Impact of systemic anticancer therapy in pediatric optic pathway glioma on visual function: a systematic review

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Abbreviations:

CEBM	Centre for Evidence-Based Medicine
CT	Chemotherapy
ICO	International Council of Ophthalmology
JBI-CA	Joanna Briggs Institute - Critical Appraisal tool
LGG	Low grade glioma
LogMAR	Logarithm of the minimum angle of resolution
MRI	Magnetic resonance imaging
MAPK	Mitogen Activated Protein Kinase
(M)DC	(Modified) Dodge Classification
NF1	Neurofibromatosis type 1
nNF1	No association with Neurofibromatosis type 1
OCT	Optical Coherence Tomography
OPG	Optic pathway glioma
OS	Overall survival
PFS	Progression-free survival
RNFL	Retinal nerve fiber layers
SAT	Systemic anticancer therapy
VA	Visual acuity
VEGF	vascular endothelial growth factor
VF	Visual field
VD	Ventricular drainage

Abstract:

Background: Systemic anticancer therapy (SAT) is the standard treatment for unresectable (progressive) pediatric optic pathway glioma (OPG), which can seriously affect visual function. New SAT modalities have been introduced the last decennium.

Methods: MEDLINE and EMBASE (Ovid) were searched for studies reporting on change in visual acuity and visual field after start of treatment with SAT for OPG (1990-August 2020).

Results: In 11 studies including 358 patients improvement of binocular VA was found in 0-45%, stability in 18-77% and decrease in 0-82% of patients. Considerable heterogeneity among included studies made a meta-analysis not appropriate. Studies on VEGF and MAPK signaling inhibition did not meet the eligibility criteria.

Conclusion. This systematic review suggests a positive impact of SAT on pediatric OPG. However, the wide ranges reported in efficacy of SAT and the observed heterogeneity highlight the need for prospective studies with uniform definitions.

1 Introduction

Optic pathway glioma (OPG) are considered a rare subtype of pediatric low grade glioma (LGG) located in the optic pathway from optic nerve to optic tract. OPG present on average at age of 3-9 year (range 0-17yr), either in association with neurofibromatosis type 1 (NF1) (incidence: 10-50%) or without NF1 (nNF1). Treatment is indicated in case of radiologic or clinical progression with significant visual deterioration or neurological symptoms [1], as OPG may remain stable in volume (presumed mostly NF1) or, rarely, regress spontaneously in case of NF1 OPG.

Regardless of the high rate of overall survival (OS) after treatment (91-100%), loss of visual function can be extensive with significant impact on the quality of life [2].

Systemic anticancer treatment (SAT), mostly chemotherapy, is considered the first choice treatment for progressive OPG, because surgery is often limited or not feasible due to the risk of damage of visual, neurologic or endocrine function [3]. As 35-65% of OPG progress during or after first line SAT, successive systemic treatment is often necessary [4]. Maximum delay in application of radiotherapy is preferred because of its long-term side effects, considering endocrine deficiencies, vasculopathy, and neurocognitive impairment [5-7]. Many different first or next line SAT regimens have been introduced since first results were published since 1976 [4, 8-11], with increased frequency from 1990 on. Initial therapy is

frequently carboplatin-based. The anti-vascular endothelial growth factor (anti-VEGF) agent bevacizumab was introduced since 2009 as next order treatment for progressive OPG [12], as angiogenesis plays a vital role in growth of LGG. Results on treatment outcome show a rapid radiological response with anecdotal profound visual improvement [13, 14]. Bevacizumab is globally not part of the standard of care for progressive pediatric OPG, as progression after discontinuation is frequent [14-16] and toxicity profiles are still being studied. Currently, the effect of targeted inhibition of the MAPK pathways is increasingly studied clinically on dose, treatment duration, effectiveness and toxicity [17-21].

Decrease of visual function, mostly more prominent than neurologic dysfunction, is frequently the leading indicator for start of treatment for OPG [22] and is often the main invalidating outcome parameter after treatment. As several studies, mainly on NF1 patients, have not found a correlation between radiologic response and change in visual function after SAT [22-24], focus on the effect of therapy on visual function is essential. Diverse components contribute to overall visual function, eg. central visual acuity (VA), visual field (VF), colour vision and contrast sensitivity. To date, VA is the only visual outcome parameter which has shown to be sensitive to change with treatment [23]. Visual field is assumed to mirror function of VA [23], but sufficient evidence is lacking to substantiate this statement.

In 2010, Moreno et al [25] published a systematic review to evaluate the effect of SAT on VA, which suggested a trend in improvement in 14%, stability of VA in 47% and decrease in 39% of patients after CT. No statistical analysis could be performed due to heterogeneity of included studies. The authors concluded an urge for standardisation of treatment indications.

In 1997 the NF1 OPG Task force consensus statement provided rational guidelines for diagnosis and treatment of OPG in NF1 [26]. Updates in 2007 and 2017 have added focus on visual function via VA measurement, which included proposal of usage of validated test modalities to measure VA suitable per age category and definitions of an age-base norm for normal VA [27-29]. To date, no consensus exists on the definition of change of VA as an outcome parameter to evaluate the effect of SAT for pediatric OPG. Therefore, the aim of this systematic review is twofold: 1) to evaluate the effect of SAT for OPG on VA and VF; 2) to evaluate the definitions on change in VA applied in studies on treatment of OPG with SAT.

2 Methods

2.1 Search Strategy

This study was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analyses) [30] and registered in the PROSPERO international prospective register of systematic reviews (reg. no. CRD42020125576).

A medical information specialist (JL) performed a comprehensive search of OVID MEDLINE and OVID EMBASE from January 1990 until August 5, 2020. Conference abstracts were excluded in EMBASE. Detailed searches for both databases are available (SUPPLEMENT TABLE 1 and 2). Reference lists and citing articles of included papers and relevant reviews were crosschecked for additional relevant studies.

Titles, abstracts and full−text articles were screened independently by two authors (CB and LW). Differences in opinion were resolved through discussion; if necessary, a third author (PS) was consulted.

2.2 Eligibility criteria

The primary endpoint of this review was the percentage and range of OPG patients with change of VA after SAT, divided in 3 categories: Improvement/ stability/ decrease of VA. The secondary endpoint was change in VF.

Studies were included when: 1) reporting on change of visual acuity in children (≤ 18 year) after receiving SAT for OPG; 2) including a minimum of 10 patients per study; 3) reporting any language, as long as the original authors were willing to translate their manuscript to English; 4) reporting on patients with or without surgical treatment (biopsy/ ventricular drainage (VD)/ tumor resection) prior to SAT. Studies containing results of patients that requiring additional therapy after SAT were also included.

Studies reporting on radiotherapy prior to SAT were excluded. When studies suggested overlap in study results, the study with most recent data was included.

2.3 Data collection

The following data were extracted: TABLE 1 and 2 present study characteristics, patient characteristics, variables regarding visual function and prognostic factors for decrease of VA and/or VF.

2.4 Critical appraisal

Assessment of methodological quality was performed in parallel by two authors (CB, PS). Study quality was weighed with the Oxford Centre for Evidence-Based Medicine (CEBM) evidence rating system. If studies were case series, the Joanna Briggs Institute Critical Appraisal (JBI-CA) tool for case series—"Checklist for Case Series" [31] was used, in which bias is evaluated in 10 questions answered with *yes, no* or *unsure*. As multiple included studies did not primarily focus on the effect of SAT, we performed critical appraisal pointed on the primary endpoint of this review. If no statistical analysis was performed, question 10 was evaluated as unsure. We considered a low risk of bias if the answers "yes" were ≥50%, a high risk of bias if the answers "no" were ≥50%, and uncertain risk of bias if the "unclear" answers were ≥50%.

2.5 Statistical Analysis

Study characteristics, patient characteristics and definition of change of VA and VF between start and after treatment with SAT were reported descriptively. Data regarding change of VA were reported as range (percentage) and cumulative proportion (number and percentage of change) (see discussion) are calculated.

3 Results

3.1 Search results

The search strategy identified a total of 818 studies. After full text evaluation, 11 studies were included. One study was excluded due to suggested overlap [32]. The PRISMA selection flowchart is presented in FIGURE 1.

3.2 Study, patient and treatment characteristics

All 11 included studies were case studies. The studies presented results of 1336 patients, of which 427 received SAT. Data for analysis of change in VA were available in 358 patients. Patient characteristics are presented in TABLE 1. Type of SAT, type of visual test and prognostic factors are shown in TABLE 2. In 6 studies NF1 status (77%) could only be extracted from the total study population (see TABLE 1), which also included patients not treated with SAT. Median/ mean age at start of SAT varied from 3.2-8 years (range 0.3-17.2 years).

All studies reported on start of treatment with first line SAT. Various SAT combinations were applied among studies (see TABLE 3), SAT regimes were carboplatin-based in 326 of 427 patients (76%). Studies on VEGF or MAPK signaling inhibition did not match inclusion criteria, due to study volume < 10 patients or outcome parameters not matching our inclusion criteria [13, 33].

3.3 Critical appraisal

All studies were judged as grade 4 evidence according to the Oxford CEBM [34]. Critical JBI-CA appraisal of all case series revealed 6 studies with a low risk of bias (see SUPPELEMENTARY TABLE 3).

The focus on change of VA as outcome parameter was variable among studies: 4 studies presented change of VA as primary or secondary outcome parameter [22-24, 35], in other studies change in VA was published as higher order outcome parameter, mainly accompanied by a lack of information on definition in change in VA.

194

195 **3.4 Outcome, definition and prognostic factors on change in visual function**

196 After treatment with SAT, 11 included studies (N=358) showed binocular improvement of VA within
197 the range of 0-45 %, stability in 18-77% and decrease of VA in 0-82%.

198

199 Within diverse studies *change of VA* contained a large diversity of variables:
200 All studies presented results on binocular change in VA. Four studies presented both binocular and
201 monocular change [23, 24, 35, 36] (see TABLE 3).
202 Five studies reported on change in binocular VA from start to within 3 months after end of SAT [23, 24,
203 35, 37, 38], of which 3 studies also published long term data [24, 35, 38]. Nine studies published long term
204 results (range median follow up: 2.2- 8 year after start of SAT (see TABLE 1)). In 6 of these 9 studies
205 tumor progression after 1th line SAT was registered: 86 of 159 patients (54%). Only in 2 studies
206 information was available for between-group analysis on progressed vs. non-progressed OPG, which
207 we did not perform as volumes were too small (18 of 30 progressed) and studies were non-comparable
208 [36, 39].
209 Change in VA was evaluated in patients with diverse anatomic tumor locations with no stratification
210 per anatomic location (see TABLE 1). Only Falzon et al. and Fisher et al. evaluated change of VA per
211 anatomic location of which the results are discussed below.

212

213 Change in VF was evaluated in 2 studies [23, 35]. Fisher et al. reported on outcome of VF in 26 patients:
214 19% improved, 38% remained stable, 42% decreased . Dodgshun et al. published 7/35 (20%)
215 abnormalities at diagnosis of which 2/ 7 (29%) improved after SAT and in 5/7 (71%) VF defects
216 persisted. Both studies did not report on the extent of VF loss, age of the tested population, type of VF
217 test and the definition of change in VF.

218

219 Four different definitions of change in VA were used in 4 studies (see TABLE 1). First, Fisher et al.
220 applied change $\leq = \geq 0.2$ Snellen lines [23] and second, Falzon et al. $\leq = \geq 0.2$ LogMAR [22]. We consider

these definitions as equal, as mostly similar VA cards in both studies were used, which are (partially) validated for conversion to the linear representation of VA: logarithmic minimum angle of resolution (LogMAR) and $\leq = \geq$ *0.2 in Snellen lines* is equal to $\leq = \geq$ *0.2 LogMAR*. In these 2 studies the time interval between starting point and evaluation highly varied (3 months after cessation of SAT [23]– median 6.5 year [22]). Third, change per ICO category (International Council of Ophthalmology: reporting visual loss in research [40]):change of 0.3 LogMAR per category. Fourth, change per category in the WHO Childhood Visual Impairment Scale: change of 0.4 LogMAR per category [24]. Seven studies applied no definition in change of VA, nonetheless reporting about its change.

Both Falzon and Fisher et al. performed uni- and multivariate analyses for prognostic factors on decrease of VA after SAT (see TABLE 2).

4. Discussion

This first systematic review in the past decade on the impact of SAT in the treatment of pediatric OPG on VA and VF, representing visual function, found improvement of binocular VA in 0-45%, stability in 18-77% and decrease in 0-82% of patient after median follow up after start of SAT of 3.7 year (range: cessation of SAT – 8.2 years).

SAT is currently widely applied for progressive pediatric OPG. More than a decade ago, Moreno et al. performed a systematic review on the effect of SAT on visual outcome (1990-2008) [25]. All included studies were of low methodologic quality and were highly heterogeneous. A cumulative decrease of VA after SAT was found in 38% of 174 patients. No analysis was performed on the definitions applied on change of VA/ VF. Stratification for anatomic location or NF1 status was impossible due to insufficient information. Our systematic review (search 1990-2020), shows a significant increase of the cumulative population (N=358). The urge in upgrading future study protocols persists, but additionally included studies show an increase in focus on the effect of SAT on visual function.

No international guidelines are available on the definition of significant change in visual function in the field of pediatric brain tumors. At present, in pediatric OPG studies, VA is accepted as the overarching parameter to represent visual function [41]. This review showed that no uniform definition on change of VA was applied so far, as 4 definitions were used in 4 studies and no definition was stated in 5 studies. International agreement on definition for change in visual function is necessary in the field of OPG, to produce comparable outcome parameters to evaluate effectiveness of therapy. We strongly support to implement the definition in change of VA $\leq$ or $\geq$0.2 LogMAR in future studies on pediatric OPG, already applied in protocols of ongoing studies [18].

We intended to perform cumulative analysis on the effect of SAT on visual function, which could not be justified in our opinion, as diverse variables as monocular/ binocular evaluation, anatomic location, definition in change of VA/ VF and term of follow up were highly disparate. We do understand that in

reviews cumulative proportions are a clinically preferred outcome parameter [25] used to inform patients and physicians. In case of coming towards clinicians' request, we suggest to stratify on a first variable, interval of follow up: cumulative analysis on 5 studies on VA change within 3 months after cessation of SAT, renders 27% improvement of VA (N=47), 52% stability (N=90) and 20% (N=20) of decrease of VA. Long term evaluation of 9 studies (follow up range 2.2–8 year) shows improvement in 19% (N=48), stability in 42% (N=105) and decrease in 39% (N=99). However, these percentages should be interpreted with caution.

A second variable contributing to the definition on change in VA, is the distinction on monocular or binocular analyses of VA. Clinical experience suggests that analysis of 1 or 2 eyes may differ in the course of OPG, as the anatomic location may result in an asymmetric burden on VA per eye. For example, in case of a unilateral optic nerve glioma (stage 1 (M)DC), monocular VA can seriously decrease due to progression of OPG, but as visual function of the other eye is not affected, binocular change in VA can be unaffected. In this review, monocular change was variably defined among studies, therefore outcome was non comparable. Future assessment of both monocular and binocular status should evaluate therapy effect through per-eye analysis and evaluate functional visual disability through 2 eye-analysis.

A third variable, anatomic location of OPG, requires stratified analysis as location of (NF1) OPG posterior to the chiasm appears to be a prognostic factor for decrease of VA after SAT [22, 23] and variety appears to exist in progression-free survival (PFS) among different anatomic locations [42].

The fourth variable contributing to the definition on change in VA, is age at start of treatment: The combination of ongoing natural development of childhood visual function and known risk factors for progression of OPG (age (<1 year [42]) or VA decrease after SAT (age < 5yr [22, 23]) require stratification for different age categories. In this review, age at start of treatment (median 3.2-8 year (range 0.4-17.2 year)) and duration of follow up after SAT (median 3,7 year (range 0-8,2 year)) widely varied. As

diverse studies applied different age categories and individual patient outcome data were limited, stratified analysis effect was impossible.

Optic pathway glioma located in the chiasm and optic tract mostly results in a combination of defects in central (VA) and peripheral vision (VF). In literature, both VA and VF are considered to mirror each other's function [23]. This assumption could not be substantiated in this review, as only 2 studies (33 patients) reporting on these parameters could not determine any association between VA and VF. In addition, definition on change of VF was lacking. Performing VF tests at young age (< 7 year) or children with limited cooperation is highly challenging with high risk for bias, which could explain the discrepancy between wide integration of VF examination in study protocols and low level of presentation of results [23].

As currently 2D volume changes on MRI are poorly predictive for visual function [22, 23], other forms of (more) objective examination like Optical Coherence Tomography (OCT) gain increased attention. OCT has proven to be a potent biomarker for visual loss in case of screening for (NF1) OPG [43]. Regarding monitoring treatment effect, retinal nerve fiber layers (RNFL) appear to be associated with change in visual function, however larger volume studies on correlation of change in VA and RNFL or ganglion cell layer-inner plexiform layer are required [43].

Since 2008 treatment options for recurrent pediatric OPG have expanded with VEGF and MAPK pathway inhibitors. In this systematic review regarding studies on the effect of SAT on VA change, these treatment modalities were not included as these series are still very small (<10 patients) [13, 44] or as outcome parameters had no focus on the effect of visual function. Future studies on the application of MAPK signaling inhibitors require attention to evaluate treatment effect in the field of visual function.

The findings of this review should be interpreted in light of several limitations. First, included studies presenting outcome on change in VA are highly heterogeneous regarding age at presentation, NF1

germline, combination of CT, tumor locations and VA outcome measures. The rarity as well as diversity of OPG characteristics make it difficult to perform high-quality prospective studies in this field.

Second, we included studies with surgical intervention prior to SAT, which may bias the effect on change in VA. Tumor resection or reducing intracranial pressure by VD can affect visual function and requires days to several months to evaluate this effect. In 5 studies, prior start of treatment, OPG had been resected, biopsied or VD had been placed (see TABLE 2 [11, 22-24, 35]). No information was available on the time interval after surgery, extension of resection or surgical effect on VA before start of SAT. Three studies presented no data on prior surgical therapy [9, 38, 45]. Only Shofty et al. excluded prior surgery. Surgical intervention frequently needs to be followed by short term start of SAT, limiting separate evaluation of the surgical effect on VA and creating bias on the effect on SAT on change in VA.

Third, in this review in 6 out of 9 studies long term follow up was presented including result on successive progression; 54% of OPG progressed of which a majority received sequential therapy of which no cumulative proportion could be calculated due to missing data. Within this interval different parameters may affect visual function, positively (e.g. individual potential of visual maturation, which continues until age of 18 years), or negatively, like further decrease of VA at progression leading to subsequent treatment of OPG.

Fourth, in our series the incidence of NF1 patients is high (77%), which we consider an unreliable representation. In 6 studies NF1 status was derived from the total study population, including OPG that received no or other non-SAT treatment. Several multicenter studies on various treatments for OPG report on lower incidence of NF1 association of 6-27% [46-48]. Treatment with SAT renders a higher PFS for NF1 associated OPG compared to nNF1 OPG (RR 0.39; CI 0.19-0.79, P= 0.07 [49]), which was contradicted in other studies.

Stratified analysis on outcome for NF1/ nNF1 was not performed, due to missing data on VA outcome per NF1 status. The only comparative results on NF1 status were available from Falzon et al.: NF1 is

associated with a decrease of VA after SAT when diagnosed with OPG at age ≤ 5 year (OR 5.27 (CI: 1.04-26.7) P=0.04) [22].

Conclusion:

This systematic review on the treatment effect of SAT on visual function for pediatric OPG presented improvement of binocular VA in 0-45%, stability in 18-77% and decrease in 0-82% in 358 patients. Treatment was carboplatin based in 76% of OPG. No studies reporting on change in visual function after VEGF or MAPK signaling inhibition met the eligibility criteria. Future studies on the effect of these relatively new modalities on visual function are needed. The variable range in outcome was substantiated by a high level of heterogeneity of variables made a meta-analysis not appropriate. International consensus on VA monitoring protocols evaluating the effect of SAT on the course of visual function is needed to substantiate methodologic structures on future studies to determine prognostic factors on visual function.

Conflict of Interest Statement:

Carlien A.M Bennebroek: no conflict of interest

Laura E. Wijninga: no conflict of interest

Jaqueline Limpens: no conflict of interest

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LEGENDS:

TABLE 1:

Abbreviations:
CVI: Childhood Visual Impairment; CT: chemotherapy; FU: follow-up; ND: no data; NEP: no extraction possible; NF1: Neurofibromatosis type 1; nNF1: No systemic association with Neurofibromatosis type 1; (M)DC: (Modified) Dodge Classification; SD: standard deviation; TX: treatment, VA: visual acuity.

*: monocular;

[a]: results only available from total population of study ;

[b]: age at diagnosis, age at start of tx not available;

[c]: interval age at diagnosis- final VA

[D]: long term data available, change of VA not registered in this table: see TABLE 3

TABLE 2:

Abbreviations: AC; actinomycin, BFP: binocular fixation preference; CB: carboplatin; CI: confidence interval; Cispl: cisplatin; DC: dactinomycin; ETO: etoposide; HOTV: HOTV eye test chart; (M)DC: (Modified) Dodge Classification; ND: no data; NF1: Neurofibromatosis type 1; nNF1 No systemic association with Neurofibromatosis type 1; P: P-value; PCZ: procarbazine; OR: odds ratio; RT: radiotherapy; SAT: Systemic Antitumor Therapy; SX: surgery; TAC: Teller Acuity Cards; TPCV: thioguanine, procarbazine, lomustine and vincristine; TX: treatment; VA: visual acuity; VB: vinblastine; VC: vincristine; VD: Ventricular drain; VF: visual field

[A] : results only available of total population that received SAT

[B] : subpopulation that received SAT

TABLE 3:

Abbreviations; binoc: binocular, mono: monocular, VA: visual acuity

*: time interval not presented

Grey boxes: time of measurement < 3 months after completion of SAT cycle

White boxes: time of measurement median 3.7 years after start of SAT

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547 SUPPLEMENT TABLE 3:
548 Light grey boxes: low risk of bias.

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