an anti-angiogenic agent. Bevacizumab is administered intravenously at 10 mg/kg per dose every 2 to 3 weeks, depending on response and adverse effects. We report 4 cases of pediatric OPGs that demonstrated marked VA/visual field (VF) recovery with bevacizumab-based therapy.

Report of Cases

Case 1

An 11-year-old girl with NF1 and a chiasmatic OPG exhibited radiographic progression. The child had no visual complaints and her previous ophthalmologic examination findings had been reported as stable (see **Table** for prior treatments). At our institution, her VA was 20/20 OD, but automated perimetry demonstrated dense temporal VF loss (**Figure 1**, left panel). The duration of the VF loss was unknown because the patient had never completed automated perimetry and offered no ophthalmologic concerns. Treatment with bevacizumab/irinotecan was initiated and within 7 months, her VF and tumor size had improved (Figure 1, middle panel). Her VF continued to improve and remained stable 6 months after treatment was discontinued (Figure 1, right panel).

Case 2

A 13-year-old girl with a sporadic (non-NF1–related) OPG presented with a decline in VA and VF 7 months after proton-beam therapy. Her chiasmatic OPG was treated initially at age 7 years with carboplatin/vincristine and temozolomide. At age 11.5 years, she again demonstrated radiographic progression so proton-beam radiotherapy was administered. Before radiotherapy, her VA was 20/20 (OD/OS), with mild VF changes, most notably a left hemifield defect respecting the vertical meridian consistent with an incongruous left hemianopsia.

Four months after radiation, she presented with mild VA loss (OD, 20/40; OS, 20/50) and was treated with corticosteroids without benefit. After 3 months, her VA continued to decline (OD, 20/40; OS, 20/125), so bevacizumab monotherapy was started (**Figure 2**, left panel). Within 2 months of starting bevacizumab, her VA improved in both eyes (OD, 20/20; OS, 20/50),

Table. Treatment History, Vision Outcomes, and Radiographic Response in Children With OPGs Treated With Bevacizumab

Case No.	Age at First Chemotherapy, y	Tx Prior to Bevacizumab	Age at Bevacizumab Tx, y	Bevacizumab AE[a]	F/U, mo	VA				VF		MRI Response
						Pre-Tx		Post-Tx				
						OD	OS	OD	OS	Pre-Tx	Post-Tx	
1	3	Carboplatin/vincristine	11[b]	HTN	6	20/20	NA[c]	20/20	NA[c]	Temporal loss	WNL	Decrease in size/enhancement
2	7	Carboplatin/vincristine, temozolamide, PBR, bevacizumab/irinotecan, vinblastine	13[d]		12	20/40	20/125	20/20	20/20	Bitemporal and central loss	WNL OD, temporal depression OS	Decrease in size/enhancement
3	4.5	Bevacizumab/irinotecan	9[e]	PN, HTN	9	20/400	20/50	20/125	20/20			Decrease in enhancement
4	0.5	Carboplatin/vincristine, temozolamide, vinblastine, Tarceva, rapamycin, PBR	6[f]	PN	9	CF 10′	20/100	20/400	20/50			Decrease in size/enhancement

Abbreviations: AE, adverse effect; CF, counting fingers; F/U, follow-up; HTN, hypertension; MRI, magnetic resonance imaging; NA, not applicable; OD, right eye; OPGs, optic pathway gliomas; OS, left eye; PBR, proton-beam radiation; PN, proteinuria; Tx, treatment; VA, visual acuity; VF, visual field; WNL, within normal limits.

[a] All AEs resolved after discontinuing bevacizumab therapy.

[b] Duration of bevacizumab treatment was 7 months.

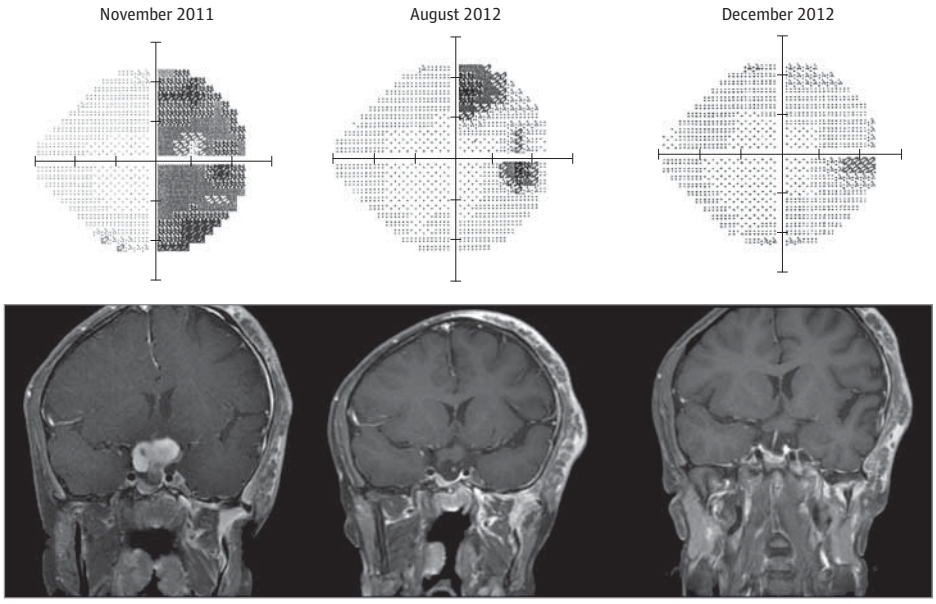
[c] Left eye enucleated at 3 years of age secondary to neurofibroma-related proptosis.

[d] Duration of bevacizumab treatment was 4 months.

[e] Duration of bevacizumab treatment was 9 months.

[f] Duration of bevacizumab treatment was 3 months.

Figure 1. Resolution of Temporal Visual Field Loss Following Bevacizumab Treatment in a Child With a Neurofibromatosis Type 1–Related Optic Pathway Glioma



Chiasmatic optic pathway glioma in an 11-year-old girl (case 1) with neurofibromatosis type 1 with dense temporal visual field loss (left panel). Improvement was seen in the visual field and tumor size/enhancement within 7 months of treatment with bevacizumab/irinotecan (middle panel). The visual field continued to improve and remained stable 6 months after treatment was discontinued (right panel).

along with mild improvement in the OD VF (Figure 2, middle panel). After 4 months of therapy, her VA had returned to normal (OD/OS, 20/20) and remained stable at 12 months (Figure 2, right panel), along with a magnetic resonance image demonstrating decreased enhancement and tumor size.

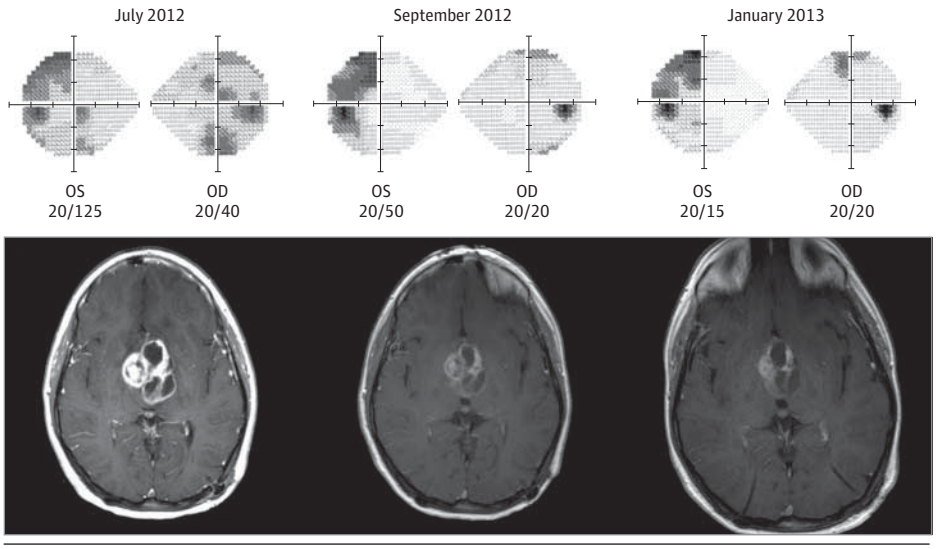
Case 3

A 9-year-old girl with an NF1-related chiasmatic OPG presented with acute vision loss (OD, 20/400; OS, 20/50) and was found to have increased enhancement and growth of her OPG. She started treatment with a regimen of bevacizumab monotherapy every 2 weeks (as previously reported[3]). Despite previous bevacizumab/irinotecan exposure at 4.5 years of age, within 6 weeks (3 doses), her vision improved (OD, 20/100; OS, 20/30); the dosing interval was lengthened to every 3 weeks without deterioration of vision (OD, 20/125; OS, 20/20) and has remained stable for the past 9 months after discontinuing bevacizumab treatment. Automated perimetry was attempted but was unreliable with 50% false-negative errors.

Case 4

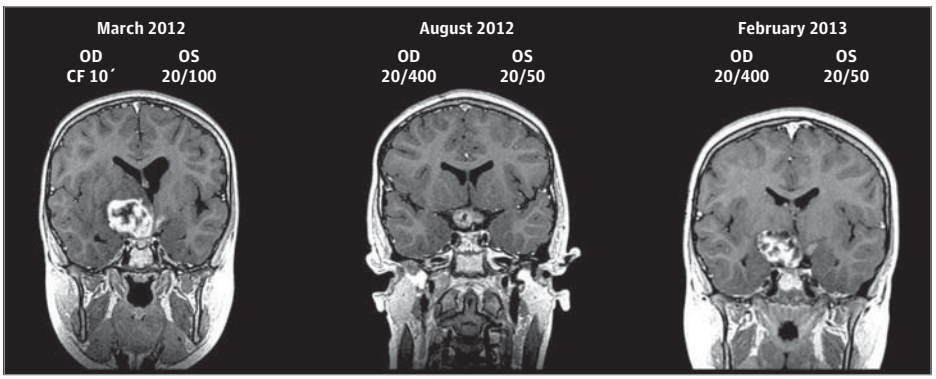
A 6-year old girl with a sporadic chiasm/hypothalamic OPG presented with a decline in VA 4 months after proton-beam therapy. Proton-beam radiation was initiated because of pre-

Figure 2. Resolution of Visual Acuity Loss Secondary to a Sporadic Chiasmatic-Hypothalamic Optic Pathway Glioma Following Bevacizumab Treatment



Sporadic (non–neurofibromatosis type 1–related) optic pathway glioma in a 13-year-old girl (case 2) with previously normal visual acuity (20/20, OD/OS) that presented with a decline in visual acuity and a left hemifield defect respecting the vertical meridian 7 months after proton-beam therapy (left panel). Improvement in vision and tumor size/enhancement occurred within 2 months of starting bevacizumab treatment (middle panel) and remained stable at 12 months (right panel).

Figure 3. Improved Visual Acuity and Gadolinium Enhancement Following Bevacizumab Treatment



Sporadic chiasmatic/hypothalamic optic pathway glioma in a 6-year-old girl (case 4), with a decline in visual acuity 4 months after proton-beam therapy (left panel). Within 5 months of starting bevacizumab, her visual acuity improved, along with a noticeable decrease in tumor size and enhancement (middle panel). Bevacizumab was discontinued because of a positive treatment response. Vision remained stable despite an increase in size and enhancement (right panel) 9 months after discontinuation of bevacizumab. CF indicates counting fingers.

vious treatment failure, subsequent radiographic progression, and VA deterioration (OD, 20/200; OS, 20/60).

Four months after radiation, she presented with continued VA loss (OD, counting fingers at 10 ft; OS, 20/100) and so bevacizumab monotherapy was started (**Figure 3**, left panel). After starting bevacizumab, her VA improved in both eyes, along with a noticeable decrease in tumor size and enhancement (Figure 3, middle panel). Bevacizumab was discontinued because of a positive treatment response. Vision remained stable despite an increase in size and enhancement 9 months after discontinuation (Figure 3, right panel).

Discussion

First-line treatment of OPGs using carboplatin/vincristine results in modest visual improvement (ie, 0.2 logMAR) in no more than 30% of children.[1,2] In our cohort, we demonstrated near-complete resolution of VF defects in 1 patient (case 1) and complete resolution of VA loss in another (case 2). All 3 patients with VA loss experienced moderate (0.3 logMAR) to significant (0.8 logMAR) VA improvement in at least 1 eye. Two patients experienced VA/VF loss from tumor progression, while VA/VF loss in 2 patients (cases 2 and 4) may have been due to postradiation effects (ie, pseudoprogression) or progression. Regardless, patients had marked improvement in their vision shortly after starting treatment with bevacizumab.

The resolution of the right temporal field loss in case 1 was particularly interesting as the duration of VF loss was unknown (Figure 1). While there was radiographic improvement, the near-complete resolution of her VF was unexpected.

Bevacizumab-based therapy in children can be complicated by variable adverse effects. Three of our patients experienced adverse effects requiring dose-interval modification

(extended to every 3 weeks instead of 2 weeks), whether with bevacizumab alone (n = 3) or in combination with irinotecan (n = 1). Three patients had previously received bevacizumab-based treatment, yet each experienced significant visual improvement when retreated, suggesting that response to bevacizumab may occur regardless of previous exposure.

Tumor-mediated impairment of visual function may be secondary to both direct tumor expansion, as well as a significant inflammatory response, both causing injury to the optic pathway. The anti-angiogenic activity and resulting decreased blood vessel permeability from bevacizumab may cause visual improvement by addressing each of these causes.[4,5] Although it is unclear what contribution the use of irinotecan adds to either the antitumoral effect or visual improvement, in most of our patients, visual response occurred with bevacizumab monotherapy.

Given that most patients with OPG-related visual impairment will show modest or no visual improvement with standard chemotherapy, the incorporation of bevacizumab in these cases may greatly improve visual outcomes and should be considered in appropriate clinical situations. Confirmation is warranted and will require prospective evaluation involving standardized and detailed ophthalmologic assessment.

ARTICLE INFORMATION

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Acquisition of data: Avery, Jakacki.
Analysis and interpretation of data: All authors.
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