Neurosurgical Focus

**Neurosurg Focus 4 (4):**Article 3, 1998

# Phase II study of carboplatin (CBDCA) in progressive low-grade gliomas

**Albert Moghrabi, M.D., Henry S. Friedman, M.D., David M. Ashley, M.B.B.S., Ph.D., Krystal S. Bottom, M.D., Tracy Kerby, C.C.R.A., Elizabeth Stewart, R.N., M.S.N., Carol Bruggers, M.D., James M. Provenzale, M.D., Martin Champagne, M.D., Linda Hershon, R.N., Melody Watral, R.N., M.S.N., C.P.N.P., Janis Ryan, R.N., M.S.N., C.P.N.P., Karima Rasheed, PAC, Shelley Lovell, PAC, David Korones, M.D., Herbert Fuchs, M.D., Timothy George, M.D., Roger E. McLendon, M.D., Allan H. Friedman, M.D., Edward Buckley, M.D., and Darryl C. Longee, M.D.**

*Department of Pediatrics, Hôpital Sainte-Justine, Montreal, Quebec, Canada; Departments of Pediatrics, Neurosurgery, Radiology, Pathology, and Ophthalmology, Duke University Medical Center, Durham, North Carolina; Department of Pediatrics, University of Utah Medical Center, Salt Lake City, Utah; and Department of Pediatrics, University of Rochester, Rochester, New York*

In this study, the authors sought to investigate the response rate and toxicity of carboplatin in patients with progressive low-grade glioma (LGG). Thirty-two patients with progressive LGG were treated with carboplatin at a dosage of 560 mg/m$^2$. Treatment was given at 4-week intervals and continued until the disease progressed, unacceptable toxicity supervened, or for 12 additional courses after achieving maximal response. Patients with stable disease were treated with a total of 12 cycles. All patients were treated as outpatients. Patients were evaluated for response to treatment and toxicity.

All patients received a minimum of two cycles of carboplatin, and were examined for response. A partial response was achieved in nine patients (28%) and a minimal response in two (6%), for an overall response rate of 34% (11 of 32 patients). Eighteen patients (56%) had stable disease. A partial response was achieved in the nine patients after a median of six cycles (range 4-11 cycles), a minimal response was achieved in the two patients after five cycles. Glioma progression was noted in three patients after three, five, and five cycles, respectively. The 11 patients in whom some response was achieved had either an optic pathway tumor or a juvenile pilocytic astrocytoma. Twenty-six of the 32 patients had those characteristics, making the response rate in that group 42% (11 of 26 patients). Thirty-two patients received a total of 387 cycles of chemotherapy. Hematological toxicity was moderate. Twenty-one patients developed thrombocytopenia (platelet count < 50,000/µl); three patients required one platelet transfusion each. Nine patients developed neutropenia (absolute neutrophil count < 500/µl); one developed fever and required administration of antibiotic agents. One dose adjustment in each of the patients prevented further thrombocytopenia and neutropenia. Two patients with stable disease died of respiratory complications. One patient developed Grade III ototoxicity after receiving five cycles, one patient developed hypersensitivity to carboplatin, and none developed nephrotoxicity.

Carboplatin given at a dosage of 560 mg/m$^2$ every 4 weeks has activity in patients with progressive LGG. This drug regimen is relatively simple and well tolerated. Further investigation and longer follow-up study are warranted.

**Key Words * brain tumor * low-grade glioma * carboplatin**

Low-grade gliomas (LGGs) are a group of tumors that, although morphologically benign, may have a heterogeneous biological behavior. Juvenile pilocytic astrocytoma (JPA) illustrates this point well. This World

Health Organization (WHO) Grade I tumor is typically seen as a well-demarcated lesion in the posterior fossa and as an infiltrating tumor in the optic pathway (OPT); it can, albeit rarely, metastasize throughout the neuraxis. Surgery is the treatment of choice for LGG and is curative if a complete resection is achieved.[11] However, when the disease is unresectable, such as when it occurs in eloquent areas or as an infiltrating tumor, other therapies such as irradiation or chemotherapy are usually used in an attempt to control disease progression. The role of these therapies in newly diagnosed patients is still undefined; no benefit has been seen with radiotherapy administered following initial partial resection rather than at the time of disease progression.[4] Unfortunately, toxicity to the pediatric brain associated with irradiation can be profound, with major long-term neurocognitive sequelae.[6]

The role of chemotherapy in the treatment of LGGs has been evaluated predominantly in the pediatric population because of the desire to spare children from the toxicity of radiotherapy. A diverse spectrum of agents have been used in the treatment of LGGs in the pediatric population, including vincristine, actinomycin D, etoposide, carboplatin, carmustine, and combinations of these regimens, particularly carboplatin and vincristine.[3,5,7-10] We previously reported a single institution experience in which carboplatin was used to treat children with progressive optic pathway glioma.[5] The success of this approach, coupled with its modest toxicity as a single agent, has led us to use carboplatin to treat both children and adults harboring progressive LGGs. We now report our experience with the first 32 patients treated in this fashion.

## CLINICAL MATERIAL AND METHODS

### *Patient Selection and Characteristics*

To be eligible for enrollment in the study, patients were required to: 1) have histological confirmation of a LGG, unless it involved the optic pathway (chiasma and optic radiations); 2) have radiographically demonstrated evidence of tumor progression (25% volume increase in the previous 3-4 months) or in case of optic pathway tumors, to have experienced progressive visual loss; and 3) have a signed informed consent form from a parent or legal guardian. Patients previously treated with chemotherapy or radiotherapy were eligible for enrollment. This study was approved by the Institutional Review Board of the participating institutions.

Thirty-two patients were enrolled in the protocol. There were 14 males and 18 females with a median age of 6.5 years (range 0.5-42 years). There were 30 patients who were younger than 14 years of age. Twenty-one patients had OPTs; 10 patients had neurofibromatosis type 1 (NF1) (Table 1).

TABLE 1
CLINICAL FEATURES AND RESPONSE TO TREATMENT IN 32 PATIENTS WITH PROGRESSIVE LGGs*

| Case No. | Sex | Age at Dx (yrs) | Age at Last Tx (yrs) | Age at Tx w/ Carbo (yrs) | Location of Tumor | Tumor Histology | Prior Tx | Response | No. Cycles to Response | Total No. Cycles & Follow Up Posttreatment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 7.5 | | 7.5 | thalamus | | | PD | | 5 cycles, died 25 mos post |
| 2 | M | 7.5 | 7.5 | 9 | lt CPA | JPA | total resection | PR | 11 | 23 cycles, alive 14 mos post |
| 3 | F | 10.5 | 10.5 | 12 | OPT, suprasellar | Grade II | Bx RT | PR | 5 | 20 cycles, alive 15 mos post |
| 4 | F | 1 | 1 | 3 | OPT | JPA | partial resection, IFO | SD | | 2 cycles, stopped at parents' request, RT, alive 30 mos post |
| 5 | M | 1 | | 1 | OPT | JPA | Bx | SD | | 2 cycles, stopped at parents' request, died 29 mos post |
| 6 | F | 1.2 | 1.2 | 4.5 | OPT | JPA | partial resection, VCR/AMD | PR | 5 | 8 cycles, ototoxicity, RT, alive 21 mos post |
| 7 | F | 8 | 8 | 12 | tectal plate | JPA | VP shunt, Bx | MR | 5 | 19 cycles, alive 12 mos post |
| 8 | F | 10 | | 10 | OPT | JPA | Bx | PR | 6 | 18 cycles, alive 12 mos post |
| 9 | F | 0.8 | 4 | 5.5 | lt frontotemporal | Grade II | 2 resections | SD | | 12 cycles, alive 17 mos post |
| 10 | M | 2.5 | | 2.5 | OPT | | NF1 | SD | | 12 cycles, alive 17 mos post |
| 11 | F | 14 | | 14 | OPT | JPA | Bx | SD | | 12 cycles, alive 17 mos post |
| 12 | M | 4 | 6 | 8 | midbrain | JPA | 2 resections | SD | | 12 cycles, alive 15 mos post |
| 13 | F | 5.5 | | 5.5 | OPT | | NF1 | SD | | 12 cycles, alive 12 mos post |
| 14 | F | 2 | | 2 | OPT | | | PR | 4 | 16 cycles, alive 10 mos post |
| 15 | M | 10.5 | | 10.5 | thalamus | | | PD | | 5 cycles, RT, died 20 mos post |
| 16 | M | 1.5 | | 1.5 | OPT | | NF1 | SD | | 10 cycles, stopped at parents' request, lost to follow up |
| 17 | F | 7 | | 7 | thalamus | JPA | Bx | PR | 8 | 20 cycles, alive 5 mos post |
| 18 | M | 3.2 | 3.7 | 12.5 | pontomedullary | JPA | 2 resections | SD | | 12 cycles, alive 11 mos post |
| 19 | F | 7 | | 7 | OPT | JPA | Bx | SD | | 10 cycles, died during therapy for respiratory distress of unknown etiology |
| 20 | M | 1.5 | | 1.5 | OPT | | NF1 | SD | | 12 cycles, alive 10 mos post |
| 21 | F | 4 | | 4 | OPT | | NF1 | SD | | 8 cycles, stopped at parents' request, alive 12 mos post |
| 22 | F | 5.5 | | 5.5 | OPT | | NF1 | PR | 11 | 19+ cycles |
| 23 | F | 4 | | 4 | OPT | | NF1 | PD | | 3 cycles, alive 15 mos post |
| 24 | F | 7 | | 7 | OPT temp lobe | LGG | NF1 Bx | PR | 11 | 19+ cycles |
| 25 | F | 37.7 | 37.7 | 42 | lt temp lobe | oligo | partial resection | SD | | 12 cycles, alive 5 mos post |
| 26 | M | 0.5 | | 0.5 | OPT | | | PR | 8 | 17 cycles |
| 27 | F | 1 | 1.5 | 4 | OPT | | CCNU/VCR/AMD | SD | | 4 cycles, died of apnea post, VP shunt replacement |
| 28 | M | 1 | | 6 | OPT | | NF1 | SD | | 5 cycles, stopped at parents' request |
| 29 | M | 6 | 6 | 7 | OPT | JPA | partial resection | MR | 5 | 15+ cycles |
| 30 | M | 5 | | 22 | OPT | | NF1 malig schwann BP at age 13, VACA/RT/surg | SD | | 12 cycles, alive 1 mo post, hypersensitivity to carboplatin |
| 31 | M | 2.5 | | 2.5 | thalamus | LGG | Bx | SD | | 12 cycles |
| 32 | M | 6 | 7 | 7.5 | lt temp lobe | PXA | 2 resections | SD | | 12 cycles |

* AMD = actinomycin D; BP = brachial plexus; Bx = biopsy; CCNU = lomustine; CPA = cerebellopontine angle; Dx = diagnosis; IFO = ifosfamide; malig schwann = malignant schwannoma; NF1 = neurofibromatosis type 1; oligo = oligodendroglioma; RT = radiation therapy; PXA = pleomorphic xanthoastrocytoma; temp = temporal; Tx = therapy; VACA = vincristine, actinomycin D, cyclophosphamide, and adriamycin; VCR = vincristine.

Tumor histology was confirmed in 18 patients: 12 had JPAs (WHO Grade I), four had WHO Grade II gliomas, one had a pleomorphic xanthoastrocytoma (WHO Grade I), and one had an oligodendroglioma (WHO Grade II).

Previous treatment included biopsy sampling in nine patients, resection in nine patients, radiation in one patient 4

months prior to progression, and chemotherapy in three patients (8 months, 2 years, and 3 years before treatment with carboplatin).

### *Chemotherapy Protocol*

Carboplatin (560 mg/$m^2$) was administered intravenously in 5% dextrose in one-half normal saline over a 1-hour period, preceded and followed by 1 hour of intravenous hydration (total fluid volume delivered during the 3-hour period was 900 ml/$m^2$). Carboplatin was given at 4-week intervals and continued in successive cycles until the disease progressed, unacceptable toxicity supervened, or for 12 additional cycles after achieving a maximum response. Patients with stable disease were treated with a total of 12 cycles. All patients were treated as outpatients.

Prior to instituting therapy, the following parameters were examined in each patient: complete blood cell count, serum creatinine, hepatic transaminase, and bilirubin levels. Retreatment with chemotherapy was not begun until the absolute granulocyte count was greater than 750/µl, the platelet count was greater than 100,000/µl, and the creatinine level was less than 1.5 mg/dl. Patients received a 25% dose reduction if the previous course resulted in a platelet count nadir of less than 50,000/µl. A 25% dose escalation was instituted if the prior course resulted in an absolute granulocyte count nadir of more than 1500/µl and/or a platelet count nadir of more than 100,000/µl.

### *Evaluation of Toxicity and Response to Therapy*

Neurological and ophthalmological examinations were performed before each course of therapy was initiated. Magnetic resonance imaging was performed before therapy was started, after the initial two cycles, and then after every three cycles. After completion of treatment, magnetic resonance images were obtained every 3 months. Audiograms were performed before the first course and every 6 months thereafter. Complete blood cell counts were obtained weekly during treatment. Prior to every course, serum creatinine, hepatic transaminase, and bilirubin levels were measured. Toxicity was graded and recorded following the Pediatric Oncology Group toxicity criteria.

The response criteria were defined objectively on magnetic resonance imaging as follows: complete response (CR), complete disappearance of disease; partial response (PR), a decrease of 50% or more in tumor size; minimal response (MR), a decrease of 25% or more, but less than 50% in tumor size; stable disease (SD), no change, or less than 25% change in tumor size; and progressive disease (PD), greater than 25% increase in tumor size. Tumor size was assessed using the product of the longest measured perpendicular diameters of the enhancing component as well as the $T_2$-weighted signal change of the nonenhancing component of the tumor.

## RESULTS

### *Response to Treatment*

All 32 patients received a minimum of two cycles of chemotherapy. A PR was achieved in nine patients (28%) and an MR was achieved in two (6%), for an overall response rate of 34% (11 of 32 patients). The PRs were achieved after a median of six cycles (range 4-11 cycles) and the MRs after five cycles. Four of the patients in whom a PR was achieved and one in whom an MR was achieved have now survived a median of 11.5 months after completions of therapy (range 5-13 months) and their status remains unchanged.

Eighteen patients (56%) had SD. Three are still undergoing therapy and eight completed therapy a median of 11 months ago (range 1-17 months). Five patients refused further therapy after receiving two, two, five, eight, and 10 cycles, respectively. Two patients died of respiratory complications: one of increased apnea after four cycles and one from respiratory distress of unknown cause after 10 cycles.

Tumor progression was seen in three patients after three, five, and five cycles, respectively. Patients in whom some response was achieved were among the 26 patients harboring either an OPT or a JPA, making the response rate of that group 42% (11 of 26 patients). Of the remaining six patients, there were four with SD and two with PD.

### *Toxicity Assessment*

The 32 patients underwent a total of 387 cycles of chemotherapy. Twenty-one patients developed thrombocytopenia (platelet count < 50,000/μl), five of them did so following a 25% dose increase. Three patients needed platelet transfusions. One dose adjustment prevented further thrombocytopenia.

Nine patients developed neutropenia (absolute neutrophil count < 500/μl), one patient did so following a 25% dose increase. Only one patient developed fever with neutropenia. One dose adjustment prevented further neutropenia.

A Grade III ototoxicity occurred in one patient after five cycles of chemotherapy. One patient developed a hypersensitive reaction during the 12th and final cycle of carboplatin. No nephrotoxicity was encountered in any patient.

## DISCUSSION

Low-grade gliomas form a group of tumors that are morphologically well differentiated (astrocytomas, WHO Grades I and II) but that can be clinically "malignant," infiltrating eloquent areas of the brain, acting as space-occupying lesions with mass effect, and occasionally, metastasizing. Surgical resection is the treatment of choice for localized disease with patient survival correlating with the degree of resection.[11] Unfortunately, patients with infiltrating tumors or with tumors located at crucial sites, having considerable residual disease after surgery, may derive little benefit from this therapy. The role of adjuvant therapy for residual disease is poorly defined. Therapeutic measures are difficult to assess because these tumors behave slowly, and sometimes erratically. Radiation therapy, the "standard" adjuvant therapy in adults, may bring objective responses, but may not produce an ultimate increase in patient survival.[1,2,12] In a recent study patients with LGGs who received radiotherapy following a subtotal resection were compared with patients who underwent radiotherapy at the time of disease progression, and the investigators found no difference in patient survival times.[4] Furthermore, pediatric patients are particularly sensitive to the neurotoxicity produced by radiotherapy, supporting efforts to defer radiotherapy for as long as possible in this population.[6]

There have been previous reports in which the efficacy of chemotherapy to treat progressive LGGs in the pediatric population has been detailed. These chemotherapy regimens have included actinomycin and vincristine,[8] carboplatin,[3,5] carboplatin and vincristine,[7] and a five-drug treatment incorporating procarbazine, 6-thioguanine, dibromodulcitol, lomustine, and vincristine.[10] The largest study to date, in which carboplatin and vincristine were administered to children with newly diagnosed progressive LGGs, was recently updated by Packer, et al.[7] This regimen produced a progression-free survival rate of 75 ± 6% at 2 years and 68 ± 7% at 3 years in 78 children, who ranged in age between 3 months and 16 years. A partial or complete response was achieved in 33% of these patients, with another 23% achieving a minimal response. These results are very encouraging and suggest that chemotherapy may well be effective in delaying radiotherapy for the majority of young children with LGG.

Our current study supplies further evidence for a role for carboplatin in the treatment of patients with progressive LGG. The toxicity of the therapy is minimal, and, of note, the CR and PR response rate in our study is identical to that achieved with the regimen of carboplatin and vincristine used by Packer, et al.[7] Furthermore, patients harboring OPTs or JPAs had an even higher response rate of 42% compared with no response in the other six patients harboring other types of LGGs in different sites of the brain. Although few conclusions can be drawn based on the results in those six patients, there were nevertheless four patients with SD after 12 cycles of carboplatin. Two of these four patients have just completed therapy, and two continue to sustain SD, 5 and 17 months posttreatment, respectively.

Our treatment regimen involves the monthly administration of carboplatin on an outpatient basis. This may be a more practical approach because it allows the patient to avoid weekly chemotherapy. Carboplatin is not associated with the potential neurotoxic effect of vincristine. Patients participating in our study show persistent disease control following termination of chemotherapy. Disease progressed in only three patients and although two additional patients died of toxicity, it was believed to be independent of the carboplatin.

## CONCLUSIONS

We can infer from these results that patients with progressive LGG may be managed effectively with carboplatin in lieu of alternative interventions. The toxicity associated with radiotherapy and the observation that the delay of radiotherapy does not alter the overall patient survival time supports the use of chemotherapy as a front-line approach in patients with progressive LGG following surgical intervention.

---

## References


1. Alvord EC Jr, Lofton S: Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site, and treatment. **J Neurosurg 68:**85-98, 1988

2. Conway PD, Oechler HW, Kun LE, et al: Importance of histologic condition and treatment of pediatric cerebellar astrocytoma. **Cancer 67:**2772-2775, 1991

3. Friedman HS, Krischer JP, Burger P, et al: Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study. **J Clin Oncol 10:**249-256, 1992

4. Leighton C, Fisher B, Bauman G, et al: Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. **J Clin Oncol 15:**1294-1301, 1997

5. Moghrabi A, Friedman HS, Burger PC, et al: Carboplatin treatment of progressive optic pathway gliomas to delay radiotherapy. **J Neurosurg 79:**223-227, 1993

6. Mulhern RK, Hancock J, Fairclough et al: Neuropsychological status of children treated for brain tumors: a critical review and integrative analysis. **Med Pediatr Oncol 20:**181-191, 1992

7. Packer RJ, Ater J, Allen J, et al: Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. **J Neurosurg 86:**747-754, 1997

8. Packer RJ, Sutton LN, Bilaniuk LT, et al: Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. **Ann Neurol 23:**79-85, 1988

9. Pons MA, Finlay JL, Walker RW, et al: Chemotherapy with vincristine (VCR) and etoposide (VP-16) in children with low-grade astrocytoma. **J Neurooncol 14:**151-158, 1992

10. Prados MD, Edwards MSB, Rabbitt J, et al: Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. **J Neurooncol 32:**235-241, 1997

11. Schneider JH Jr, Raffel C, McComb JG: Benign cerebellar astrocytomas of childhood. **Neurosurgery 30:**58-63, 1992

12. Shaw EG, Scheithauer BW, Gilbertson DT, et al: Postoperative radiotherapy of supratentorial low-grade gliomas. **Int J Radiat Oncol Biol Phys 16:**663-668, 1989


---


Manuscript received February 26, 1998.

Accepted in final form March 23, 1998.



Address reprint requests to: Albert Moghrabi, M.D., Hôpital Sainte-Justine, 3175 Côte Ste-Catherine, Montreal, Quebec H3T 1C5, Canada. email: moghraba@medclin.umontreal.ca


---