

Efficacy of different salvage regimens in progressive unresectable pediatric low-grade glioma

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Abstract. Multiple salvage chemotherapy regimens are used in progressive low-grade glioma (LGG), with no single regimen being more effective than any other. In the present study, different salvage therapies were compared with regard to the response rate, overall survival (OS) rate, event-free survival (EFS) rate and visual outcome in 70 patients with pediatric LGG. Age was found to significantly affect the EFS and OS rates ($P < 0.001$). The visual outcome was the same between the three regimens. The 2-year EFS and OS rates of the vincristine/carboplatin, monthly carboplatin and weekly vinblastine regimens were 64.7 and 70.6%, 71.0 and 85.0%, and 56.0 and 62.7%, respectively ($P = 0.6$ for EFS; $P = 0.56$ for OS). Overall, the present study demonstrated that age had a significant impact on survival. The three salvage regimens used were equally effective with regard to the radiological response and visual outcome. However, further randomized controlled trials are required to detect the optimal salvage therapy.

Introduction

Pediatric low-grade gliomas (pLGGs) represent one-third of all central nervous system tumors (1). Pathologically, pLGG is graded by the World Health Organization into either grade I or II (2). The main management is via gross total resection (GTR) whenever feasible. Deeply seated and locally infiltrative tumors pose a challenge to effective surgical resection, as surgery can further compromise certain functions, such as vision in the case

of hypothalamic-optic pathway gliomas (OPGs). Diagnosis may depend only on the radiological findings (3).

Although overall survival (OS) rates have reached as high as 98% at 5 years, approximately one-half of the affected patients will require adjuvant therapy, with a progression-free survival (PFS) rate of ~50% (4). Lower survival rates have been observed in infants <1 year of age at diagnosis, for those with disseminated tumors or spinal cord tumors, and for those without complete surgical excision, with a mean event-free survival (EFS) rate of ~54% for the three groups. Infants <1 year of age with OPG have a lower EFS rate than infants with tumors of the cerebellum and cerebral hemispheres (5).

Patients with neurofibromatosis type 1 (NF1)-associated pLGGs have a higher EFS rate than those with non-NF1-associated pLGGs (6). The majority of NF1-associated pLGGs are located in anatomical regions where surgery is associated with complications and may lead to severe sequelae, mainly in hypothalamic-optic pathway primary sites (7).

First-line chemotherapy with the vincristine/carboplatin (VC) regimen achieves a 5-year PFS rate of 53%, and this is higher for NF1-associated tumors. Progression after first-line therapy is associated with the risk of developing subsequent progression (4). There is no current standard salvage regimen available for progressive LGG (8). The present study aimed to analyze the different salvage regimens used in progressive LGG and to determine their efficacy in terms of the clinical and radiological response, and the impact on survival.

Patients and methods

Patient population. The present retrospective study included 70 pediatric patients with pLGG (<18 years of age) who developed progression (radiological and/or clinical) and received one of the following salvage chemotherapy regimens: Weekly vinblastine, monthly carboplatin or a re-challenge with VC. All patients had a pathological confirmation of LGG or had undergone magnetic resonance imaging that was suggestive of LGG without biopsy (either in patients with NF1 or

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non-NF1-associated pLGG) and were not amenable for biopsy due to a poor general condition or risky procedure. All patients received the Children Oncology Group protocol (COG A9952) (NCT00002944) as first-line therapy, consisting of 10 weeks of VC induction followed by a maintenance period of eight cycles of VC (1.5 mg/m² intravenous vincristine and 175 mg/m² intravenous carboplatin) (9). Treatment was administered in the Children's Cancer Hospital Egypt (Cairo, Egypt) between July 2007 and December 2019, and the patients were followed-up until June 2021.

Treatment regimens. The salvage regimen was selected according to the time elapsed since the end of therapy and the social situation of the patient. A VC regimen was considered if the progression occurred >1 year from the end of the first-line therapy. Monthly carboplatin and weekly vinblastine were considered if progression occurred <1 year from the end of therapy. If the social issue was difficulty regarding transportation, monthly carboplatin was the preferred regimen to decrease the number of visits to the hospital.

The present study aimed to compare the efficacy of different salvage chemotherapeutic regimens in patients with unresectable progressive LGG, as measured by the disease response rate at 6, 12 and 24 months from the end of the salvage therapy, and also the 2-year EFS rate. The retrieval and collection of data were performed using the stage 6 Cerner computer system by the health care information and management systems society analytics.

The following data were collected: Age, sex, initial presentation, duration of symptoms, family history, NF status, initial Karnofsky performance status (KPS) score (10), tumor location and extension to the surrounding structures. The visual acuity and field were assessed using the method of following objects and visual evoked potential testing in infants. Unique visual charts and instruments were used in older children to calculate optical power to be translated into seven grades as follows: Normal vision, ≥ 0.8 ; mild vision loss, ≥ 0.3 and < 0.8 ; moderate visual loss, ≥ 0.125 and < 0.3 ; severe visual loss, ≥ 0.05 and < 0.125 ; profound visual loss, ≥ 0.02 and < 0.05 ; near-total loss (near blindness), < 0.02 till >no light perception (NLP); and total vision loss (NLP) (11).

Initial management data, such as the extent of surgical resection [GTR, subtotal resection (STR) and biopsy], pathological subtypes and grading, first-line chemotherapy (number of cycles and treatment duration) were collected. Data for the type of response post-therapy were collected both clinically and radiologically. The clinical response was defined as measuring variations in the quality of life, reduction in the frequency of seizures, reduction in steroid dosage and modification of the KPS score. The radiological response was defined according to the Response Assessment in Pediatric Neuro-Oncology criteria (12) as follows: i) Complete response: Complete disappearance of the target lesion and all areas of metastatic disease on T2-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging; ii) major response: A $\geq 75\%$ reduction in the target lesion, but an insufficient response to qualify as a complete response; iii) partial response: A $\geq 50\%$ reduction in the target lesion, typically on T2-weighted and T2-weighted FLAIR imaging; iv) stable disease: An increase or a decrease in the target

lesion that is not sufficient to qualify as progressive disease or responsive disease; and v) progressive disease: A $>25\%$ increase in the target lesion, usually assessed on T2-weighted and T2-weighted FLAIR imaging, or the development or substantial growth ($>25\%$) of new or metastatic lesions. Both an increased and decreased enhancement (one or both) do not contribute to the response type (12). The date of maximum radiological response was also collected.

Recurrence and progression data (type of progression either clinical and/or radiological, timing, tumor location and extent, visual re-assessment upon progression in the optic pathway and suprasellar gliomas) were collected and analyzed. The salvage chemotherapy regimen (type, number of cycles and treatment duration), response assessment, date of maximum response, visual re-assessment post-salvage chemotherapy, and KPS at the time of progressive disease and post-salvage were also collected as essential response indicators. Complete response, major response, partial response and stable disease were considered together to indicate non-progressive disease. The toxicity of the different salvage regimens was also revised using the Common Terminology Criteria for Adverse Events (CTCAE) IV (13).

Statistical analysis. The data are presented as the median and interquartile range, counts and percentages. OS time was defined as the time from the date of the first progression to the date of death from any cause or the last follow-up. EFS time was defined as the time from the date of the first progression to the date of the second progression of the tumor, death or the last follow-up. Kaplan-Meier curves were used for survival analysis, while the log-rank test was used to compare the curves. The χ^2 or Fisher's exact tests were used to analyze categorical variables (such as the radiological and clinical responses), and the Kruskal-Wallis test measured the KPS score outcome. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using R Statistical Environment (version 4.0.2) supported by the R Core Team and the R Foundation for Statistical Computing.

Results

Patient characteristics. The present study included 70 patients (43 males and 27 females), with a male-to-female ratio of 1.6:1. The age of the patients ranged from 0.3-11 years (median, 4 years). Initially, the duration of symptoms ranged from 4-6.7 months (median, 4.5 months). In total, 14 patients (14/70; 20.0%) had the clinical stigmata of NF1. The median number of cycles of first-line chemotherapy was eight. As the majority of the included patients had tumors located on the midline, no one was subjected to GTR initially or upon progression. Initially, 48 patients (48/70; 68.6%) underwent either STR (two patients) or only a biopsy (46 patients), and the remaining patients were diagnosed radiologically. The most common primary tumor sites were the suprasellar/optic chiasm (54.3%), thalamus (17.1%), cerebral cortex (11.4%) and isolated optic nerve (10%), whereas other sites had lesser frequency. Following first-line therapy, 11 patients (15.7%) exhibited a major response, a partial response was documented in 23 patients (32.9%) and 24 patients (34.3%) had stable disease.

Table I. Clinicopathological data of the studied patients (n=70).

| Characteristics | Value |
|---|--------------|
| Median age (IQR), years | 4 (0.3-11.0) |
| Age group, n (%) | |
| <1 years | 12 (17.1) |
| 1-8 years | 50 (71.4) |
| >8 years | 8 (11.4) |
| NF1 status, n (%) | |
| Positive | 14 (20.0) |
| Negative | 56 (80.0) |
| Sex, n (%) | |
| Male | 43 (61.4) |
| Female | 27 (38.6) |
| Family history of cancer, n (%) | |
| Positive | 9 (12.9) |
| Negative | 61 (87.1) |
| NF1 status, n (%) | |
| Positive | 14 (20.0) |
| Negative | 56 (80.0) |
| Initial surgery, n (%) | |
| Yes | 48 (68.6) |
| No | 22 (31.4) |
| Extent of resection, n (%) ^a | |
| STR | 2 (4.2) |
| Biopsy | 46 (95.8) |
| Site, n (%) | |
| Suprasellar/OPG | 38 (54.3) |
| OPG | 2 (2.9) |
| Isolated optic nerve | 7 (10.0) |
| Cerebral cortex | 8 (11.4) |
| Spine | 2 (2.9) |
| Thalamus | 12 (17.1) |
| Brain stem | 1 (1.4) |
| Tumor pathology, n (%) | |
| Pilocytic | 19 (27.1) |
| Pliomyxoid | 16 (22.9) |
| Ganglioglioma | 5 (7.1) |
| Others | 12 (17.1) |
| Type of initial response, n (%) | |
| Major response | 11 (15.7) |
| Partial response | 23 (32.9) |
| Stable disease | 24 (34.3) |
| Progressive disease | 12 (17.1) |
| Type of progression, n (%) | |
| Clinical | 27 (38.6) |
| Radiological | 26 (37.1) |
| Both | 17 (24.3) |
| Extent of the tumor on progression, n (%) | |
| Local | 67 (95.7) |
| Metastatic | 3 (4.3) |
| Re-surgery, n (%) | |
| No | 65 (92.9) |
| Yes | 5 (7.1) |

Table I. Continued.

| Characteristics | Value |
|------------------------|-----------|
| Type of salvage, n (%) | |
| Rechallenge with VC | 17 (24.3) |
| Monthly carboplatin | 22 (31.4) |
| Weekly vinblastine | 31 (44.3) |

^an=48. VC, vincristine/carboplatin; OPG, optic pathway glioma; STR, subtotal resection.

The median time to maximum response was 3.47 months (range, 2.8-8.5 months). A total of 12 patients (17.1%) had progressive disease post-induction. The median KPS score of the studied patients following first line therapy was 80.

Upon progression, 27 patients (38.6%) exhibited clinical progression, 26 patients (37.1%) exhibited radiological progression, and 17 patients (24.3%) exhibited both clinical and radiological progression. In total, 67 patients (95.7%) had localized disease and three patients (4.3%) exhibited spinal cord metastatic disease. In addition, five patients (7.1%) underwent STR.

The VC, monthly carboplatin and weekly vinblastine regimens were used in 17 (24.3%), 22 (31.4%) and 31 (44.3%) patients, respectively. The median time to progression was 24.5 months (range, 11.7-42.3 months). All clinicopathological data are summarized in Table I.

Prognostic factors. Age was found to have a significant impact on the outcome post-salvage, with a 2-year EFS rate for patients aged <1, 1-8 and >8 years of 19.4% (95% CI, 5.7-66.4), 68.4% (95% CI, 17.9-81.1) and 87.5% (95% CI, 56.3-83.2), respectively (P<0.001). The OS rate in same age groups was 38.1% (95% CI, 66.0-90.0), 77.1% (95% CI, 67.3-100.0) and 87.5% (95% CI, 67.3-100.0), respectively (P<0.001). However, sex, tumor pathology, primary tumor site and radiological response did not affect the outcome, regardless of the salvage regimen used (Table II). The effect of the extent of resection upon progression could not be assessed due to the small number of patients who underwent surgical intervention.

The median number of cycles for the VC and monthly carboplatin regimens was four and eight cycles, respectively, whereas the median number of weeks on the vinblastine arm was 48 weeks. The VC, monthly carboplatin and weekly vinblastine protocols exhibited a median time to maximum response of 3.3, 4.5 and 3.5 months, respectively. A total of three patients (4.3%) were not evaluated, as they succumbed to the disease before the end of therapy.

VC, weekly vinblastine and monthly carboplatin exhibited a radiological response (major and partial response) of 58.8, 46.5 and 27.3%, respectively (P=0.25; data not shown). Non-progressive disease was reported in 89.3% of patients treated with weekly vinblastine, in 88.2% of patients treated with VC and in 77.3% of patients treated with the monthly carboplatin regimen (Table III). No single patient achieved a complete radiological response.

Table II. Association between prognostic factors of included patients and survival.

| Variable | 2-year EFS rate (%) | P-value | 2-year OS rate (%) | P-value |
|--|---------------------|---------|--------------------|---------|
| Age, years | | <0.001 | | <0.001 |
| <1 | 19.4 | | 38.1 | |
| 1-8 | 68.4 | | 77.1 | |
| >8 | 87.5 | | 87.5 | |
| Sex | | >0.99 | | 0.3 |
| Male | 60.8 | | 75.6 | |
| Female | 64.6 | | 70.2 | |
| Site ^a | | 0.7 | | 0.7 |
| Cerebral cortex | 60 | | 60 | |
| Optic pathway glioma | 60.8 | | 71.4 | |
| Others | 66.5 | | 80 | |
| Pathology | | 0.5 | | 0.3 |
| Pilocytic | 70.7 | | 82 | |
| Pilomyxoid | 60.6 | | 73.7 | |
| Ganglioglioma | 60 | | 60 | |
| Others | 41.7 | | 50 | |
| Radiological response | | 0.6 | | 0.8 |
| Responders (major response and partial response) | 75 | | 75.5 | |
| Stable disease | 66.4 | | 75 | |
| Progressive disease | 52.3 | | 65.5 | |

^aThalamus, spine, brain stem as midline structure were placed in one group; optic pathway is the most common category and was considered as a separate entity followed by the cortical primary sites. EFS, event-free survival; OS, overall survival.

Table III. Different types of response with varying salvage regimen.

| Salvage regimen | Partial response, n (%) | Major response, n (%) | Stable disease, n (%) | Progressive disease, n (%) | Total, n |
|---------------------|-------------------------|-----------------------|-----------------------|----------------------------|----------|
| Rechallenge with VC | 4 (23.5) | 6 (35.3) | 5 (29.4) | 2 (11.8) | 17 |
| Monthly carboplatin | 2 (9.1) | 4 (18.2) | 11 (50.0) | 5 (22.7) | 22 |
| Weekly vinblastine | 5 (17.9) | 8 (28.6) | 12 (42.8) | 3 (10.7) | 28 |

VC, vincristine/carboplatin.

The KPS score did not differ significantly following the salvage regimens, with a median score of 80, 70 and 80 for the VC, monthly carboplatin and weekly vinblastine arms, respectively (P=0.99; data not shown).

In total, 47 patients had suprasellar and OPGs. In addition, 13 patients were re-initiated on the VC protocol (four of them had radiological progression), five of the 13 patients (38.5%) exhibited visual improvement, six (46.2%) exhibited stable vision and two (15.4%) had deteriorated vision. A total of 13 patients received monthly carboplatin (four of them had radiological progression). Visual improvement, stability and deterioration were reported in two, four and seven patients, respectively. A total of 18 patients (18/44; 40.9%) received weekly vinblastine (two of them had documented radiological progression). In addition, five of these 18 patients (27.8%) exhibited visual improvement, eight (44.4%) exhibited stable

vision and five (27.8%) experienced deteriorated vision. There was no significant difference in the visual outcome between the three regimens (P=0.16; data not shown).

A total of four patients (4/9; 44.4%) with NF1-associated OPG and 10 patients (10/35; 28.6%) with non-NF1-associated OPG had documented visual deterioration following salvage therapy (P=0.43; data not shown).

The disease status was assessed in patients with OPG at 6, 12 and 24 months following the end of salvage treatment. At 6 months, 12 (12/13; 92.3%), 11 (11/13; 84.6%) and 15 patients (15/18; 83.3%) exhibited non-progressive disease on the VC, monthly carboplatin and weekly vinblastine arms, respectively. A total of two patients on the weekly vinblastine arm were not assessed. However, one patient on the VC and weekly vinblastine arms, and two patients on the monthly carboplatin arm exhibited progressive disease (P=0.81; data not shown).

At 12 months, non-progressive disease was documented in 11 patients in both the VC and monthly carboplatin regimens. In addition, 12 patients on the weekly vinblastine arm did not exhibit progressive disease ($P=0.52$). Furthermore, two patients on the monthly carboplatin and weekly vinblastine arm were not evaluated due to clinical deterioration, which did not permit the radiological assessment.

At 24 months, 10 (83.3%), 7 (77.7%) and 9 (81.8%) patients in the VC, monthly carboplatin and weekly vinblastine arms, respectively, did not exhibit progressive disease ($P=0.99$; data not shown).

In addition, one patient on the VC arm, four patients on the monthly carboplatin and seven patients on the weekly vinblastine arms were not assessed due to disease-related severe morbidity with marked clinical deterioration.

There was no significant difference in the rate of non-progressive OPG between the three arms at the 6-, 12- and 24-month evaluations ($P=0.81$ at 6 months, $P=0.52$ at 12 months and $P=0.99$ at 24 months) (Fig. 1).

All patients with NF1-associated OPG did not exhibit any progression until 24 months after the salvage regimens. There was no significant difference observed in the progression rate following salvage therapy at the time of data collection beyond 24 months of follow-up between the patients with NF1-associated and non-NF1-associated OPG; one patient (1/9) and seven patients (7/28) developed progressive disease in the NF1-associated and non-NF1-associated groups, respectively ($P=0.99$; data not shown).

When taking into consideration all patients with or without NF1-associated OPG, irrespective of the site, no significant difference was observed in the rate of disease progression between the NF1-associated and non-NF1-associated groups at 6, 12 and 24 months from the end of treatment ($P=0.60$, $P=0.32$ and $P=0.29$, respectively; data not shown). In addition, one patient with NF1-associated disease (1/14; 7.1%) developed disease progression versus 21 patients (21/53; 39.6%) in the non-NF1 group.

Toxicity of therapy. The primary toxic effects observed with weekly vinblastine were hematological, mainly neutropenia. Grade 3 and 4 fever and neutropenia were documented in 5% of patients, with confirmed infection in 2% of cases. Grade 3-4 peripheral neuropathy was noted in three patients. Monthly carboplatin treatment was associated with grade 3-4 hematological toxicity, mainly neutropenia, in 20% of patients. The VC regimen was associated with allergies in 15% of cases, with grade 4 hypersensitivity reported in 5% of patients. Grade 3 or 4 peripheral neuropathy was reported in 15% of cases, leading to temporary discontinuation of therapy, and grade 3-4 neutropenia in 10% of patients (data not shown).

Survival outcomes. A total of 16 patients (16/70) were deceased at the time of the analysis. Of note, 15 patients succumbed due to progressive disease and one patient succumbed due to septic shock following salvage therapy with monthly carboplatin. All patients with metastatic disease are still alive.

There was no statistically significant difference in the EFS and OS between the patients with NF1-associated and non-NF1-associated OPG ($P=0.27$ for EFS and $P=0.16$ for OS) (Figs. 2 and 3).

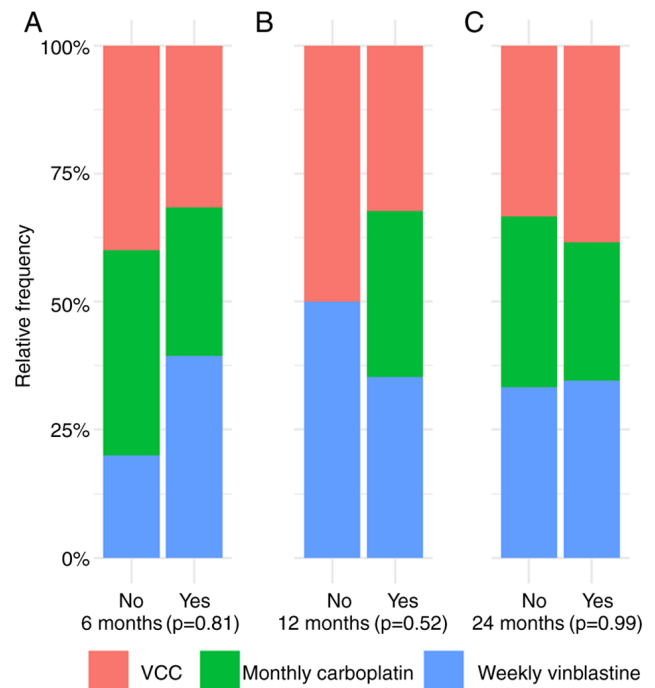


Figure 1. Rate of non-progressive optic pathway glioma in the three regimens at (A) 6-, (B) 12- and (C) 24-month evaluations. VCC, low-grade glioma rechallenge with vincristine/carboplatin.

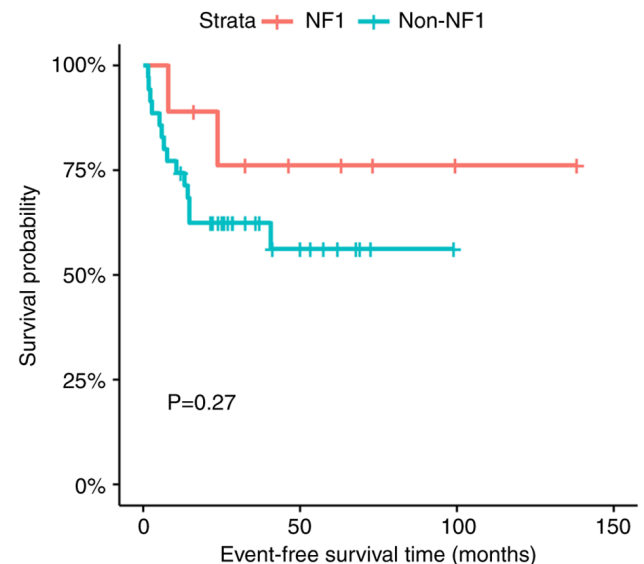


Figure 2. Survival curve for the 2-year event-free survival of patients with NF1 and non-NF1 optic pathway glioma. NF1, neurofibromatosis type 1.

The 2-year EFS rates of the VC, monthly carboplatin and weekly vinblastine regimens were 64.7% (95% CI, 45.5-91.9), 71.0% (95% CI, 53.8-93.6) and 56.0% (95% CI, 40.4-77.5), while the 2-year OS rates for the three regimens were 70.6% (95% CI, 51.9-95.9), 85.0% (95% CI, 70.6-100) and 62.7% (95% CI, 47.2-83.1), respectively ($P=0.60$ for EFS and $P=0.56$ for OS) (Figs. 4 and 5).

In the present study, 22 patients (22/70; 31.4%) developed disease progression following salvage therapy, 16 of which did not survive (data not shown).

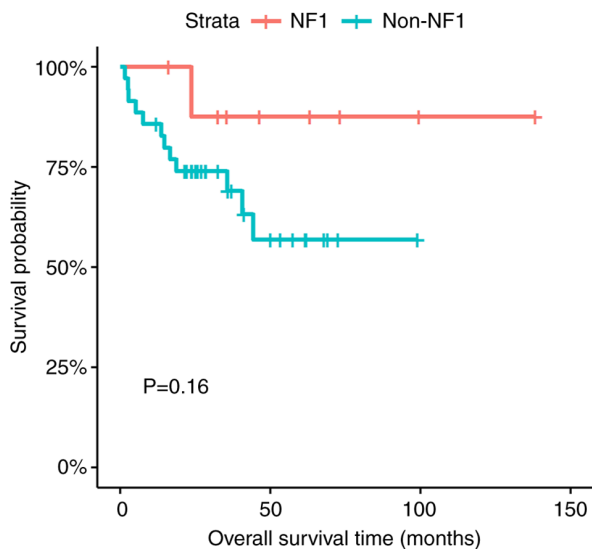


Figure 3. Survival curve for the 2-year overall survival of patients with NF1 and non-NF1 optic pathway glioma. NF1, neurofibromatosis type 1.

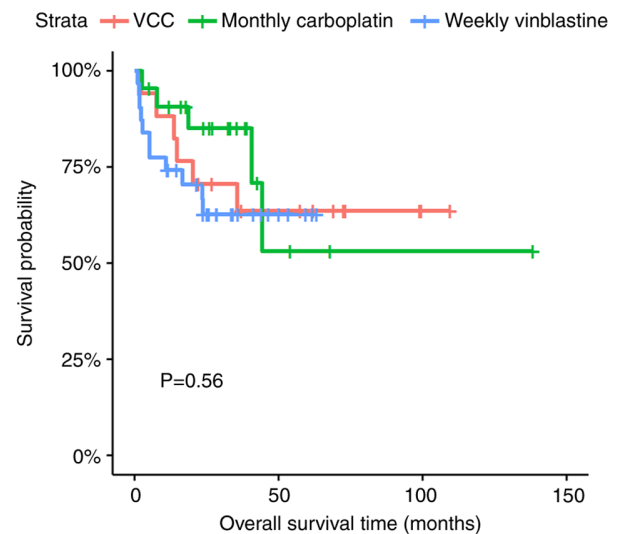


Figure 5. Survival curve for the 2-year overall survival of the studied patients in relation to the different salvage regimens. VCC, low-grade glioma rechallenge with vincristine/carboplatin.

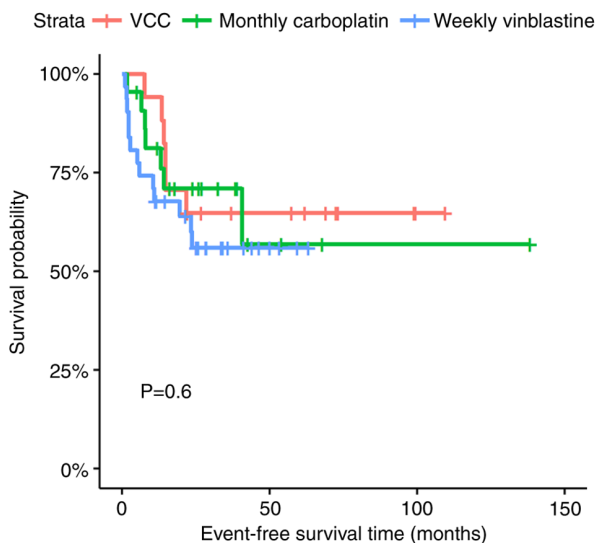


Figure 4. Survival curve for the 2-year event-free survival of the studied patients in relation to the different salvage regimens. VCC, low-grade glioma rechallenge with vincristine/carboplatin.

Discussion

Progressive LGG is considered a challenging disease to treat. To the best of our knowledge, there are no data available in the literature comparing the efficacy of different salvage strategies. Scheinemann *et al* (14) reported irrelevant differences in the PFS after the second, third and fourth lines of chemotherapy. A pilot study by Bouffet *et al* (15) reported the efficacy of weekly vinblastine in patients with progressive LGG. Another phase II study confirmed the efficacy and safety of monthly carboplatin in progressive LGG (16). The present study provided data on the efficacy of different salvage regimens in order to reach a consensus for the standard salvage regimens in progressive LGG. The median age at diagnosis was close to that reported in the study by Gururangan *et al* (16) (4 years), but lower than the median age reported in the study by Bouffet *et al* (15) (7 years).

Age was a significant prognostic factor for survival in the present study, with patients <1 year of age exhibiting the worst outcome, which coincided with the data in the study by Kandels *et al* (5), where an age <1 year was a risk factor for progression and a lower PFS time. Ater *et al* (17) reported that an age <3 years and a residual tumor >3 cm² in volume were independent poor prognostic factors. The poor outcome of the younger age group may be associated with the high prevalence of canonical BRAF alterations (97% of cases), particularly BRAF V600E in midline infantile LGG, as reported by Stucklin *et al* (18).

In the present study, sex, tumor site, pathological subtypes and radiological response did not affect the outcome. In total, 20% of the studied patients had clinical stigmata of NF1, similar to the study by Gururangan *et al* (16), although with a lower frequency than the studies by Ater *et al* (17) and Manoharan *et al* (19), which had 30 and 33% of patients with progressive LGG associated with NF1, respectively.

The three salvage regimens used in the present study according to frequency were weekly vinblastine, followed by monthly carboplatin and then VC which differs from the findings of the study by Moorman *et al* (8), which collected data from multiple North American centers, where the VC regimen was the most common, followed by weekly vinblastine then monthly carboplatin across different tumor sites.

Packer *et al* (20) reported that non-progressive disease occurred in 74% of patients on the VC regimen, which was lower than the rate observed in the present study. Ater *et al* (17) found that 76% of patients (NF1 and non-NF1) had non-progressive disease following the VC regimen. Non-progressive disease was reported in 86% of patients in the studies by Bouffet *et al* (15) and Dodgshun *et al* (21), which used weekly vinblastine and monthly carboplatin, respectively. These results were similar to those of the weekly vinblastine arm outcome (89.3%), but higher than those of the monthly carboplatin arm (77.3%), observed in the present study.

Patients with NF1-associated disease did not exhibit any sign of radiological progression until 1 year after salvage therapy

in the three regimens. Stokland *et al* (6) concluded that NF1 was not a risk factor for progression, which is in accordance with the findings of the present study. There was no difference in the response rate between patients with NF1-associated and non-NF1-associated disease in the three regimens, coinciding with the findings of Bouffet *et al* (22). Scheinmann *et al* (14) reported radiological progression in 50% of patients with NF1-associated disease following treatment with second-line salvage regimens (vinblastine, vincristine/etoposide, or thio-guanine, procarbazine, lomustine and vincristine).

Gururangan *et al* (16) and Packer *et al* (20) did not find a significant difference in the EFS rate of patients with OPG associated with or without NF1, as in the present study. By contrast, Stokland *et al* (6) reported a significantly improved PFS rate for patients with OPG associated with NF1 compared with that in patients with non-NF1-associated disease (70 vs. 46.7%; $P<0.001$).

There are limited data available regarding the visual outcome post-OPG/suprasellar primary tumor progression. In the present study, visual deterioration was reported in 32% of progressive OPG tumors in all salvage regimens, which was lower than the rate reported in the study by Shofty *et al* (23), where 47.2% of these patients had deteriorated vision and 13.8% of the studied patients had improved vision with the VC regimen.

In the population in the present study, visual improvement was highest with the VC regimen (38.5%), followed by the weekly vinblastine (27.8%) and monthly carboplatin (15.4%) regimens, although without statistical significance. Bouffet *et al* (22) reported visual deterioration in one patient. The study by de Haas *et al* (24), which used VC, vinblastine and radiotherapy for progressive OPG, reported that six patients (6/33) had become blind, nine children had deteriorated vision and 18 children had stable vision. The patients with preserved vision were equally distributed between the chemotherapy and radiotherapy groups (24). Visual improvement was observed in 20% of patients with OPG, as documented by Lassaletta *et al* (25), when using single-agent vinblastine therapy.

In the present study, visual deterioration in patients with NF1-associated OPG occurred in 44.4% of patients, which was a higher rate than that in the non-NF1 counterparts (28.6%), and was also in accordance with the study by Scheinmann *et al* (14). This previous study reported severe visual impairment in 35% of patients, while in the NF1 group, 75% of the patients had severely impaired vision. The discrepancy between the absence of radiological progression in patients with NF1-associated OPG, regardless of the site, until 1 year post-therapy, and the visual deterioration in almost half of patients with NF1-associated disease, emphasizes the hypothesis that the radiological response does not usually match the visual outcome, as reported by Ullrich *et al* (26).

In the present study, there was no significant difference in the progression rate between patients with NF1-associated and non-NF1-associated disease at 6, 12 and 24 months of salvage therapy. Gururangan *et al* (16) reported a 3-year PFS rate of 72 and 62% for patients with non-NF1-associated and NF1-associated glioma, respectively ($P=0.39$). By contrast, Bouffet *et al* (22) found a significant difference in PFS rates between patients with NF1 (75%) and non-NF1 (37%) disease ($P=0.04$). Ater *et al* (17) reported the COG 9952 data, with a

superior EFS rate in patients with NF1-associated in comparison to those with non-NF1-associated disease ($P<0.001$).

In the present study, the 2-year EFS rate of patients on the weekly vinblastine arm (56%) was lower than that of the patients on the other two regimens, although with no significant difference. Kandels *et al* (4) reported 3-year PFS rates of 48 and 8% following salvage vinblastine monotherapy in patients with NF1-associated and non-NF1-associated disease, respectively. Lassaletta *et al* (25) reported a 5-year OS and PFS rate of 94.4 and 53.2%, respectively, using vinblastine single-agent therapy.

In the present study, the 2-year EFS and OS rates of the monthly carboplatin group were 71 and 85%, respectively, which is comparable to the results in the study by Dogdshun *et al* (21), which reported a 3-year PFS of 65% with monthly carboplatin treatment.

In the present study, 22 patients (22/70; 31.4%) developed disease progression following salvage therapy, of which 16 did not survive; this rate of progression was lower than that observed in the study by Kandels *et al* (4), which reported 58% progression following salvage therapy, and only 8/86 of the patients succumbed to the disease.

There are some limitations to the present study due to its retrospective design, such as the relatively small number of patients in each therapy group, the absence of a precise method for visual assessment in young patients and the lack of fixed clinical indication for recruitment in each therapy group. Although there was some selection bias as the salvage regimen was selected according to the time elapsed from the end of therapy and the social situation of the patient, the homogeneity of the study population in each group regarding age, midline location and inaccessibility for surgery decreased this bias.

In conclusion, according to the present results, there is no standard regimen for pLGG. Due to its benign course, the outcome of progressive disease is good. The present study showed that an age <1 year was associated with a poor survival rate. Other prognostic factors, such as sex, tumor site, pathology and radiological response did not affect the outcome. There was no significant difference in efficacy between the three regimens. The NF1 status did not affect the rate of progression following salvage therapy, although it was associated with poor visual outcomes, regardless of the salvage regimen. One of the important causes of tumor progression is underlying molecular abnormality, so molecular testing is mandatory to detect chemo-resistant tumors that may benefit from targeted therapy. Randomized prospective clinical trials are required to detect the most effective salvage chemotherapy regimen for progressive LGG.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AEH was involved in the conception of the study. OA and FA were involved in data curation. AEH and FA confirmed data accuracy. AEH was involved in the data analysis. OA was involved in the study methodology. FA provided the software and was involved in the data validation. OA and AEH were involved in the writing of the original draft. OA, AEH, HT, AR and ME were involved in designing the study, and writing, reviewing and editing the manuscript. AEH and OA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Children's Cancer Hospital Egypt 57357 (Cairo, Egypt; approval no. CCHE IRB 12-2020). Informed verbal consent was obtained by phone from the guardians of all patients involved in the study, as most of the patients were from remote areas with difficulties in transportation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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