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RESEARCH ARTICLE

Optic pathway gliomas in children: Clinical characteristics, treatment, and outcome of 95 patients in a single center over a 31-year period. Can we avoid radiotherapy?

Rejin Kebudi[1] | **Ulku Miray Yildirim**[1] | **Ayça İribaş**[2] | **Samuray Tuncer**[3]

[1]Division of Pediatric Hematology Oncology, Oncology Institute, Istanbul University, Istanbul, Turkey

[2]Department of Radiation Oncology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

[3]Department of Ophthalmology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Correspondence
Rejin Kebudi, Division of Pediatric Hematology Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey.
Email: rejinkebudi@yahoo.com

Abstract

Background: Optic pathway gliomas (OPG) are rare tumors in children. Lesion extent, visual functions, neurofibromatosis 1 (NF1), and age are factors that guide treatment. This study evaluates the clinical characteristics, treatment, and outcome of children and adolescents with OPG treated over a 31-year period in a single center.

Methods: Ninety-five patients with OPG diagnosed between January 1990 and December 2021 were retrospectively evaluated. First-line chemotherapy regimen consisted of vincristine and carboplatinum for 1 year. Radiotherapy was not used as first-line treatment and tried to be avoided in the ones who progressed after first-line treatment.

Results: Ninety-five children (44 male, 51 female) with a median age of 52 (1–216) months were evaluated. Sixty-three (66.3%) had NF1 and 10 (10,5%) diencephalic syndrome. The most common presenting symptoms were visual abnormalities and/or proptosis, nistagmus, and behavioral changes. Twenty-one (22.1%) patients with NF1 had stable disease throughout the follow-up period and received no treatment. Sixty-three of 74 patients received treatment at diagnosis and 11 due to progression during follow-up. Only one adolescent received radiotherapy at progression. Patients who progressed, received further line systemic treatment (vinblastine; bevacizumab; vincristine–cisplatinum–etoposide). Ten-year overall survival in all patients, in patients with NF1, and without NF1 were 97.2%, 98%, and 95.8% ($p > .05$), respectively; 10-year progression-free survival (PFS) in all patients, in patients with NF1, and without NF1 were 71.6%, 85.7%, and 54.2% ($p = .001$), respectively.

Conclusions: In children with symptomatic/progressive OPG, chemotherapy consisting of vincristine–carboplatinum (VC) is effective. Radiotherapy may be avoided, especially in patients with NF1.

Abbreviations: BV, bevacuzimab; CVE, carboplatin, vincristin, etoposide; DS, diencephalic syndrome; NF1, neurofibromatosis 1; OPG, optic pathway gliomas; OS, overall survival; PFS, progression-free survival; V, vincristine; VC, vincristine, carboplatin.

KEYWORDS
bevacizumab, chemotherapy, diencephalic syndrome, neurofibromatosis 1, optic pathway glioma, spinal metastasis

1 | INTRODUCTION

Optic pathway gliomas (OPG) constitute approximately 3%–5% of all central nervous system tumors in children.[1] Histologically, they are typically low-grade gliomas, and majority of them are pilocytic astrocytomas and may be located in the optic nerve, optic chiasm, hypothalamus, or retrochiasmal visual pathway.[2,3] Clinical signs and symptoms vary according to the localization of the tumor. Gliomas confined to the optic nerves cause visual abnormalities, proptosis, or exophthalmos. Chiasmatic-hypothalamic tumors may cause hydrocephalus, focal neurologic deficits, behavioral and intellectual changes, and endocrinological disorders such as panhypopituitarism and diabetes insipidus. Diencephalic syndrome (DS) may also be seen when the tumor extends to the hypothalamic area and has been suggested to be associated with frequent leptomeningeal involvement.[1,4,5]

OPG are the most common brain tumors among individuals with neurofibromatosis 1 (NF1), with a prevalence of about 15%–20%. In individuals with NF1, the increased susceptibility to develop malignancies, the potential risks associated with radiotherapy should be considered.[6] The OPGs may remain stable for several years, or may progress rapidly, resulting in severe morbidity and even mortality, occasionally they may even spontaneously regress.[1,7]

The use of chemotherapy as first-line treatment has become the mainstay of treatment with progressive or unresectable OPGs in young children. Radiotherapy has been used by some groups as the standard treatment in OPGs, especially in older children and adolescents. Many studies have demonstrated the late side effects of radiotherapy such as endocrinopathies, vasculopathies, neurocognitive disorders, and secondary malignancies, especially in patients with NF1, thus, radiotherapy has been recommended to be preserved for limited cases, especially in the younger age group.[8–11]

In this study, we aim to evaluate the demographic, clinical characteristics, treatment, and outcome of the children and adolescents with OPG treated in a single center with an institutional adapted protocol consisting of chemotherapy for symptomatic/progressive cases and avoiding radiotherapy, over a 31-year period.

2 | METHODS

Between January 1990 and December 2021, 95 patients with OPG younger than 19 years of age, diagnosed and treated at the Istanbul University, Institute of Oncology, were retrospectively evaluated. Their demographic and clinical characteristics, treatment details, and outcome were assessed (Table 1).

This clinical study was approved by the local ethics committee.

Presence of a tumor in the optic nerve or hypothalamus/optic chiasm was considered sufficient to make the diagnosis of OPG without histopathological diagnosis.[12]

Tumor location was classified according to Dodge criteria: stage 1: optic nerves only; stage 2: chiasm involved (with or without optic nerve involvement); and stage 3: hypothalamic involvement and/or other adjacent structures.[13]

Radiological assessment by cranial and orbital magnetic resonance imaging (MRI) with contrast were performed at diagnosis. A spinal MRI was performed at diagnosis for all patients with DS and those who had leptomeningeal disease in cranial MRI. Radiological response evaluation was performed in accordance with the International Society of Paediatric Oncology criteria.[14] Complete response (CR), partial response (PR), stable disease (SD), progression and/or relapse (PD) were noted in the files. CR was defined as no evidence of disease at the primary tumor site or of metastases. PR was defined as a reduction in size of all unequivocal residual tumor manifestations of more than 50% radiographically and no progression at any site and no appearance of new tumor lesions. SD was defined as a less than 50% reduction of residual tumor size measured radiographically, and no progression at any site and no appearance of new tumor lesions. Progression and/or relapse (PD) was defined as a more than 25% increase of tumor size radiographically or the emergence of new lesions. A more than 25% but less than 50% reduction in size, which was defined as SD in the SIOP criteria, was additionally noted as minimal response in our adapted institutional protocol.

Indications for systemic treatment were severe/progressive clinical sign and symptoms (such as DS, nystagmus, proptosis, visual impairment), and/or measurable radiologic tumor growth (confirmed by follow-up scans to exclude transient growth with SD afterwards). Threshold for treatment in visual impairment was less than 0.6 decimal confirmed by the ophtalmology department.

All asymptomatic cases were diagnosed during the surveillance of patients with NF1 and followed-up without treatment. NF1 was diagnosed with clinical criteria according to National Institutes of Health (NIH), which include the most frequent disease manifestations (cafe-au-lait macules, freckling, neurofibromas, and Lisch nodules), specific disease complications (OPG, sphenoid dysplasia, cortical thinning of long bones with/without pseudarthrosis), and a first-degree relative with NF1.[15]

First-line chemotherapy consisted of three cycles of induction consisting of vincristine (V) 1.5 mg/m^2/dose and carboplatinum (C) 550 mg/m^2/dose with 21 days of interval, followed by nine cycles consolidation with vincristine–carboplatin (VC) every 28 days for a total of 12 cycles. All patients were evaluated in the weekly multidisciplinary pediatric tumor board. Radiotherapy was not recommended as primary treatment in children, nor adolescents in our institutional protocol. In

TABLE 1 Details of the patients who progressed after first-line treatment.

Patient number	NF status (yes/no), age at diagnosis (months), Dodge classification (I, II, III)	First-line treatment	Time to first progression and second-line treatment	Time to second progression and third-line treatment	Time to third progression and fourth-line treatment	Latest status
1[a]	No, 87, III	STR+VC	10 m/VBL	9 m/SR+CVE	5 m/TMZ	Clinical and radiological stable disease, AWD
2	No,6, III DS	STR+VC	13 m/VBL	1 m/STR+CVE	20 m/CVE+BV	Clinical recovery, radiological partial remission, AWD
3	Yes, 37, I	VC	12 m/VBL			Clinical recovery, radiological stable disease, AWD
4	No, 41, I	VC	8 m/VBL			Clinical and radiological stable disease, AWD
5	No, 72, III	VC	21 m/VBL			Clinical and radiological stable disease, AWD
6	No, 103, I	VC	9 m/VBL			Clinical and radiological stable disease, AWD
7	No, 11, III	VC	10 m/VBL	12 m/CVE	32 m/VC+BV	Clinical recovery, radiological partial remission, AWD
8	No, 8, III, DS	VC	3 m/VBL+BV			Clinical recovery, radiological partial remission, AWD
9	Yes, 69, III	VC	31 m/STR+BV	12 m/STR		Clinical and radiological stable disease, AWD
10	No, 1, III, DS	VC	2 m/VC+BV			Gained weight, radiological partial remission
11	Yes, 37, III	SR	96 m/VC			Clinical recovery radiological stable disease, AWD
12	No, 72, I	VC	42 m/CVE, GTR			Clinical recovery, radiological partial remission, AWD
13	No, 60, III	STR+VC	50 m/CVE	2 m/BV		Clinical recovery, radiological partial remission, AWD
14	No, 52, I	VC	4 m/CVE			Improvement in vision, radiological stable disease, AWD
15	No, 192, I	VC	7 m/RT			Clinical and radiological stable disease, AWD
16	No, 8, II	VC	53 m/TMZ			Clinical and radiological stable disease, AWD
17[b]	Yes, 128, II	VC	9 m/TMZ	24 m/BV	12 m/NTZ	Clinical and radiological stable disease, AWD
18	Yes, 108, II	VC	42 m/STR			Clinical and radiological stable disease, AWD
19	Yes, 30, II, DS	VC	69 m/STR			Clinical and radiological progressive disease, DOD
20	Yes, 40, III	SR+VC	22 m/STR			Clinical and radiological stable disease, AWD
21	No, 178, III	VC	8 m/none			Clinical and radiological progressive disease, DOD

Abbreviations: AWD, alive with disease; BV, bevacizumab; CVE, cisplatin, vincristine, etoposide; DOD, dead of disease; DS, diencephalic syndrome; GTR, gross total resection; m, months; NTZ, nimotuzumab; RT, radiation therapy; SR, shunt replacement; STR, subtotal resection; TMZ, temozolomide; VBL, vinblastine; VC, vincristine, carboplatin.

[a]Underwent STR 4 months after cessation of TMZ.

[b]Also had LGG of the frontal lobe, which was resected and FMF. His vision deteriorted after 13 cycles of NTZ and received CVE. His vision was stable after 12 cycles of CVE.

case of further progression, weekly vinblastine; vincristine, etoposide, cisplatinum (CVE); and/or bevacizumab alone or in combination with chemotherapy were used as further treatment (Table 1).

The patients were evaluated by physical examination, complete blood count, and biochemical tests before each cycle. Tumor response was evaluated with an MRI, and in patients older than 5 years with visual field acuity testing.

The survival analysis was performed by the Statistical Package for Social Sciences (SPSS) version 13.0. The Kaplan–Meier analysis was used for evaluation of survival rates, and the log-rank test was used for comparing survival among the groups such as age, gender, disease stage. Overall survival (OS) was estimated as the time interval from the date of diagnosis to the date of death from any cause or time of latest follow-up. Progression-free survival (PFS) was defined as the time between the date of diagnosis and the date of first progression or death from any cause. Multivariate analysis for prognostic factors was performed with the Cox regression model.

3 | RESULTS

Between January 1990 and December 2021, among 720 patients younger than 19 years of age, diagnosed with central nervous system (CNS) tumors at the Istanbul University, Institute of Oncology, 95 (13.2%) were diagnosed with OPG. The median age of the 95 patients (44 male, 51 female) was 52 months (range: 1–216 months). Eleven patients (11,5%) were infants (≤12 months of age); 23 (24.2%) were 1–3 years old, 47 (49.5%) were 3–10 years of age, and 14 (14.7%) were ≥10 years old.

Sixty-three patients (66.3%) had NF1, and 10 had DS (10.5%). Two patients had spinal metastasis, both were infants and had DS. Histopathologic evaluation was available in a total of 17 patients; 14 patients had pilocytic astrocytoma, one pilomyxoid astrocytoma, and one neurocytoma, and in one no viable tumor was observed when operated due to progression and complication after chemotherapy (Table 1). Twelve of these had underwent biopsy/resection at diagnosis, the other five at progression.

According to Dodge classification, 27 (28.4%) had Dodge 1, 29 (30.5%) Dodge 2, and 39 (41.1%) Dodge 3 disease. Median follow-up time was 119.42 months (0.53–264 months).

Radiological response assessment was scheduled at Week 12 and repeated every 12 weeks and regularly thereafter.

Assessment of ophthalmological function was done in the ophtalmology department. The ophtalmologic response was noted in all the oncology files as "better, same, worse," depending whether the visual acuity was improved, stable, or detoriated.

Figure 1 shows the details of the initial management for the 95 patients. Twenty-one patients (all had NF1) were diagnosed with OPG under surveillance, and received no treatment since diagnosis and no progression was observed on follow-up.

The other 74 patients (42 had NF1) in the study received treatment either at diagnosis or at progression (59 chemotherapy only, 15 surgery ± chemotherapy). Of these 74 patients, 63 (85.1%) required treatment at diagnosis, and 11 (14.9%) received treatment due to clinical and/or radiological progression during their follow-up at a median of 37.2 (range: 7–163) months from diagnosis of OPG.

A total of four patients underwent surgical intervention without chemotherapy, one of whom underwent subtotal resection (STR) at diagnosis, and three (one gross total resection [GTR], one STR, and one ventriculoperitoneal shunt [VPS] replacement each) were subsequently treated due to progression on follow-up. Of these, the patient who underwent VPS replacement progressed at 96th month, he was given chemotherapy (VC), and clinical improvement was observed after chemotherapy.

A total of 70 patients received VC as chemotherapy (62 at diagnosis, eight at progression). The response to chemotherapy was as follows: 30 had clinical response (regression of proptosis, weight gain in DS, better vision), 34 were clinically stable, and six deteriorated. Radiological evaluation revealed partial response in 11 patients (including complete regression of leptomeningeal metastasis in one), SD in 50 patients (including SD in OPG and complete regression of leptomeningeal metastasis in one), and progressive disease in nine.

Of the 63 who had an indication for treatment at diagnosis, one underwent only STR and is under follow-up without any further treatment, 11 received chemotherapy after surgical intervention (three VPS replacemet, eight STR), and 51 received only chemotherapy. In 62 patients who received chemotherapy, radiological evaluation revealed improvement/partial remission in 10 patients, leptomeningeal metastases disappeared in two patients with DS, SD in 44, and progression in eight. Clinical findings improved in 28 out of 62 patients (45.2%), were stable in 29 (46.7%), and worsened in five (8.1%) (Table 1).

Eleven of the 74 patients (14.8%) who were under observation since diagnosis required treatment due to clinical deterioration with or without radiological progression during follow-up; three underwent surgery alone (one gross total resection [GTR], subtotal resection [STR], and ventriculoperitoneal shunt replacement [VPS] each), eight received chemotherapy alone. In these eight patients, vision improved in two patients, was stable in five, and vision deteriorated in one patient. Two of 11 patients needed further treatment due to progression on follow-up (Table 1, Patients 11 and 17).

Two patients died of progressive disease (35 and 70 months after diagnosis), one of whom had DS and the other patient who refused treatment after progression (Table 1, Patients 19 and 21).

Two patients with DS and spinal metastasis, had complete response of the spinal metastasis after chemotherapy (one after VC, the other after VC+bevacuzimab [BV]). Clinical response was evaluated in 74 patients who received treatment (chemotherapy and/or surgery): clinical improvement was observed in 30 (40.6%), stable clinical findings in 39 (52.7%), and deterioration in five patients (6.8%).

Clinical and/or radiological progression was observed in 21 of 74 patients (28.4%) at a median of 12 months (range: 2–96 months) and required further treatment after first-line treatment, as shown in Table 1. Out of these 21 patients, seven received vinblastine, one received vinblastine with bevacizumab, and in one patient with DS and spinal metastasis, who had clinical progression despite SD of the intracranial tumor on MRI, bevacizumab was added to her current

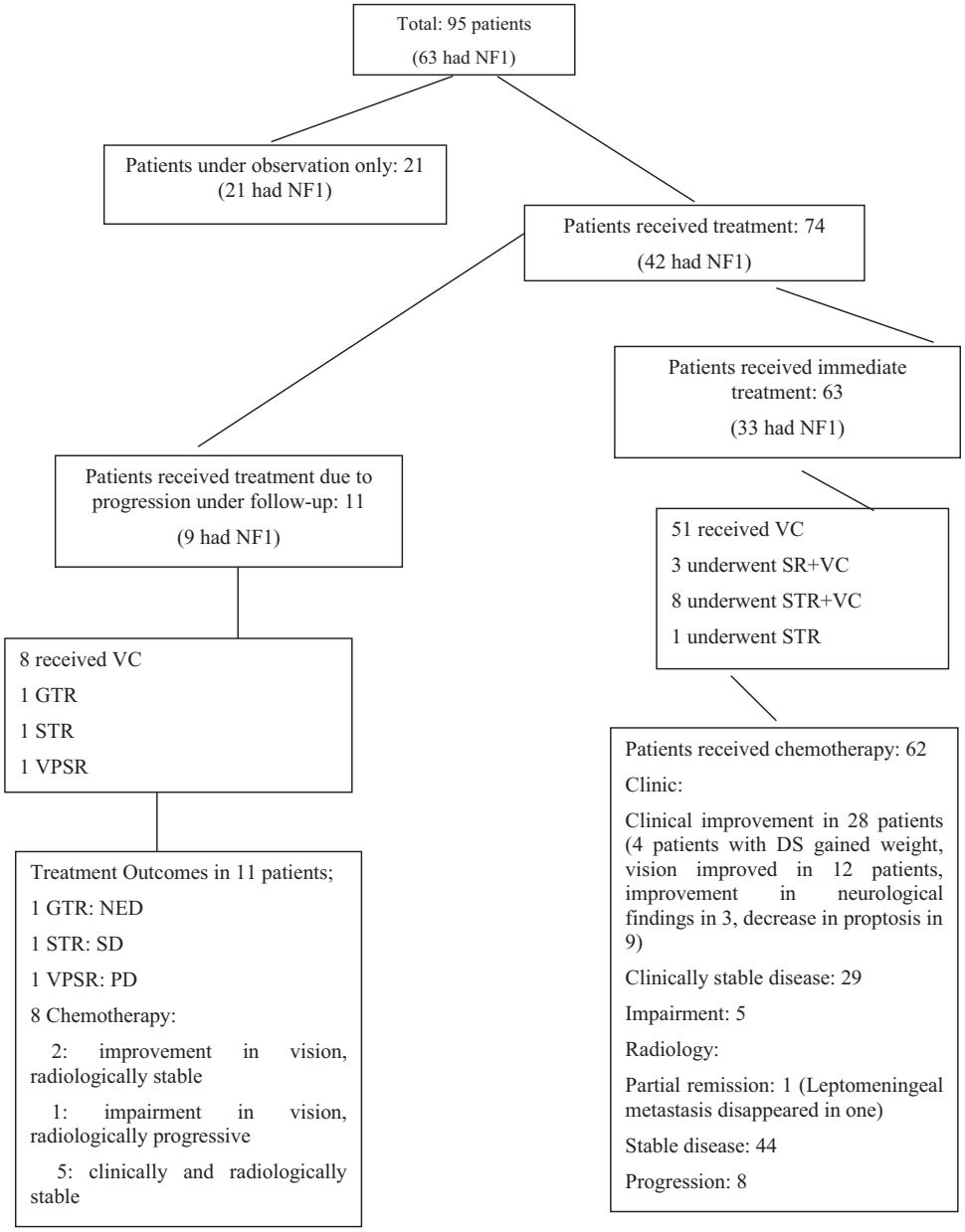

FIGURE 1 Details of the initial management for the 95 patients. NF1: neurofibromatosis type 1; SR, shunt replacement; STR, subtotal resection; GTR: gross total resection; VC, vincristine, carboplatin; VPSR, ventriculoperitoneal shunt replacement.

treatment. Two months after VC+BV treatment, significant clinical response (gained weight, neurological development improved) and radiological response were attained (partial response of the intracranial tumor and complete response of the spinal metastases) (Patient 10).

Of the seven patients who received vinblastine as second-line, three required further treatment on follow-up (VPS repalcement, STR, vincristine, cisplatin and etoposide [VCE], BV, temozolamide) (Table 1).

Three patients without NF1 received CVE as second-line treatment (Table 1, Patients 12–14). In 16 of the 21 patients who had progressive disease (76.1%), clinical and/or radiological improvement and/or SD status were achieved with second-line treatment and did not require further treatment. Five patients received third-line treatment and only one achieved clinical recovery with radiological partial remission, while the other four patients required further treatment due to clinical and/or radiological progression. Full visual acuity was achieved in one of the six patients who received CVE. Bevacizumab was used in a total of seven patients (two had NF1), and all obtained clinical and/or radiological response, only one (with NF1) experienced progression at 12 months (Patient 9). Radiotherapy was given (50.4 Gy) to only one adolescent patient with a tumor on the optic nerve at the intraconal level on the left side who had previously received chemotherapy at progression, resulting in clinical and radiologically SD, with no vision on the left before and after radiotherapy (Patient 15).

The 5- and 10-year OS were 98.8% and 97.2% for all patients, 100% and 98% for patients with NF1, 95.8% and 95.8% for patients without NF1 ($p > .05$).

The 5- and 10-year PFS of all patients were 82.9% and 71.6% and were significantly lower in patients without NF1 than in patients with NF1 (54.2% and 54.2% vs. 88% and 85.7%, respectively; $p = .001$).

Among the patients without NF1, the 5- and 10-year PFS of patients under 1 year of age or DS or metastatic was 41.7%.

Two patients with NF1 and OPG had concurrent brainstem gliomas (BSG) diagnosed radiologically. One of these patients who was under follow-up without treatment for OPG, showed regression in his OPG on follow-up; however, the BSG that was stable for years progressed after 12 years and he received chemotherapy (vincristine, carboplatinum) with minimal regression on MRI and significant clinical improvement. He graduated from high school. The other patient who had OPG and BSG has been under observation alone with no treatment and SD for 17 years, she graduated from university.

4 | DISCUSSION

OPG are rare tumors of childhood and constitute 3%–5% of all intracranial tumors.[1] Although they are frequently slow-progressing tumors and rarely spontaneous remissions have been reported, they may occasionally present with a rapid or irregular growth pattern.[17] Factors such as age at diagnosis, tumor location, and presence of NF1 have been suggested as prognostic factors.[18]

OPG are the most common central nervous system tumors in individuals with NF1, with a prevalance of about 15%–20%. Our center is a reference center for NF1-related tumors as well as neuro-oncology. Thus, the percentage of NF1 in our cohort of OGs (66% in our cohort) is high. A limited number of studies have shown significant differences between sporadic and NF1-related OPGs in regard to clinical manifestations and natural history. Increased intracranial pressure and decreased visual acuity at presentation are also more common in sporadic cases compared to cases with NF1, and therefore sporadic cases are more often symptomatic.[19] Consistent with the results of the study by Nicolin et al., all of the asymptomatic cases in our study that did not require treatment at diagnosis and during the follow-up period were individuals with NF1, and also the majority of patients (13 of 21 patients, 61.9%) who progressed after the initial treatment and required further treatment were without NF1, which indicates favorable effect of coexistance of NF1 on the disease course.[5]

OPGs can be managed with surgery, chemotherapy, radiotherapy alone, or with combinations of these treatment modalities; however, some cases may be followed-up with no treatment. Considering the various clinical manifestations of these tumors, balancing carefully the benefits of treating tumors that may lead to serious morbidities such as hydrocephalus and vision loss, and treatment-related long-term side effects, especially in patients with NF1, is crucial.[20]

Although gross total resection is a curative approach, and had been used more often in the past, it is often not possible nor recommended due to the location of these tumors and the possible morbidities. Primary surgical intervention is indicated in the presence of a tumor causing increased intracanial pressure or hydrocephalus.[21,22]

Radiotherapy has been used by some groups as the standard treatment in OPGs especially in older children and adolescents, with 10-year PFS rates reported between 69% and 89%. Many studies have demonstrated the late side effects of radiotherapy on the immature brain in younger children and the role of chemotherapy in the management of OPGs; but the adolescent age group is often not included in these studies. Considering that OPGs are low-grade tumors and long-term side effects of radiotherapy such as endocrinopathies, vasculopathies, neurocognitive disorders, and secondary malignancies, especially in patients with NF1, radiotherapy has been recommended to be preserved for limited cases especially in the younger age group.[8–11]

Chong et al. in a retrospective study from two centers in Canada, reported that among patients treated with chemotherapy, as first-line treatment or after prior nonchemotherapy treatment failure, the PFS of the adolescent age group (aged ≥10 years) was more favorable than that of children under 10 years of age, albeit nonsignificant statistically (PFS 62.9 vs. 38.9 months, $p = .16$). They recommended that chemotherapy shall be considered as first-line therapy in adolescents also, avoiding potential radiation-associated morbidities.[23] Similarly, in our institutional protocol, we have not used radiotherapy for children nor for adolescents as first-line treatment.

However, radiotherapy may be indicated for selected conditions such as nonresectable tumors when serious morbidity is expected in case of minimal growth, for tumors localized where the risk of treatment-related cognitive dysfunction is low, and in the presence of clinical/radiological progressive or disseminated disease for which even salvage chemotherapy may not be beneficial.[22,24,25] It has been demonstrated in some studies that early initiation of radiation therapy in the context of progressive disease is associated with stabilization or improvement in visual acuity. In a study investigating long-term visual acuity outcomes after radiation therapy for sporadic optic glioma, where all patients had their baseline visual acuity tested within 3 months before starting radiation therapy and were monitored for an average of 5 years, the 5-year cumulative incidence of visual acuity decline or improvement was around 17.9% versus 13.5% for the worse eye and 11.5% and 10.6% in the better eye, respectively. The authors concluded that these findings support the ongoing use of radiation therapy to prevent visual acuity deterioration, and emphasize its potential to enhance visual acuity in selected patients.[26]

Due to the potential morbidities associated with surgery and radiotherapy, the use of chemotherapy as first-line treatment has become the mainstay of treatment with progressive or unresectable OPGs. Although chemotherapy is not often curative in the treatment of OPG, the main goal is to stabilize or reduce the tumor size and improve clinical findings and PFS rates.[27]

Table 2 summarizes various chemotherapy regimens used over the past few decades. Packer et al. used vincristine and carboplatin therapy for the first time in a total of 78 patients with newly diagnosed progressive low-grade glioma (15 with NF1). The 2- and 3-year PFS rates were found to be 75% and 68%, respectively, and it was reported

TABLE 2 Summary of some pediatric studies using chemotherapy on optic pathway gliomas.

Reference (study title and/or country) chemotherapy regimen	Number of patients	PFS, % (years)		OS, % (years)
Packer et al.[28] VC	78	75 ± 6 (2)	68 ± 7 (3)	97 (3)
	15 (NF+)	79 ± 11 (2)		
	63 (NF−)	75 ± 6 (2)		
COG A9952[31]	274 (NF−)	45 ± 3.2[a] (5)		86 ± 3 (5)
CV arm	137	39 ± 4[a] (5)		86 ± 3 (5)
TPCV arm	137	52 ± 5[a] (5)		87 ± 7 (5)
HIT-LGG-1996[32]	1031	51% (5), 47% (10)		96 (5), 94 (10)
Chemotherapy arm	216	47 (5), 44 (10)		
Radiation therapy arm	147	65 (5), 62 (10)		
SIOP-LGG 2004[33]	497 (NF−)			
VC arm	249	46.1% (5)		89.2 (5)
VCE arm	248	45.3% (5)		88.8 (5)
Canadian phase II VBL[29]	54	53.2% (5)		94.4% (5)
	13 NF (+)	85.1% (5)		
	41 NF (−)	42% (5)		
BBSFOP[34]	148	71% (5), 58% (10)		96% (5), 90% (10)
	7 NF (+)			
	141 NF (−)			
Massimino et al.[16]	37	60 ± 9.6 (5)		86.4 ± 8 (5)
	7 NF (+)			
	30 NF (−)			
Our instutional protocol	59	70.4% (5), 70.4% (10)		98% (5), 9 5.3% (10)
	37 NF (+)	82.9% (5), 82.9% (10)		100% (5), 96.4% (10)
	22 NF (−)	46.8% (5), 46.8% (10)		93.3% (5), 93.3% (10)

Abbreviations: BBSFOP, Baby Brain protocol of the French Society of Pediatric Oncology; COG, Children's Oncology Group; CV, carboplatin and vincristine; EFS, event-free survival; HIT-LGG-1996, the Hirntumorstudien (HIT)-LGG-1996 protocol; NF, neurofibromatosis; OS, overall survival; PFS, progression-free survival; TPCV, thioguanine, procarbazine, lomustine, and vincristine; VBL, vinblastine; VC, vincristine, carboplatin; VCE, vincristine, carboplatin, etoposide.

that vincristine and carboplatin treatment had at least a delaying effect on radiotherapy, especially in the younger age group.[28] Chemotherapy protocols containing VC are still used most frequently. Vinblastin has been used as first-line treatment in Canada with considerably favorable results. With the various chemotherapy regimens that have been used over the past few decades, similar response rates were obtained as summarized in Table 2, with differences in terms of their side effect profiles such as carboplatinum allergy, vincristine neurotoxicity, and increased risk of secondary malignancy due to etoposide.[29]

There are several limitations of this study. This is a retrospective study over a long duration of time. The detailed ophtalmologic evaluations (visual acuity, visual fields, and other) could not be presented, similar to some other trials that have been done in the past decade as during the long time span of the study, detailed results were not always noted in the files; however, a note as better, stable, worse was noted in the files and those were considered in the clinical evaluation.

Considering the chronicity of the disease process, the treatment protocols to be used should be the most effective, the easiest to apply, and have the most tolerable side effect profile. Patients and families should be informed that the main aim is to improve clinical findings such as vision and achieve SD or response, which is mostly not a complete response. Recently, advances in molecular studies have led to the use of targeted treatment in some brain tumors as well as OPG such as antiBRAF medications and MEK inhibitors, which are promising.[30] In our cohort, only 17 had a histopathologic diagnosis. Recently, we began to do molecular studies on tumor specimens, of nine patients in whom we could do a molecular study, a pathogenic variant in which a targeted treatment is available was not found.

In this study, our institutional protocol with first-line chemotherapy with VC in symptomatic/progressive optic gliomas in children and adolescents, avoiding radiotherapy resulted in a high 10-year OS of over 95% in both, patients with NF1 or without. The use of further lines of systemic treatment (such as vinblastin, BV, vincristine–cisplatinum–etoposide) in 21 refractory/progressive patients has been effective in most, avoiding radiotherapy. The 10-year PFS was over 85% in patients with NF1 versus 54% in ones with no NF1. The outcome of the patients with DS or infants or metastasis was considerably better than in some large series.[31]

In conclusion, OPGs are indolent and slowly progressive tumors in children, but may cause serious morbidities. Chemotherapy has an important role in treatment. Clinical evaluation and visual examination along with radiological imaging are important in the decision to start and guide treatment. An adapted chemotherapy protocol consisting of VC for 1 year, which may be administered as ambulatory treatment, avoiding radiotherapy, as first-line treatment even in adolescents, is effective and tolerable, results in a high OS, and considerably high PFS. Considering that OPGs are low-grade tumors and long-term side effects of radiotherapy such as endocrinopathies, vasculopathies, neurocognitive disorders, and secondary malignancies, especially in patients with NF1, radiotherapy should be preserved for limited cases. Considering the slightly more aggressive clinical course in sporadic cases than in cases with NF1, individualized clinical and therapeutic approach should be established for each patient, especially if there is progression after first-line treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Rejin Kebudi https://orcid.org/0000-0003-4344-8174
Ulku Miray Yildirim https://orcid.org/0000-0003-0585-5123
Ayça İribaş https://orcid.org/0000-0002-1686-7114
Samuray Tuncer https://orcid.org/0000-0001-7491-8613

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