Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03549-x

CLINICAL STUDY

Retrospective analysis of combination carboplatin and vinblastine for pediatric low-grade glioma

Anandani Nellan[1,4] · Erin Wright[2] · Kristen Campbell[1] · Kurtis D. Davies[3] · Andrew M. Donson[1] · Vladimir Amani[1] · Alexis Judd[2] · Molly S. Hemenway[1] · Jennifer Raybin[1] · Nicholas K. Foreman[1] · Sarah Rush[2] · Kathleen Dorris[1]

Received: 26 March 2020 / Accepted: 29 May 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Introduction Low-grade glioma (LGG) represent the most common pediatric central nervous system tumor. When total surgical resection is not feasible, chemotherapy is first-line therapy in children. Multiple pediatric LGG chemotherapy regimens have been investigated with variable 2-year event free survival (EFS) rates of 39–69%. To date, treatment of pediatric LGG with a carboplatin and vinblastine (C/VBL) chemotherapy regimen has only been evaluated in a phase 1 dose-finding study.

Methods A retrospective review of pediatric patients with LGG who were treated with C/VBL at Children's Hospital of Colorado or Akron Children's Hospital from 2011 to 2017 was conducted. Data collected included patient demographics, tumor location, disease response, neurofibromatosis 1 (NF1) status, therapy duration and toxicities. Response to therapy was determined by objective findings on imaging and treating physicians' evaluation.

Results Forty-six patients were identified for analysis, all of whom were chemotherapy-naive. Only five patients treated in this cohort had NF1. BRAF fusion was identified in 65% (22/34) of tested tumors. Best therapy response was partial response in nine patients and stable disease in twenty-five patients. Twelve patients had progressive disease. One-year, 3-year, and 5-year EFS probabilities for all patients were 69.6%, 39.4%, and 34.5%, respectively. Nine patients had admissions for febrile neutropenia and seven patients experienced one delay in chemotherapy due to neutropenia. Only two patients had to discontinue this chemotherapy regimen because of treatment-related toxicities [carboplatin allergy (n = 1) and vinblastine neuropathy (n = 1)].

Conclusion C/VBL achieves similar EFS rates to other single-agent and combination cytotoxic chemotherapy regimens for pediatric LGG with manageable toxicities.

Keywords Low-grade glioma · Pediatrics · Brain tumor · Chemotherapy

Abbreviations

LGG	Low-grade gliomas
NF1	Neurofibromatosis 1
EFS	Event free survival
C/VBL	Carboplatin and vinblastine
CNS	Central nervous system
CV	Carboplatin and vincristine
TPCV	Thioguanine, procarbazine, lomustine, and vincristine
PFS	Progression free survival

Anandani Nellan and Erin Wright are co-first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11060-020-03549-x) contains supplementary material, which is available to authorized users.

✉ Anandani Nellan
anandani.nellan@childrenscolorado.org

[1] Department of Pediatrics, Morgan Adams Foundation Pediatric Brain Tumor Research Program, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[2] Division of Hematology Oncology, Akron Children's Hospital, One Perkins Square, Akron, OH 44308, USA

[3] Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[4] Center for Cancer and Blood Disorders, Morgan Adams Foundation Pediatric Brain Tumor Research Program, University of Colorado School of Medicine, 13123 East 16th Avenue, Box B115, Aurora, CO 80045, USA

Published online: 06 June 2020

OS Overall survival
NA Not reachable

Introduction

Low-grade glioma (LGG) is the most common type of pediatric brain tumor. It represents about 17% of all pediatric central nervous system (CNS) tumors [1]. The mainstay of treatment involves maximal safe surgical resection and, when feasible, a gross total resection can prevent disease recurrence in most patients [2]. Gross total resection is not an option for a significant portion of patients based on tumor location, and therefore chemotherapy has become first-line therapy for children with unresectable LGGs [3]. Radiotherapy has shown good overall outcomes with estimated progression free survival (PFS) of 62–80%, however this therapeutic modality is associated with significant long term morbidity especially when delivered at a younger age [4–6]. To date, there is no clear standard of care for the treatment of recurrent or progressive LGGs, though recent recommendations were published by the International Society of Pediatric Oncology (SIOP) [7, 8]. Management strategies include more surgery, first-line or repeated chemotherapy, targeted therapies and radiation.

Various chemotherapy regimens have been evaluated demonstrating event free survival (EFS) or PFS rates of anywhere from 39 to 69% [3, 6, 9–14]. Carboplatin and vincristine (CV) has become one of the common first line chemotherapy regimens based on the randomized Children's Oncology Group (COG) study comparing CV to thioguanine, procarbazine, lomustine, and vincristine (TPCV) in patients without neurofibromatosis 1 (NF1). The reported 5-year EFS was 39% for CV and 52% for TPCV. The latter regimen had increased toxicity, so CV became the treatment regimen of choice [11, 15]. Patients with NF1 were non-randomly treated with CV and demonstrated a much higher 5-year EFS rate of 69% [10]. Notable other LGG chemotherapy regimens include weekly vinblastine which was well tolerated and showed a 5-year PFS of 42–53% [12, 16, 17] and monthly carboplatin with a 3-year failure free survival of 64% [18]. While chemotherapy is widely used for the treatment of unresectable and progressive pediatric LGGs, no chemotherapy regimen has demonstrated a significant improvement in EFS or PFS from any other regimen.

One of the major toxicities of using the combination of CV in pediatric LGG is significant neurotoxicity including neuropathic pain, cranial neuropathies, motor weakness and constipation from autonomic neuropathy [15, 19, 20]. Grade 3 neurotoxicity from the combination of CV was recently reported to occur in 38% of patients [15], which is double the previously published rate from this regimen [11]. Vinblastine has decreased neurotoxic effects compared to vincristine but can have more profound effects on the bone marrow leading to prolonged cytopenias [17]. A chemotherapy regimen using carboplatin and vinblastine (C/VBL) has been evaluated in a phase 1 dose-finding study by the Children's Oncology Group to determine the safety of giving these medications in combination and to find a safe dosing regimen with acceptable toxicities [21]. The goal of our retrospective case series was to describe the experience of treating pediatric patients with LGG using carboplatin and vinblastine (C/VBL).

Methods

A retrospective chart review was performed at Children's Hospital Colorado, Aurora, CO and Akron Children's Hospital, Akron, OH. Patients were identified from the Neuro-Oncology databases at each respective institution. Inclusion criteria included patients ages 0–18 years at time of diagnosis who were diagnosed between January 2011 and December 2017 with a LGG and received treatment with carboplatin (400 mg/m^2 on day 1 of every 4-week cycle) and vinblastine (4 mg/m^2 on days 1, 8, and 15 of every 4-week cycle) for up to 12 cycles [21]. C/VBL was the institutional standard for first line chemotherapy at each institution during the study time frame above in non-NF patients diagnosed with low-grade glioma.

Data collected

Demographic data including age at diagnosis, gender, NF1 status, age at initiation of treatment, date of death and date of last follow up was obtained for each patient. Pathology diagnosis, as defined by WHO classification 2007 or 2016, and BRAF fusion testing results were included if they were available. Information about location of tumor, extent of surgical resection at diagnosis, age at treatment, timing of therapy, best response to therapy, delays due to toxicity, cytopenias, neuropathy, admissions for febrile neutropenia, number of hypersensitivity reactions, date of relapse/progression and relapse therapy was also collected. Response to therapy was determined by retrospective review of documentation by the neuroradiologists' findings on MRI of the brain with and without contrast and any neuro-oncology tumor board/physician documentation of the evaluation of therapy response.

Statistics

Summary statistics were reported with counts and proportions for categorical variables. Skewed continuous variables were summarized with median and interquartile range, and normally distributed variables were summarized with mean and standard deviation. Kaplan–Meier plots were generated

to estimate overall survival (OS) and event-free survival (EFS). Event free survival was equivalent to a time-to-relapse analysis, as all deaths were preceded by disease progression or relapse. Log-rank tests were used to test for differences in EFS by the following covariates: NF1, BRAF fusion, age at diagnosis (≤ 3 vs. > 3), metastatic disease status, presence of V600E mutation and grade of astrocytoma (grade II vs. grade I). Median time-to-event and 95% confidence intervals were reported. Estimated survival proportions at 1, 3 and 5 years were reported. All analyses were performed using R version 3.5.1, and the significance level was set to 0.05.

Results

Forty-six patients (28:18; male:female) met the inclusion criteria and were identified for analysis and demographic data was obtained (Table 1). Detailed information about each subject including tumor histology, grade, metastatic status, NF1 status, BRAF fusion/mutation status, and indication for treatment is listed in Supplemental Table 1. Pathologic diagnosis consisted of pilocytic astrocytoma (n = 26, 59%), astrocytoma/diffuse glioma WHO Grade II (n = 9, 20%), pilomyxoid astrocytoma (n = 5, 11%), and low-grade glioma NOS (n = 4, 9%) (Table 1). Two patients with NF1 were diagnosed by imaging only and histology is not available. BRAF-KIAA1549 fusion or other BRAF fusion was identified in 22/34 (65%) tumor samples tested (Table 1). Twenty-one patients had a BRAF-KIAA1549 fusion and one patient had a BRAF-GIT2 fusion [22], which has been previously described in the literature. Two patients had a BRAF V600E mutation of 11 tested for the mutation. Only five (11%) patients treated in this cohort had NF1. Tumors were located in the optic pathway/chiasm/hypothalamus (n = 22, 48%), supratentorial cerebral hemispheres (n = 13, 28%), posterior fossa (n = 8, 17%), and spine (n = 5, 11%). Four patients had metastatic or multi-focal disease at time of initiation of C/VBL therapy (Table 1).

Table 1 Baseline characteristics

Characteristic	Statistic	All (n = 46)
Male	n (%)	28 (61%)
Age at diagnosis, years	Mean ± sd	6.8 ± 4.7
Pathology	n (%)	
Pilocytic astrocytoma		26 (59%)
Astrocytoma/diffuse glioma Grade II		9 (20%)
Pilomyxoid astrocytoma		5 (11%)
Low grade glioma, NOS		4 (9%)
BRAF KIAA1549 fusion or other BRAF fusion	n (%)	
Y		22 (65%)
N		12 (35%)
Missing		12 (26%)
Neurofibromatosis 1 (NF1)	n (%)	
Y		5 (11%)
N		41 (89%)
Location (check all that apply)	n (%)	
Optic pathway/Chiasm/Hypothalamus (OPCH)		22 (48%)
Supratentorial (ST)		13 (28%)
Posterior fossa (PF)		8 (17%)
Spine		5 (11%)
Metastatic/Multifocal	n (%)	4 (9%)
V600E	n (%)	
Y		2 (4%)
N		9 (20%)
Missing		35 (76%)

The majority of patients underwent a biopsy only at diagnosis (n = 22, 50%), the next most common upfront surgical intervention was a subtotal resection (n = 16, 36%), followed by a gross total resection (n = 6, 14%) (Table 2). The median time from diagnosis to treatment start was 1 year (interquartile range (IQR), 0.8 year–1.1 years), and the median duration on chemotherapy was 10.5 months (IQR, 6–11 months) (Table 2). Twenty-four patients (52%) completed all 12 cycles of chemotherapy. Thirty-seven patients were treated with C/VBL at time of diagnosis and nine at the time of disease progression. All individuals who were treated with C/VBL at disease progression were chemotherapy-naive, as their upfront therapy involved only surgical resection. Best therapy response was partial response in nine patients (20%) and 25 patients (54%) showed stable disease throughout C/VBL therapy. Twelve patients (26%) had progressive disease during therapy. Nine patients had admissions for febrile neutropenia and only 7/46 (15%) patients experienced at least one delay in starting a chemotherapy cycle due to neutropenia (Table 2). Only two patients had to stop this chemotherapy regimen because of treatment-related toxicities [carboplatin allergy (n = 1) and vinblastine neuropathy (n = 1)].

Twenty-nine patients (63%) experienced at least one relapse after receiving C/VBL therapy (Table 3). Three patients in this cohort died from progressive disease. The median time from start of chemotherapy to death for these patients was 1.8 years (IQR 1.4, 2.3 years) (Table 3). The 5-year OS for the entire cohort was 92% (95% CI 83.8%, 100%) (Fig. 1a). The median EFS time for the entire cohort was 2.2 years (95% CI 1.6, NA). 1-year, 3-year, and 5-year EFS probabilities for all patients were 69.6% (95% CI 57.5%, 84.2%), 39.4% (95% CI 26.9%, 57.7%), and 34.5% (95% CI 21.7%, 54.7%), respectively (Fig. 1b).

When comparing EFS by NF1 status, the 1-year, 3-year, and 5-year EFS probabilities for the five patients with NF1

Table 2 Treatment

Characteristic	Statistic	All (n = 46)
Surgery extent	n (%)	
Biopsy		22 (50%)
Subtotal resection (STR)		16 (36%)
Gross total resection (GTR)		6 (14%)
Years from diagnosis to treatment start	Median (IQR)	1 (0.8, 1.1)
Months on carboplatin	Median (IQR)	10.5 (6, 11)
Best response to upfront therapy	n (%)	
Stable disease (SD)		25 (54%)
Progressive disease (PD)		12 (26%)
Partial response (PR)		9 (20%)
Number of fever and neutropenia admissions on therapy	n (%)	
0		37 (80%)
1		5 (11%)
2		3 (7%)
3		1 (2%)
Number of delayed cycles due to neutropenia	n (%)	
0		39 (85%)
1		7 (15%)

Table 3 Outcomes

Characteristic	Statistic	All (n = 46)
Relapse (at least 1)	n (%)	29 (63%)
Time from start of chemo to relapse, years	Median (IQR)	1.1 (0.3, 1.9)
Death	n (%)	3 (7%)
Time from start of chemo to death	Median (IQR	1.8 (1.4, 2.3)

was 60% (95% CI 29.3%, 100%) at all timepoints (Fig. 2). Whereas those without NF1 had 1-year, 3-year, and 5-year EFS probabilities of 70.7% (95% CI 58.1%, 86.1%), 36.2% (95% CI 23.3%, 56.2%), and 30.2% (95% CI 10.2%, 50.4%). Time to relapse did not differ significantly by NF1 status (p = 0.368). Thirty-four patients had BRAF fusion testing, with the remaining 12 patients excluded from analysis. The median EFS time for patients with a BRAF fusion

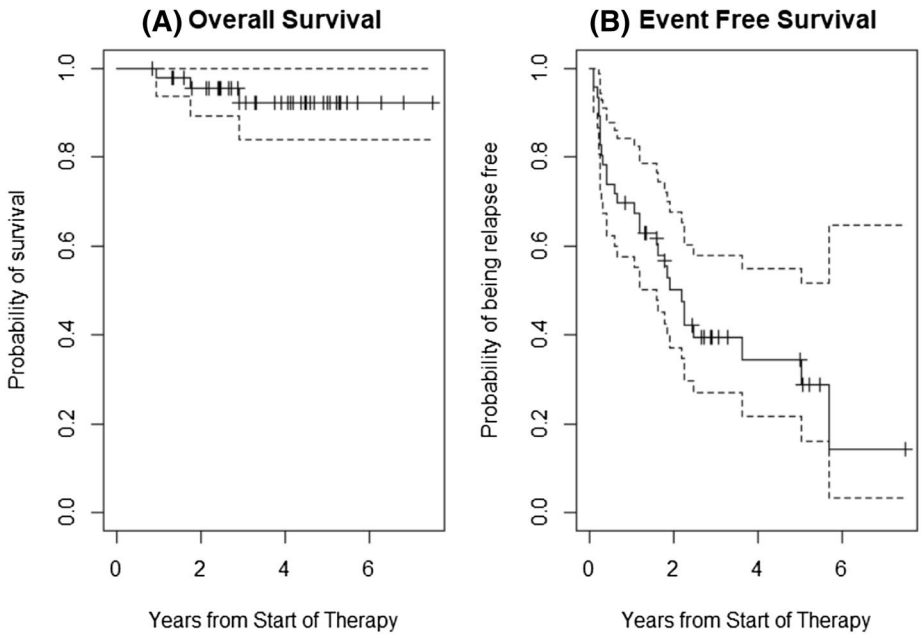

Fig. 1 **a** Kaplan–Meier curve for overall survival (OS). The black tick marks represent censoring and the dotted lines represent the 95% confidence interval. The 5-year estimated survival probability was 92% (95% CI 83.8%, 100%). **b** Kaplan–Meier curve for event free survival (EFS). The median EFS time was 2.2 years (95% CI 1.6, NA) for all patients. 1-year, 3-year, and 5-year EFS probabilities for all patients were 69.6% (95% CI 57.5%, 84.2%), 39.4% (95% CI 26.9%, 57.7%), and 34.5% (95% CI 21.7%, 54.7%)

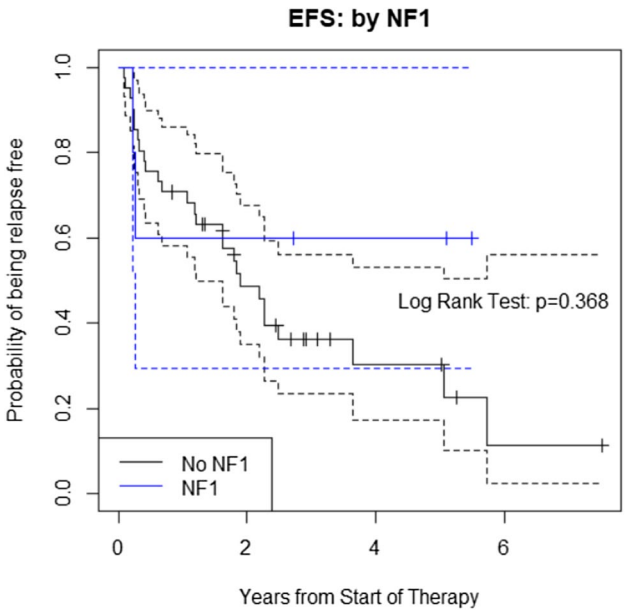

Fig. 2 Kaplan–Meier curve for EFS stratified by neurofibromatosis 1 (NF1) status. Log-rank test statistic reported to test for differences in EFS by NF1 status. The 1-year, 3-year, and 5-year EFS probabilities for the five patients with NF1 was 60% (95% CI 29.3%, 100%) at all timepoints. The 1-year, 3-year, and 5-year EFS probabilities in patients without NF1 were 70.7% (95% CI 58.1%, 86.1%), 36.2% (95% CI 23.3%, 56.2%), and 30.2% (95% CI 10.2%, 50.4%)

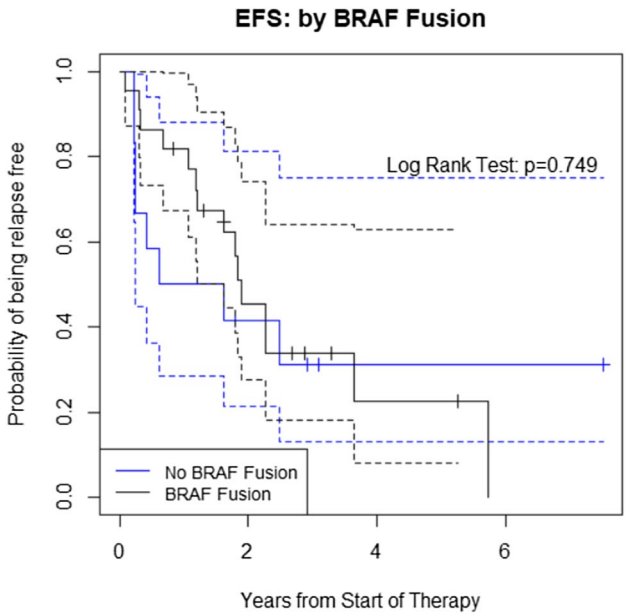

Fig. 3 Kaplan–Meier curve for EFS stratified by BRAF fusion status. Thirty-four patients had BRAF fusion testing, with the remaining 12 patients excluded from analysis. The median EFS time for patients with a BRAF fusion was 1.9 years (95% CI 1.61, NA). One-year, 3-year, and 5-year EFS probabilities for the 22 patients with a BRAF fusion tumor were 81.8% (95% CI 67.2%, 99.6%), 33.9% (95% CI 18.0%, 64.0%), and 22.6% (95% CI 8.1%, 62.8%)

(BRAF-KIAA 1549, n = 21, BRAF-GIT2, n = 1) was 1.9 years (95% CI 1.61, NA) (Fig. 3). 1-year, 3-year, and 5-year EFS probabilities for the 22 patients with a BRAF fusion tumor were 81.8% (95% CI 67.2%, 99.6%), 33.9% (95% CI 18.0%, 64.0%), and 22.6% (95% CI 8.1%, 62.8%), respectively (Fig. 3). This did not differ significantly from those without a BRAF fusion (p = 0.749). EFS did not differ significantly by age at diagnosis (≤ 3 vs. > 3), metastatic disease status, presence of V600E mutation or grade of astrocytoma (grade II vs. grade I).

Discussion

Chemotherapy is a frontline therapy for unresectable pediatric low-grade glioma and various chemotherapy regimens published to date demonstrate similar EFS rates (Supplemental Table 2). Carboplatin and vincristine is a combination chemotherapy regimen that is widely used as upfront chemotherapy for pediatric LGG but is associated with neurotoxicity. Our study demonstrates that a combination chemotherapy regimen with carboplatin and vinblastine has similar efficacy to other single-agent and combination chemotherapy regimens in pediatric low-grade glioma and has the potential for decreased neurotoxicity compared to a CV regimen. One of the limitations of this analysis is the fact that it is a retrospective review compared to historic controls; therefore, this study cannot determine superiority between C/VBL and other chemotherapy regimens.

Our results show that nine patients (20%) demonstrated partial response to the therapy, which is lower than previous studies that identified 35% and 30% response rates for CV regimens and TPCV respectively. However, the rate of progressive disease in our cohort (n = 12, 27%) is similar to rates on study for CV and TPCV (32%). Therefore, there does not appear to be an increased rate of on-therapy progression in our patients compared to historic controls. The 1-year, 3-year, and 5-year EFS probabilities for all patients were 69.6%, 39.4%, and 34.5%, which is very similar to the previously reported 5-year EFS of 39% for patients treated with carboplatin and vincristine [11]. A potential drawback of our study, inherent to retrospective reviews, is that response was not prospectively defined using set criteria such as RANO criteria and therefore may be subject to interpreter bias in evaluation of the MRI images. As therapy decisions were made due to the evaluation of response at that time, retrospective re-evaluation of the tumors was not performed with more defined criteria.

We did test for associations between known risk factors for poor outcomes in pediatric low-grade glioma and EFS to determine if our cohort further supported these trends. However, there was no difference in EFS/OS for patients based

on age, metastatic status, or tumor grade. We also evaluated the effect of BRAF V600E on EFS due to previous studies showing worse outcomes for these patients [23]. While both patients with known BRAF V600E mutation did relapse, statistical significance was not achieved. We think the small number of patients with a tumor harboring a BRAF V600E mutation (n = 2) is due to the fact that this was not routinely tested for during the timeframe of our study.

The patients in our study tolerated the chemotherapy well and disease progression was the most common reason for discontinuation of the C/VBL treatment regimen. An unusual finding in our study was that only 1 of 46 (2%) patients developed a carboplatin hypersensitivity reaction. Previous studies have reported carboplatin reactions in up to 6–78% of patients receiving chemotherapy for low-grade glioma [24]. In the COG study A9952, 26 patients (19%) who received carboplatin were removed from study due to carboplatin hypersensitivity. The study was even amended to allow patients with Grade 1 and 2 hypersensitivity reactions to continue to receive the medication. This rate of hypersensitivity reactions is significantly higher than the rate observed in our study. One explanation is that the dose and timing of carboplatin administration in the C/VBL regimen (400 mg/m^2 of carboplatin on day 1 every 4 weeks) compared to the CV regimen (175 mg/m^2 of carboplatin weekly for 4 weeks every 6 weeks) may be less prone to the development of hypersensitivity. These differences may also be secondary to the shorter overall timeframe of therapy compared to single agent carboplatin or the low number of NF1 patients in our study as these have also been factors reported to influence hypersensitivity [13, 25]. However, none of the patients in our cohort with NF1 experienced carboplatin allergy. These dosing regimens need to be compared directly on a larger scale to determine whether this difference is still observed. As we have shown, C/VBL is an efficacious potential first line therapy in line with other traditional chemotherapy agents for upfront therapy of low-grade glioma. Thirty-six of our patients had evaluation for BRAF alterations including either the BRAF fusion, V600E mutation, or both. The remaining ten patients did not have this evaluation due to lack of tissue or the timing of their diagnosis as this has only recently become a more widespread part of upfront evaluation in low-grade glioma. Targeted agents, such as MEK inhibitors, are newer agents that show promise in early phase clinical trials and case reports treating patients with relapsed and refractory pediatric low-grade gliomas with BRAF fusions [26, 27]. Numerous consortia throughout the world are developing trials to compare these targeted therapies with conventional chemotherapy directly to determine the most appropriate upfront treatment for these patients. Until results from those trials are available, this retrospective analysis supports the use of C/VBL as an effective treatment regimen for patients with pediatric LGG, as it produces similar EFS rates to other published chemotherapy regimens with a potentially more favorable side effect profile to other first line regimens. This retrospective review supports the use of carboplatin and vinblastine as both a tolerable and comparably effective regimen to treat patients with pediatric low-grade glioma.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AN, EW, KC, AJ, and KD. The first draft of the manuscript was written by AN and EW. All authors commented on previous versions of the manuscript and all authors read and approved the final manuscript.

Funding This study was funded by the Morgan Adams Foundation. This work was supported by the Molecular Pathology Shared Resource of the University of Colorado (National Cancer Institute Cancer Center Support Grant No. P30-CA046934).

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

Compliance with ethical standards

Conflict of interest Kurtis D. Davies has received sponsored travel from ArcherDx. All other authors declare that they have no conflict of interest.

Ethical approval The use of data and biological material in this study was approved by the Akron Children's Hospital Institutional Review Board (IRB), Colorado Multiple Institutional Review Board (IRB), IRB for the University of Colorado Denver/Anschutz Medical Campus and affiliates. We certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Johnson KJ, Cullen J, Barnholtz-Sloan JS et al (2014) Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomark Prev 23(12):2716–2736
2. Wisoff JH, Sanford RA, Heier LA et al (2011) Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68(6):1548–1554 **(discussion 1554–1545)**
3. Packer RJ, Lange B, Ater J et al (1993) Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 11(5):850–856
4. Saran FH, Baumert BG, Khoo VS et al (2002) Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood. Int J Radiat Oncol Biol Phys 53(1):43–51
5. Marcus KJ, Goumnerova L, Billett AL et al (2005) Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. Int J Radiat Oncol Biol Phys 61(2):374–379
6. Gnekow AK, Falkenstein F, von Hornstein S et al (2012) Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and

adolescents of the German speaking society of pediatric oncology and hematology. Neuro-Oncology 14(10):1265–1284
7. Scheinemann K, Bartels U, Tsangaris E et al (2010) Feasibility and efficacy of repeated chemotherapy for progressive pediatric low-grade gliomas. Pediatr Blood Cancer 57(1):84–88
8. Gnekow AK, Kandels D, Tilburg CV et al (2019) SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. Klin Padiatr 231(3):107–135
9. Chintagumpala M, Eckel SP, Krailo M et al (2015) A pilot study using carboplatin, vincristine, and temozolomide in children with progressive/symptomatic low-grade glioma: a Children's Oncology Group Study†. Neuro Oncol 17(8):1132–1138
10. Ater JL, Xia C, Mazewski CM et al (2016) Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the Children's Oncology Group. Cancer 122(12):1928–1936
11. Ater JL, Zhou T, Holmes E et al (2012) Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 30(21):2641–2647
12. Bouffet E, Jakacki R, Goldman S et al (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30(12):1358–1363
13. Gnekow AK, Walker DA, Kandels D et al (2017) A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma—a final report. Eur J Cancer 81:206–225
14. Dodgshun AJ, Maixner WJ, Heath JA, Sullivan MJ, Hansford JR (2016) Single agent carboplatin for pediatric low-grade glioma: a retrospective analysis shows equivalent efficacy to multiagent chemotherapy. Int J Cancer 138(2):481–488
15. Rosca L, Robert-Boire V, Delisle J-F, Samson Y, Perreault S (2018) Carboplatin and vincristine neurotoxicity in the treatment of pediatric low-grade gliomas. Pediat Blood Cancer 65:e27351
16. Lassaletta A, Scheinemann K, Zelcer SM et al (2016) Phase II weekly vinblastine for chemotherapy-naïve children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium Study. J Clin Oncol 34(29):3537–3543
17. Nelson RL (1982) The comparative clinical pharmacology and pharmacokinetics of vindesine, vincristine, and vinblastine in human patients with cancer. Med Pediatr Oncol 10(2):115–127
18. Gururangan S, Cavazos CM, Ashley D et al (2002) Phase II Study of carboplatin in children with progressive low-grade gliomas. J Clin Oncol 20(13):2951–2958
19. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ (2003) Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs 63(15):1549–1563
20. van de Velde ME, Kaspers GL, Abbink FCH, Wilhelm AJ, Ket JCF, van den Berg MH (2017) Vincristine-induced peripheral neuropathy in children with cancer: a systematic review. Crit Rev Oncol/Hematol 114:114–130
21. Jakacki RI, Bouffet E, Adamson PC et al (2011) A phase 1 study of vinblastine in combination with carboplatin for children with low-grade gliomas: a Children's Oncology Group phase 1 consortium study. Neuro Oncol 13(8):910–915
22. Helgager J, Lidov HG, Mahadevan NR, Kieran MW, Ligon KL, Alexandrescu S (2017) A novel GIT2-BRAF fusion in pilocytic astrocytoma. Diagn Pathol 12(1):82
23. Lassaletta A, Zapotocky M, Mistry M et al (2017) Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. J Clin Oncol 35(25):2934–2941
24. Wiesner A, Zucol F, Lauener RP, Grotzer MA (2004) Hypersensitivity reactions to carboplatin in children with low-grade gliomas. J Pediatr Neurol 2(3):151–155
25. Hernáiz Driever P, von Hornstein S, Pietsch T et al (2010) Natural history and management of low-grade glioma in NF-1 children. J Neurooncol 100(2):199–207
26. Kieran MW, Bouffet E, Broniscer A et al (2018) Efficacy and safety results from a phase I/IIa study of dabrafenib in pediatric patients with BRAF V600–mutant relapsed refractory low-grade glioma. J Clin Oncol 36(15_suppl):10506–10506
27. Kondyli M, Larouche V, Saint-Martin C et al (2018) Trametinib for progressive pediatric low-grade gliomas. J Neuro-Oncol 140:435–444
28. Prados MD, Edwards MS, Rabbitt J, Lamborn K, Levin RL (1997) Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neuro-Oncol 32(3):235–241

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.