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Single agent carboplatin for pediatric low-grade glioma: A retrospective analysis shows equivalent efficacy to multiagent chemotherapy

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Pediatric low-grade gliomas (LGG) that are unresectable often require adjuvant chemotherapy such as carboplatin/vincristine. Small Phase II studies have suggested equivalent efficacy of single agent 4-weekly carboplatin. A single-institution retrospective review captured all patients aged 0 to 18 years diagnosed with LGG between 1996 and 2013 and treated with carboplatin monotherapy. The response and survival according to tumor site was compared to published results for multiagent chemotherapy. Of 268 children diagnosed with LGG diagnosed in this period, 117 received chemotherapy and 104 children received single agent carboplatin as first line chemotherapy. All patients received carboplatin at 560 mg/m^2, four-weekly for a median of 12 courses. The mean age at diagnosis was 5.8 years (range 3m–16y) and 32% had neurofibromatosis type 1. With a mean followup of 54 months, 86% of patients achieved stabilisation or better (SD/PR/CR). 3-year progression free survival (PFS) 66% (95% CI 57–76%), and 5-year PFS was 51% (95% CI 41–63%). 5-year overall survival was 97%. Multivariate analysis showed poorer PFS for those with chiasmatic/hypothalamic tumors. In this retrospective analysis single agent carboplatin shows comparable efficacy to historical multiagent chemotherapy for the treatment of patients with unresectable LGG. Equivalent outcomes are achieved with less chemotherapy, reduced side effects and fewer hospital visits. Further research is required to establish the place of this simplified regimen in the up-front treatment of unresectable LGG.

Low-grade gliomas (LGG) are the most common central nervous system tumors in children. They occur throughout childhood, arise in many locations and, while heterogeneous in their histology, are characterized by an indolent clinical behavior.[1]

The optimal management of most LGG is surgical resection which carries excellent event-free survival (EFS).[2] Where complete resection is not possible the best therapeutic approach remains unclear. While radiotherapy has been used widely in this setting and is effective,[3] the long-term toxicity is significant[4] particularly in young children. Newer radiotherapy techniques are being utilized to minimise toxicity[5] but radiotherapy is generally avoided in young children if at all possible, particularly in children with neurofibromatosis type I (NF-1).

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Several chemotherapy protocols have been developed to delay or potentially avoid radiotherapy altogether. The most commonly used combination of carboplatin and vincristine showed an objective response rate of 56% and a 3-year progression-free survival (PFS) of 68% in a cohort of 78 children with a mean age of 3 years.[6] PFS in this study was age dependent with those under 5 years having a 3-year PFS of 74% whereas older children had a 3-year PFS of 39%. In the HIT-LGG-1996 Study, 216 patients who were treated with 12 months of vincristine and carboplatin had a 5-year PFS of 51% with outcome influenced by extent of surgical resection and tumor location.[7]

A large randomized study comparing TPCV (Thioguanine/procarbazine/lomustine/vincristine) to carboplatin/vincristine found a nonstatistically significant improvement in 5-year EFS in favor of TPCV (52% *vs.* 39%)[8] but there is a concern that TPCV may increase the long-term risk of second malignancy and infertility, especially in patients with NF-1.

Following an initial study comparing single agent carboplatin with iproplatin in children with progressive or recurrent brain tumors,[9] two Phase II studies reported the efficacy of single agent carboplatin in children with newly diagnosed LGG.[10,11] Both studies treated patients with single agent carboplatin at 560 mg/m^2 for a planned 12 treatments. In the first study of 12 children with optic pathway gliomas 3-year

What's new?

There may be a simpler chemotherapy option for children with low-grade glioma. When the tumor cannot be completely removed by surgery, chemotherapy can stave off recurrence. Currently recommended chemotherapy regimens, which include multiple agents, are costly and difficult for patients. In this paper, the authors report on a simplified chemotherapy regiment, carboplatin alone. Analyzing data collected from 18 years' worth of patients, they show that carboplatin monotherapy worked just as well as conventional multiagent therapies, with similar survival rates but fewer hospital visits and less severe side effects.

EFS was 83%. The second, larger, study reports on 81 patients receiving single agent carboplatin for LGG in all locations. They report an 85% rate of disease stabilisation or better and a 3-year failure free survival of 64%.

Here we report our experience with a large cohort of patients with LGG treated with a simplified regimen of single agent carboplatin given four-weekly and compare the outcome with published multiagent chemotherapy regimens. After contributing to the larger Phase II trial,[13] this protocol became standard of care in our institution after the study closed. This protocol continued to be used to determine indications for and modifications to treatment.

Material and Methods

All patients (0–18 years) at our institution diagnosed with LGG between 1996 and 2013 were identified from hospital databases and the relevant clinical, diagnostic and treatment data were abstracted from the clinical record. The review was conducted with institutional ethics approval. Patients without a biopsy were included if the clinical features and tumor imaging were consistent with the diagnosis of LGG.

Clinical features recorded included age at diagnosis, gender, and the presence or absence of NF-1, while treatment details included the date and nature of surgical intervention, the degree of resection and the dose and timing of chemotherapy. Clinical outcome data recorded included any disease- or treatment-related events, visual acuity, the measured MRI tumor response and calculated time to tumor progression.

Response evaluations were recorded during and on completion of therapy and best response was recorded. Complete response, partial response and stable disease were ascertained using the revised RECIST criteria.[12] Time to tumour progression, time to death and time to censoring were all calculated from the date of starting treatment with carboplatin. Progression was defined as the decision to institute further therapy by the treating clinician, be it based on radiological progression, visual deterioration or the development of other clinical symptoms such as to warrant therapy.

The most recent 20 patients' charts were interrogated to determine number of outpatient consults, number of outpatient infusional visits, number of inpatient days required due to therapy toxicity, number of transfusions of red blood cells and platelets and number of visits for toxicity monitoring (*e.g.*, audiograms). This was compared to 10 patients treated according to the SIOP LGG 04 study using carboplatin and vincristine.

Statistical analysis was completed using the "survival"[13] package in the R language.[14] Kaplan–Meier analysis of survival was used throughout with univariate p values generated using the log-rank test. Cox proportional hazards model was used for multivariate analysis.

Results

268 children aged 0-18 years were diagnosed with LGG at our institution over the 18 year period from 1996 to 2013. Of these, 117 children received chemotherapy as part of their treatment and 104 children received single agent carboplatin as their first line of nonsurgical therapy. The remaining 13 patients had other first line therapy and were not included in the analysis. The 151 children who did not receive chemotherapy either had surgery alone or observation only. All patients receiving carboplatin were treated according to the schedule described by Gururungan *et al.*[13] This involves infusion of 560 mg/m^2/dose of carboplatin on a four-weekly schedule for a planned 12 doses. Criteria for starting therapy were progressive or recurrent LGG in patients aged under 18 years old. Histologic confirmation was not required in tumors which had clinical and radiological characteristics consistent with LGG and biopsy was deemed to carry excessive risk.

Indication to start treatment was radiological progression/recurrence in 76 courses (73%), visual decline in 23 (22%), proptosis in 3 (3%) and diencephalic syndrome in 2 (2%). As this was a retrospective review, dose or drug alterations were not mandated by a prospective protocol but patients were managed by the same clinicians over the period studied and conformed very closely to the modifications described in the Phase II study of carboplatin monotherapy.[13]

Patient characteristics are summarized in Table 1 and are consistent with other reported cohorts of patients receiving treatment for LGG.[7,8] The mean age of the carboplatin cohort was 5.8 years (range 3 months–16 years), 48% were male and 32% met diagnostic criteria for NF-1. The majority of biopsied tumors were pilocytic astrocytomas or low grade astrocytoma of unclear subtype. Biopsies were not possible or not done in 36 children (35%), 25 of these had lesions in the optic pathway, eight in the brainstem and three in the

Table 1. Demographics, location, histology, previous therapies of children with low grade glioma treated with carboplatin

Age at diagnosis		
Mean		5.8 years
Range		3 months–16 years
Less than 1 year	6	6%
1–5 years	50	48%
Greater than 5 years	48	16%
Sex		
Male	50	48%
Female	54	52%
Neurofibromatosis I		
Present	33	32%
Absent	71	68%
Location		
Brainstem	23	22%
Cerebellum/4th ventricle	15	14%
Central (nonchiasmatic)	11	10%
Spine	10	10%
Hemisphere	1	1%
Optic pathway	(39)	(38%)
– Chiasmatic/hypothalamic	18	17%
– Nonchiasmatic/hypothalamic	21	20%
Disseminated	5	5%
Histology		
Pilocytic astrocytoma	52	50%
Fibrillary astrocytoma	1	1%
Low grade astrocytoma NOS	12	12%
Oligodendroglioma	1	1%
Pilomyxoid astrocytoma	1	1%
Pleiomorphic xanthroastrocytoma	1	1%
No histology	36	35%

Table 2. Serious reactions to carboplatin

CTCAE	Hypersensitivity	Hearing loss	Hematuria
Grade II	2	1	1
Grade III	2	0	0
Grade IV	0	0	0
Total	4 (4%)	1 (1%)	1 (1%)

spinal cord. The clinical presentation and radiological findings of all unbiopsied tumors was consistent with LGG. There were 18 children (17%, 12 with NF-1) with chiasmatic/hypothalamic tumors, defined as gliomatous involvement of the optic chiasm with extension into hypothalamus or other central structures. There were 11 children with central, nonchiasmatic tumors, defined as involving either thalamus, hypothalamus or basal ganglia with no involvement of the optic chiasm.

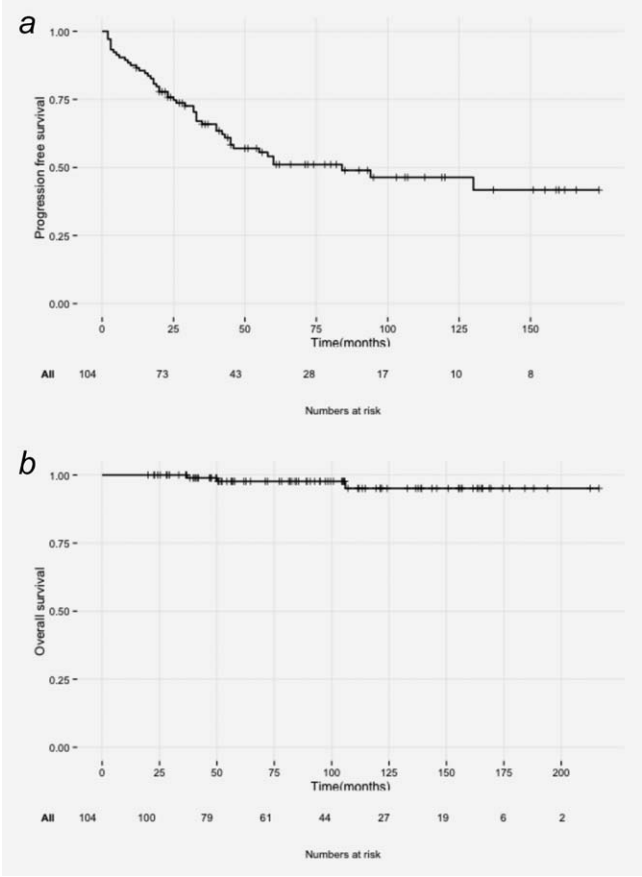

Figure 1. Progression free survival (*a*) and overall survival (*b*) of children treated with carboplatin for low grade glioma.

Patients received a median of 12 doses (4-weekly) with a range of 1–15 doses. Serious reactions to carboplatin were rare with four hypersensitivity reactions (3.8%), 1 case of treatment related hearing loss and one case of hematuria (Table 2). In two cases of hypersensitivity which occurred at or after dose 10 treatment was stopped early. For the remaining four patients treatment was changed—to temozolomide in three cases and to TPCV in another.

Radiological response evaluation was possible in all treatment courses. Stable disease was achieved in 79 patients, partial response in nine and complete response in one. Overall 86% achieved stabilisation of disease or better (SD/PR/CR).

Mean follow-up was 54 months. Kaplan–Meier analysis showed a 3-year PFS of 66% (95% CI 57–76%), a 5-year PFS of 51% (95% CI 41–63%) and the overall survival for the whole cohort was 97% at 5 years (95% CI 93–100%) (Fig. 1). Table 3 shows the 5-year PFS along with univariate and multivariate analysis. On univariate analysis there was no difference by response to chemotherapy (p – 0.44), no difference by year of treatment (p – 0.63) and no age-related association with PFS in our cohort (p – 0.62). Although numbers were small, children under the age of 1 had similar outcomes to

Table 3. Univariate (log rank) and multivariate (Cox proportional hazards) analysis for children with LGG treated with carboplatin

	5 year PFS	95% CI	Log-rank *p* values (Univariate)	Hazard ratio	95% CI	Wald *p* value (Multivariate)
All patients	51%	41–63%				
NF-1						
Absent	46%	35–61%	0.18	REFERENCE	0.37–4.54	0.69
Present	63%	47–83%		1.3		
Response						
CR/PR	65%	40–100%	0.44	REFERENCE	0.50–6.59	0.36
SD	58%	48–73%		1.82		
Site						
All other sites	56%	45–70%	0.2	REFERENCE		
Central nonchiasmatic	50%	26–95%		1.36	0.35–5.36	0.66
Chiasmatic/hypothalamic	34%	17–68%		3.75	1.40–10.05	**<0.01**[1]
Age						
Over 5 years	46%	32–66%	0.62	REFERENCE		
Under 1 year	50%	58–100%		0.89	0.24–3.36	0.87
1–5 years	55%	42–72%		0.59	0.26–1.36	0.22
Histology						
Pilocytic astrocytoma	38%	25–55%	**0.02**[1]	REFERENCE		
No histology	70%	54–90%		0.26	0.07–1.01	0.05
Nonpilocytic LGG	53%	33–86%		0.66	0.23–1.89	0.44
Year of treatment						
2008–2013	54%	37–77%	0.63	REFERENCE		
1996–2001	51%	36–72%		1.44	0.55–3.82	0.46
2002–2007	48%	34–70%		3.04	0.97–9.50	0.06

[1]Statistically significant, $p < 0.05$.

those over 1 year, as did children under the age of 5 compared with older children. Those patients who had not had biopsy had better outcome on univariate analysis (p – 0.02) but this did not retain statistical significance on multivariate analysis. There was a nonsignificant trend to better outcome in children with NF-1 ($p = 0.18$) (Fig. 2*a*) but this was not borne out in multivariate analysis.

Differences by site were observed and were significant. Figure 2*b* shows the comparative outcome of children with pre-chiasmatic optic pathway tumors and those with chiasmatic/hypothalamic tumors. The 5-year PFS of children with prechiasmatic optic pathway tumors was 68%, whereas those with chiasmatic/hypothalamic tumors had a PFS of 34%, a statistically significant difference (p – 0.02). When chiasmatic/hypothalamic gliomas were compared with all other sites the trend remained but this did not retain statistical significance ($p = 0.08$) (Fig. 2*d*). Central, nonchiasmatic tumors involving either the thalamus, hypothalamus or basal ganglia, but with no involvement of the optic chiasm, had a 5-year PFS for this group was 50%, no different from with the 5-year PFS for noncentral tumors of 56% ($p = 0.74$) (Fig. 2*c*).

Subset analysis of patients without NF-1 showed similar patterns to the overall cohort with no difference in PFS by response, age or year of treatment. Chiasmatic/hypothalamic tumors trended to poorer PFS but numbers were small and this did not reach significance (p – 0.22). Subset analysis of children with NF-1 showed no difference in PFS by response, age or year of treatment but the difference in PFS between chiasmatic/hypothalamic gliomas and other sites was significant (p – 0.04).

Multivariate analysis showed that only chiasmatic/hypothalamic site retained statistical significance for a poorer PFS with a hazard ratio of 3.75 (Table 3). Central, nonchiasmatic tumors had no detectable difference to other sites.

Visual assessments were available on 37/39 children who started treatment for optic pathway tumors. Visual acuity was derived from logMAR charts or Kay pictures depending on age and ability of the child. Five children were infants at the time of starting therapy and visual acuity was unable to be quantified. Five had normal vision before and after therapy (treatment was started for nonvisual reasons). When the indication for treatment was visual decline, the majority

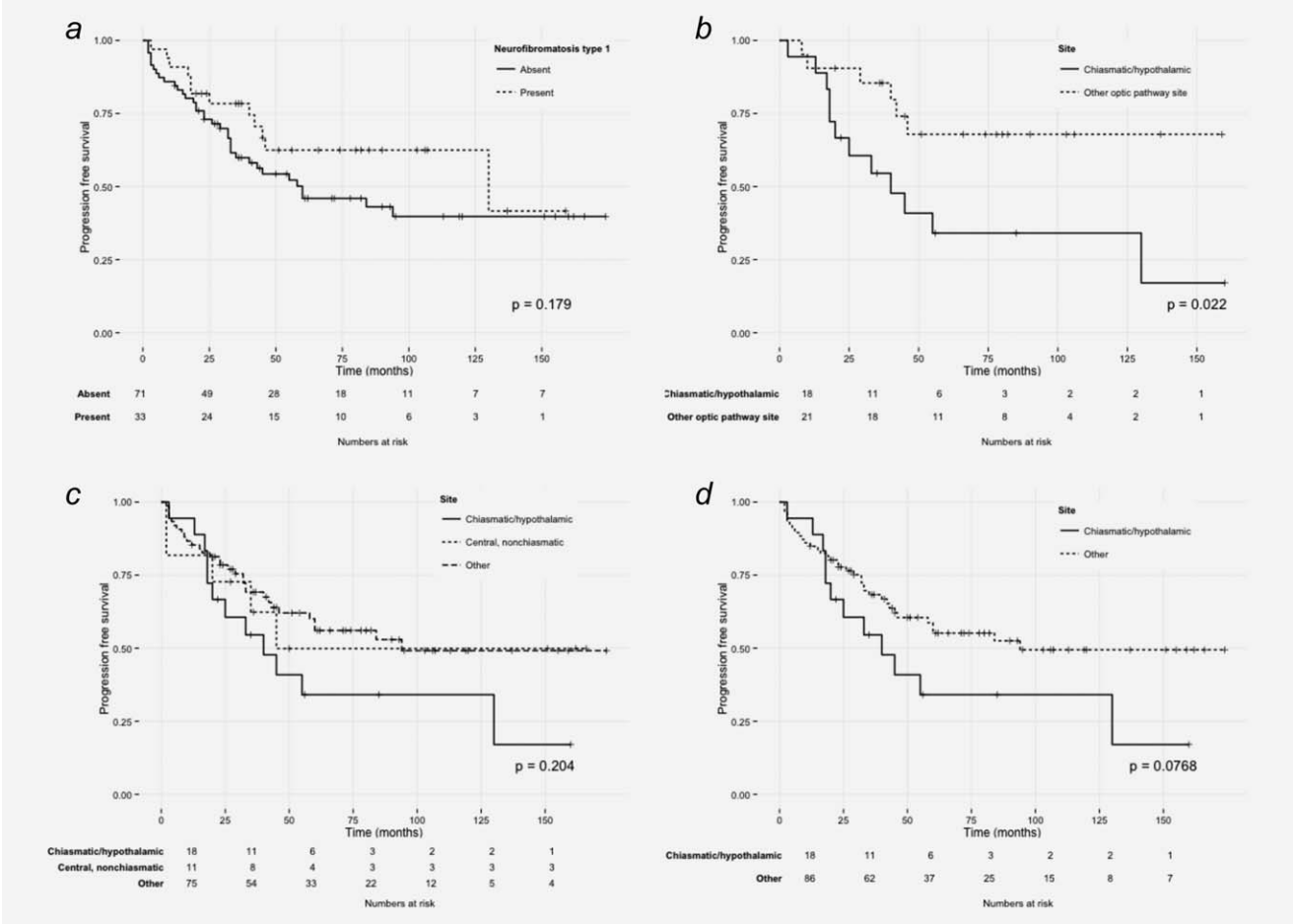

Figure 2. Progression free survival by NF-1 status (*a*), for optic pathway tumors by site (*b*), for chiasmatic/hypothalamic tumors compared with other central tumors and all other tumors (*c*) and for chiasmatic/hypothalamic tumors compared with all other tumors (*d*).

(70%) showed no change in vision, while 19% improved and 11% deteriorated.

There were 13 patients with LGG who received first line treatment other than single agent carboplatin. Treatment was carboplatin/vincristine in nine cases, radiotherapy in 1 and other chemotherapy regimens for the remaining 3. Mean age of this group was younger at 3.6 years (range 5 months – 11 years). Fewer had NF-1 (two patients, 15%) and more had tumors in central locations (5 patients, 38%). 5-year PFS in this group was 35% (95% CI 15–82%) and 5-year OS was 89% (95% CI 71–100%). When the groups receiving carboplatin and not receiving carboplatin were combined – an analysis of all 117 patients receiving first line nonsurgical therapy—the 3-year PFS was 65% (95% CI 57–75%) and 5-year PFS was 49% (95% CI 40–60%).

We compared the mean number of outpatient visits per patient to that of children treated in our institution with vincristine and carboplatin (SIOP LGG 04 protocol) in order to assess the impact of treatment on the patient and family. For patients treated with carboplatin monotherapy the mean number of outpatient visits during treatment was 15, this compares with 26 for those treated on the SIOP LGG protocol. Mean number of infusional visits was 12 compared with 43 for patients following SIOP LGG 04. There was no difference in mean number of inpatient days (3 days) by regimen, nor transfusion requirements.

Discussion

We report the largest cohort of patients with unresectable LGG treated with a simplified regimen of single agent carboplatin given four-weekly and have compared the outcome with published multi-agent chemotherapy regimens. Although complete surgical resection is the optimal approach for most LGG, many of these tumors cannot be safely removed. While radiotherapy is effective its toxicity precludes its use in young children for these low grade tumors. This leaves many young children with a chronic relapsing-remitting disease requiring treatment over many years.[15] Reducing therapy and simplifying the treatment of LGG should make treatment less onerous on the patient and family while minimising long-term treatment related toxicity.

Carboplatin and vincristine has a published 5-year PFS of between 39%[8] and 51%[7] and TPCV has a published 5-year PFS of 52%.[8] We have shown that the 5-year PFS for carboplatin monotherapy is 51% (95% CI 41–63%), comparing favourably with established regimens in this disease. This also confirms the results of previous Phase II studies using carboplatin monotherapy.[13] Of particular note, single agent carboplatin used here achieved excellent outcomes for children with pre-chiasmatic optic pathway tumors, however, the efficacy of single agent therapy appears site specific with relatively poor long-term outcome for patients with chiasmatic/hypothalamic tumors.

Central or diencephalic tumors have been shown in other studies to have poorer outcomes.[7,13] Much of this adverse prognosis has been attributed to the limited options for surgical resection in this location but in our series we showed a sharp distinction in outcome between unresectable central tumors located within and outside the optic pathway. In our series, central tumors not involving the optic pathway had a PFS identical to noncentral tumors. It is unlikely that this result is due to the chemotherapy regimen given and it more likely reflects the biology of these tumors.

In this analysis, when chiasmatic/hypothalamic gliomas are grouped with other optic pathway gliomas—which have an excellent PFS—the combined PFS for all optic pathway tumors is equivalent to other locations. When grouped with the small number of central, nonchiasmatic tumors the combined PFS for all diencephalic tumors is poorer than other locations. As can be seen in Figure 2*c*, the behavior and outcome of these central, nonchiasmatic tumors in this analysis more closely matches that of noncentral tumors than chiasmatic/hypothalamic tumors. It may be that the biology of central, nonchiasmatic tumors more closely mirrors noncentral tumors and so the behavior also mirrors tumors in these other locations. Most published research groups chiasmatic/hypothalamic tumors and other central tumors together in outcome analysis.[6,13] Those that separate the groups demonstrate a difference in prognosis with chiasmatic/hypothalamic tumors having a poorer outcome.[7]

The histology of central, nonchiasmatic tumors in this cohort was 73% pilocytic astrocytoma, 18% astrocytoma NOS, 9% oligodendroglioma and the histology of biopsied chiasmatic/hypothalamic tumors in this cohort was 82% pilocytic astrocytoma and 18% astrocytoma NOS. Given that histological appearance does not explain difference in behavior, it may be that molecular analysis will provide greater insight into this apparent distinction in behavior and outcome.

Unlike other studies we found no significant difference in outcome by age or histology. There was no age group which separated from other age groups in terms of PFS. Other studies have shown variable effect of age on PFS, with some showing better outcome for those under 5 years[6] but others showing poorer outcome for those diagnosed under 5 years.[8] While outcome by NF-1 status in our series showed a trend for improved PFS for those with NF-1 this did not reach statistical significance. This may reflect a true difference which was unable to be brought to statistical significance by the limitation of numbers in this series as other large studies consistently report a better PFS for patients with NF-1.[7,16]

Response evaluation in this group was reported using RECIST 1.1 criteria[14] and we report a relatively low rate of partial and complete responses at 10% of the total group. There is no one agreed way to measure tumor response in this tumor type. RECIST uses the sum of the diameters of the tumor, some response assessments use maximal 2-dimensional cross-sectional area[13] and others use 3-dimensional methods.[16] Even within any one method, some use contrast enhancing components[16] and others use T2/FLAIR sequences,[8] variable targets are set for meeting criteria for a partial response and sometimes a category of "minor response" is included.

RECIST sets a relatively high threshold for assigning a partial response and there is no minor response category. This may explain the lower rate of partial responses seen in our series compared with others published reports. Of note, as shown in other series,[6] response was not correlated with PFS with no difference in outcome between those who achieved partial or complete response compared to stable disease.

Comparisons between chemotherapeutic regimens are difficult to interpret in light of the large number of potential confounding variables. Differences in the proportion of tumors in different locations, heterogeneous histopathology, age, prior treatment and the proportion of patients with NF-1 all may influence the interpretation of data and the comparison of different studies. In addition the clinical behavior of these tumors means the risk of progression persist beyond 5 years, so comparative analysis of PFS at 3 years may be less meaningful and longer periods of follow-up are required. Comparative efficacy of contemporary regimens with reported PFS to at least 4 years are summarized in Table 4.

What can be seen in this comparison is that all regimens have very similar 5-year PFS, between 39 and 52%. Both of these figures forming the ends of the range are from the randomized trial reported by Ater *et al.*[8] comparing vincristine/carboplatin (39%) and TPCV (52%). In the discussion of this paper, the largest published randomized trial of chemotherapy in pediatric LGG, the authors note that the planned analysis by stratified log-rank test did not reach statistical significance and only the secondary, data-driven analysis showed a significant difference between regimens, casting doubt on the true difference between regimens.

What is clear is that in the past 20 years there has been no conclusive proof of the superiority of one chemotherapy regimen over another in the treatment of LGG. With this in mind, we believe the focus for determining treatment should be on quality of life, avoidance of toxicity and late effects for children with these indolent tumors. Reducing short and long term treatment related toxicity is a common goal across the childhood cancer spectrum especially where the rate of cure is high. Here, we show the use of single agent carboplatin is

Table 4. Comparison of response and 5 year EFS/PFS rate for chemotherapy regimens

Regimen	Stabilisation rate (SD/PR/CR)	Reported EFS/PFS	Patient number	Patient population
Carboplatin (current study)	86%	51% (95% CI 41–63%) at 5 years	104	All locations, first line therapy
Vincristine/carboplatin (Packer)	68%	39% (95% CI 35–43%) at 5 years[8]	274	All locations other than nonchiasmatic OPG
Vincristine/carboplatin (HIT)	92%	51% (CI not reported) at 5 years[7]	216	All locations, first line therapy
TPCV	68%	52% (95% CI 47–57%) at 5 years[8]	274	All locations other than nonchiasmatic OPG

associated with a very low incidence of acute carboplatin related hypersensitivity (4%) compared to the frequency seen in other published studies using more frequent carboplatin dosing. Hypersensitivity reactions are well documented in adults[17,18] and children[19,20] receiving carboplatin, and the reported cumulative incidences vary from 7 to 32% for children receiving carboplatin for LGG.[6,7] Moreover, we have avoided the use of vincristine, with its associated acute and medium term neurotoxicity, especially given the uncertainty of its efficacy in the treatment of this class of brain tumor.

The reason for the low rate of hypersensitivity in this group is not clear. The mechanism for carboplatin hypersensitivity has never been clearly elucidated and attempts to prevent it occurring have not been successful.[21] We speculate that the reduced frequency of carboplatin dosing compared with other schedules, allowing for a greater washout period, may result in less immunogenicity of the drug.

Visual function is variably reported in children with optic pathway gliomas. A systematic review published in 2010[22] showed that in 174 children across eight published studies, 14% showed visual improvement with chemotherapy, 47% remained stable and 39% experienced deterioration. Fewer children in this review who started chemotherapy for visual decline experienced a deterioration in vision (11%) and similar numbers experienced an improvement in vision (19%).

Many large metropolitan pediatric oncology centres service geographically diverse and remote regions. Decreasing the frequency and intensity of treatment minimises the disruption of schooling and work, the cost and the dislocation of patients and families who need to travel to treatment centres when patients are treated with weekly chemotherapy. Moreover, reducing the frequency of carboplatin related hypersensitivity by less frequent carboplatin dosing may make it safer for selected patients to be treated in local treatment centres closer to their home. Our study supports the use of less intense therapy for these patients. The mean number of outpatient consultations over a 12 months course of treatment was 50% fewer than other regimens and the number of chemotherapy infusion visits was 75% fewer than regimens using combined carboplatin and vincristine. Cost saving has not been calculated as this will differ markedly between institutions and countries but the impact for patients needing to travel from rural and regional centres for treatment is clear.

There are some important limitations to this study. As a retrospective study this analysis is vulnerable to selection bias. Over the period studied there was a complete data capture of all patients receiving nonsurgical therapy ($n = 117$). When comparing those who received carboplatin as first line therapy and those who did not it is clear that there are more central tumours receiving other therapies and the mean age is younger. This may explain the apparent good outcome of central tumors receiving carboplatin except that of the five patients with central tumors receiving other therapies the 5-year PFS was similar with only one progression within 5 years of starting treatment. Clearly the effect of selection bias may be present although a combined analysis of all 117 patients receiving nonsurgical therapy suggests the impact is small.

Another limitation to the study is that there was no central review of radiology or pathology. It is conceivable that a small subset of unbiopsied tumors had histology other than low grade glioma, particularly the 11 nonoptic pathway tumors. Progression is difficult to quantify for a number of reasons. As there was no prospective central review and mandated indications for further treatment the analysis relies on treating clinicians to decide when progression is sufficient to warrant further therapy. Radiological characteristics alone do not adequately detail an indication for treatment as a 25% growth of a large central tumour is likely to be defined as significant progression by a treating clinician and lead to further therapy whereas the same percentage growth of a small posterior fossa nodule may lead to further watchful waiting. Progressive visual symptoms without radiological progression may also warrant further therapy. Due to these complexities the only meaningful way to define progression in this retrospective cohort is to rely on clinician expertise. This is a potential source of bias in our study. Additionally the proportion of patients with NF-1 is slightly higher than other reported series.[7] The reason for this is not clear, although it is unlikely to reflect selection bias, rather our underlying population, as the proportion of patients with NF-1 in the total cohort of 117 is also high.

Our analysis supports previous Phase II studies on the efficacy of single agent four-weekly carboplatin in the treatment of LGG and we suggest that this warrants further research, ideally in a randomized controlled trial, as an option for frontline therapy especially when the goal is to reduce potential treatment related toxicity and the healthcare burden on families. This therapeutic approach is currently being planned for an upcoming Phase III trial for upfront therapy in unresectable pediatric LGG in Australasia.

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