

Feasibility and Efficacy of Repeated Chemotherapy for Progressive Pediatric Low-Grade Gliomas

Katrin Scheinemann, MD,^{1,2} Ute Bartels, MD,¹ Elena Tsangaris, BSc,¹ Cynthia Hawkins, MD, PhD,³ Annie Huang, MD, PhD,¹ Peter Dirks, MD, PhD,⁴ Iris Fried, MD,¹ Eric Bouffet, MD,¹ and Uri Tabori, MD^{1*}

Background. Chemotherapy is widely accepted as first-line therapy for pediatric low-grade gliomas (LGG). Treatment modalities for further progression are not clearly established. The aim of the study was to determine the feasibility and long-term outcome of repeated chemotherapy for children with recurrent LGG. **Methods.** The study group consisted of patients who received a second line of chemotherapy at progression of their LGG. We compared toxicity, progression-free survival (PFS), and overall survival (OS) of patients treated with chemotherapy at the time of initial diagnosis and patients who received another treatment with chemotherapy at further progression. **Results.** Between 1985 and 2009, 118 patients received chemotherapy as primary treatment for LGG, 38 had repeated chemotherapy at further progression. Chemotherapy was tolerated extremely well. Ninety-two

percent of patients completed their second line protocol and toxicity was comparable between initial and second line chemotherapy. Five-year OS and PFS were $86 \pm 6\%$ and $37 \pm 8\%$, respectively, which were similar to first-line chemotherapy ($P = 0.14$). Repeated chemotherapy courses were not associated with worsening of visual, neuroendocrine, or other long-term organ sequelae. **Conclusion.** This study demonstrates high feasibility and low mortality of repeated chemotherapy treatment for progressive LGG. The chronic nature of LGG concerning tumor progression justifies consideration of non-toxic second-line treatment regimens at the time of recurrence. Prospective studies focusing on toxicity and long-term outcome are needed to substantiate this approach. *Pediatr Blood Cancer* © 2010 Wiley-Liss, Inc.

Key words: chemotherapy; children; grade glioma; low recurrence; outcome

INTRODUCTION

Low-grade gliomas (LGG) are the most common brain tumor in children [1]. Surgery is the main treatment modality and curative when complete removal is possible [1]. Since surgery for deep-seated tumors is often restricted to debulking procedures or image-guided biopsies, radiation therapy was traditionally applied for such tumors.

After initial anecdotal observations in the 1970s [2], chemotherapy has gained an important role as primary treatment of LGG, particularly in young children. Most of the early series were using a single agent approach [3,4], with either alkylating or platinum-based chemotherapies. More recently, combination therapies over extended periods were developed to potentially address the biological pattern of these slow growing tumors [5–7].

The initial indication for the use of chemotherapy was a salvage approach in the setting of a progressive tumor following radiation treatment [8]. However, several prospective studies [4,9] have demonstrated safety and efficacy of chemotherapy as the first-line treatment for LGG. The primary goal with this approach is to avoid or at least postpone radiotherapy [10,11], which will then be reserved for recurrent/progressive tumors. Since radiation therapy is known to affect neurocognitive and endocrine function and growth [12–14] and may trigger malignant transformation [15], there is increasing interest in considering repeated chemotherapy at further progression of LGG, particularly in young children [5,7,11,16].

The approach of repeated chemotherapy for progressive LGG is still controversial. Many institutions still prefer radiation therapy at progression of LGG; however, other institutions more frequently apply more aggressive chemotherapies at recurrence. Here we report the feasibility, effectiveness, and long-term outcome of patients treated with multiple courses of chemotherapy for progressive LGG. Our findings highlight the importance of pondering alternate treatment options to avoid additional morbidities in a mostly not life threatening disease.

PATIENTS AND METHODS

We performed a retrospective population based study of LGG in the MRI era (1985–2009) at a single center. Databases from the

Division of Pathology, the Division of Pediatric Oncology, the Pediatric Brain Tumor Program, and the Neurofibromatosis Clinic were used to identify the patients. Data on demographics, location, histology, interventions, outcome, and long-term sequelae were collected for each patient. Our study group consisted of patients who received chemotherapy at the time of their recurrence/progression after having completed one chemotherapy course as a first line treatment option. Inclusion criteria were (i) age at diagnosis less than 18 years, and (ii) grade I or II glial tumor as per WHO criteria. Patients referred from other centers or treated in other centers or patients who received other medical, surgical or irradiation therapies were excluded from this study. For comparison of toxicity and feasibility, newly diagnosed LGG patients currently enrolled on the Trans-Canadian Phase II study consisting of weekly vinblastine were used as a the control group.

The Kaplan–Meier method was used to estimate probabilities of progression-free survival (PFS) and overall survival (OS) with standard errors calculated according to Greenwood's formula. Groups were compared using the log-rank test. P -value <0.05 was considered statistical significant. All statistical analyses were performed using the SPSS v12 statistical program.

RESULTS

Overall, 733 children were diagnosed and treated for a low grade glioma at Sickkids from 1985 to June 2009. Neurofibromatosis I as an underlying condition was found in 107 patients (14.6%). One

¹Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Canada; ²Division of Hematology/Oncology, McMaster Children's Hospital, Hamilton, Canada; ³Division of Pathology, The Hospital for Sick Children, Toronto, Canada; ⁴Division of Neurosurgery, The Hospital for Sick Children, Toronto, Canada

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*Correspondence to: Dr. Uri Tabori, MD, Division of Hematology/Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON Canada M5G 1X8. E-mail: uri.tabori@sickkids.ca

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hundred eighteen (24.7%) patients received chemotherapy as initial treatment (with or without surgery) and are defined as the first line chemotherapy group (FLC). Seventy-six (15.9%) patients were treated with radiation treatment as a first line treatment and 9 (1.9%) patients with a combined approach of chemo- and radiotherapy as first line treatment. These 9 patients were all treated prior to 1995. Further details of patient management and outcome are shown in Figure 1A–C.

Repeated Chemotherapy

Our study cohort comprised 38 of 118 patients treated with initial chemotherapy who received repeated chemotherapy courses at progression and were defined as multiple line chemotherapy group (MLC). Median follow-up time from start of repeated chemotherapy was 4.46 years (range 0.23–14.64 years). Further clinical and epidemiological data on this group are shown in Table I. Median age at the start of second-line chemotherapy was 5.33 years (range of 1.21–

TABLE I. Clinical Characteristics of Patients With Repeated Chemotherapy

| Characteristics | Second line chemotherapy (n = 38) |
|---|-----------------------------------|
| Age in years at first diagnosis, median (range) | 2.94 (0.01–9.64) |
| Age in years at progression, median (range) | 5.33 (1.21–12.42) |
| Follow-up in years from initial diagnosis, median (range) | 7.49 (0.98–17.94) |
| Gender | |
| Male | 31.6% |
| Female | 68.4% |
| Tumor location | |
| Optic pathway | 22 (44.7%) |
| Brainstem | 7 (18.4%) |
| Spinal | 4 (10.5%) |
| Disseminated | 3 (7.9%) |
| Thalamus | 2 (5.3%) |
| Phakomatosis | NF I 4 (10.5%) |
| Histological diagnosis | |
| No histology* | 5 (13.2%) |
| Grade I astrocytoma | 27 (71%) |
| Ganglioglioma | 2 (5.3%) |
| Pilomyxoid glioma | 3 (7.9%) |
| Oligoastrocytoma | 1 (2.6%) |
| Chemotherapy courses | |
| n = 2 | 38 |
| n = 3 | 12 |
| n = 4 | 6 |
| n = 5 | 1 |
| n = 7 | 1 |
| Death (due to tumor progression) | 4 (10.5%) |

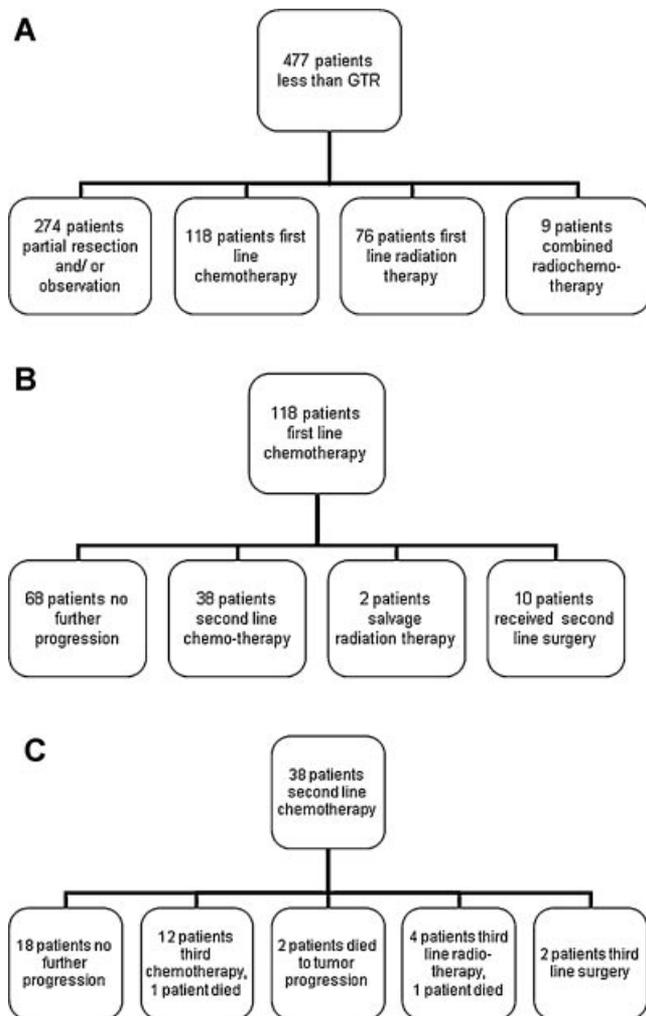


Fig. 1. Summary of treatment and outcome for our patients. From a total of 733 patients 256 patients received gross total resection and were excluded. The additional treatment for the remaining 477 patients is shown in (A). Chemotherapy was initiated as first line in 118 patients—their outcome is shown in (B). At least two rounds of chemotherapy were given in 38 patients (study group) and their outcome is shown in (C).

NF I, neurofibromatosis type I. *Diagnosis made by imaging only, location within optic pathway or thalamus.

12.42 years). Fifteen patients (46.9%) were under the age of 5 years, while only six patients (18.8%) were older than 10 years. This age distribution was not significantly different from the FLC group. Median time from FLC to MLC was 2.22 years (1.32–9 years); the median time to the third course of chemotherapy was slightly shorter at 1.7 years (0.97–5 years) ($P = NS$).

The majority of FLC patients (76%) were treated with vincristine/carboplatin according to the CCG 9952 arm A regimen. For the MLC group the majority of patients (60%) were treated with weekly vinblastine and enrolled into the ongoing Canadian phase II study for recurrent LGG. Seven patients received vincristine/carboplatin as per CCG 9952 arm A, seven patients received TPCV (CCG 9952 arm B), and one patient was treated with the combination of vincristine/etoposide. Further details are shown in Table II. Twelve patients received at least three different lines of chemotherapy including TPCV or temozolamide.

Feasibility and Toxicity

Thirty-five of 38 (92%) MLC patients completed their second line chemotherapy. The causes of withdrawal from therapy were procarbazine allergy in one patient and further tumor progression in two.

Second line chemotherapy was tolerated well with a low toxicity profile. In order to better assess tolerability of administering further chemotherapy to our patients, we compared two subsets of children

TABLE II. Chemotherapy Protocols Used in the Study Cohort

| Drugs | Number of patients |
|------------------------|--------------------|
| Chemotherapy I | |
| VCR/CARBO | 29 |
| CARBO | 3 |
| VCR/VP 16 | 1 |
| VBL | 3 |
| TPCV | 2 |
| Chemotherapy II | |
| VBL | 23 |
| TPCV | 7 |
| VCR/CARBO | 7 |
| VCR/VP 16 | 1 |

VCR, vincristine; CARBO, carboplatin; TPCV, thioguanine/procarbazine/lomustine/vincristine; VP 16, etoposide; VBL, vinblastine.

treated with the same regimen (vinblastine) as initial or second line chemotherapy. Of the 20 MLC patients who were on the vinblastine study at first recurrence, only two patients (10%) did not complete the protocol, both due to tumor progression. Fourteen patients (61%) needed dose reductions due to neutropenia. By comparison, of the 20 FLC patients treated with vinblastine as FLC, 4 (20%) patients did not complete the protocol due to tumor progression. Thirteen patients (65%) needed dose reductions due to neutropenia plus/minus infection ($P = 1$).

Outcome

Following second line chemotherapy, 18 (47%) of patients did not experience further tumor progression. Four patients died due to tumor progression. Two patients had invasive and disseminated ganglioglioma and progressed despite multiple treatments including irradiation and two infants less than 1 year at diagnosis had presented with a large and disseminated grade II astrocytoma. OS and PFS for MLC at 5 years were $86 \pm 6\%$ and $37 \pm 8\%$, respectively. Comparison of FLC and MLC groups did not reveal a significant difference in PFS ($P = 0.14$, Fig. 2). Furthermore, FLC patients had continuous late recurrences up to 12 years from treatment as demonstrated by lack of plateau in their PFS while MLC patients did not experience further progression after 4 years (Fig. 3). Further comparison of second, third, and fourth line chemotherapies did not reveal change in PFS upon repeated progressions. Out of 20 patients with neurofibromatosis type 1 who were initially treated with chemotherapy, only 4 required second line chemotherapy. Two of them experienced further progression after second line chemotherapy and needed further treatment, but all patients are alive.

Long-Term Sequelae

For analysis of long-term outcome data from 30 (79%) out of the 38 patients were available. Eight patients (26.7%) had growth retardation with a measured height below the 5th percentile. Of those eight patients, six had an optic pathway glioma (OPG), one patient suffered from brainstem, and another from spinal cord glioma. Four patients, all with chiasmatic/hypothalamic OPGs, were diagnosed with panyhypopituitarism. Visual outcome for the OPG group revealed severe visual impairment or blindness in 6 (35%) 17 patients and only 2 patients had documented a normal vision. Within the group of

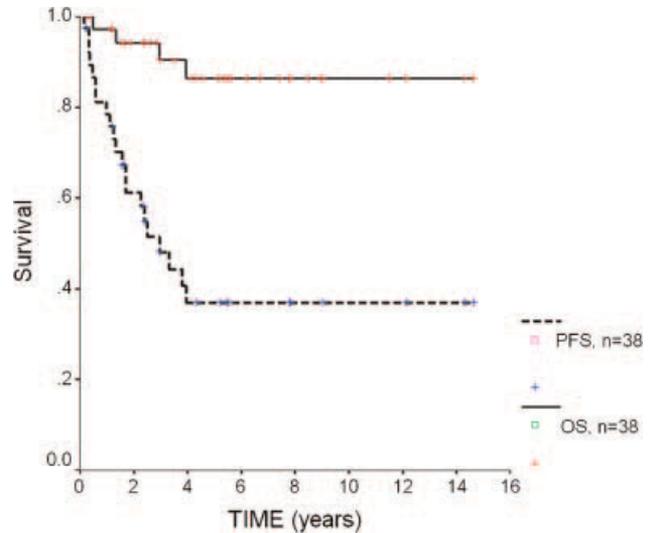


Fig. 2. Kaplan–Meier figure for overall (OS) and progression free survival (PFS) for 38 patients with second line chemotherapy. Five-year OS $86 \pm 6\%$, 5-year PFS $37 \pm 8\%$.

neurofibromatosis type 1 only one patient has a documented normal vision, two of them have severely impaired vision, and one is blind. However, detailed longitudinal analysis of these patients revealed that visual loss was present at presentation or before second line chemotherapy in all children and at a mean time of 5.5 years none suffered further deterioration after completion of second line chemotherapy.

DISCUSSION

Since the introduction of chemotherapy in the early 1990s [4], the landscape of LGG has dramatically changed [9]. In our institution, the majority of patients (85%) treated with radiotherapy were

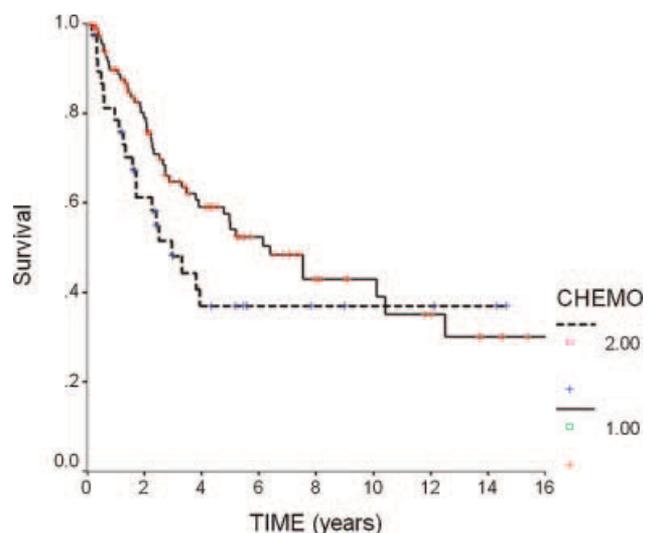


Fig. 3. Kaplan–Meier figure for progression free survival for first (1) and second line (2) chemotherapy. First line chemotherapy 5-year EFS $52 \pm 6\%$, second line chemotherapy 5-year EFS $37 \pm 8\%$ ($P = 0.14$).

diagnosed before 2000. Since 2000 chemotherapy has become the initial treatment for progressive PLGG and radiation therapy is reserved for aggressive life threatening tumors only. The safety, effectiveness, and long-term outcome of this change in practice have never been addressed. This paper presents and evaluates a large cohort of LGG patients treated with repeated chemotherapy approach.

Strikingly, as opposed to other brain tumors in which PFS after recurrence is dramatically shorter than at diagnosis, similar outcome were observed between FLC, second line of chemotherapy and even successive chemotherapy treatments. The CCG 9952 protocol [18] reported a 5-year PFS of $41.7 \pm 3.4\%$ in non-NF1 patients and $68.7 \pm 4.8\%$ in NF1 patients. Since our cohort had similar PFS to CCG 9952 in patients with FLC, the results of the MLC group can be regarded as representative and are unlikely the result of a selection bias. These results are even more intriguing as almost half of the patients were less than 5 years old at the time of progression and young age is known to constitute a negative prognostic factor. This highlights the unique biology of LGGs which do not become more aggressive, and generally do not progress to high grade tumors at subsequent relapse [15].

The relatively benign phenotype and similar response to MLC courses suggest lack of drug resistance in recurrent LGG. Despite the use of the same drug group (vinca alkaloid) for the first and second line chemotherapy, there was no significant difference in PFS. Therefore, when choosing chemotherapy for recurrent LGG, a trial of less toxic therapy is justified. Earlier studies demonstrated high toxicity using etoposide [19,20] and idarubicin [17] for progressive/recurrent LGG with no evidence of increased efficacy. Temozolamide, an alkylating agent introduced into the treatment of LGG more recently [21,22] did not demonstrate evidence of better control or prolonged PFS. However, concerns with regard to hematological toxicity and potential long-term side effects should be considered.

These studies suffer from a heterogeneous patient population, particularly regarding previous treatments, ranging from surgery alone to prior radiation or multiple lines of chemotherapy. Nevertheless, OS and PFS are surprisingly similar, matching our findings (Figs. 2 and 3) and suggesting that LGG should be treated as a chronic continuous disease with specific care of host toxicity and long-term outcome.

In our cohort, previous chemotherapy did not result in higher toxicity for MLC compared to FLC group. Moreover, 92% of patients completed their second line chemotherapy protocol which was comparable with the same regimen given as first line option. This highlights that choosing appropriate chemotherapy for progressive LGG is essential for feasibility and prevention of long-term sequelae. In addition, MLC therapies compared favorably with FLC platinum based protocols which report higher rates of hematotoxicity and allergic reactions resulting in lower completion rates [5,7,10,16,23,24].

Since OS in LGG is high, the main concern is long-term morbidity. As expected, this is highly dependent on tumor location. For our OPG patients, visual impairment is a significant burden and is not reversible [25]. However, careful examination of timing revealed that visual impairment occurred early, and repeating chemotherapy did not result in continuous loss of vision due to lack of tumor control. Long-term endocrinopathies were low in our OPG group suggesting effective prevention of this significant complication by avoiding radiation therapy at progression [26]. Further support to this concept is demonstrated by a recent paper from Merchant et al. [27] which

revealed high neuroendocrine deficits in LGG patients who underwent radiation therapy. Unfortunately, growth retardation was significant in our cohort irrespective of endocrine function and tumor location. We observed similar long-term morbidities in spinal LGG [28] adding to the complexity of LGG and its management.

Neurocognitive and social outcomes are a major concern of childhood brain tumors. A recent publication [29] revealed significant psychological and cognitive dysfunction in LGG survivors who were treated with surgery only. Therefore, tumor size and the location might influence these children's long-term functional outcome and the additional toxicity of medical treatment (chemotherapy or radiation therapy) must be taken into careful considerations in the management of these patients. Since most recurrent LGG in our cohort are very young, neurocognitive impairment is an ongoing concern. The role of repeated chemotherapy and neurocognitive outcome needs to be assessed in a prospective setting.

The future approach to PLGG should include careful observation and one or several courses of relatively non-toxic therapies with the ultimate aim of avoiding long-term deficits in most patients. For the small group of persistent growing LGGs, with risk of significant visual or other organ dysfunction, novel targeted therapies should be pursued [30].

In summary our results highlight the feasibility and favorable outcome of repeated chemotherapy for progressive LGG. The relatively benign nature of LGG justifies implementation of second-line chemotherapy as the primary treatment modality at progression. Since most children with LGG will experience tumor progression following initial chemotherapy, a comprehensive prospective multi-institutional study which includes all age groups, tumor locations, and incorporates long-term growth, neuropsychological and functional assessments, is warranted in order to address the appropriate treatment modality for these children.

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