

Original Article

mTOR inhibitor everolimus versus conventional chemotherapy in pediatric low-grade gliomas

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Abstract: Standard chemotherapy in pediatric low-grade gliomas (pLGG) has limited efficacy and substantial toxicity, while clinical data on everolimus are lacking. This study compared the efficacy of everolimus and traditional chemotherapy in patients with pLGG, and evaluated the treatment response, survival, and the frequency and severity of adverse events. This single-center retrospective cohort study analyzed 279 patients with pathologically confirmed World Health Organization (WHO) grade 1-2 pLGG (Jan 2014-Jan 2021): 126 received everolimus and 153 received standard carboplatin-vincristine (CV) chemotherapy. The primary efficacy endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR). In the optic pathway glioma subgroup, visual function changes were assessed using the pediatric eye questionnaire (PedEyeQ) scale along with objective ophthalmic indicators including best-corrected visual acuity, visual field assessment, and optic nerve atrophy grading. Safety was evaluated by recording adverse events according to the CTCAE v5.0 criteria, with exposure-adjusted rates calculated per 100 patient-years to account for differential treatment duration, and long-term pediatric safety was assessed through 5-year follow-up of growth, bone metabolism, and endocrine function. The follow-up period was 5 years. The median PFS was 49.00 months (95% CI: 37.00-55.00) in the everolimus group and 41.00 months (95% CI: 28.00-55.00) in the CV group, with no significant difference (Log-rank $\chi^2=0.162$, $P=0.688$) and a hazard ratio (HR) of 0.939 (95% CI: 0.684-1.288). OS did not differ significantly between the everolimus and CV groups (Log-rank $\chi^2=0.423$, $P=0.515$), with an HR of 0.778 (95% CI: 0.365-1.662). No significant differences were observed in ORR, DCR, or CBR (all $P>0.05$). In the optic pathway glioma subgroup, the 5-year PedEyeQ scores were significantly higher in the everolimus group than in the CV group ($P<0.001$), and objective ophthalmic assessments consistently demonstrated better visual preservation with everolimus. In terms of safety, the incidence of grade 3-4 adverse events was significantly lower in the everolimus group than in the CV group (22.22% vs. 44.44%, $P<0.001$). The incidence of hematologic toxicity (26.19% vs. 52.94%, $P<0.001$) was significantly lower in the everolimus group; non-hematologic toxicities, including nausea, vomiting, and alopecia, were also significantly lower in the everolimus group. The most common adverse events in the everolimus group were oral mucositis (49.21%), hyperlipidemia (38.10%), and rash (25.40%), most of which were grade 1-2 and manageable. Exposure-adjusted safety analyses confirmed these findings, and 5-year follow-up showed no significant between-group differences in growth, bone metabolism, or endocrine function. For pLGG patients, everolimus is comparable to carboplatin in terms of efficacy, but has significantly better safety and fewer serious adverse events, along with potential advantages in visual function preservation and reduced health-care resource utilization.

Keywords: Pediatric low-grade gliomas, everolimus, mammalian target of rapamycin inhibitor, conventional chemotherapy, retrospective cohort study, visual function

Introduction

Pediatric low-grade glioma (pLGG) is the most common tumor of the central nervous system in children, accounting for 30%-50% of all pediatric brain tumors [1]. It mainly comprises World

Health Organization (WHO) grade I-II glioma, of which pilocytic astrocytoma is the main subtype [2]. These tumors are often located in areas such as the optic pathway, brainstem, and hypothalamus, and cannot be completely removed, so some patients need to receive

long-term systemic treatment to control tumor progression [3]. The long-term sequelae caused by the treatment process, including visual impairment, hypothalamic dysfunction and cognitive defects, will seriously damage the patient's quality of life [4].

At present, the core of pLGG's treatment strategy is still to achieve maximum safe resection [5, 6]. However, for cases that cannot be completely removed or relapse/progress after surgery, systemic treatment becomes an important choice [7]. Routine chemotherapy is an important part of the first-line standard therapy [8]. Among them, carboplatin-vincristine (CV) regimen is currently the most widely used regimen [9]. In the HIT-LGG-1996 trial (n=1,032), 363 patients received chemo/radiotherapy (216 on CV regimen), yielding CR 3.8%, PR 31.6%, overall response/SD 56.5%, and 5-year PFS 47% [10].

The clinical value of traditional chemotherapy in pLGG treatment is limited. About 50% of patients will have tumor recurrence or resistance to the initial therapy after treatment [11]. Traditional chemotherapy regimens are accompanied by significant cumulative toxic reactions, including hematological toxicity, neurotoxicity, ototoxicity and carboplatin hypersensitivity [12, 13]. Cumulative toxicity may reduce the patient's tolerance, which may lead to treatment interruption or dose adjustment, compromising therapeutic efficacy [14]. During chemotherapy, patients need to be hospitalized frequently for treatment and monitoring, which will interfere with their normal study, daily life and psychological development [15]. Therefore, the current research focus has shifted to treatment strategies with accurate therapeutic effect, good safety and little impact on the quality of life.

In recent years, due to rapid developments in the fields of molecular biology and precision oncology, the molecular features of pLGG have become gradually well understood [16, 17]. The key roles of abnormally active mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathways in initiating and supporting the diseases in pLGG patients are well established [18, 19]. mTOR is a serine/threonine kinase that lies in the downstream pathway of PI3K/AKT signaling and it

has a role in regulating various cellular activities such as cell proliferation, growth, and metabolism, besides, the processes of angiogenesis and autophagy [20]. These tumor types where neurofibromatosis type 1 (NF1) genes are affected, are the NF1-related optic pathway gliomas and the tuberous-sclerosis-complex (TSC)-associated subependymal giant cell astrocytomas. The loss-of-function mutations in NF1 and TSC1 or TSC2 can lead to a situation in which mTOR is constitutively active, which could result in uncontrolled cell proliferation and cell survival [21, 22]. The discovery of the molecular pathways involved in regulating cell growth and death offers a theoretical basis that justifies the development and use of mTOR inhibitors as a therapy for pLGG.

Everolimus, a rapamycin derivative, works through a selective inhibition of mTOR. It exerts antitumor effects through mTORC1 inhibition and the downstream dephosphorylation of S6 ribosomal protein and 4E-BP1 blocking the protein synthesis and cell proliferation [23]. Everolimus was approved by the U.S. Food and Drug Administration (FDA) in 2010. The drug reached the Chinese market in 2014 for TSC-associated subependymal giant cell astrocytomas (SEGA) [24, 25]. Since SEGA and pLGG share the molecular mechanistic characteristics - characterized by a dysregulated mTOR signaling - everolimus use has raised great interest as therapy in pLGG.

Although several previous clinical trials and case reports have suggested that everolimus is an antitumor agent in certain types of pLGG, and that radiographic tumor shrinkage or tumor stability can be achieved by this drug in a certain portion of the patients, direct head-to-head studies contrasting everolimus with standard chemotherapy regimens for pLGG cases are scarce [26]. At present, most of the published material on the subject relates either to single-arm trials or small-sample pilot studies without follow-up, rather than large cohort studies evaluating the various aspects between everolimus and chemotherapeutics by factors of their effectiveness, survival advantages, and safety profiles [27].

Therefore, the study at hand was a single-center, retrospective cohort of patients with pLGG who had received everolimus or conventional chemotherapy between January 2014 and

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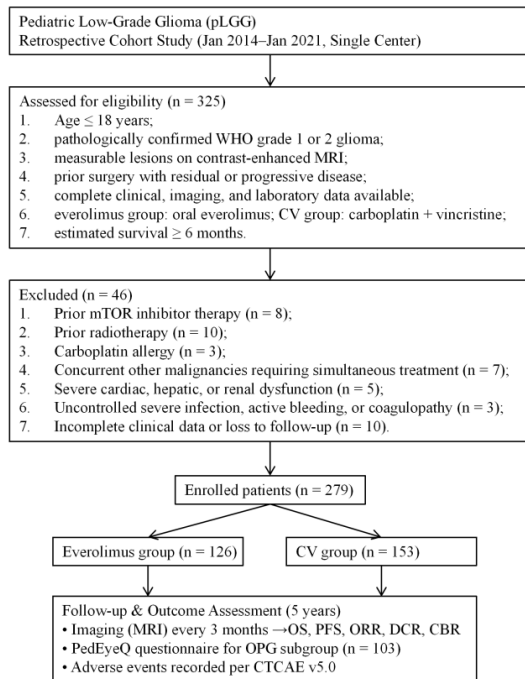


Figure 1. Study flowchart. Notes: pLGG, pediatric low-grade gliomas; CV, carboplatin-vincristine; mTOR, mammalian target of rapamycin.

January 2021. This study mainly compared the differences between the two therapies in terms of therapeutic effect, survival outcome and functional retention. At the same time, adverse events were carefully recorded and analyzed to clarify their safety characteristics and provide clearer evidence for clinicians to guide treatment decisions. The findings of this study are expected to provide evidence for individualized treatment decision-making in pLGG, particularly in the context of pursuing a therapeutic goal that balances efficacy and quality of life, by exploring the feasibility of mTOR inhibitors as an alternative or supplement to conventional chemotherapy, thereby optimizing the comprehensive management strategy for pLGG and improving patients' long-term prognosis and quality of life.

Methods

Study design

In this single-center retrospective cohort study, pLGG patients treated at our center between January 2014 and January 2021 were classified into the everolimus or CV group. This study was conducted in accordance with the Declaration of Helsinki and was approved by the

Ethics Committee of the First Clinical College, Liaoning University of Traditional Chinese Medicine (Approval No.: KY-2026-03-102). The requirement for informed consent was waived by the ethics committee due to the retrospective study design and use of de-identified data. The study flow flowchart is presented in **Figure 1**.

Inclusion criteria

(1) Age ≤ 18 years; (2) Histopathologically confirmed as WHO grade 1 or 2 gliomas according to the WHO Classification of Central Nervous System Tumors [28]; (3) B-Raf proto-oncogene V600 (BRAF V600) mutation-negative status confirmed by molecular testing, with evidence of downstream mTOR pathway activation; (4) Presence of measurable lesions, with imaging evaluation performed using contrast-enhanced MRI; (5) Prior surgical treatment with postoperative residual disease or recurrent/progressive disease; (6) Complete clinical data, imaging follow-up records, and laboratory test results available; (7) Patients in the everolimus group received oral everolimus therapy, while those in the CV group received carboplatin plus vincristine chemotherapy; (8) Estimated life expectancy ≥ 6 months.

Exclusion criteria

(1) Prior treatment with mTOR inhibitors; (2) Prior radiotherapy; (3) History of carboplatin hypersensitivity reactions; (4) Concurrent other malignancies requiring concomitant treatment; (5) Severe cardiac, hepatic, or renal dysfunction; (6) Uncontrolled severe infections, active bleeding, or coagulation disorders; (7) Incomplete clinical data or loss to follow-up.

Sample size calculation

This retrospective cohort study included consecutively enrolled patients meeting eligibility criteria between January 2014 and January 2021. Assuming a 10% improvement in 5-year PFS for everolimus over the CV group (historical rate $\sim 40\%$ [10]), sample size was calculated using a two-sided log-rank test, with $\alpha=0.05$, power=80%, and an estimated dropout rate of 10%. The calculation indicated that approximately 101 evaluable patients per group were required. Finally, 126 patients in the everolimus group and 153 in the CV group were included.

Treatment regimens

Everolimus group: Everolimus was taken orally once a day. The dose was calculated based on body weight: 2.5 mg per day for patients weighing <30 kg, and 5 mg per day for patients weighing ≥30 kg. During treatment, regular monitoring of blood trough concentrations was performed, aiming to maintain levels between 3 and 8 ng/mL. Dose adjustments were made based on the results of therapeutic drug monitoring and the occurrence of adverse events. Treatment was continued until disease progression, development of intolerable toxicity, withdrawal of consent by the patient or guardian, or completion of the planned treatment course.

CV Group: Patients in the CV group received a carboplatin-based conventional chemotherapy regimen (carboplatin plus vincristine).

(1) Induction phase: Vincristine was administered at 1.5 mg/m² as an intravenous push once weekly for a total of 10 doses (weeks 1-10). Carboplatin was administered at 550 mg/m² as a 1-hour intravenous infusion once every 3 weeks for a total of 4 doses (administered at weeks 1, 4, 7, and 10).

(2) Consolidation phase: Ten cycles were administered, with each cycle lasting 6 weeks. Vincristine was administered at 1.5 mg/m² as an intravenous push on days 1, 8, and 15 of each 6-week cycle. Carboplatin was administered at 550 mg/m² as a 1-hour intravenous infusion on day 1 of each 6-week cycle. The total treatment duration was 18 months.

Dose Adjustments for Special Populations: For children weighing <10 kg, the carboplatin dose was modified to 18.3 mg/kg, and the vincristine dose was modified to 0.05 mg/kg. For infants aged <6 months, a further one-third dose reduction was recommended in addition to the above adjustments.

Clinical outcome measures

Efficacy assessment criteria: Tumor response was evaluated using contrast-enhanced MRI according to International Society of Pediatric Oncology (SIOP) criteria [29], with measurements performed using the bidimensional (product of the two largest perpendicular diameters) method on axial images, consistent with

the recommendations of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group for pediatric low-grade glioma. The response categories were defined as: complete response (CR): disappearance of all target lesions, no new lesions; partial response (PR): ≥50% volume reduction; minor response (MR): 25%-50% reduction; stable disease (SD): volume change within ±25%; progressive disease (PD): ≥25% increase or new lesions. Imaging assessments were performed at baseline (prior to treatment initiation) and every 3 months during treatment, and were evaluated independently by two radiologists blinded to the grouping. In cases of disagreement, a third senior radiologist made the final determination.

Primary endpoint: Progression-free survival (PFS) was measured from treatment initiation to first documented PD (by SIOP imaging criteria) or death from any cause.

Secondary efficacy endpoints: (1) Overall survival (OS): from treatment initiation to death or last follow-up; (2) Objective response rate (ORR): proportion achieving CR or PR; (3) Disease control rate (DCR): proportion achieving CR, PR, MR, or SD; (4) Clinical benefit rate (CBR): proportion achieving CR, PR, MR, or SD lasting ≥6 months.

Functional outcome measure: Visual function was assessed in the optic pathway glioma subgroup (n=103) using a multimodal approach combining (1) the pediatric eye questionnaire (PedEyeQ) [30] and (2) standardized ophthalmic objective examinations. The PedEyeQ is applicable to children aged 0-18 years and comprises 40 items across 5 domains assessing functional vision and quality of life, completed either through child self-report or parent proxy. Scores range from 0 to 100, with higher scores indicating better outcomes. Objective ophthalmic quantitative indicators were evaluated by a single pediatric ophthalmologist blinded to treatment allocation at baseline and at each annual follow-up visit, including: Best-corrected visual acuity (BCVA) measured by age-appropriate methods (Lea symbols or Snellen chart) and converted to the logarithm of the minimum angle of resolution (logMAR) for analysis; Visual field assessed by automated perimetry or confrontation field testing depending on developmental age, with results categorized as improved, stable, or deteriorated rela-

tive to baseline; Optic nerve atrophy grading based on fundoscopic examination using a 4-point scale: Grade 0 (no pallor), Grade 1 (temporal pallor), Grade 2 (diffuse pallor involving $\geq 50\%$ of the disc), and Grade 3 (severe pallor involving the entire disc). Progression was defined as an increase of ≥ 1 grade from baseline.

Safety outcomes: All adverse events (AEs) occurring during treatment were recorded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria: (1) Hematologic toxicities, including neutropenia, thrombocytopenia, and anemia; (2) Metabolic abnormalities, including hyperlipidemia, hypertriglyceridemia, and hyperglycemia; (3) Non-hematologic toxicities, including oral mucositis, rash, diarrhea, nausea and vomiting, fatigue, elevated liver enzymes, proteinuria, and infections. The time of onset, severity, management measures, and outcomes of all AEs were documented. Special attention was paid to the incidence of grade 3-4 adverse events. To account for the difference in actual treatment duration between groups, exposure-adjusted AE rates were calculated as the number of patients experiencing at least one event divided by the total cumulative patient-years of follow-up, expressed per 100 patient-years. Total patient-years were computed as the sum of individual treatment durations (from treatment initiation to discontinuation or last follow-up) divided by 12. Long-term pediatric safety outcomes were evaluated over the 5-year follow-up to assess growth, bone metabolism, and endocrine function. Growth was monitored using height standard deviation score (height Z-score), with short stature defined as height Z-score < -2 . Bone metabolism was assessed by lumbar spine bone mineral density (BMD) Z-score measured by dual-energy X-ray absorptiometry (DXA), with low BMD defined as BMD Z-score < -2 , and by serum calcium and phosphorus levels. Endocrine function was evaluated by serum free thyroxine (FT4). Assessments were performed at baseline, 3 years, and 5 years.

Follow-up: All patients were followed from treatment start through outpatient visits, telephone interviews, and chart reviews. Follow-up assessments comprised physical examination, laboratory tests, tumor markers, cranial MRI, and quality of life measures. Follow-up continued until death or loss to follow-up, with a total period of 5 years.

Exploratory health economic endpoints: (1) Treatment Exposure and Adherence. Actual treatment duration: time from treatment initiation to discontinuation (months). Reasons for discontinuation were categorized as: disease progression, intolerable toxicity, or parent/patient preference. Dose Intensity (DI): percentage of the actual cumulative dose received relative to the planned cumulative dose. Everolimus group: actual exposure based on weight-adjusted dosing; CV group: actual carboplatin/vincristine exposure based on body surface area. Relative dose intensity (RDI): The percentage of the actual dose intensity to the planned dose intensity, with $< 85\%$ indicating insufficient dose. Oral drug compliance was calculated as (actual medication days/theoretical medication days) $\times 100\%$, with $\geq 80\%$ as good compliance.

(2) Medical resource utilization: including annual number of hospitalizations, annual length of hospital stays (days), rate of unplanned hospitalizations, annual number of outpatient visits, annual number of emergency department visits, proportion of ED visits related to adverse events, transfusion support, granulocyte colony-stimulating factor (G-CSF) use.

Statistical analysis

Statistical analyses were performed using SPSS 26.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (IQR), and categorical variables expressed as n (%). Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous data were compared by independent t-test; non-normal data by Mann-Whitney U test. Categorical variables were compared by chi-square or Fisher's exact test. PFS and OS curves were generated using the Kaplan-Meier method and compared by log-rank test. Patients lost to follow-up were censored at the date of their last documented clinical or imaging assessment. To further quantify the treatment effect, the hazard ratio (HR) and its 95% confidence interval (CI) were estimated using the univariable Cox proportional hazards regression model. To adjust for potential confounding variables, multivariable Cox proportional hazards regression models were constructed separately for PFS and OS. The following clinically relevant covariates were entered into the models simultaneously: treatment group (everolimus vs. conventional che-

motherapy), age, tumor location, histology, WHO grade, and extent of resection. The proportional hazards assumption was verified using Schoenfeld residual tests, and no violation was detected ($P>0.05$ for all covariates). Results were presented as HR with 95% CI. To compare PFS and OS rates at specific time points (1, 3, and 5 years), separate log-rank tests were performed. These analyses were considered exploratory and descriptive; therefore, no adjustments for multiple comparisons (e.g., Bonferroni correction) were applied. Consequently, the results from these time-point comparisons should be interpreted with caution, as the uncorrected testing may inflate the probability of Type I errors. All other tests were two-sided, and $P<0.05$ was considered statistically significant.

The subgroup analysis of optic pathway glioma patients using the PedEyeQ scale was not pre-specified in the study protocol but was conducted as an exploratory post-hoc analysis. No separate sample size calculation was performed for this subgroup ($n=103$). Accordingly, the results from this subgroup should be interpreted as hypothesis-generating and warrant confirmation in future prospective studies. Furthermore, given the incomplete NGS data across the cohort, pre-specified subgroup analyses based on molecular driver genes (e.g., NF1, TSC, FGFR) were not conducted, as the sample size in each genetic subgroup was insufficient to achieve adequate statistical power. Therefore, our efficacy comparisons are presented as overall cohort analyses without genotype-driven stratification, and the results should be considered exploratory. Adverse event rates were compared using crude incidence proportions (number of patients with at least one event/total patients in each group). For health-care resource utilization metrics, data were summarized as median (IQR) and compared between groups using the Mann-Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate. These analyses were considered exploratory and hypothesis-generating.

Results

Baseline patient characteristics

The two groups were comparable in baseline characteristics, including age, sex, tumor location, histological subtype, and extent of surgical resection (all $P>0.05$; **Table 1**).

PFS

The median PFS was 49.00 months (95% CI: 37.00-55.00) in the everolimus group and 41.00 months (95% CI: 28.00-55.00) in the CV group, with no statistically significant difference (Log-rank $\chi^2=0.162$, $P=0.688$) and an HR of 0.939 (95% CI: 0.684-1.288). Comparison of PFS rates at various time points showed that the 1-year, 3-year, and 5-year PFS rates were 73.81%, 58.73%, and 45.24%, respectively, in the everolimus group, and 68.63%, 54.90%, and 43.14%, respectively, in the CV group. No statistically significant differences were observed at any time point (all $P>0.05$). The Kaplan-Meier survival curves demonstrated that the PFS curves of the two groups were largely overlapping, suggesting that everolimus had comparable efficacy to conventional chemotherapy in delaying disease progression. See **Table 2** and **Figure 2**.

OS

The OS did not differ significantly between the everolimus and CV groups (Log-rank $\chi^2=0.423$, $P=0.515$), with HR of 0.778 (95% CI: 0.365-1.662). Comparison of OS rates at various time points demonstrated that the 1-year, 3-year, and 5-year OS rates were 97.62%, 94.44%, and 91.27%, respectively, in the everolimus group, and 96.08%, 92.81%, and 88.89%, respectively, in the CV group. No statistically significant differences were observed at any time point (all $P>0.05$). The Kaplan-Meier survival curves showed that the OS curves of the two groups were largely overlapping, indicating that everolimus and conventional chemotherapy were comparable in terms of prolonging OS in patients. See **Table 3** and **Figure 3**.

Multivariable Cox regression analysis

Multivariable Cox regression analysis was performed to adjust for baseline clinical covariates. After adjustment, everolimus treatment was not identified as an independent predictor of PFS (adjusted HR=0.928; 95% CI: 0.675-1.275; $P=0.644$). None of the other covariates, including age, tumor location, histology, WHO grade, or extent of resection reached statistical significance (all $P>0.05$). In the multivariable Cox regression model for OS, everolimus treatment did not demonstrate a statistically significant association with improved overall survival

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Table 1. Comparison of baseline characteristics between the two groups

Characteristics	Total (n=279)	Everolimus group (n=126)	CV group (n=153)	Statistic	P	SMD
Age (years)	7.00 (5.00, 10.00)	7.00 (5.00, 10.00)	7.00 (5.00, 10.00)	Z=-0.095	0.924	0.045
Sex				$\chi^2=0.353$	0.552	0.071
Male	156 (55.91)	68 (53.97)	88 (57.52)			
Female	123 (44.09)	58 (46.03)	65 (42.48)			
Tumor location				Z=0.451	0.978	0.081
Cerebral hemisphere	28 (10.04)	12 (9.52)	16 (10.46)			
Cerebellar hemisphere	78 (27.96)	36 (28.57)	42 (27.45)			
Sellar region	123 (44.09)	57 (45.24)	66 (43.14)			
Brainstem	13 (4.66)	5 (3.97)	8 (5.23)			
Ventricle	37 (13.26)	16 (12.70)	21 (13.73)			
Histology				Z=0.287	0.991	0.065
Pilocytic astrocytoma	157 (56.27)	72 (57.14)	85 (55.56)			
Pilomyxoid astrocytoma	31 (11.11)	14 (11.11)	17 (11.11)			
Diffuse astrocytoma	43 (15.41)	19 (15.08)	24 (15.69)			
Oligodendroglioma	35 (12.54)	16 (12.70)	19 (12.42)			
Astrocytoma NOS	13 (4.66)	5 (3.97)	8 (5.23)			
WHO grade				$\chi^2=0.006$	0.936	0.010
Grade I	172 (61.65)	78 (61.90)	94 (61.44)			
Grade II	107 (38.35)	48 (38.10)	59 (38.56)			
Extent of resection				Z=0.417	0.937	0.078
Gross total resection	40 (14.34)	18 (14.29)	22 (14.38)			
Subtotal resection	110 (39.43)	52 (41.27)	58 (37.91)			
Partial resection	89 (31.90)	38 (30.16)	51 (33.33)			
Biopsy	40 (14.34)	18 (14.29)	22 (14.38)			

Notes: SMD, standardized mean difference.

Table 2. Comparison of PFS between the two groups

PFS	CV group (n=153)	Everolimus group (n=126)	Statistic	P
Median (95% CI)	41.00 (28.00-55.00)	49.00 (37.00-55.00)		
1-year PFS rate (%)	105 (68.63)	93 (73.81)	$\chi^2=0.901$	0.343
3-year PFS rate (%)	84 (54.90)	74 (58.73)	$\chi^2=0.412$	0.521
5-year PFS rate (%)	66 (43.14)	57 (45.24)	$\chi^2=0.124$	0.725

Notes: PFS, progression-free survival; CI, confidence interval; CV, carboplatin-vincristine.

(adjusted HR=0.742; 95% CI: 0.346-1.593; P=0.444). Similarly, none of the other covariates, including age, tumor location, histology, WHO grade, or extent of resection, showed independent prognostic value for OS (all P>0.05), as summarized in **Table 4**.

Tumor response assessment

No significant differences were observed in ORR, DCR, or CBR (all P>0.05). The ORR was 37.30% in the everolimus group and 35.29% in the CV group; the DCR was 89.68% and 86.27%, respectively; and the CBR was 85.71%

and 81.70%, respectively. The distribution of each response category (CR, PR, MR, SD, PD) was also similar, suggesting that everolimus was comparable to conventional chemotherapy in terms of antitumor efficacy. See **Table 5**.

Functional outcomes in the optic pathway glioma subgroup

In the optic pathway glioma subgroup (n=103), there were 48 patients in the everolimus group and 55 patients in the CV group. The baseline PedEyeQ scores were balanced and comparable (P=0.778). As shown in **Table 6**, the two

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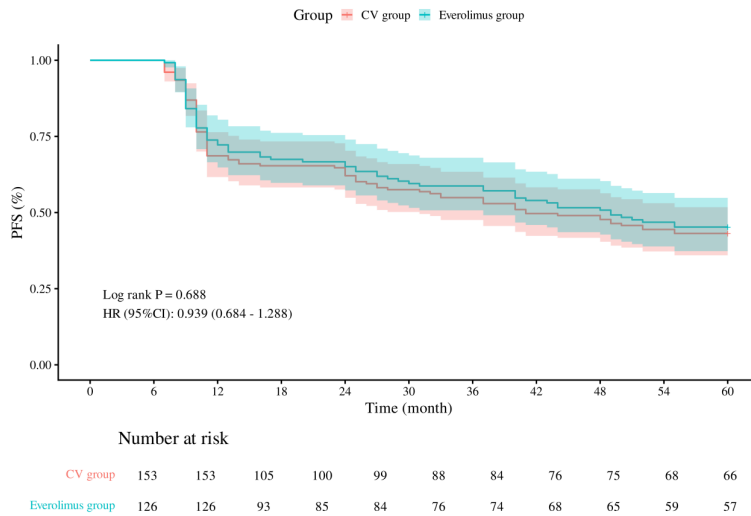


Figure 2. Comparison of PFS between the two groups. Notes: PFS, progression-free survival; CV, carboplatin-vincristine; CI, confidence interval.

Table 3. Comparison of OS between the two groups

OS	CV group (n=153)	Everolimus group (n=126)	Statistic	P
Median (95% CI)	-	-		
1-year OS rate (%)	148 (96.08)	124 (97.62)	-	0.611
3-year OS rate (%)	142 (92.81)	119 (94.44)	$\chi^2=0.306$	0.580
5-year OS rate (%)	136 (88.89)	115 (91.27)	$\chi^2=0.434$	0.510

Notes: OS, overall survival; CI, confidence interval; CV, carboplatin-vincristine.

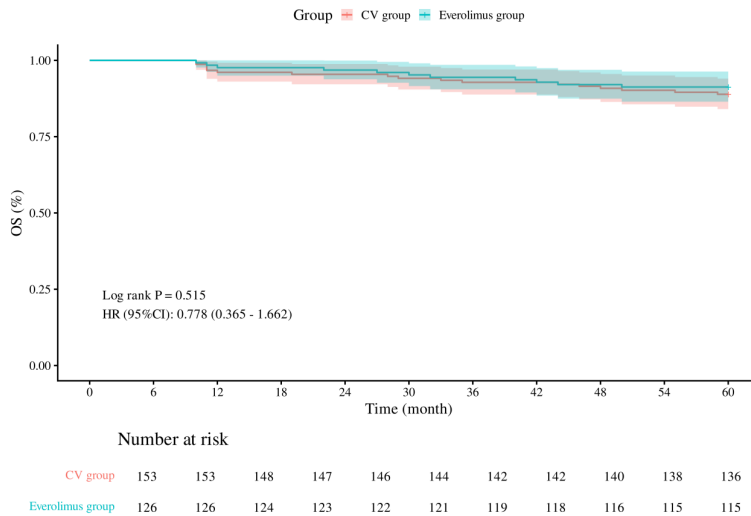


Figure 3. Comparison of OS between the two groups. Notes: OS, overall survival; CV, carboplatin-vincristine; CI, confidence interval.

groups were well balanced with respect to baseline characteristics, including age, sex, NF1 status, tumor location, extent of prior surgery, and baseline PedEyeQ scores (all $P>0.05$).

Improvement was significantly higher in the everolimus group at 1 year ($P=0.022$), 3 years ($P=0.002$), and 5 years ($P<0.001$). Furthermore, the cumulative incidence of optic nerve atrophy

Longitudinal assessments at the 1-, 3-, and 5-year follow-up visits demonstrated that patients in the everolimus group showed progressive and sustained improvement in visual function: the PedEyeQ score increased to 58.60 ± 7.80 at 1 year after treatment initiation (a 12.07% improvement from baseline, $P<0.05$), further increased to 61.40 ± 7.51 at 3 years (a 17.42% improvement from baseline, $P<0.01$), and reached 63.19 ± 6.98 at 5 years (a 20.85% improvement from baseline, $P<0.05$), indicating continuous functional gain over time rather than a static endpoint difference. In contrast, patients in the CV group showed limited visual function improvement. Between-group comparisons showed that the PedEyeQ score of the everolimus group was significantly better than that of the CV group at 1- ($P=0.008$), 3- ($P=0.001$) and 5-year ($P<0.001$) follow-up visits (Table 7).

To complement the subjective PedEyeQ findings, objective ophthalmic indicators were analyzed in the same optic pathway glioma subgroup (Table 8). Baseline BCVA, visual field status, and optic nerve atrophy grades were well balanced between the two groups (all $P>0.05$).

At the 5-year follow-up, the everolimus group demonstrated a significant improvement in BCVA compared to baseline ($P<0.001$). The between-group difference at 5 years was statistically significant ($P<0.001$). Consistently, the proportion of patients with visual field improvement was significantly higher in the everolimus group at 1 year ($P=0.022$), 3 years ($P=0.002$), and 5 years ($P<0.001$). Furthermore, the cumulative incidence of optic nerve atrophy

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Table 4. Multivariable Cox proportional hazards regression analysis for PFS and OS

Variable	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Treatment				
Chemotherapy	Reference		Reference	
Everolimus	0.928 (0.675-1.275)	0.644	0.742 (0.346-1.593)	0.444
Age (per year increase)	1.026 (0.976-1.079)	0.306	1.079 (0.962-1.210)	0.193
Tumor location				
Cerebral hemisphere	Reference		Reference	
Cerebellar hemisphere	1.029 (0.539-1.965)	0.931	0.505 (0.094-2.728)	0.427
Sellar region	0.699 (0.416-1.177)	0.179	0.697 (0.215-2.256)	0.547
Brainstem	0.753 (0.466-1.215)	0.245	0.617 (0.207-1.843)	0.387
Ventricle	0.820 (0.349-1.928)	0.649	0.507 (0.058-4.435)	0.539
Histology				
Pilocytic astrocytoma	Reference		Reference	
Pilomyxoid astrocytoma	1.433 (0.619-3.320)	0.401	1.430 (0.186-11.021)	0.731
Diffuse astrocytoma	1.938 (0.761-4.935)	0.165	1.978 (0.211-18.583)	0.551
Oligodendroglioma	1.220 (0.486-3.058)	0.672	0.951 (0.095-9.470)	0.966
Astrocytoma NOS	1.490 (0.583-3.806)	0.405	1.635 (0.174-15.356)	0.667
WHO grade				
Grade I	Reference		Reference	
Grade II	1.194 (0.852-1.673)	0.303	1.096 (0.500-2.401)	0.819
Extent of resection				
Gross total resection	Reference		Reference	
Subtotal resection	0.903 (0.504-1.619)	0.733	0.631 (0.146-2.733)	0.538
Partial resection	0.881 (0.543-1.429)	0.607	0.874 (0.295-2.588)	0.808
Biopsy	0.824 (0.498-1.363)	0.45	0.838 (0.268-2.620)	0.761

Notes: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Table 5. Comparison of best overall response assessment between the two groups [n (%)]

Indicators	Everolimus group (n=126)	CV group (n=153)	Statistic	P
CR	5 (3.97)	6 (3.92)	$\chi^2=0.000$	0.984
PR	42 (33.33)	48 (31.37)	$\chi^2=0.122$	0.727
MR	28 (22.22)	32 (20.92)	$\chi^2=0.070$	0.791
SD	38 (30.16)	46 (30.07)	$\chi^2=0.000$	0.987
PD	13 (10.32)	21 (13.73)	$\chi^2=0.750$	0.386
ORR	47 (37.30)	54 (35.29)	$\chi^2=0.121$	0.728
DCR	113 (89.68)	132 (86.27)	$\chi^2=0.750$	0.386
CBR	108 (85.71)	125 (81.70)	$\chi^2=0.809$	0.368

Notes: CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; ORR, objective response rate (CR+PR); DCR, disease control rate (CR+PR+MR+SD); CBR, clinical benefit rate (CR+PR+MR+SD lasting ≥ 6 months).

progression (increase ≥ 1 grade) was lower in the everolimus group at 5 years ($P=0.040$). These objective metrics corroborate the Ped-EyeQ findings, suggesting that the visual func-

tional benefit observed with everolimus reflects genuine anatomical and physiological preservation rather than solely subjective perception.

Safety analysis

The adverse event profiles of the two groups differed markedly. The incidence of grade 3-4 adverse events was 22.22% (28/126) in the everolimus group, which was significantly lower than that in the CV group (44.44%; 68/153) ($P<0.001$). The incidence of hematologic toxicity was 26.19% in the everolimus group, significantly lower than the 52.94% in the CV group ($P<0.001$); the incidence rates of grade 3-4 neutropenia were 3.97% and 27.45%, respectively ($P<0.001$). Adverse events specific to the everolimus group included oral mucositis (49.21%, of which grade 3-4 accounted for 5.56%),

Everolimus vs. chemotherapy in pediatric LGG

Table 6. Baseline characteristics in the optic pathway glioma subgroup

Characteristics	Everolimus (n=48)	CV (n=55)	Statistic	P	SMD
Age (years)	8.00 (5.00, 10.25)	7.00 (5.00, 9.00)	Z=1.066	0.287	0.199
Sex			$\chi^2=0.001$	0.969	0.008
Male	26 (54.17)	30 (54.55)			
Female	22 (45.83)	25 (45.45)			
Tumor location			$\chi^2=0.189$	0.663	0.086
Cerebral hemisphere	8 (16.67)	11 (20.00)			
Sellar region	40 (83.33)	44 (80.00)			
NF1 status			$\chi^2=0.149$	0.699	0.076
Positive	28 (58.33)	30 (54.55)			
Negative	20 (41.67)	25 (45.45)			
Prior surgery			$\chi^2=0.109$	0.947	0.065
Subtotal resection	11 (22.92)	14 (25.45)			
Partial resection	15 (31.25)	16 (29.09)			
Biopsy	22 (45.83)	25 (45.45)			
Baseline PedEyeQ score	52.29±8.43	51.80±9.12	t=0.283	0.778	0.057

Notes: PedEyeQ, Pediatric Eye Questionnaire; NF1, neurofibromatosis type 1; SMD, standardized mean difference; CV, carboplatin-vincristine.

Table 7. Functional outcomes in the optic pathway glioma subgroup

Indicators	Everolimus group (n=48)	CV group (n=55)	Statistic	P	95% CI
1 year	58.60±7.80*	54.20±8.67	t=2.695	0.008	1.162-7.646
3 years	61.40±7.51*	55.80±8.89	t=3.423	0.001	2.353-8.839
5 years	63.19±6.98*	53.56±9.22	t=6.013	<0.001	6.448-12.800

Notes: *P<0.05, compared with baseline. PedEyeQ, Pediatric Eye Questionnaire; CI, confidence interval; CV, carboplatin-vincristine.

Table 8. Objective ophthalmic outcomes in the optic pathway glioma subgroup

Indicators	Everolimus group (n=48)	CV group (n=55)	Statistic	P
BCVA (logMAR)				
Baseline	0.82±0.35	0.85±0.38	t=-0.414	0.680
1 year	0.71±0.32*	0.89±0.41	t=-2.624	0.010
3 years	0.65±0.30*	0.94±0.44	t=-3.962	<0.001
5 years	0.58±0.28*	1.02±0.48	t=-5.429	<0.001
Visual field improvement [n (%)]				
1 year	15 (31.25)	7 (12.73)	$\chi^2=5.235$	0.022
3 years	20 (41.67)	8 (14.55)	$\chi^2=9.524$	0.002
5 years	24 (50.00)	9 (16.36)	$\chi^2=13.318$	<0.001
Optic nerve atrophy progression [n (%)]				
1 year	4 (8.33)	10 (18.18)	-	0.164
3 years	6 (12.50)	16 (29.09)	$\chi^2=4.200$	0.040
5 years	8 (16.67)	19 (34.55)	$\chi^2=4.236$	0.040

Notes: *P<0.05, compared with baseline within-group paired t-test. BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CV, carboplatin-vincristine.

hyperlipidemia (38.10%), hypertriglyceridemia (33.33%), and rash (25.40%), most of which were grade 1-2 and manageable with symptom-

atic treatment. The incidences of nausea and vomiting (58.17%) and alopecia (50.98%) in the CV group were significantly higher (both

Table 9. Comparison of treatment-related AEs of any grade between the two groups [n (%)]

Any-grade AEs	Everolimus group (n=126)	CV group (n=153)	Statistic	P
Hematologic toxicity	33 (26.19)	81 (52.94)	$\chi^2=20.462$	<0.001
Neutropenia	23 (18.25)	74 (48.37)	$\chi^2=27.625$	<0.001
Thrombocytopenia	11 (8.73)	34 (22.22)	$\chi^2=9.298$	0.002
Anemia	16 (12.70)	44 (28.76)	$\chi^2=10.557$	0.001
Nausea/vomiting	16 (12.70)	89 (58.17)	$\chi^2=60.870$	<0.001
Alopecia	4 (3.17)	78 (50.98)	-	<0.001
Oral mucositis	62 (49.21)	13 (8.50)	$\chi^2=58.260$	<0.001
Rash	32 (25.40)	8 (5.23)	$\chi^2=22.884$	<0.001
Diarrhea	23 (18.25)	23 (15.03)	$\chi^2=0.521$	0.471
Fatigue	20 (15.87)	34 (22.22)	$\chi^2=1.785$	0.182
Elevated liver enzymes	13 (10.32)	13 (8.50)	$\chi^2=0.271$	0.603
Proteinuria	8 (6.35)	4 (2.61)	-	0.147
Infection	11 (8.73)	19 (12.42)	$\chi^2=0.979$	0.322
Hyperlipidemia	48 (38.10)	4 (2.61)	-	<0.001
Hypertriglyceridemia	42 (33.33)	5 (3.27)	$\chi^2=44.588$	<0.001
Hyperglycemia	16 (12.70)	8 (5.23)	$\chi^2=4.904$	0.027

Notes: AE, adverse event; CV, carboplatin-vincristine.

Table 10. Comparison of grade 3-4 treatment-related AEs between the two groups [n (%)]

Grade 3-4 AEs	Everolimus group (n=126)	CV group (n=153)	Statistic	P
Hematologic toxicity	5 (3.97)	42 (27.45)	$\chi^2=27.201$	<0.001
Neutropenia	5 (3.97)	42 (27.45)	$\chi^2=27.201$	<0.001
Thrombocytopenia	2 (1.59)	9 (5.88)	-	0.119
Anemia	1 (0.79)	5 (3.27)	-	0.227
Nausea/vomiting	1 (0.79)	13 (8.50)	-	0.004
Alopecia	0 (0.00)	0 (0.00)	-	1.000
Oral mucositis	7 (5.56)	1 (0.65)	-	0.025
Rash	2 (1.59)	0 (0.00)	-	0.203
Diarrhea	3 (2.38)	2 (1.31)	-	0.661
Fatigue	2 (1.59)	4 (2.61)	-	0.693
Elevated liver enzymes	2 (1.59)	1 (0.65)	-	0.591
Proteinuria	0 (0.00)	0 (0.00)	-	1.000
Infection	2 (1.59)	4 (2.61)	-	0.693
Hyperlipidemia	4 (3.17)	0 (0.00)	-	0.041
Hypertriglyceridemia	3 (2.38)	0 (0.00)	-	0.091
Hyperglycemia	1 (0.79)	0 (0.00)	-	0.452
Any grade 3-4 adverse events	28 (22.22)	68 (44.44)	$\chi^2=15.119$	<0.001

Notes: AE, adverse event; CV, carboplatin-vincristine.

P<0.001). Details are shown in **Tables 9** and **10**.

Given the significantly longer median treatment duration in the everolimus group (43.0 vs. 38.0 months, P<0.001), we performed an exposure-adjusted safety analysis using Poisson rate comparison (Wald test) to control for differen-

tial follow-up time. The cumulative patient-years of exposure were 451.5 in the everolimus group and 484.5 in the CV group. The exposure-adjusted rates (per 100 patient-years) largely confirmed the favorable safety profile of everolimus. Notably, after exposure adjustment, hyperglycemia of any grade (P=0.077) and grade 3-4 oral mucositis (P=0.061) no longer

Table 11. Comparison of exposure-adjusted treatment-related AEs of any grade between the two groups (per 100 patient-years)

Any-grade AEs	Everolimus group (n=126)	CV group (n=153)	Rate ratio	P
Total patient-years	451.5	484.5	-	-
Hematologic toxicity	7.31	16.72	0.44	<0.001
Neutropenia	5.09	15.27	0.33	<0.001
Thrombocytopenia	2.44	7.02	0.35	0.002
Anemia	3.54	9.08	0.39	0.001
Nausea/vomiting	3.54	18.37	0.19	<0.001
Alopecia	0.89	16.10	0.06	<0.001
Oral mucositis	13.73	2.68	5.12	<0.001
Rash	7.09	1.65	4.3	<0.001
Diarrhea	5.09	4.75	1.07	0.818
Fatigue	4.43	7.02	0.63	0.103
Elevated liver enzymes	2.88	2.68	1.07	0.865
Proteinuria	1.77	0.83	2.14	0.214
Infection	2.44	3.92	0.62	0.211
Hyperlipidemia	10.63	0.83	12.87	<0.001
Hypertriglyceridemia	9.30	1.03	9.01	<0.001
Hyperglycemia	3.54	1.65	2.15	0.077

Notes: AE, adverse event; CV, carboplatin-vincristine.

Table 12. Comparison of exposure-adjusted grade 3-4 treatment-related AEs between the two groups (per 100 patient-years)

Grade 3-4 AEs	Everolimus group (n=126)	CV group (n=153)	Rate ratio	P
Total patient-years	451.5	484.5	-	-
Hematologic toxicity	1.11	8.67	0.13	<0.001
Neutropenia	1.11	8.67	0.13	<0.001
Thrombocytopenia	0.44	1.86	0.24	0.066
Anemia	0.22	1.03	0.21	0.159
Nausea/vomiting	0.22	2.68	0.08	0.016
Oral mucositis	1.55	0.21	7.42	0.061
Rash	0.44	0.00	-	0.203
Diarrhea	0.66	0.41	1.62	0.597
Fatigue	0.44	0.83	0.53	0.465
Elevated liver enzymes	0.44	0.21	2.15	0.535
Infection	0.44	0.83	0.53	0.465
Hyperlipidemia	0.89	0.00	-	0.041
Hypertriglyceridemia	0.66	0.00	-	0.091
Hyperglycemia	0.22	0.00	-	0.452
Any grade 3-4 adverse events	6.20	14.03	0.44	<0.001

Notes: AE, adverse event; CV, carboplatin-vincristine.

reached statistical significance, whereas severe neutropenia ($P<0.001$), nausea/vomiting ($P=0.016$), and any grade 3-4 AE ($P<0.001$) remained significantly less frequent with everolimus. Details are shown in **Tables 11** and **12**.

Long-term pediatric safety: growth, bone metabolism, and endocrine function

To evaluate the long-term pediatric safety of chronic therapy, we compared growth, bone metabolism, and thyroid function between the two groups at baseline, 3 years, and 5 years (**Table 13**). Baseline characteristics were comparable between groups (all $P>0.05$). At 5 years, the proportion of patients with short stature was 3.97% (5/126) in the everolimus group and 6.54% (10/153) in the CV group, with no statistically significant difference ($P=0.429$). Similarly, the proportion of patients with low BMD at 5 years was 4.76% (6/126) in the everolimus group and 9.80% (15/153) in the CV group; this difference did not reach statistical significance ($P=0.112$). Serum calcium and phosphorus levels remained stable throughout the 5-year follow-up in both groups, with no significant between-group differences at any time point (all $P>0.05$). Endocrine function, as assessed by serum free T4, was also comparable between the two groups at all evaluated time points (all $P>0.05$). Overall, no significant between-group differences were observed in long-term growth, bone metabolism, or thyroid function during the 5-year follow-up. These findings suggest that, within the observed time-frame, everolimus and conventional chemotherapy had comparable profiles regarding these pediatric safety endpoints.

Comparison of treatment exposure and adherence

Table 14 compares treatment exposure and adherence. The everolimus group had a signifi-

Table 13. Comparison of long-term growth, bone metabolic, and endocrine outcomes between the two groups

Indicators	Everolimus group (n=126)	CV group (n=153)	Statistic	P
Height Z-score <-2 at 5 years	5 (3.97)	10 (6.54)	-	0.429
BMD Z-score <-2 at 5 years	6 (4.76)	15 (9.80)	$\chi^2=2.524$	0.112
Serum calcium (mmol/L)				
Baseline	2.35±0.13	2.33±0.14	t=1.242	0.215
3 years	2.33±0.13	2.31±0.15	t=0.849	0.396
5 years	2.33±0.13	2.32±0.16	t=0.002	0.998
Serum phosphorus (mmol/L)				
Baseline	1.42±0.18	1.40±0.20	t=1.059	0.290
3 years	1.40±0.19	1.38±0.22	t=0.576	0.565
5 years	1.39±0.18	1.37±0.23	t=0.412	0.681
Free T4 (pmol/L)				
Baseline	15.84±3.22	15.65±3.55	t=0.440	0.660
3 years	15.57±3.45	14.98±3.85	t=1.312	0.191
5 years	15.64±3.35	15.18±3.61	t=1.119	0.264

Notes: CV, carboplatin-vincristine.

Table 14. Comparison of treatment exposure and adherence between the two groups

Indicators	Everolimus group (n=126)	CV group (n=153)	Statistic	P
Actual treatment duration (months)	43.00 (35.00, 51.00)	38.00 (28.00, 47.00)	Z=3.636	<0.001
Completion of planned treatment courses	89 (70.63)	102 (66.67)	$\chi^2=0.504$	0.478
Reasons for discontinuation				
Disease progression	21 (16.67)	38 (24.84)		
Intolerable toxicity	8 (6.35)	10 (6.54)		
Parent/patient preference	8 (6.35)	3 (1.96)		
DI	91.00 (88.00, 93.00)	75.00 (69.00, 87.00)	Z=9.249	<0.001
RDI	88.00 (86.00, 90.00)	86.00 (75.00, 89.00)	Z=3.961	<0.001
RDI<85%	22 (17.46)	60 (39.22)	$\chi^2=15.759$	<0.001
Good adherence	101 (80.16)			

Notes: DI, dose intensity; RDI, relative dose intensity; CV, carboplatin-vincristine.

cantly longer median treatment duration (43.0 vs. 38.0 months, $P<0.001$), higher DI (91.00% vs. 75.00%, $P<0.001$) and RDI (88.00% vs. 86.00%, $P<0.001$), and a lower proportion of patients with RDI<85% (17.46% vs. 39.22%, $P<0.001$), indicating better treatment delivery and tolerance with everolimus.

Comparison of healthcare resource utilization

Table 15 compares the utilization of medical resources. The everolimus group had a significant fewer annual hospitalizations (2.0 times vs. 4.0 times, $P<0.001$), shorter hospital stays (4.0 days vs. 9.0 days, $P<0.001$), fewer ED visits (1.0 times vs. 3.0 times, $P<0.001$), and

lower rates of unplanned hospitalization, fewer AE-related ED visits, and less need for blood transfusion and G-CSF (all $P<0.001$), indicating that everolimus can significantly reduce the healthcare burden.

Discussion

For pLGG, the most common central nervous system tumor in children, treatment has shifted from cytotoxic chemotherapy to targeted therapy over the past few decades [31]. Although chemotherapy is still the first choice, its efficacy is limited and its toxicity is concerning [32]. The discovery of the MAPK and PI3K/AKT/mTOR pathways has made mTOR inhibitors

Table 15. Comparison of medical resource utilization between the two groups

Indicators	Everolimus group (n=126)	CV group (n=153)	Statistic	P
Annual number of hospitalizations	2.00 (1.00, 3.00)	4.00 (3.00, 4.00)	Z=-5.946	<0.001
Annual length of hospital stays (days)	4.00 (3.00, 6.00)	9.00 (6.00, 13.00)	Z=-9.588	<0.001
Rate of unplanned hospitalizations	12 (9.52)	45 (29.41)	$\chi^2=16.812$	<0.001
Annual number of outpatient visits	7.00 (6.00, 9.00)	8.00 (6.00, 9.00)	Z=-0.749	0.454
Annual number of emergency department visits	1.00 (1.00, 1.75)	3.00 (2.00, 4.00)	Z=-13.125	<0.001
Proportion of ED visits related to adverse events	20 (15.87)	90 (58.82)	$\chi^2=53.373$	<0.001
Transfusion support	0	16 (10.46)	Z=8.234	<0.001
G-CSF	3 (2.38)	42 (27.45)	-	<0.001

Notes: ED, emergency department; G-CSF, granulocyte colony-stimulating factor; CV, carboplatin-vincristine.

such as everolimus a promising option. This study retrospectively analyzed 279 patients with pLGG who received everolimus or chemotherapy over a 7-year period, and compared the differences in efficacy, prognosis and safety between the two treatment regimens to guide individualized treatment in the real world.

This study revealed no significant difference in PFS between everolimus and CV. This finding suggests that everolimus exhibits comparable efficacy to carboplatin-based conventional chemotherapy in terms of delaying disease progression. The study by Haas-Kogan et al. [27] indicated that in the PNOC001 phase II clinical trial for recurrent or progressive pLGG, the 6-month PFS rate with everolimus treatment reached 67.4%, with a median PFS of 11.1 months, and the 48-month OS rate for the overall population was as high as 91.9%, confirming the disease control value of this agent in refractory pLGG. Ullrich et al. [33] further found in a phase II clinical trial of NF1-associated recurrent/progressive pLGG that among 23 patients treated with everolimus, 68% achieved tumor shrinkage or disease stabilization, and all patients remained alive at a median follow-up of 33 months, with no treatment discontinuation due to toxicity. In the present study, the 5-year PFS rate in the everolimus group was 45.24%, which largely overlapped with the 43.14% in the CV group; this figure is highly consistent with the 5-year PFS rates of CV regimens reported in previous literature [10], further supporting the potential feasibility of everolimus as an alternative to conventional chemotherapy in first-line or second-line settings.

Regarding secondary outcomes, no significant differences in ORR, CBR, or DCR were observed

between everolimus and CV groups. Notably, ORR was not significantly higher with everolimus than with chemotherapy, yet CBR and DCR of everolimus were still high, exceeding 85%. Hütt-Cabezas et al. [34] highlighted that the antitumor effects of mTOR inhibitors in pLGG are primarily attributed to their ability to suppress cell proliferation and inhibit angiogenesis. This is in contrast to the main action of conventional chemotherapeutic agents which is to induce apoptosis. This is particularly important for pLGG, in which patients often have prolonged survival with minimal deterioration in function and quality of life. In this setting, even a small prolongation of survival can dramatically change outcomes as well as preserve patients' neurological function and quality of life.

Optic pathway gliomas are among the most difficult types of pLGG to treat clinically, and the objective for these tumors is not only disease control but also maintaining or enhancing the children's visual function in the most optimal way. The results in the optic pathway glioma subgroup (n=103) in this study warrant emphasis. Patients who had everolimus therapy showed significantly better PedEyeQ scores at 1, 3 and 5 years than in the CV group, indicating that the effect of everolimus was more visible as treatment period extended. This finding has important clinical translational significance. As previously shown, visual deficits in patients with optic pathway gliomas may be caused not only by direct tumor compression of optic nerve/optic chiasm but also by tumor-induced swelling, systemic chemotoxicities, and the comprehensive influence of hospitalization on the patient's physiological status [35-37]. The inclusion of objective ophthalmic metrics sub-

stantiates the subjective PedEyeQ findings. The significant improvement in BCVA and the higher rate of visual field improvement in the everolimus group provide concrete evidence that the functional benefit translates into measurable anatomical preservation. Moreover, the lower cumulative incidence of optic nerve atrophy progression suggests that everolimus may exert a neuroprotective effect beyond mere tumor cytostasis, possibly through reduction of peritumoral edema and decreased mechanical compression on the optic pathway.

The sustained visual function improvement observed in the everolimus-treated OPG subgroup warrants further mechanistic exploration. Notably, the serial PedEyeQ measurements revealed a widening intergroup difference over time (from 4.4 points at 1 year to 9.6 points at 5 years), suggesting that the functional benefit of everolimus is not merely a one-time effect but accumulates with prolonged treatment exposure. The observed combination of sustained tumor stabilization (5-year PFS of 45.24%) and progressive visual recovery in the everolimus-treated OPG subgroup supports a mechanistic hypothesis. Ullrich et al. [38] assessed visual outcomes in children with NF1-associated optic pathway gliomas treated with everolimus and found that the majority maintained stable vision, with a subset demonstrating measurable improvement. We propose a dual-mechanism hypothesis to explain these findings. First, everolimus directly inhibits mTORC1, blocking ribosomal S6 kinase and 4E-BP1 phosphorylation, thereby suppressing tumor cell proliferation in NF1- or TSC-deficient glial cells [33]. This cytostatic effect likely underlies the comparable PFS between everolimus and conventional chemotherapy. Second, and more speculatively, mTOR inhibition may reduce tumor-associated vascular permeability through downregulation of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1- α (HIF-1 α) [33, 39], thereby alleviating peritumoral edema and secondary mechanical compression on the optic pathway. This indirect effect could explain the progressive improvement in PedEyeQ scores observed exclusively in the everolimus group - an advantage not shared by CV chemotherapy, which, despite achieving similar tumor control, lacks anti-edema activity and carries cumulative neurotoxic and ototoxic burdens. Additionally, the oral route of everoli-

mus administration avoids chemotherapy-related systemic inflammatory reactions and reduces repeated intravenous puncture trauma, both of which may contribute to long-term visual preservation. However, we acknowledge that these mechanistic interpretations remain speculative in the absence of paired tissue or animal model validation. Future studies incorporating patient-derived organoid cultures or NF1-mutant genetically engineered mouse models are urgently needed to dissect the relative contribution of anti-proliferative versus anti-edema effects of everolimus, and to determine whether baseline mTOR pathway activation levels predict functional recovery.

Safety evaluation is another major aspect of this report. Results indicated that only 22.22% of the cases treated with everolimus presented with grade 3-4 AEs compared to 44.44% for the other regimen group ($P < 0.001$). Differences were striking for hematological events (26.19% vs. 52.94%) and grade 3-4 neutropenia (3.97% vs. 27.45%). Using targeted therapy versus conventional chemotherapy regimens for pLGG, Cooney et al. [40] in a clinical controversy debate remarked that conventional chemotherapy protocols lead to myelotoxicity, neurotoxicity, and also ototoxicity, and have the possibility of causing secondary malignant neoplasm, the factors which seriously influence patients' treatment tolerance and the overall well-being of patients' life; in contrast, the side effect profile of targeted therapeutic agents, such as mTOR inhibitors, mitogen-activated protein kinase kinase (MEK) inhibitors, and B-Raf proto-oncogene (BRAF) inhibitors, is quite distinct, mainly characterized by metabolic imbalances, mucocutaneous lesions, and cardiovascular adverse events.

Our study found a high rate of patients experiencing nausea/vomiting (58.17%) and alopecia (50.98%) in the CV group. This combination of side effects not only significantly decreased patients' well-being but may also have affected treatment continuity by reducing food intake and the deterioration of nutritional status. In contrast, everolimus was not associated with significant cytopenias or alopecia, a feature that could be particularly important for safety of children under critical stages of growth and development. Also, no patients permanently discontinued treatment due to severe adverse events in either group, suggesting both regi-

ments were well tolerated by patients under close supervision and timely intervention.

The adverse event profile specific to the everolimus group included oral mucositis (49.21%), hyperlipidemia (38.10%), hypertriglyceridemia (33.33%), and rash (25.40%). However, in most cases, the events were mild and the conditions could be handled with supportive care. PNOC001 Trial by Haas-Kogan et al. [27] reported comparable toxicity profile as well. In this study, oral mucositis and metabolic abnormalities were the most common treatment-related adverse events, while grade ≥ 3 toxic reactions were rare and no new safety problems occurred. However, it is well known that mTOR inhibitors are associated with risks, especially hyperlipidemia and hyperglycemia, and therefore need to be monitored regularly. It is worth noting that although the overall safety performance of everolimus is better, its incidence of severe (grade 3-4) oral mucositis (5.56%) and hyperlipidemia (3.17%) is still higher than that in the CV group. However, the absolute incidence of both is less than 6%, and almost all cases can be controlled by standard treatment. Mucositis can be alleviated by local irrigation and symptomatic treatment. Hyperlipidemia can be controlled by diet adjustment or lipid-lowering drugs. No patient required permanent discontinuation. Second, when weighed against the substantially higher rates of grade 3-4 hematologic toxicities, alopecia, and severe nausea/vomiting in the CV group - toxicities that directly impair children's nutritional status, growth, and psychosocial well-being during critical developmental stages - the class-specific metabolic and mucosal side effects of everolimus appear more acceptable and less disruptive to long-term quality of life. Therefore, despite a higher severe-grade incidence for these two particular AEs, the overall safety profile of everolimus remains favorable and clinically advantageous, especially in the context of chronic treatment for a disease with favorable long-term prognosis. Overall, in the field of pediatric oncology, where diseases such as pLGG are likely to have good overall results and long expected survival, treatment regimens should be based on their potential long-term effects on patients' cognition, psychosocial adjustment, and quality of life for both patients and their families. In this context, the oral route of administration of everolimus, reduced need for frequent chemo-

therapy visits, and significantly reduced risk of serious (grade 3-4), side effects provide unique benefits in tailoring treatment of the patient and thereby reducing the healthcare resource burden.

To address the concern that differential treatment exposure might confound safety comparisons, we calculated exposure-adjusted AE rates per 100 patient-years. After this adjustment, the safety advantage of everolimus was not only preserved but, for several toxicities, more pronounced. For instance, the rate of grade 3-4 neutropenia was 0.13 times that in the CV group, reinforcing the clinical relevance of the observed difference. Conversely, the higher exposure-adjusted rates of metabolic abnormalities and mucocutaneous events with everolimus underscore the importance of long-term metabolic monitoring in children receiving chronic mTOR inhibition. Regarding long-term pediatric safety, our 5-year follow-up data showed no significant between-group differences in height Z-score, BMD, serum calcium/phosphorus, or free T4 levels. The proportions of patients with short stature or low BMD were low in both groups and did not differ statistically. These findings suggest that, within the 5-year horizon, everolimus does not confer a demonstrable advantage over CV chemotherapy in preserving linear growth or bone health, nor does it appear to exert a disproportionately negative impact on these axes relative to conventional cytotoxic therapy. However, the conclusion of comparable long-term safety should be considered preliminary, and prospective trials with predefined endocrine and metabolic monitoring are needed to definitively address this question.

In addition to safety and efficacy, everolimus also improves treatment compliance and reduces the use of medical resources. Patients taking everolimus had longer treatment time, higher dose intensity, and a lower proportion with RDI<85%, reflecting better compliance with oral drugs. In addition, the drug also reduced the number of annual hospitalizations, shortened hospital stays, reduced the frequency of emergency visits, and reduced the need for blood transfusion or G-CSF support. These advantages reduce the burden on families, reduce medical costs, enable children to maintain normal academic and daily life, and make

everolimus a more practical long-term treatment option for pLGG patients.

Limitations

Several limitations of this study must be acknowledged. First and foremost, this is a single-center retrospective cohort study with inherent selection bias. Most critically, we did not have complete NGS molecular typing data for all enrolled patients. Although we excluded the BRAF V600E mutant subgroup, we were unable to perform stratified efficacy analyses based on other key driver genes such as NF1, TSC, or FGFR alterations. Given that these molecular subtypes are known to exhibit differential sensitivity to mTOR inhibition versus cytotoxic chemotherapy, the absence of this stratification significantly limits our ability to draw genotype-specific conclusions. Our results, therefore, primarily reflect the overall clinical response in a mixed molecular population, which may obscure heterogeneous treatment effects. The small sample sizes within individual genetic subgroups precluded any meaningful multivariable adjustment for molecular markers. We strongly emphasize that our findings should be considered hypothesis-generating, and future prospective trials with mandatory NGS-based enrollment criteria are urgently needed to validate whether everolimus offers a preferential benefit in specific molecular subsets (e.g., TSC-mutant vs. NF1-associated pLGG).

Second, although we have now incorporated exposure-adjusted AE rates to mitigate the confounding effect of differential treatment duration, the retrospective design precludes definitive causal inference. Additionally, while we have added longitudinal data on growth, bone metabolism, and endocrine function over the 5-year follow-up, these assessments were not part of the original prospective protocol and were extracted from routine clinical records. Consequently, the timing of these measurements varied between patients. Moreover, 5 years remains an intermediate timeframe for a pediatric population with excellent long-term prognosis; we did not systematically collect data on cognitive function, neuropsychological development, or secondary malignancy risk beyond this period. Therefore, our conclusions regarding the long-term safety of everolimus should be interpreted as preliminary, and prospective randomized controlled trials with pre-

defined neuropsychological batteries, growth charts, and endocrine monitoring are required to confirm these findings.

Conclusion

In summary, for pLGG patients, there was no significant differences between everolimus and CV in PFS, OS, or ORR, indicating that everolimus provides antitumor efficacy comparable to traditional chemotherapy. In addition, everolimus showed better visual function retention in the optic pathway glioma subgroup and was associated with fewer grade 3-4 adverse events, especially hematologic toxicity.

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Disclosure of conflict of interest

None.

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