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Novel "T-Dimension" Therapies for Pediatric Optic Pathway Glioma: A Timely, Targeted, and Tailored Treatment Trend

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Keywords
Bevacizumab · MEK inhibitors · mTOR inhibitors · Optic pathway glioma · Proton beam radiotherapy · Stereotactic radiosurgery · Target therapy

Abstract
Introduction: Novel targeted and tailored therapies can substantially improve the prognosis for optic pathway glioma (OPG), especially when implemented in a timely manner. However, their tremendous potential remains underestimated. Therefore, in this study, we provide an updated overview of the clinical trials, current trends, and future perspectives for OPG's novel therapeutic strategies. ***Methods:*** We completed an extensive literature review using the PubMed, MEDLINE, and ClinicalTrials.gov databases. We analyzed and reported the data following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. ***Results:*** Thioguanine, procarbazine, lomustine, and vincristine/vinblastine, as well as cisplatin-etoposide, provided excellent results in advanced-phase trials. Selumetinib and trametinib, two oral MEK inhibitors, have been approved for recurrent or refractory OPGs in association with the angiogenetic inhibitor bevacizumab. Among the mTOR inhibitors, everolimus and sirolimus showed the best results. Stereotactic radiosurgery and proton beam radiation therapy have advantages over conventional radiotherapy regimens. Timely treatment is imperative for acute visual symptoms with evidence of tumor progression. This latest evidence can help define a novel "T-Dimension" for pediatric OPG therapies. ***Conclusion:*** The novel "T-Dimension" for pediatric OPGs is based on recent evidence-based treatments, including combination chemotherapy regimens, molecular targeted therapies, stereotactic radiosurgery, and proton beam radiation therapy. Additional clinical trials are essential for validating each of these new therapies.

Introduction

Optic pathway gliomas (OPGs) account for 2–5% of all pediatric neoplasms [1–4]. Regardless of their sporadic or neurofibromatosis type 1 (NF1)-associated form, 70% of

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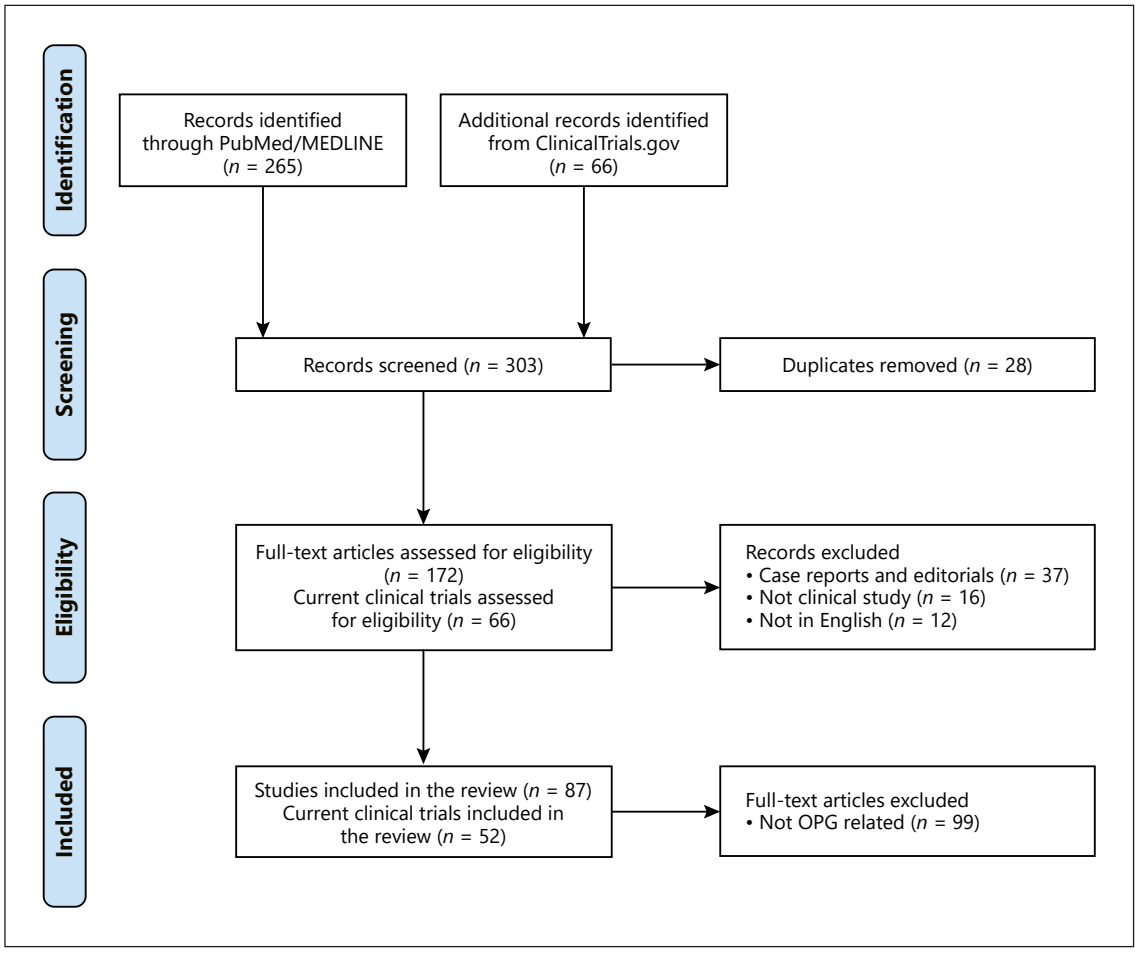

Fig. 1. PRISMA flowchart.

OPGs occur in patients <5 years old [5–8], arising from the pre-cortical visual pathways and involving the optic nerves, chiasm, optic tracts, and hypothalamus [9, 10]. Apart from visual impairment, the potential of OPGs to involve the supra- and parasellar areas is responsible for associated endocrinological disorders [10, 11]. Although their growth is generally slow, OPGs can behave unpredictably [4, 12].

Conventional treatment options historically have included chemoradiotherapy, surgical resection, and radiotherapy [13–21]. Nevertheless, recent advances in the field of neuro-oncology have led to a dramatically wider spectrum of cures, mainly through the refinement of epigenetics and techniques in regenerative medicine [12, 22–31].

Combined chemotherapy regimens, such as stereotactic and proton beam radiotherapy, and molecularly targeted agents, such as Ras blockers and antiangiogenetic inhibitors, are currently being evaluated in clinical trials and are showing promise for efficacy, safety, and treatment feasibility. However, their potential remains largely unknown or underestimated.

In this extensive literature review, we summarize the innovative therapeutic strategies for sporadic and NF1-related OPGs while analyzing the results of the clinical trials reported to date. We also discuss current trends and future perspectives.

Methods

We conducted an online literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. We accessed the PubMed and MEDLINE (https://pubmed.ncbi.nlm.nih.gov; accessed March 1, 2021) databases using the following Medical Subject Heading terms: "optic pathway glioma;" "visual pathway neoplasms;" "therapies, inves-

tigational;" "chemotherapy;" "radiation therapy;" "target therapy;" "angiogenesis inhibitors;" "Ras-related pathway inhibitors;" "mitogen-activated protein kinase pathway inhibitors;" and "mTOR inhibitors." The inclusion criteria for the selected articles were randomized trials, clinical studies, review articles, and meta-analyses written in or translated into English. We excluded case reports and editorials. We further sorted these studies on the basis of the best match and relevance inferred from the titles and abstracts.

On ClinicalTrials.gov (https://clinicaltrials.gov; accessed February 25, 2021), we searched the following keywords and phrases: "optic pathway glioma," "visual pathway glioma," and "optic pathway tumors." We reviewed the titles and abstracts, with no limits for study date, phase, or recruitment status. We excluded the duplicates.

The treatment endpoints, applied to quantify the therapeutic efficacy and survival measures, were the progression-free survival (PFS) and the overall survival (OS) both set at 2-, 3-, and 5 years. The radiological response was evaluated through the Response Assessment in Neuro-Oncology (RANO) criteria, systematized into 4 categories as follows: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Results

Literature Volume and Clinical Trials

Our literature search returned 265 records and 66 clinical trials identified through the PubMed or MEDLINE and the ClinicalTrials.gov databases, respectively. After removing the duplicates, 303 items remained, with 87 articles and 52 clinical trials. Figure 1 shows the PRISMA flowchart for the review, and the online supplementary Table 1 (see www.karger.com/doi/10.1159/000524873 for all online suppl. material) the PRISMA checklist.

Twenty (39%), 9 (18%), 17 (33%), 5 (10%), and one clinical trial were phase 1, mixed phases 1 and 2, phase 2, phase 3, and not available, respectively. Twenty (38%) were recruiting, 14 (27%) were completed, 11 (21%) were active and not recruiting, 3 (6%) were terminated, 3 (6%) were unknown, and 1 (2%) was withdrawn. Overall, 26 (50%) trials involved molecularly targeted therapies, 23 (44%) a combination of chemotherapy regimens, and 3 (6%) radiation therapy strategies (Fig. 2). Table 1 synthesizes the results of all the clinical trials on optic pathways.

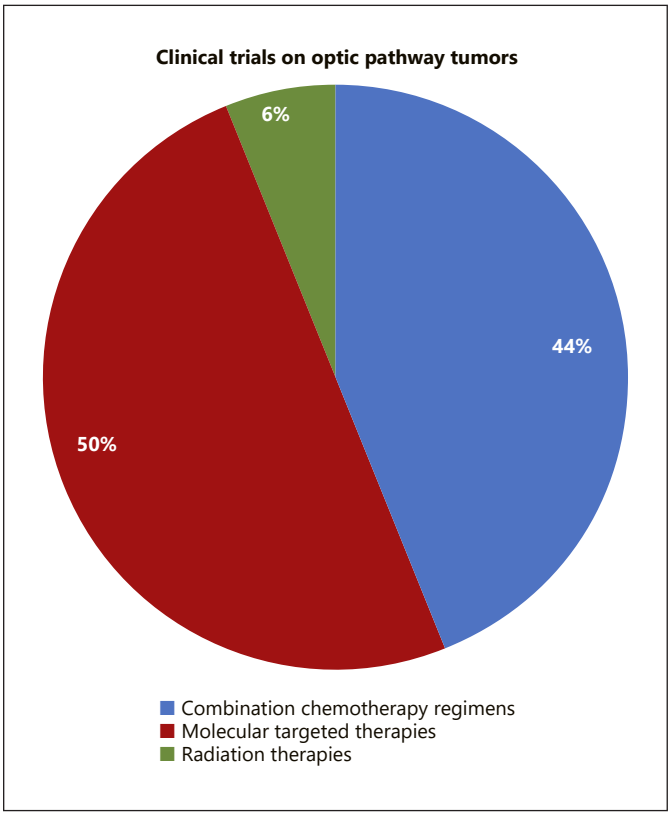

Fig. 2. Pie graph showing the incidence of the ongoing clinical trials on optic pathway tumors.

Combination Chemotherapy Regimens

Historically, the carboplatin-vincristine (CV) protocol has been considered the "gold standard" for chemotherapy of OPGs. In 1993, Packer and his team conducted a clinical trial with the aim to validate the CV therapy for OPGs in young children. Ninety-three percentage of treated patients did not experience a progression of the tumor (PD) [33]. A further study carried out in 1997, reported a 2-years PFS (2Y-PFS) of 75% and a 3Y-PFS of 68% for OPGs underwent CV therapy, without distinction between sporadic with NF1-related tumors [34].

Subsequent evidence and further clinical studies verified an average 5Y-PFS ranging between 35% and 50% and 69% for sporadic and NF1 OPGs, respectively. The protocol included 10 weeks of induction and 45 weeks of maintenance [33–37]. In the light of this background, CV therapy is the reference used to compare the most recent combined regimens.

Thioguanine, procarbazine, lomustine, and vincristine/vinblastine (TPCV) were proposed as alternatives to the standard approach. Randomized clinical studies employed the TPCV protocol for OPGs and reported an average 5Y-OS and 5Y-PFS of 52% and 39%, respectively [37, 38].

A phase 2 clinical trial tested the vinblastine as monotherapy for recurrent or refractory OPGs. The administration dose was 6 mg/m weekly for 1 year. 36% of patients achieved a CR and PR with a 5Y-OS of 93.2% and a 5Y-PFS of 42.3%. For the remaining patients, PD was

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Table 1. Clinical trials on optic pathway tumors

#	ClinicalTrials.gov identifier	Title	Phase	Status	Number of patients enrolled	Pathological conditions	Treatment	Country
1	NCT00003765	O6-benzylguanine and Carmustine in Treating Children with Refractory CNS Tumors	1	Completed	36	Brain and CNS tumors	O6-benzylguanine, carmustine	USA
2	NCT00503724	Enzastaurin in Treating Young Patients with Refractory Primary CNS Tumors	1	Completed	32	Brain and CNS tumors Neuroblastoma	Enzastaurin hydrochloride	USA
3	NCT01158300	PTC299 in Treating Young Patients with Refractory or Recurrent Primary Central Nervous System Tumors	1	Completed	28	Brain and CNS tumors	VEGF inhibitor PTC299	USA
4	NCT01273090	Imetelstat Sodium in Treating Young Patients with Refractory or Recurrent Solid Tumors or Lymphoma	1	Completed	34	Brain and CNS tumors Lymphoproliferative disorder	Imetelstat sodium	USA
5	NCT00623077	MT2004-30: Tomotherapy for Solid Tumors	1	Terminated	23	Brain and CNS tumors Retinoblastoma Sarcoma	Filgrastim, busulfan, etoposide, ifosfamide, melphalan, thiotepa, stem cell transplantation, mesna	USA
6	NCT00002944	Combination Chemotherapy in Treating Children with Progressive Brain Tumors	3	Completed	428	CNS tumors	Carboplatin, lomustine, procarbazine hydrochloride, thioguanine, vincristine sulfate	USA
7	NCT00002749	Carboplatin in Patients with Progressive Gliomas	2	Completed	25	Brain and CNS tumors	Carboplatin	USA
8	NCT00445965	Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients With Central Nervous System Cancer or Leptomeningeal Cancer	2	Active, not recruiting	78	Brain and CNS tumors Retinoblastoma, sarcoma	Iodine I 131 monoclonal antibody 3F8	USA
9	NCT03363217	Trametinib for Pediatric Neuro-oncology Patients with Refractory Tumor and Activation of the MAPK/ERK Pathway	1/2	Recruiting	150	LGG Plexiform neurofibroma CNS glioma	Trametinib	Canada
10	NCT00003015	Carboplatin Plus Vincristine in Treating Children and Adolescents with Low Grade Glioma	3	Unknown	200	Brain and CNS tumors	Carboplatin, vincristine sulfate, conventional surgery, radiation therapy	IT, UK, Germany
11	NCT00004078	Irinotecan in Treating Children with Refractory Solid Tumors	2	Completed	181	Childhood brain and CNS tumors	Irinotecan hydrochloride	USA
12	NCT00101270	Oxaliplatin and Irinotecan in Treating Young Patients with Refractory Solid Tumors or Lymphomas	1	Completed	24	Childhood brain and CNS tumors	Irinotecan hydrochloride, oxaliplatin	USA
13	NCT00326664	AZD2171 in Treating Young Patients with Recurrent, Progressive, or Refractory Primary CNS Tumors	1	Completed	55	Childhood brain and CNS tumors	Cediranib maleate	USA
14	NCT00012181	Flavopiridol in Treating Children with Relapsed or Refractory Solid Tumors or Lymphomas	1	Completed	30	Childhood brain and CNS tumors	Alvocidib	USA
15	NCT00638898	Busulfan, Melphalan, Topotecan Hydrochloride, and a Stem Cell Transplant in Treating Patients with Newly Diagnosed or Relapsed Solid Tumor	1	Active, not recruiting	25	Brain and CNS tumors	Busulfan, melphalan, topotecan hydrochloride, filgrastim	USA
16	NCT00929903	Pazopanib Hydrochloride in Treating Young Patients with Solid Tumors That Have Relapsed or Not Responded to Treatment	1	Completed	55	Childhood brain and CNS tumors	Pazopanib hydrochloride	USA
17	NCT00994500	Vorinostat and Bortezomib in Treating Young Patients with Refractory or Recurrent Solid Tumors, Including Central Nervous System Tumors and Lymphoma	1	Completed	20	Childhood brain and CNS tumors	Vorinostat, bortezomib	USA
18	NCT01088763	Gamma-Secretase Inhibitor RO4929097 in Treating Young Patients with Relapsed or Refractory Solid Tumors, CNS Tumors, Lymphoma, or T-Cell Leukemia	1	Terminated	129	Childhood brain and CNS tumors	Gamma-secretase/notch signaling pathway inhibitor RO4929097, dexamethasone	USA

Table 1 (continued)

#	ClinicalTrials.gov identifier	Title	Phase	Status	Number of patients enrolled	Pathological conditions	Treatment	Country
19	NCT02780804	Entinostat in Treating Pediatric Patients with Recurrent or Refractory Solid Tumors	1	Active, not recruiting	36	Brain stem neoplasm, pineal region neoplasm, recurrent/refractory malignant solid neoplasm Recurrent/refractory primary CNS neoplasm Recurrent/refractory visual pathway glioma	Entinostat	USA
20	NCT02415153	Pomalidomide in Treating Younger Patients with Recurrent, Progressive, or Refractory Central Nervous System Tumors	1	Active, not recruiting	29	NF1, recurrent childhood brain stem glioma, recurrent childhood visual pathway glioma Recurrent/refractory primary CNS neoplasm	Pomalidomide	USA
21	NCT01089101	Selumetinib in Treating Young Patients with Recurrent or Refractory Low-Grade Glioma	1/2	Active, not recruiting	220	LGG, recurrent childhood pilocytic astrocytoma, recurrent/refractory NF1, recurrent/refractory visual pathway glioma, NF1	Selumetinib	USA
22	NCT03871257	A Study of the Drugs Selumetinib Versus Carboplatin/Vincristine in Patients with Neurofibromatosis and Low-Grade Glioma	3	Recruiting	290	LGG, NF1, visual pathway glioma	Carboplatin, selumetinib sulfate, vincristine sulfate	USA
23	NCT03326388	Intermittent Dosing of Selumetinib In Childhood NF1 Associated Tumors	1/2	Recruiting	30	NF1, plexiform neurofibroma, optic nerve glioma	Selumetinib	UK
24	NCT01338857	Sorafenib in Children and Young Adults with Recurrent or Progressive Low-Grade Astrocytomas	2	Terminated	12	NF1, recurrent or progressive OPG, recurrent or progressive LGG	Sorafenib	USA
25	NCT01260103	Phase 3 Study of ANP Therapy versus TMZ for Optic Pathway Glioma	3	Withdrawn	0	Optic nerve glioma	TMZ, ANP therapy	NA
26	NCT01553149	Low-Dose or High-Dose Lenalidomide in Treating Younger Patients with Recurrent, Refractory, or Progressive Pilocytic Astrocytoma or Optic Pathway Glioma	2	Active, not recruiting	75	NF1, recurrent childhood pilocytic astrocytoma, recurrent childhood visual pathway glioma	Lenalidomide	USA
27	NCT00003477	Antineoplaston Therapy in Treating Children with Visual Pathway Glioma	2	Completed	12	Visual pathway glioma	Antineoplaston therapy (atengenal + astugenal)	USA
28	NCT02343224	Pegylated Interferon ALFA-2b in Children with Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas	2	Recruiting	20	Juvenile pilocytic astrocytomas, OPGs	Pegylated interferon alpha-2b	USA
29	NCT01331135	Aflac ST0901 CHOANOME – Sirolimus in Solid Tumors	1	Completed	18	Childhood brain and CNS tumors	Sirolimus	USA
30	NCT04238819	A Study of Abemaciclib (LY2835219) in Combination with Temozolomide and Irinotecan and Abemaciclib in Combination with Temozolomide in Children and Young Adult Participants with Solid Tumors	1	Recruiting	60	Relapsed solid tumor Refractory solid tumor	Abemaciclib, irinotecan, TMZ	USA
31	NCT02124772	Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects with Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects with Cancers Harboring V600 Mutations	1/2	Active, not recruiting	139	Cancer	Trametinib, dabrafenib	USA
32	NCT02684058	Phase II Pediatric Study with Dabrafenib in Combination with Trametinib in Patients with HGG and LGG	2	Recruiting	142	Brain and CNS tumors	Dabrafenib, trametinib, carboplatin, vincristine	USA
33	NCT01734512	PNOC 001: Phase II Study of Everolimus for Recurrent or Progressive Low-grade Gliomas in Children	2	Active, not recruiting	65	Pediatric recurrent progressive LGGs Pediatric progressive LGGs	Everolimus	USA
34	NCT03871257	A Study of the Drugs Selumetinib versus Carboplatin and Vincristine in Patients with Low-Grade Glioma	3	Recruiting	220	Astrocytoma LGG	Carboplatin, selumetinib sulfate, vincristine sulfate	USA
35	NCT04185038	Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	1	Recruiting	70	Brain and CNS tumors	SCRI-CARB7H3(s); B7H3-specific CAR T cel	USA

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Table 1 (continued)

#	ClinicalTrials.gov identifier	Title	Phase	Status	Number of patients enrolled	Pathological conditions	Treatment	Country
36	NCT02372409	Using MRI-Guided Laser Heat Ablation to Induce Disruption of the Peritumoral Blood-Brain Barrier to Enhance Delivery and Efficacy of Treatment of Pediatric Brain Tumors	2	Recruiting	12	Brain and CNS tumors	Doxorubicin, etoposide	USA
37	NCT01748149	Vemurafenib in Children with Recurrent/Refractory BRAF Gene V600E (BRAFV600E)-Mutant Gliomas	1	Active, not recruiting	40	Pediatric recurrent/refractory BRAFV600E-mutant gliomas	Vemurafenib	USA
38	NCT03206021	COZMOS: Phase I/Ib Trial of Combined 5′ Azacitidine and Carboplatin for Recurrent/Refractory Pediatric Brain/Solid Tumors	1	Recruiting	46	Recurrent childhood CNS tumor, ependymoma, recurrent childhood, childhood solid tumor	5 azacytidine	USA, Australia
39	NCT03245151	Study of Lenvatinib in Combination with Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors	1/2	Recruiting	120	Recurrent and refractory solid tumors	Lenvatinib, everolimus	USA
40	NCT02840409	Vinblastine +/– Nevacizumab in Children with Unresectable or Progressive Low-Grade Glioma (LGG)	2	Recruiting	150	LGG	Vinblastine, bevacizumab	USA
41	NCT03698994	Ulixertinib in Treating Patients with Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders with MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial)	2	Recruiting	49	Brain and CNS tumors	Ulixertinib	USA
42	NCT02839720	Selumetinib in Treating Patients with Neurofibromatosis Type 1 and Cutaneous Neurofibroma	2	Recruiting	24	Cutaneous neurofibroma, NF1 Optic nerve glioma	Selumetinib	USA
43	NCT03330197	A Study of Ad-RTS-hIL-12 + Veledimex in Pediatric Subjects with Brain Tumors Including DIPG	1/2	Recruiting	45	Pediatric brain tumor DIPG	Ad-RTS-hIL-12, oral veledimex – arm 1 (pediatric brain tumor), oral veledimex – arm 2 (DIPG)	USA
44	NCT04065776	Evaluation of Hippocampal-Avoidance Using Proton therapy in Low-Grade Glioma	NA	Recruiting	74	Childhood brain and CNS tumors	Hippocampal-avoidance proton therapy	USA
45	NCT01288235	Proton Radiotherapy for Pediatric Brain Tumors Requiring Partial Brain Irradiation	2	Active, not recruiting	100	Brain and CNS tumors	Proton radiotherapy	USA
46	NCT01188096	A Trial of Poly-ICLC in the Management of Recurrent Pediatric Low-Grade Gliomas	2	Unknown	23	Brain tumors	Poly ICLC	USA
47	NCT03194906	Memantine for Prevention of Cognitive Late Effects in Pediatric Patients Receiving Cranial Radiation Therapy for Localized Brain Tumors	2	Recruiting	50	Glioma of brain, craniopharyngioma, ependymoma, germ cell tumor	Memantine	USA
48	NCT02285439	Phase I/II Study of MEK162 for Children with Ras/Raf Pathway Activated Tumors	1/2	Active, not recruiting	105	LGGs, malignant neoplasms, brain, soft tissue neoplasms	MEK162	USA
49	NCT04201457	A Trial of Dabrafenib, Trametinib and Hydroxychloroquine for Patients With Recurrent LGG or HGG With a BRAF Aberration	1/2	Recruiting	75	LGG of brain with BRAF aberration HGG of the brain with BRAF aberration LGG of brain with NF1	Dabrafenib, trametinib, hydroxychloroquine	USA
50	NCT03429803	TAK-580 In Gliomas and Other Tumors	1	Recruiting	53	LGG	TAK-580	USA
51	NCT01661400	Anti-Angiogenic Therapy Post Transplant (ASCR) for Pediatric Solid Tumors	2	Recruiting	12	Glioma, neuroectodermal tumors, primitive Wilms tumor, rhabdomyosarcoma, sarcoma, Ewing, osteosarcoma, retinoblastoma	Metronomic cyclophosphamide, thalidomide	USA
52	NCT01837862	A Phase I Study of Mebendazole for the Treatment of Pediatric Gliomas	1/2	Unknown	36	Brain and CNS tumors	Mebendazole, vincristine, carboplatin, TMZ, bevacizumab, irinotecan	USA

CAR, chimeric antigen receptor; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; ERK, extracellular signal-regulated kinase; HGG, high-grade glioma; IT, Italy; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; NF1, neurofibromatosis Type 1; TMZ, temozolomide; UK, United Kingdom; USA, United States of America; VEGF, vascular endothelial growth factor; OPG, optic pathway glioma.

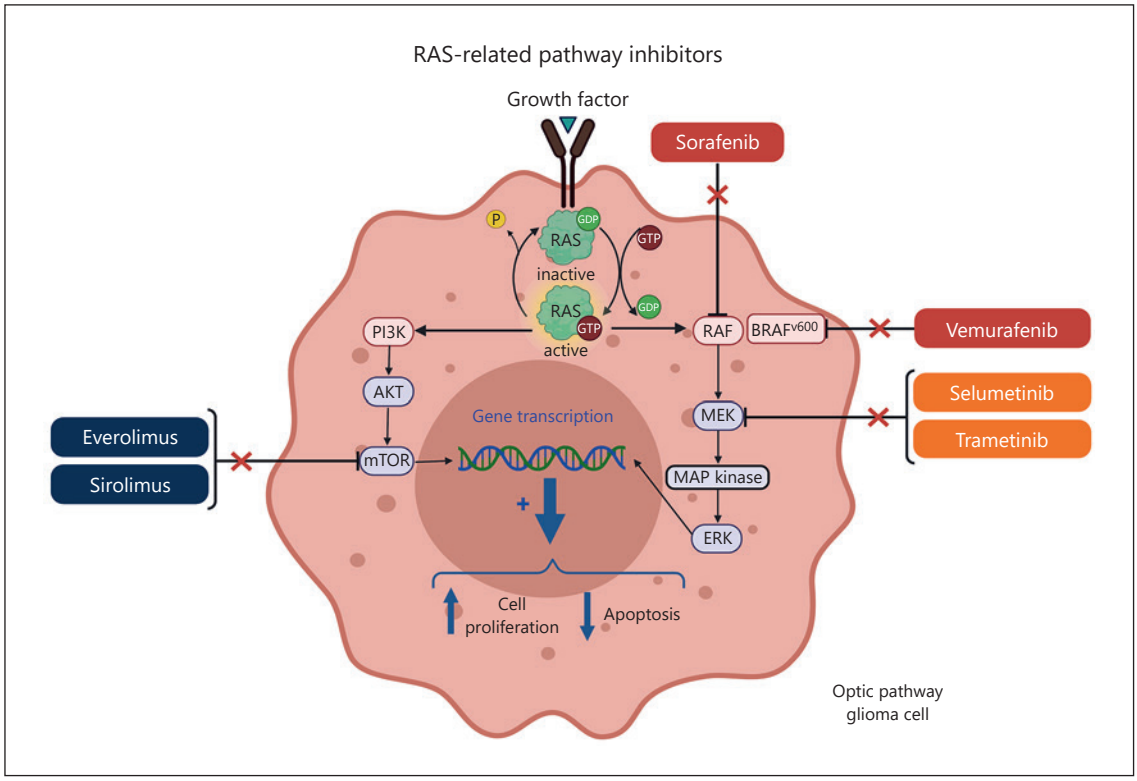

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Fig. 3. Mechanism of action of Ras-related pathway inhibitors. AKT, protein kinase B; ERK, extracellular signal-regulated kinase; GDP, guanosine 5′-diphosphate; GTP, guanosine 5′-triphosphate; MAP, mitogen-activated protein kinase; MEK, mitogen-activated protein; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase.

reported [39]. Additional study purposed the sole vinblastine for refractory OPGs in childhood. The protocol was effective in 87% of patients, in which PR, CR, and SD were reported, with a 5Y-OS and 5Y-PFS of 94.4% and 53.2%, respectively. An improvement in the visual field was seen in 20% of cases [40].

Cisplatin plus etoposide (CE) was also suggested for sporadic and NF1 unresectable OPGs. After 10 months of treatment, CR was encountered in 70% of patients with a 3Y-PFS of 80% [41].

Conversely, thalidomide, lenalidomide, and pomalidomide were tested unsuccessfully in recurrent pediatric OPGs (#NCT01661400, #NCT01553149, #NCT024151-53). In addition, nitrogen mustards, such as the intravenous carmustine (#NCT00003765) and the oral lomustine (#NCT00002944), temozolomide (#NCT01260103, #NCT01837862, #NCT04238819), irinotecan (#NCT-00004078, #NCT00101270), filgrastim, busulfan, melphalan, and thiotepa (#NCT00623077, #NCT00638898), are under investigation as monotherapies or in combinations.

Molecular Targeted Therapies

Ras-Related Pathway Inhibitors

The Ras/RAF/MEK/MAPK cascade was found to be upregulated in both sporadic and NF1-related OPGs, especially for the BRAFV600E mutants [42, 43]. Vemurafenib, a selective inhibitor of the BRAFV600E used in late-stage melanoma treatment, has been studied in a clinical trial on recurrent or refractory BRAFV600E-mutant pediatric gliomas (#NCT01748149) [44].

Selumetinib, an oral MEK inhibitor (MEKi), has been tested in some clinical trials for the treatment of low- or high-grade OPGs and NF1 neurofibromas (#NCT03326388, #NCT02839720, #NCT01089101). A hhase 1/2 study has examined selumetinib for use in young patients with recurrent or refractory OPGs (#NCT01089101) for dose-limiting toxicities (25 mg/m^2/dose) and radiological response. A recruiting phase 3 trial has compared selumetinib to the CV chemotherapy protocol (#NCT03871257). In April 2020, the overall results of these trials led to the U.S. Food and Drug Administration's (FDA's) approval of selumetinib for unresectable childhood NF1 tumors [45, 46].

Trametinib, another selective MEKi, has been tested as a monotherapy (#NCT03363217) or in combination with dabrafenib (#NCT02124772), hydroxychloroquine (#NCT04201457), and CV (#NCT02684058). Results remain unreported.

Sorafenib is a multitarget protein kinase inhibitor acting against B-RAF to prevent signal activation. One study, which terminated in February 2017, evaluated its efficacy in 12 patients with low-grade gliomas, including OPGs, and failed to demonstrate any positive effects (#NCT01338857).

Everolimus and sirolimus, Ras/phosphatidylinositol 3-kinase/AKT-mammalian targets of rapamycin (mTOR) blockers, are currently under investigation for pediatric progressive gliomas (#NCT01734512, #NCT01331135) [47]. A recruiting phase 1/2 clinical trial is testing the combination of everolimus and lenvatinib for the treatment of solid childhood central nervous system (CNS) tumors, including OPGs (#NCT03245151). Despite having a good safety profile, none of these have demonstrated a satisfactory increase in the OS and PFS rates. Figure 3 summarizes the mechanisms of the Ras-related pathway inhibitors used for OPGs.

Angiogenesis Inhibitors

Bevacizumab, a humanized selective monoclonal antibody that is the mainstay of the vascular endothelial growth factor (VEGF) inhibitors [48], has been approved by the FDA as a second-line treatment for malignant brain glioma, comprising OPGs [49–52]. Recent studies reported advances in survival and visual acuity after long-term treatment with bevacizumab in pediatric OPGs [53–56]. Hwang and colleagues [53] conducted a retrospective review on 14 low-grade gliomas, including OPGs. The patients' average age was of 5 years and bevacizumab-based treatment lasted 1 year. Twelve children responded to therapy in about 9 weeks [53]. In 2014, Avery et al. [55] reported an early gain of vision in 4 pediatric OPGs after bevacizumab administration. All patients fully recovered from visual symptoms [55]. Yamasaki et al. [56], in 2020, obtained encouraging advancements in the visual field after long-term bevacizumab administration. Bevacizumab de facto improved vision in 2 children affected by OPGs, independently from radiological response [56].

Furthermore, bevacizumab is on testing in many ongoing clinical trials. A recruiting phase 2 study is administering bevacizumab in combination with vinblastine for low-grade glioma treatment, involving unresectable OPGs. The estimated study completion date is in August 2026 and early improvements have already been verified in cases of reduced visual acuity (#NCT02840409). A phase 1/2 non-randomized clinical trial is studying the combination of bevacizumab and vincristine, carboplatin, temozolomide, and irinotecan for brain gliomas (#NCT01837862). Preliminary results showed a two-year PFS rate of 30–50% for OPGs. Bevacizumab-based therapy demonstrated strong antiangiogenic properties, decreased vascular permeability, arterial caliber, and tortuosity with improved visual symptomatology in >80% of cases. The estimated study completion date is in April 2023.

Cediranib and pazopanib target the vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, inhibiting all the proangiogenetic intracellular pathways; however, data for these remain unknown (#NCT00326664, #NCT00929903). Enzastaurin hydrochloride, which has been used in new trials on OPGs with positive but premature results, binds selectively to the protein kinase C, an intracellular mediator of the VEGF pathway, inhibiting glioma cell survival, proliferation, and abnormal angiogenesis (#NCT00503724). Figure 4 condenses the molecular pathways of the angiogenesis inhibitors tested for OPGs.

Radiation Therapies

Stereotactic radiosurgery and proton beam radiation therapy are under investigation in two ongoing clinical studies [57]. A recruiting phase 2 study is testing the feasibility of using proton therapy with low-grade optic gliomas (#NCT04065776). Another phase 2 trial is focusing on the assessment of the long-term neurological, endocrinological, and otologic sequelae in 100 children with brain tumors, including OPGs, treated with proton therapy. This study's estimated completion date is September 2022 (#NCT01288235).

Discussion

This review is an updated overview of the novel and most promising therapeutic strategies for pediatric newly diagnosed and recurrent or refractory OPGs. The choice of the most appropriate approach is still controversial. As recommended, treatment plans should be tailored to patient and tumor characteristics, as well as to clinical onset [58]. Treatment should be multidisciplinary, involving neurosurgeons, pediatricians, and oncologists. Management options include observation, chemotherapy, radiotherapy, and surgical resection [13, 14, 16, 17, 19, 21].

Clinical observation is the currently favored starting option. The "wait-and-see" strategy has been found to be

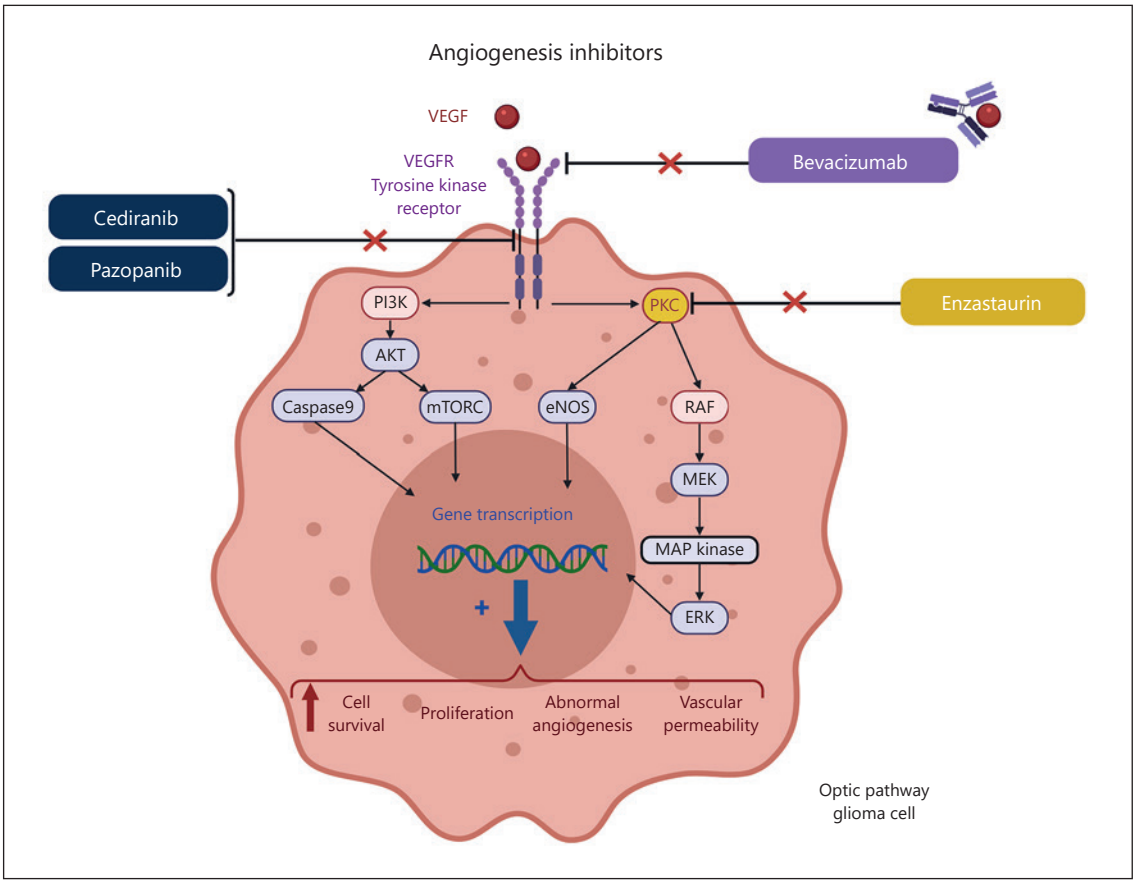

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Fig. 4. Mechanism of action of angiogenesis inhibitors. AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; MAP, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol-3-kinase; PKC, protein kinase C; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

successful, especially in NF1 and asymptomatic patients [1, 7, 20, 59–62]. Active interventions are not recommended in patients with NF1 because tumors are often multiple and rarely grow after the first decade [5, 63, 64]. In 2003, Astup et al. reported an excellent OS rate for 25 patients subject only to clinical observation, describing spontaneous radiological tumor regressions [65]. Conversely, rapid intervention is imperative for symptomatic patients with acute neurological onset, decline in visual acuity, and evidence of tumor progression.

CV chemotherapy regimen is considered as the first-line option when treatment is indicated [20]. In line with current indications, chemotherapy is suitable for patients who are <5 years old, symptomatic, and with radiological evidence of tumor progression [66]. Since 1993, Packer and colleagues [33] proved the first-line CV regimen to be effective in achieving tumor SD and CR/PR in more than 90% of cases, with a 3Y-PFS of about 70%. No differences in survival were detected between progressive sporadic and NF1-related OPGs. The only limit encountered was patients' age. Treatment was more effective in 5 years old or younger children, compared to older ones who showed a 3Y-PFS ranging between 39% and 21%. In a few cases, mild adverse effects were found like allergies and hematologic toxicity [33, 34, 62, 67].

In cases of glioma refractoriness or regrowth, second-line chemotherapeutic regimens should be planned after further updated pathological examination to confirm or rule out a malignant transformation. Several authors have reported combined multidrug chemotherapy as adjuvant agents for progressive or refractory OPGs, including vincristine, procarbazine, thioguanine, lomustine, and temozolomide [37, 39, 40, 68–71]. These drugs have failed to demonstrate favorable results, showing a 5Y-OS of 5%

and a 5Y-PFS lesser than 40% [3, 37, 72, 73]. In addition, chemotherapy is not free from side effects. Bone marrow suppression, long-term ototoxicity, and renal failures have been reported, risks directly proportional to the length of exposure [37–40, 74–76].

In 2002, Massimino et al. [41] proposed the CE combination as a second-line treatment for both sporadic and NF1 OPGs. They reported good results with a 3Y-PFS of 80% and significant improvements in visual symptoms [41].

In the past decade, the therapeutic trend for OPGs was toward the innovative molecular targeted therapies, as >50% of the clinical trials were based on the Ras-related pathway and angiogenesis inhibitors [12, 17, 21, 24, 26, 27, 77–81]. Among all the MEKi, selumetinib and trametinib have proven to have excellent efficacy profiles, especially for recurrent or refractory forms, with a two-year PFS rate of 70% [82]. However, MEKi has been associated with dermal toxicity, pneumonia, and gastrointestinal disorders, whereas selumetinib presents a risk of uveitis, eye neuropathy, and retinal detachment [83–87].

Therapeutic resistance represents a major challenge to this approach. The OPG microenvironment is supported by intense pathological neovascularization; VEGF and VEGFR are the basis of glioma aberrant angiogenesis [88–91].

Bevacizumab, the most widely tested antiangiogenetic agent, has been shown to be an excellent option for additional treatment in patients with refractory tumors and visual impairments [49–51, 53–56, 92]. Bevacizumab was demonstrated to improve the visual field, even in absence of imaging regression, presumably through anti-inflammatory and anti-vasculogenetic mechanisms, reducing the edema and hypertension within the optic pathway [4, 22, 55].

Accordingly, the first indication for monotherapy with bevacizumab is the decrease in visual acuity, exhibiting excellent results [53, 55, 56]. Nevertheless, sole bevacizumab did not prove to be effective for the glioma regression and radiological response, and it must be integrated into the standard chemotherapy line of treatment.

The timing of administration is still debated. Bevacizumab can be implemented in the chemotherapy regimen at any time, regardless of the treatment stage and the drug in use. After a first unsuccessful treatment course, patients may be re-treated with bevacizumab to enforce the long-term outcomes [93].

Ongoing clinical trials are aiming to establish the optimum doses and treatment schedules for pediatric OPGs to limit the potential adverse effects (#NCT02840409, #NCT01837862). The side effects of bevacizumab were hypertension, asthenia, and proteinuria, reported after about 3–6 weeks from the first administration [53, 94–97].

To sum up, our review found the TPCV and CE chemotherapeutic regimens, selumetinib and trametinib, and bevacizumab promising and effective innovative evidence-based approaches for OPGs. Other treatment strategies, proposed as an alternative to medical therapies, included radiation and surgery.

Since the 1950s, radiation therapy has been considered an elective treatment for OPGs, with up to 90% of patients having a 10-year PFS [98–101]. Radiotherapy is indicated as a neo- or adjuvant long-term treatment for OPGs in patients >10 years old and with evidence of PD [102, 103]. The main clinical trials on radiation therapy have reported an OS and 5Y-PFS of 80–85% and 80–100%, respectively [99–101]. Despite these findings, significant radiation-induced side effects, especially in children <7 years old, such as hormonal dysfunction, radio-induced tumors, vasculopathy, moyamoya disease, gliosis, and cognitive deterioration, have led to the search for new radiation strategies and sources [104–106].

Stereotactic radiation therapy, gamma knife therapy, and proton beam radiotherapy have recently been proposed to reduce these risks. All were tested in many clinical studies and demonstrated good results as adjuvant treatments for patients >10 years old with PD [57, 105, 107]. Proton beam radiotherapy is the most promising prospect, and two clinical trials are currently underway. A phase 2 study, with an estimated completion date in July 2028, is investigating the proton therapy for midline or suprasellar low-grade gliomas, including OPGs (#NCT04065776). A further trial is analyzing the efficacy of proton radiotherapy, 5 days a week, for low-grade gliomas. Dose-related endocrine dysfunctions, neurocognitive and auditory sequelae are additionally examined (#NCT01288235).

The current use of surgery for OPGs is declining and is considered only for extremely selected cases. Current surgical indications are the presence of acute symptoms, such as blindness, proptosis, pituitary, hypothalamic dysfunction, tumor mass effect, and acute hydrocephalus [18, 108, 109]. The rationale for surgery lies in the decompression of the optic pathways, symptom relief, and histological confirmation of the diagnosis. Apart from biopsy, shreds of literature evidence reported surgery did not improve patients' outcomes, even in cases of loss of visual function and glioma refractoriness to first-line chemotherapy [15, 110–112].

In 2006, Ahn and colleagues [113] reported a 17-year series of 33 patients with OPGs surgically treated, of which six were biopsied, and the remaining underwent gross- or near-total resection. These authors described a high rate of postoperative complications, such as worsening vision and cranial nerves palsy, without significant improvement in OS or PFS [113]. In 2008, Sawamura et al. [108] published the results of their surgical experience with 25 patients with OPGs and did not document a high benefit rate. In 2009, using a retrospective series of 133 patients, Nicolin and colleagues [114] proposed a combined treatment with surgical debulking and adjuvant radiochemotherapy, finding a better PFS for the latter, with an improvement in visual symptoms, as compared with surgery alone.

The future perspectives for OPG treatment are directed toward the progressive integration of standard treatment with new molecular targeted and antiangiogenetic therapies. Increasing the safety profile by limiting the possible side effects is another goal to achieve.

Limitations

This literature review has some limitations, including its retrospective nature and the heterogeneity of the patients recruited for the clinical trials. OPGs are low- and high-grade glioma subtypes, and not all the included studies were restricted to this category. Despite applying the PRISMA guidelines, this bias is the main weakness of this study. The majority of the trials included more than one medication, thus preventing conclusions about the role of every agent tested as a monotherapy.

Conclusion

Novel therapeutic strategies for OPGs include combination chemotherapy regimens, molecular targeted therapies, Ras-related pathway inhibitors, angiogenesis inhibitors, and radiation therapies. TPCV and CE have proved to be valuable options when compared with the conventional CV protocol. Selumetinib and trametinib are the most promising MEKi for recurrent or refractory OPGs, whereas mTOR inhibitors, such as everolimus and sirolimus, are still being evaluated. Bevacizumab has demonstrated an excellent efficacy and safety profile in counteracting the angiogenesis of other pediatric and adult CNS tumors. Stereotactic radiosurgery and proton beam radiation therapy have been tested to limit the radiation-induced side effects of conventional radiotherapies.

These findings establish a potential treatment trend that we defined as "The Novel T-Dimension" for OPGs. Future management perspectives, especially for recurrent or refractory OPGs, provide for the possibility of various combinations of therapies in a synergistic convergence. Additional clinical trials are essential to validate each of these new therapies.

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Statement of Ethics

The paper is exempt from Ethical Committee approval/written informed consent because neither approval of the Institutional Review Board nor patients' informed consent is required by the Ethics Committee of our institutions, namely, the University of Pavia, for a retrospective literature review.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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