Visual outcomes after chemotherapy for optic pathway glioma in children with and without neurofibromatosis type 1: results of the International Society of Paediatric Oncology (SIOP) Low-Grade Glioma 2004 trial UK cohort

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ABSTRACT

Aims To report visual acuity (VA) outcomes following chemotherapy for optic pathway glioma (OPG) in children with or without neurofibromatosis type-1 (NF1) and to analyse associated risk factors.

Methods A prospective, multicentre, cohort study involving 155 children treated between September 2004 and December 2012. Initial and final VA was used for per-eye and per-subject analysis. Correlation tests were performed to determine whether initial VA predicted final VA. Logistic regression was used to determine whether age and tumour location were associated risk factors.

Results 90 children had complete ophthalmological data. At initiation of chemotherapy, 26% and 49% of eyes with NF1-OPG and sporadic OPG, respectively, had VA of ≥0.7 log of the minimum angle of resolution (logMAR). At final visit, per eye, 49% had ≤0.2, 23% had 0.30–0.60 and 28% had VA≥0.70 logMAR in the NF1-OPG group. In the sporadic OPG group, per eye, 32% had ≤0.2, 11% had VA 0.30–0.60 and 57% had ≥0.70 logMAR. Children with sporadic OPG, per eye, were significantly less likely to have VA outcomes ≤0.60 logMAR compared with children with NF1-OPG (OR=0.30; 95% CI 0.16 to 0.56; P<0.0001). Per subject, VA improved in 24%, remained stable in 35% and worsened in 41% of children with NF1-OPG and improved in 18%, remained stable in 43% and worsened in 39% of children with sporadic OPG.

Conclusions Children with and without NF1 demonstrated the same rate of VA improvement, stabilisation or worsening; however, children with sporadic OPG had a poorer VA outcome. Better initial VA, older age, absence of postchiasm tumour and presence of NF1 were associated with improved or stable VA outcomes.

INTRODUCTION

Optic pathway gliomas (OPGs) account for 5% of paediatric intracranial tumours.[1] Most children with OPGs have neurofibromatosis type 1 (NF1), the remainder being sporadic. Although studies report over 90% 5-year overall survival (OS) rates, children with OPGs can experience significant visual impairment.[2 3] Risk factors for long-term visual impairment include younger age and chiasm tumour location.[4]

The variable, unpredictable natural history of OPGs, including possible spontaneous regression, and poor correlation between MRI and visual acuity (VA) outcomes make management decisions challenging.[5–7] The Response Evaluation in Neurofibromatosis and Schwannomatosis Visual Outcomes Committee recommends that VA should be the primary outcome measure to assess for tumour progression, guide treatment decisions and evaluate treatment effect.[8]

The purpose of our study was to investigate prospectively the long-term visual outcomes following chemotherapy in a large cohort of children with OPG, with or without NF1, and to identify any associated risk factors in each group.

METHODS

The European Paediatric Brain Tumour Group has coordinated two international low-grade glioma (LGG) studies involving the UK childhood population.[9] The first LGG study was a registry study and recruited patients for observation or treatment. The LGG 2004 trial was the first prospective randomised trial in Europe designed to establish the level of progression-free survival (PFS) in childhood LGG. Children received extended chemotherapy for 18 months. Children with NF1-OPGs received vincristine and carboplatin (VC). Children with sporadic OPGs were randomised to either VC alone or with etoposide. The addition of etoposide to VC did not improve PFS or OS.[10]

One hundred seventy-three children with OPGs were enrolled from 21 UK paediatric oncology centres between 2004 and 2012 (Cancer Research UK trial number CRUK/05/012). Children were diagnosed with NF1 using established National Institutes of Health criteria. They were enrolled from the Multidisciplinary Neurofibromatosis Clinic at each site. All centres were asked to record VA outcomes prospectively at enrolment and throughout follow-up; however, this was not mandatory.

For the purpose of this study, data were extracted from the LGG2 database. This study was conducted in accordance with the Declaration of Helsinki and the UK's Data Protection Act. Inclusion criteria included (1) MRI evidence of an OPG, (2) treatment by chemotherapy and (3) complete

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ophthalmological follow-up and VA outcomes. Children who received prior chemotherapy or radiotherapy were excluded. Data included presenting clinical features, age at diagnosis, NF1 status and tumour location at the start of therapy. VA at diagnosis and VA at last follow-up were used for analysis. One of the challenges of monitoring VA in a paediatric clinical trial is that the preferred VA testing method changes as children get older. VA was measured using Teller Acuity Card grating acuity (Stereo Optical, Chicago, Illinois, USA) in children younger than 2½ years old or with cognitive or behavioural problems. Otherwise, distance VA was measured using a Snellen or logarithm of the minimum angle of resolution (logMAR) chart (letter or LEA symbol format). Although VA results between Teller acuity and optotype tests are not identical, there is reasonable correlation in children.[8 11] VA was converted to an eight-point scale: 8 representing good and 1 representing poor VA (online supplementary table 1).

VA outcomes per eye at initial and last follow-up were grouped into three categories: ≤0.2, 0.3–0.6 and ≥0.7 logMAR based on the standardised Pediatric Eye Disease Investigator Group scale for visual impairment.[12 13] At present, there is no validated definition of clinically significant VA change. Similar to previous OPG studies, we defined a significant VA response per eye (improvement or worsening) as a ≥0.2 change in logMAR from baseline.[8 14 15] For VA response per subject, if one eye improved and the other eye remained stable, the response was defined as improvement.[14] If one eye worsened, irrespective of the response of the other eye (improvement or stable), the response was defined as worsening.[14]

OPGs are predominantly benign pilocytic astrocytomas (WHO Grade 1 tumours) and generally do not transform to more malignant tumour phenotypes. Minimum requirements for cranial MRI at diagnosis included T2-weighted, T1-weighted and contrast-enhanced T1-weighted sequences and flair-attenuated inversion recovery. No additional imaging was required if the tumour was clearly arising from the optic nerve, tract and chiasm on MRI. MRI scans were assessed by neuroradiologists at each site, and all children randomised to chemotherapy had the images sent for central radiological review and tumour volume estimation. Unequivocal increase of tumour volume was a criteria to start therapy. Biopsy was not performed routinely if they presented with typical clinical and imaging features.

Tumour location was described by the Dodge classification: optic nerve alone (stage 1), optic chiasm±optic nerve (stage 2) and postchiasm (stage 3).[16] Imaging response was defined as complete (CR; no evidence of tumour), partial (PR; >50% reduction in tumour size), objective (OR; 25%–50% reduction in tumour size), stable disease (SD; <25% reduction in tumour size, no change in size or tumour enlargement of ≤25%) or progressive disease (PD; tumour growth >25% or the appearance of new lesions).[14] As pilocytic astrocytomas may have solid and cystic components, enlargement of the cystic component alone was not considered sufficient evidence of tumour progression.

Data entry and cleaning were performed in Microsoft Excel. Data analyses were performed using Stata V.14.1. Age was divided into two groups (≤5 and >5 years). Tumour location was divided into two groups (Dodge 1 and 2 and Dodge 3). Correlation tests (Pearson correlation coefficient, *r*) were performed to determine whether initial VA predicted VA at final assessment. Logistic regression was used to determine whether age at treatment and tumour location were associated with VA response and VA outcomes. Univariate analyses were first performed. Variables that were marginally significant (P≤0.2) were entered into a multivariate model. Analyses were performed separately for subjects with and without NF1 and were performed on a per-subject or per-eye basis.

RESULTS

One hundred and fifty-five children had MRI evidence of an OPG and received treatment by chemotherapy. Ninety children (180 eyes) with complete ophthalmological follow-up and VA outcomes were included in this study. Clinical characteristics of the study population are summarised in table 1. Forty-six children (59% female) had NF1-OPG and 44 children (43% female) had sporadic OPG. Dodge stage 3 tumours were associated with a younger age in both NF1 and sporadic groups (online supplementary figure 1).

VA loss was the most frequent indication to initiate therapy in both NF1 (n=34 eyes, 74%) and sporadic (n=39 eyes, 89%) groups. Sixty per cent (n=3) and 80% (n=4) of children in the NF1-OPG and sporadic OPG groups, respectively, with raised intracranial pressure also had vision loss as an indication for treatment. The median interval from enrolment to initiation of treatment was 28 days (range: 1–292 days). Average follow-up was 6.5 years (range: 2.0–10.2 years).

At initiation of chemotherapy, 26% and 49% of eyes in the NF1 and sporadic groups respectively had VA ≥0.7 logMAR (online supplementary table 2). At completion, in the NF1-OPG group, 49% of eyes had ≤0.2 logMAR, 23% of eyes had VA 0.30–0.60 logMAR and 28% of eyes had ≥0.70 logMAR. In the sporadic OPG group, 32% of eyes had ≤0.2 logMAR, 11% of eyes had 0.30–0.60 logMAR and 57% of eyes had ≥0.70 logMAR. Children with sporadic OPG, per eye, were significantly less likely to have a VA outcome of ≤0.60 logMAR compared with children with NF1-OPG (OR=0.30; 95% CI 0.16 to 0.56; P<0.0001). At completion, per subject, VA improved, remained stable and worsened in 24%, 35% and 41% of children with NF1-OPG and 18%, 43% and 39% of children with sporadic-OPG (tables 2 and 3).

There was strong correlation between initial and final VA in NF1-OPG (*r*=0.72) and very strong correlation (*r*=0.82) in sporadic OPG (online supplementary figure 2). Per eye, patients with initial VA ≤0.60 logMAR were more likely to have a final

Table 1 Baseline characteristics

	NF1 n = 46 (%)	Sporadic n = 44 (%)
Gender		
Female	27 (59)	19 (43)
Male	19 (41)	25 (57)
Age		
Median (months)	45	38
Range (months)	9–168	5–180
<2 years	6 (13)	10 (23)
2–5 years	25 (54)	20 (45)
>5 years	15 (33)	14 (32)
Dodge classification		
Stage 1	6 (13)	3 (7)
Stage 2	20 (43)	13 (30)
Stage 3	20 (43)	28 (63)
Indications for treatment		
VA loss (or threat to vision)	34 (74)	39 (89)
Neurological symptoms	5 (11)	10 (23)
Raised intracranial pressure	5 (11)	5 (11)

NF1, neurofibromatosis type 1; VA, visual acuity.

Table 2 VA response by age at time of treatment (per subject)

	NF1				Sporadic			
Age (yr)	N	Improved	Stable	Worse	N	Improved	Stable	Worse
<2	6	1	1	4	10	2	6	2
2 to 5	25	5	8	12	20	3	6	11
>5	15	5	7	3	14	3	7	4
Total	46	11	16	19	44	8	19	17

VA of ≤0.60 logMAR in both the NF1 (OR 23.3; 95% CI 6.345 to 85.668; P<0.001) and sporadic (OR 58.3; 95% CI 15.57 to 218.15; P<0.001) groups.

Age ≤5 years (OR 25.2; 95% CI 3.02 to 209; P=0.003) and Dodge stage 3 (OR 7.14; 95% CI 2.44 to 25.0; P<0.001) at presentation were associated with VA ≥0.70 logMAR on both univariate and multivariate analysis in the NF1 group. Age ≤5 years at presentation was significant (P=0.002) in the sporadic group (table 4).

Age ≤5 years and Dodge stage 3 were associated with worsening VA at final follow-up on both univariate and multivariate, per subject and per eye analysis in the NF1 group. Age ≤5 years (P=0.35 per subject; P=0.56 per eye) and Dodge stage (P=0.91 per subject; P=0.42 per eye) were not found to be significant in the sporadic group. (table 5).

There was poor correlation between imaging and VA outcomes (n=66). Twenty-two per cent of patients with improved imaging outcomes had improved VA, whereas 30% of patients experienced worse VA despite improved or stable imaging outcomes (online supplementary table 3).

DISCUSSION

This study examined VA outcomes in a prospective trial of chemotherapy for OPG in children with or without NF1. With an average follow-up of 6.5 years, VA improved or remained stable in 59% and 61% of children with NF1 and sporadic OPGs, respectively. Our data further support the use of systemic chemotherapy to slow down or arrest tumour growth and the decline of VA in both NF1 and sporadic OPGs.[4 14 17]

A range of 20%–70% of children with OPG affecting the chiasm or postchiasm pathways present with abnormal VA at diagnosis.[18 19] Kelly *et al* found that 25% of patients with bilateral OPG had normal VA at diagnosis.[15] In our study, 46% and 22% of eyes in the NF1 and sporadic groups, respectively, had VA ≤0.20 logMAR at diagnosis. Significant correlation between initial and last measured VA was found by Kelly *et al* (r^2=0.53, P<0.001) including a meta-analysis of data from 44 patients with bilateral OPG (r^2=0.45, P<0.001).[15] Both NF1 and sporadic OPG patients with a VA ≤0.60 logMAR were more likely to retain this level of vision (P<0.001) in our study.

Sporadic OPGs are more likely to present with progressive disease and associated vision loss than NF1-OPG.[12 14 20] Following treatment, 72% of children with NF1-OPG have improved or stable VA, whereas 74% of children with sporadic OPG have evidence of visual or tumour progression.[12 14] Thirty per cent of children with sporadic OPG present with VA ≥0.70 logMAR, two-thirds have long-term vision loss, 50% have severe unilateral vision loss (≥0.70 logMAR) and a quarter have severe bilateral vision loss.[12 20] In our study, at initiation, 49% of sporadic OPG eyes had VA ≥0.7 logMAR compared with 26% of NF1-OPG eyes. Fifty-seven of sporadic OPG eyes had a VA ≥0.70 logMAR at last examination. Although children with NF1 and sporadic OPG demonstrated the same VA response in our study, children with sporadic OPG had a poorer VA outcome. This suggests pre-existing visual damage, indexed by the higher rate of poor initial VA, limits visual outcomes despite chemotherapy.

Sixty-two per cent of NF1-OPG patients with postchiasm involvement have visual loss compared with 32% of patients whose tumours are limited to the optic nerves and chiasm.[19] Chiasm and postchiasm involvement is more common in sporadic OPG. Forty-five per cent and 60% of NF1-OPG and sporadic OPG patients presented with Dodge stage 3 tumours in our cohort. Postchiasm NF1-OPGs are significantly associated with a higher likelihood of VA loss despite chemotherapy.[14] In our NF1 cohort, children with Dodge stage 3 tumours were seven times more likely to experience worsening VA and a poor final VA outcome despite treatment. Wan *et al* found that postchiasm sporadic OPGs were associated with a worse visual outcome for the less severely affected eye but not with the more severely affected eye.[12] In our sporadic OPG cohort, posterior tumour extent was not found to be a significant prognostic factor.

Younger age is a poor prognostic factor.[3 4 12] The age of highest risk is variably reported as less than 1, 2 or 5 years.[3 14] Age <2 years or >5 years is associated with poor visual outcomes in NF1-OPG.[14] Age ≤5 years was associated with a poor visual response despite treatment in NF1-OPG in our study. Age ≤5 years at presentation was a significant risk factor for a poor visual outcome in our sporadic group but was not found to be significant for visual response.

Long-term progressive visual decline may be predicted by larger tumour volume at presentation, likely reflecting the severity of pre-existing visual pathway damage.[15] There is however increasing evidence that serial changes in VA do not reliably detect tumour progression and, conversely, tumour progression does not reliably correlate with decreased VA.[8 14 15] Previous studies found that 38% and 22% of NF1-OPG and sporadic OPG subjects, respectively, had concordant visual and imaging outcomes, and 53% of patients with a decrease in tumour volume did not experience long-term VA improvement.[14 15 20] In our cohort, 35% had concordant imaging and visual outcomes and 30% of patients with improved or stable radiological outcomes experienced worsening VA. Imaging outcomes do not always correlate with visual outcomes following treatment,

Table 3 VA response by tumour location at time of treatment (per subject)

	NF1				Sporadic			
Dodge	N	Improved	Stable	Worse	N	Improved	Stable	Worse
1	6	2	2	2	3	1	0	2
2	20	5	11	4	13	2	7	4
3	20	4	3	13	28	5	12	11

NF1, neurofibromatosis type 1; VA, visual acuity.

Table 4 Prognostic factors for a poor VA outcome (0.70 logMAR or worse)

	NF1-OPG			Sporadic OPG
	Univariate	Multivariate		Univariate
	P value	OR (95% CI)	P value	P value
Age ≤5 years	0.005	25.2 (3.02 to 209)	0.003	0.002
Dodge 3	0.001	7.14 (2.44 to 25.0)	<0.001	0.56

logMAR, logarithm of the minimum angle of resolution; NF1, neurofibromatosis type 1; OPG, optic pathway gliomas; VA, visual acuity.

Table 5 Prognostic factors for worsening VA (≥0.2 logMAR decline)

	NF1-OPG						Sporadic OPG	
	Per subject			Per eye			Per subject	Per eye
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Univariate
	P	OR (95% CI)	P	P	OR (95% CI)	P	P	P
Age ≤5 years	0.05	5.27 (1.04 to 26.7)	0.04	0.03	3.80 (1.10 to 13.2)	0.03	0.35	0.56
Dodge 3	0.006	7.14 (1.75 to 33.3)	0.006	0.001	5.56 (1.92 to 16.7)	0.002	0.91	0.42

logMAR, logarithm of the minimum angle of resolution; NF1, neurofibromatosis type 1; OPG, optic pathway gliomas; VA, visual acuity.

therefore therapeutic success should be based on visual rather than imaging endpoints.[8]

Some studies report unsatisfactory visual outcomes in both NF1 and sporadic OPG following chemotherapy.[20–22] A systematic review found that chemotherapy did not improve visual outcomes in 86% of children.[21] A 9-year follow-up study found that 67% had mild deterioration of VA.[15] These studies did not differentiate between patients with or without NF1. Although they suggest that visual loss prior to OPG treatment may be irreversible, a recent study found that 72% of children with NF1-OPG had stable or improved vision following chemotherapy.[14] In our study, per subject, 59% and 61% of children with NF1-OPG and sporadic-OPG, respectively, showed stable or improved VA.

The importance of early diagnosis and identification of signs of visual deterioration is well recognised.[20] Visual deterioration during therapy may reflect pre-existing damage prior to treatment rather than continued tumour progression.[14] Early treatment was initiated in both NF1 and sporadic groups; median time from diagnosis to initiation of treatment was 35 and 21 days, respectively, with 77% and 93% of subjects, respectively, receiving treatment within 1 year of diagnosis.

Although most patients in either group had improved or stable VA after chemotherapy, 41% and 39% of children, with and without NF1, respectively, experienced a decline in VA despite treatment. At last examination, 28% and 57% of eyes with NF1 and sporadic OPG, respectively, had VA ≥0.70 logMAR. These findings raise the question as to whether chemotherapy is effective in preserving vision; it may well be that treatment after a certain point of visual deterioration cannot prevent further decline.[20 23] Spontaneous regression of large, symptomatic OPGs without treatment is well recognised and has been suggested as a consideration to withhold initiating chemotherapy in patients with vision loss.[7 24] Deterioration in visual function, which is often taken as clinical evidence of tumour progression and used to justify treatment, may not necessarily be the case and could actually indicate tumour regression.[24] However, as chemotherapy has the potential to reduce vision loss and even restore vision in many cases, early treatment of recent visual loss prior to irreversible damage may result in better functional outcomes.[14 23]

The strengths of our study include a large sample and differentiation between patients with or without NF1 using defined visual outcomes and responses. Correlation tests were performed to determine whether initial VA predicted final VA. Logistic regression analysis was used to determine whether age and tumour location were significant risk factors.

Our study has limitations. Although the LGG2 trial was a prospective trial, it remains uncontrolled and was designed to establish the level of PFS. Although all participating centres were asked to document specific ophthalmology data prospectively, including VA outcomes, to be sent to the national data collecting centre, this was not mandatory. Ninety children with complete ophthalmological follow-up and VA outcomes were included in this study. Sixty-five children were excluded. The distribution of the risk factors evaluated in this study did not differ significantly between the included and excluded patients (online supplementary table 4). This suggests that our study population was representative of the source population. Selection bias may influence which sporadic tumours are brought to clinical attention compared with NF1-OPGs, which are actively sought for in NF1 patients during surveillance. Children with sporadic OPGs are more likely than those with NF1 tumours to have poorer VA at diagnosis and poorer long-term visual outcomes for despite high rates of therapy.[12 14]

In conclusion, although children with and without NF1 experienced the same rate of VA improvement, stabilisation or worsening, children with sporadic OPG had a poorer VA outcome. Better initial VA, increasing age, absence of postchiasm tumour and presence of NF1 were associated with better VA outcomes in our study. Although visual outcomes after chemotherapy are not optimal, timely treatment arrested the decline in VA in most children, and some children regained vision.

Collaborators Jack Gormley (Leeds Teaching Hospitals); Olwyn Nelson (Leeds Teaching Hospitals); Janice Hoole (Leeds Teaching Hospitals); Danielle Guy (Leeds Teaching Hospitals); Martha Campos (Cancer Research UK Clinical Trials Unit, Birmingham); Safoora Baig (Cancer Research UK Clinical Trials Unit, Birmingham).

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