Medical and Pediatric Oncology 27:32–39 (1996)

Successful Treatment of Childhood Pilocytic Astrocytomas Metastatic to the Leptomeninges With High-Dose Cyclophosphamide

Geoffrey McCowage, MB, BS, FRACP, Robert Tien, MD, Roger McLendon, MD, Gary Felsberg, MD, Herbert Fuchs, MD, PhD, Michael L. Graham, MD, Joanne Kurtzberg, MD, Albert Moghrabi, MD, Lee Ferrell, CRA, Tracy Kerby, CRA, Margaret Duncan-Brown, RN, BSN, Elizabeth Stewart, RN, MSN, Patricia L. Robertson, MD, O. Michael Colvin, MD, Barry Golembe, MD, Darrell D. Bigner, MD, PhD, and Henry S. Friedman, MD

Leptomeningeal dissemination of childhood pilocytic astrocytoma (PA) is a rare event with little information available regarding therapy. We report here four children with disseminated PA whom we treated with high doses of cyclophosphamide with clinical benefit. The patients were aged 2.5 to 8 years. Three patients presented with PA localized in the posterior fossa, initially treated with surgical resection (n = 3) and radiotherapy (n = 1). Leptomeningeal dissemination occurred at 32, 44, and 8 months from diagnosis, respectively. The fourth patient presented with an optic pathway tumor with leptomeningeal dissemination at diagnosis. At commencement of cyclophosphamide therapy, disease was present in the subarachnoid space (intracranial, n = 2; spinal, n = 4), cerebral ventricles (n = 2), and primary site (n = 3). Histology was identical at diagnosis and recurrence in the two biopsied cases and cerebrospinal fluid was negative in all cases. Treatment was with cyclophosphamide 4–5 g/m^2/cycle given every 4 weeks for a total of two cycles (n = 1) and four cycles (n = 3). One patient achieved disease stabilization (duration 27 months at the time of publication) and three patients experienced significant reductions in tumor burden. Subsequent intrathecal therapy was administered to two patients. Two patients developed disease progression at 10 and 9 months from cessation of chemotherapy. The one re-treated patient responded to further, lower dose, cyclophosphamide. This is the first report of the use of high dose cyclophosphamide for disseminated PA. The recurrence of disease in two cases with a further response to lower dose cyclophosphamide has implications for the optimal duration of therapy for these low grade, aggressive tumors.

Key words: pilocytic astrocytoma, cyclophosphamide, leptomeninges

INTRODUCTION

Pilocytic astrocytomas (PA) are indolent, low-grade glial neoplasms, the clinical course of which is intimately related to their site of origin [1–3]. Resectable lesions, such as the juvenile cerebellar pilocytic astrocytoma, are cured with surgical intervention alone. Pilocytic astrocytomas located at more eloquent sites such as the optic pathway are more problematic, since gross resection is often not possible and tumor progression ultimately occurs in a significant proportion of these cases. Although radiotherapy can delay tumor progression, either as adjuvant therapy following initial sub-total resection or at the time of progressive disease [3–5], this modality does not cure pilocytic astrocytoma [3,6] and, when applied to the brain of younger children, may be profoundly neurotoxic [7]. Recent observations have supported the role of chemotherapy in the treatment of these tumors, and Packer et al. [8], Cohen et al. [9], Moghrabi et al. [10] and others have suggested the application of this approach to the rarer biologically aggressive pilocytic astrocytomas.

A small minority of pilocytic astrocytomas are associated with the development of a more aggressive course with metastatic spread to the leptomeninges [11–22]. The

From the Departments of Pediatrics (G.M., M.L.G., J.K., L.F., T.K., M.D.B., E.S., H.S.F.), Radiology (R.T., G.F.), Pathology (R.M., D.D.B.), and Surgery (H.F.), Duke University Medical Center, Durham, North Carolina; The Johns Hopkins Oncology Center, Johns Hopkins University, Baltimore, Maryland (O.M.C.); Hospital Sainte-Justine, Montreal, Quebec, Canada (A.M.); Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, Michigan (P.L.R.); and Nalle Clinic, Charlotte, North Carolina (B.G.).

Received August 12, 1994; accepted January 29, 1995.

Address reprint request to Henry S. Friedman, M.D., Duke University Medical Center, Box 2916 DUMC, Durham, NC 27710.

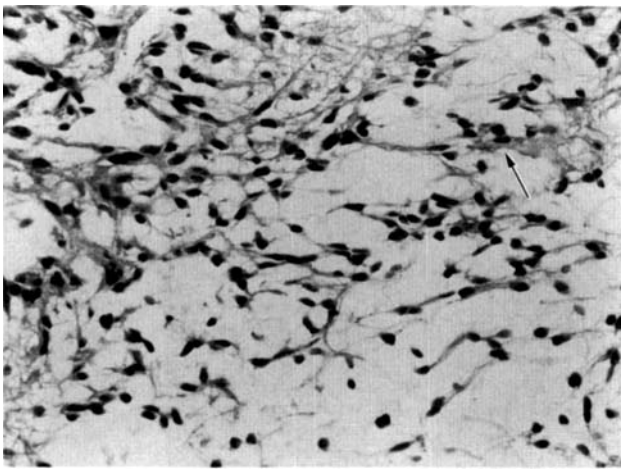

Fig. 1. The original biopsy was characterized by heterogenous appearance of bipolar spindle shaped astrocytes exhibiting clustering around vessels separated by looser, stellate arrangements. Rosenthal fibers are evident (arrow) (H&E, ×400).

few cases reported in the literature are notable for the absence of de-differentiation at the time of spread. There is minimal experience reported regarding treatment of metastatic pilocytic astrocytoma, with variable benefits seen following use of radiation therapy.

We previously described the moderate activity of a constellation of chemotherapeutic agents in the treatment of three children with optic pathway tumors metastatic to the subarachnoid space [17]. We now report four children with leptomeningeal metastases secondary to pilocytic astrocytoma who demonstrated significant benefit from high dose cyclophosphamide and discuss strategies for further improvements in the treatment of similar patients.

CASE REPORTS

Case 1

An 8-year-old boy presented in February 1989 with symptoms and signs of hydrocephalus. Subtotal resection of a third ventricular tumor was performed and a shunt was inserted. Histopathology revealed a neoplasm consisting of fibrillar elongated processes with elongated, hyperchromatic nuclei located either centrally or at one end of the cytoplasmic processes. The bipolar cells occasionally exhibited a perivascular radial orientation. Mitotic activity was not seen (Fig. 1). He received 5040 Gy external beam radiation therapy to the tumor bed which led to reduction in the size of the residual tumor.

He remained well until October 1991 when a surveillance MRI scan revealed multiple deposits of intracranial and spinal sub-arachnoid tumor. Cerebrospinal fluid analysis was negative for tumor cells. The patient was referred to Duke University Medical Center. He was treated with four cycles of chemotherapy, each comprising cyclophosphamide 2.5 g/m^2/day for two days with mesna uroprotection and subcutaneous granulocyte-macrophage colony stimulating factor (GM-CSF) 250 μg/m^2 twice daily. Chemotherapy was administered at 4-week intervals and was complicated by myelosuppression. Five months from the initiation of chemotherapy, scans revealed no change in tumor bulk. The patient was then treated with two doses of intrathecal 4-hydroxyperoxycyclophosphamide (12.4 mg) administered via an Ommaya reservoir. He has been followed with no further therapy for 19 months (27 months since initiation of chemotherapy) and serial MRI scans have demonstrated stable intracranial and spinal imaging abnormalities. He remains clinically well and is monitored with surveillance scans every 6 months.

Case 2

A 5-year-old girl presented in March 1989 with hydrocephalus and an enhancing midline cerebellar tumor measuring 5 × 4.5 cm. Gross total resection was performed followed by insertion of a ventriculoperitoneal shunt 6 days later. Cerebrospinal fluid (CSF) was negative for tumor cells. Histopathology revealed typical morphology of PA with fibrillar astrocytes exhibiting round to elongated nuclei and cytoplasmic Rosenthal fibres. There was moderate variation in cellular distribution with perivascular crowding of neoplastic cells separated by occasional microcysts. The patient was followed clinically and with serial CT scans which revealed no evidence of tumor over the 2 years following tumor resection.

In November 1992, she developed recurrent tumor measuring 2 × 1.5 cm in the midline of the cerebellum (Fig. 2A). Macroscopic gross total resection was performed and the patient made an uneventful recovery. Histopathology was similar to that at diagnosis, with typical appearance of pilocytic astrocytoma.

The patient was referred to Duke University Medical Center for further evaluation and treatment. On review of her cranial MRI scan, a small enhancing nodule was seen at the surgical bed, considered most likely to represent residual tumor (Fig. 2B), and an enhancing nodule was seen on the anterior spinal cord at the level of C2 (Fig. 3A). Spine MRI revealed two enhancing masses near the conus medullaris (Fig. 3B). CSF was negative for tumor cells. Treatment was with cycles of chemotherapy administered every 4 weeks, beginning in February 1993. Four chemotherapy cycles were administered, each comprising cyclophosphamide 2 g/m^2/day for 2 days with mesna and subcutaneous GM-CSF 250 μg/m^2 twice daily. Toxicity related to myelosuppression. Following two cycles, spine MRI revealed a minor decrease in the size of all tumor deposits. One month after the completion of chemotherapy there was complete resolution of the cervical spine nodule and no change in size of the lumbar lesions. Six months later, MRI revealed complete resolution of

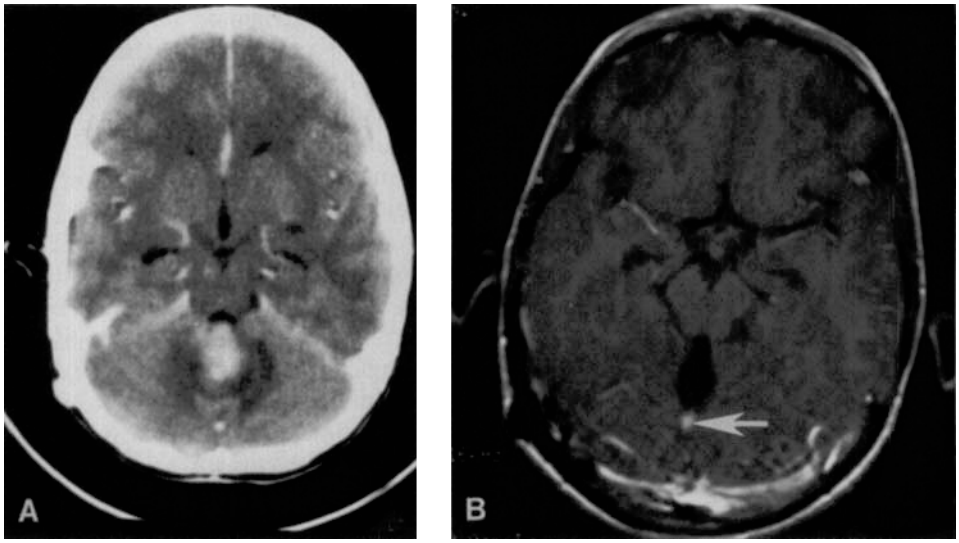

Fig. 2. **A:** Post-contrast axial CT scan of the posterior fossa performed in December 1992 on patient in Case 2 showed an enhancing mass approximately 2 × 1.5 cm in size with adjacent edema near the inferior vermis which is consistent with imaging findings of recurrent pilocytic astrocytoma. **B:** Post-contrast axial T1-weighted image performed immediately after surgery in January 1993 on patient in Case 2 demonstrates a small enhancing nodule (arrow) at the surgical bed which most likely represents residual tumor.

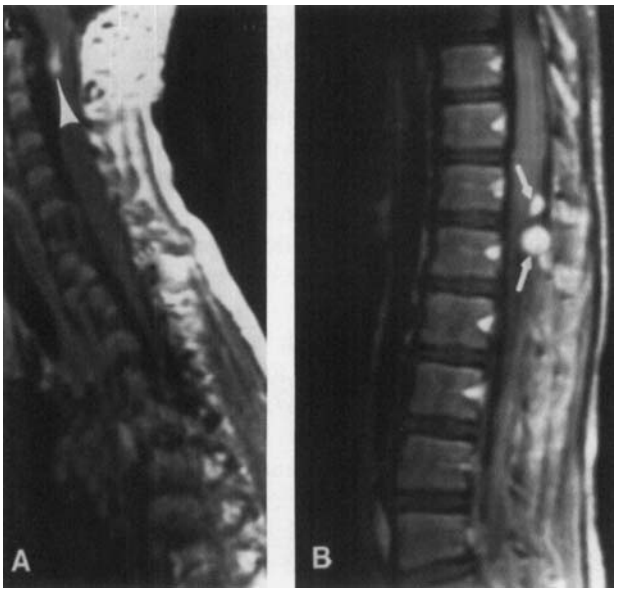

Fig. 3. **A:** Post-contrast sagittal T1-weighted image of the cervical spine performed in February 1993 on patient in Case 2 demonstrates an enhancing nodule located in the anterior portion of the cervical cord at the level of C2 (arrowhead). **B:** In the lumbar spine region, two enhancing masses are identified near the conus medullaris (arrows).

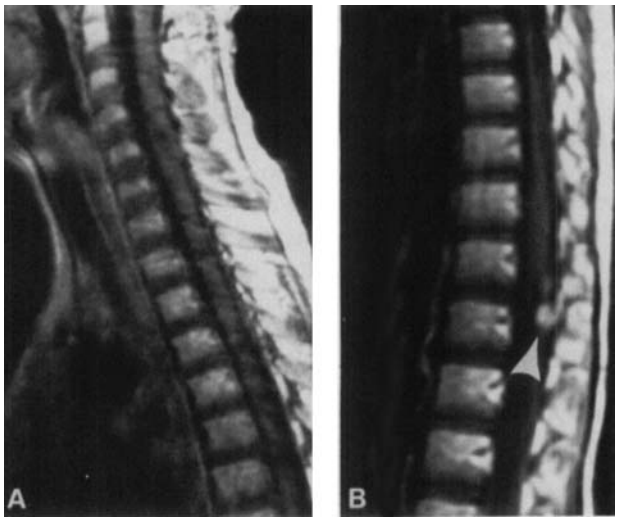

Fig. 4. Post-contrast sagittal T1-weighted images performed in December 1993 on patient in Case 2, 7 months following completion of chemotherapy, show complete resolution of tumor deposit at the level of C2 (**A**) and partial resolution of the two nodules at the level of the conus medullaris (**B**, arrowhead).

the posterior fossa lesion, continued total resolution of the cervical lesion, and a decrease in the size of the lumbar nodules (Figs. 4,5). Four months later, 10 months from completion of chemotherapy, the lumbar lesions were further reduced in size but she developed two new small posterior fossa lesions. Currently we are monitoring the patient with periodic MRI scans which have remained stable over the subsequent 4 months.

Case 3

A 2½-year-old girl presented in April 1991 with a large mass occupying the third ventricle. Gross total resection was performed. Histopathology revealed a tumor which was modestly cellular and composed of fibrillar,

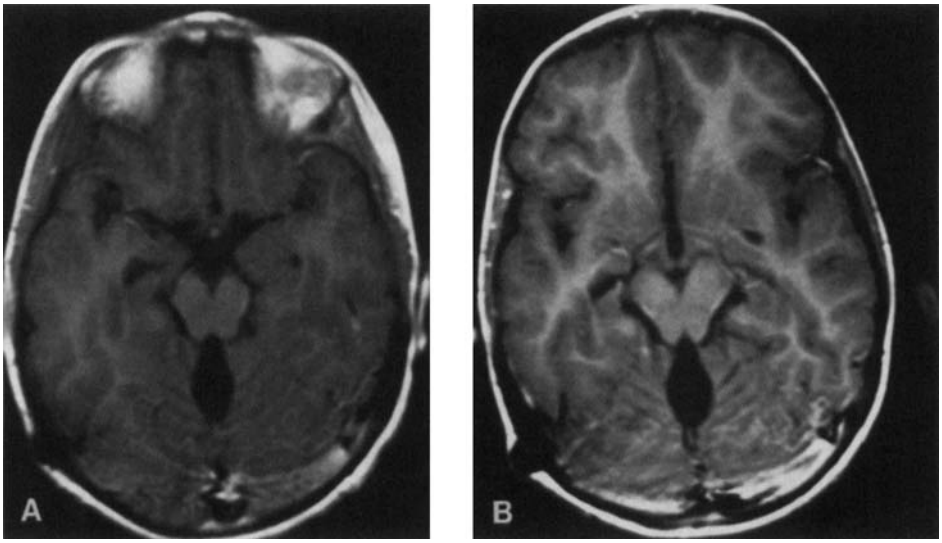

Fig. 5. Post-contrast axial T1 weighted images **(A,B)** of the posterior fossa performed on the patient in Case 2 in December 1993, 7 months following completion of chemotherapy, show total resolution of the enhancing residual tumor which was noted post-operatively (compare to Fig. 2B).

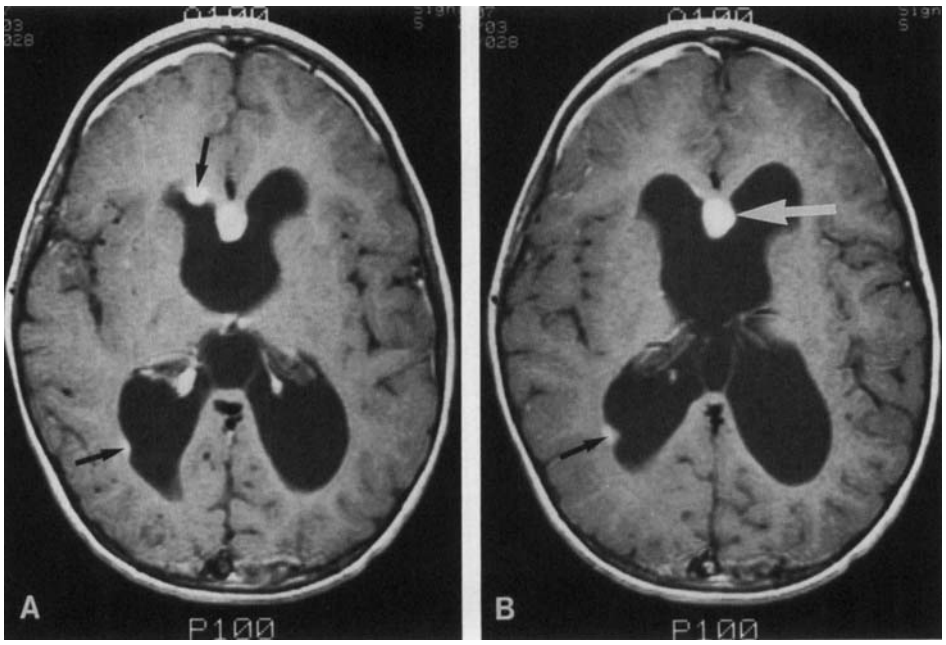

Fig. 6. Post-contrast axial T1-weighted images **(A,B)** at the level of the lateral ventricle performed on patient in Case 3 in March 1993, immediately prior to commencement of cyclphosphamide therapy, show a 1.5 × 1.0 cm enhancing module (white arrow) adjacent to the genu of the corpus callosum. Several ependymal metastatic nodules are also identified (black arrows).

bipolar astrocytes with compact and loosely woven stellate areas evident. Rosenthal fibres were common.

She remained disease-free on serial CT scans until December 1991 when a small lesion in the original tumor bed and a punctate lesion in the fourth ventricle were detected, followed 4 months later by further seeding of the fourth ventricle and the development of a single lesion in the lumbar region above the conus medullaris. Endoscopic biopsy of one of the brain lesions again revealed a low grade astrocytic neoplasm. Two months later, MRI demonstrated tumor deposits in the third, fourth, and lateral ventricles, as well as the lumbar lesion. She was

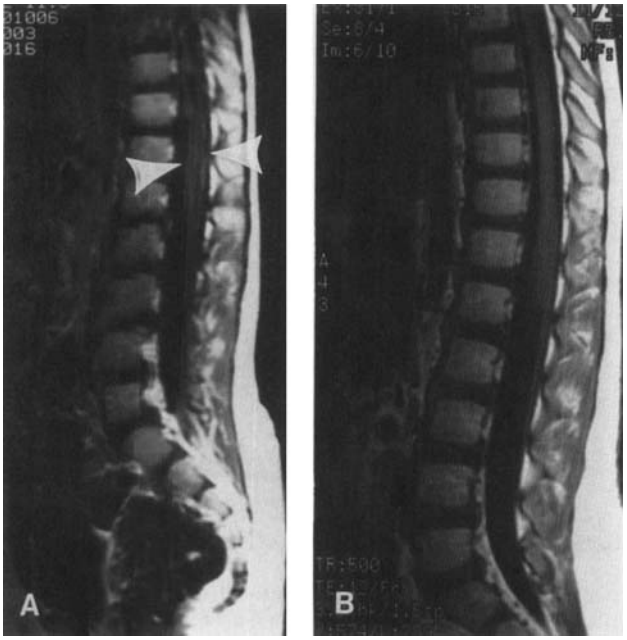

Fig. 7. **A:** Post-contrast sagittal T1-weighted image of the lumbar spine performed on patient in Case 3 in March 1993, immediately prior to commencement of cyclophosphamide therapy, shows abnormal enhancement around the conus medullaris representing metastatic disease (arrowheads). **B:** The same patient's study performed in November 1993, 4 months following completion of chemotherapy, shows total resolution of tumor. No abnormal enhancement is identified.

treated with carboplatin and vincristine with stable disease from July 1992 until March 1993 at which time progression of the ventricular lesions was detected. MRI scan revealed a 1 cm diameter mass in the fourth ventricle, an 8 × 6 mm mass in the third ventricle, a 1.5 × 1 cm mass adjacent to the genu of the corpus callosum, and several ependymal metastatic nodules (Fig. 6). The spinal lesion was unchanged in size (Fig. 7A).

The patient was referred to Duke University Medical Center in April 1993 and chemotherapy was changed to cyclophosphamide 2 g/m^2/day for 2 days with mesna and subcutaneous GM-CSF 250 μg/m^2 twice daily. A total of four cycles were administered at 4 week intervals. Toxicity related to myelosuppression. MRI scans in early October 1993, 3 months following completion of chemotherapy, demonstrated resolution of the third ventricular, subependymal, and spinal lesions and significant reduction in the size of the mass near the genu of the corpus callosum (Figs. 7B,8). In mid-October 1993, she received a single dose of I^{131}-labeled monoclonal antibody 81C6 administered via a ventricular reservoir (with communication via CSF pathways with the intracranial and spinal subarachnoid space). Her disease remained stable on serial scans until March 1994 at which time she developed new enhancing nodularity along the fourth ventricle, septum pellucidum, and lateral ventricle. Spinal MRI scan remained negative for tumor. Treatment was reinstituted with cyclophosphamide 1g/m^2/day for two days (half the previous dose) every four weeks. Cranial MRI scan obtained after two courses of this therapy revealed an approximately 60% reduction in tumor bulk. She continues on this treatment at monthly intervals.

Case 4

A 7-year-old girl presented in February 1994 with an 18-month history of behavioral problems, visual field abnormalities, dysconjugate eye movements, and nausea and vomiting. MRI scan demonstrated hydrocephalus and a large lobulated mass within the sella turcica and suprasellar region. There was extensive meningeal disease in subarachnoid and lumbar regions and intraventricular spread. Ventriculo-peritoneal shunt and tumor biopsy were performed. Histology revealed a slightly hypercellular glial neoplasm with a fibrillary background. There were round to oval nuclei with long bipolar processes with slight pleomorphism. Microcysts and myxoid material were present. The findings were consistent with the diagnosis of pilocytic astrocytoma. CSF was negative for tumor cells.

The patient was referred in May 1994 to Duke University Medical Center and two chemotherapy cycles were administered, each comprising cyclophosphamide 2 g/m^2 per day for 2 days with mesna and subcutaneous GM-CSF 250 μg/m^2 twice daily. Reevaluation in August 1994 following these two cycles revealed stable disease at the primary site, a minor reduction in intracranial leptomeningeal disease, and a dramatic reduction in the tumor burden around the spinal cord. These findings were associated with a dramatic reduction in her back pain. Treatment continues now with monthly cyclophosphamide at half of the previous dose.

DISCUSSION

The occurrence of metastatic disease from a pilocytic astrocytoma is a rare event, estimated to occur in 4% of cases [11]. These low grade tumors more typically follow an indolent course, with gross resection of surgically accessible lesions curative in a high proportion of cases. Radiotherapy, previously used for those cases which were unresectable is now frequently reserved until radiographic or clinical evidence of tumor progression is seen. However, there exists a small subset of patients with these tumors who have an aggressive clinical course, either with progressive or recurrent tumor, or with the development of disease metastatic to the leptomeninges. Several cases of leptomeningeal tumor dissemination have been described which retained the histological characteristics of pilocytic astrocytoma.

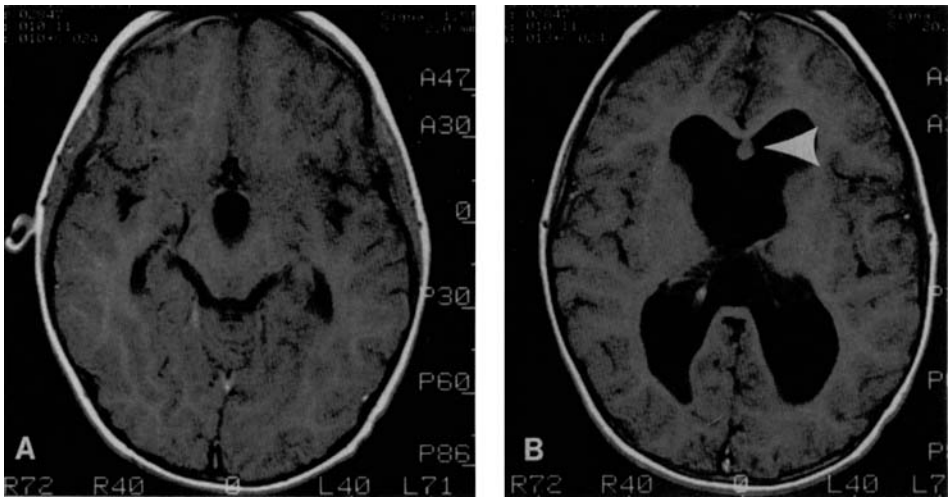

Fig. 8. Post-contrast T1-weighted images performed on patient in Case 3 in October 1993, 3 months following completion of chemotherapy, at the level of the third ventricle **(A)** and lateral ventricle **(B)**. The enhancing mass at the third ventricle (see text) has resolved. The mass adjacent to the genu of the corpus callosum (arrowhead) is significantly decreased in size compared with Figure 6, as is the ependymal nodule. These masses are also somewhat less enhancing, but this may be partially attributable to differences in technique. There is a small subdural hygroma noted in the right frontal region.

We previously reported our experience using chemotherapy for pilocytic astrocytomas, describing eleven patients who had experienced disease progression or recurrence despite conventional treatment with surgery and chemotherapy [23]. All patients had disease which had recurred within brain parenchyma, generally in close proximity to the anatomic location of the original tumor. A total of 16 different chemotherapy regimens were used on the 11 patients, with 12 regimens producing tumor stabilization or regression. The broad spectrum of regimens used precluded analysis of the role of individual agents, but of five patients receiving cisplatin or a cisplatin analogue, three had a radiographic and clinical response, and two experienced tumor stabilization. Other groups have confirmed the efficacy of chemotherapy in the treatment of these tumors, including actinomycin-D/vincristine [24], "TPDCV" (6-thioguanine, procarbazine, dibromodulcitol, lomustine and vincristine [25], "MOPP" (mechlorethamine, vincristine, procarbazine, and prednisone) [26], and carboplatin-containing combinations [8,27].

The increasing experience with the use of chemotherapy for pilocytic astrocytomas following intra-parenchymal tumor recurrence has not been extended to the treatment of leptomeningeal dissemination. The small number of cases reported in the literature have generally described the use of radiotherapy, with no clear proof of efficacy. A number of investigators have found apparent benefit following radiation therapy [11,13,16], though other have described disease progression [14,15,18,22]. The uncertain benefit of radiation therapy in this uncommon clinical setting, along with its long-term sequelae in the pediatric patient population [7], provide a rationale for exploring alternate therapeutic modalities.

Reports of chemotherapy for the treatment of leptomeningeal disease include our previous study of three patients with disseminated optic pathway gliomas [17]. One patient responded to oral 6-mercaptopurine and carmustine but developed fatal lung fibrosis as a complication of the latter agent. The second patient, who was aged 14 weeks, achieved disease stabilization with thiotepa before treatment was withdrawn by her parents. The third patient received vincristine, cyclophosphamide, cisplatin, and etoposide and responded with a greater than 50% reduction in the size of leptomeningeal tumor. Obana et al. reported a patient treated at age 16 months for pilocytic astrocytoma with subtotal resection and external beam irradiation [19]. He developed leptomeningeal disease at age 10 years with histology similar to the original lesion. Treatment was with 6-thioguanine and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and led to stabilization or reduction of all lesions over a follow-up period of 1½ years. Trigg et al. described a 3½-year-old boy who developed cerebrospinal and peritoneal seeding with tumor cells while undergoing treatment with vincristine and actinomycin-D for a previously non-metastatic optic pathway glioma [20]. In Pollack's series, two patients received chemotherapy, with impressive responses to aziridynyl benzoquinone, etoposide/5-fluorouracil, and carboplatin/vincristine, and a minor response to lomustine/procarbazine/vincristine [11]. The rarity of the disease and variety of regimens employed makes compar-

ison of the relative efficacy of these regimens, and our own, impossible.

We have now reported treatment of four patients with leptomeningeal dissemination of juvenile pilocytic astrocytoma using high dose cyclophosphamide, demonstrating three significant tumor responses and one prolonged disease stabilization. We chose cyclophosphamide for the treatment of these patients because of our earlier demonstration of activity against high-grade and low-grade gliomas [28]. Our experience is notable both for the responses obtained, and because two of the four patients described subsequently developed disease progression months following cessation of therapy. Furthermore, the re-treatment of the patient in Case 3 with lower doses of cyclophosphamide following tumor recurrence led to a prompt response. It is interesting to speculate that the optimal treatment duration of low-grade gliomas such as pilocytic astrocytoma may parallel that of childhood acute leukemia: early pre-B cell leukemia requires sustained, moderate intensity therapy for 2–3 years, while the more proliferative mature B-cell disease is curable with as little as 4 to 6 months of high intensity therapy. We plan in the future to treat patients with these low-grade disseminated brain tumors with an initial short phase of high-dose cyclophosphamide, followed by a more prolonged phase using lower doses of cyclophosphamide.

In summary, we describe four patients with disseminated leptomeningeal disease following treatment of pilocytic astrocytoma who responded to high-dose cyclophosphamide with significant reductions in tumor burden in three cases, and disease stabilization in one. The recurrence of disease in two cases after cessation of therapy, with a further response to cyclophosphamide in the one re-treated patient, has implications for duration of therapy of these low-grade, aggressive tumors.

ACKNOWLEDGMENTS

This work was partially supported by NIH grants CA 11898 and NS 20023.

REFERENCES

1. Geissinger JD: Astrocytomas of the cerebellum in children: long term study. Arch Neurol 24:125–135, 1971.
2. Gjerris F, Klinken L: Long-term prognosis in children with benign cerebellar astrocytoma. J Neurosurg 49:179–184, 1978.
3. Garcia DM, Latifi HR, Simpson JR, Picker S: Astrocytomas of the cerebellum in children. J Neurosurg 71:661–664, 1989.
4. Leibel SA, Sheline GE, Wara WM, Boldrey EB, Nielsen SL: The role of radiation therapy in the treatment of astrocytomas. Cancer 35:1551–1557, 1975.
5. Packer RJ, Savino PJ, Bilaniuk LT, Zimmerman RA, Schatz NJ, Rosenstock JG, Nelson DS, Jarrett PD, Bruce DA, Schut L: Chiasmatic gliomas of childhood. A reappraisal of natural history and effectiveness of cranial irradiation. Childs Brain 10:393–403, 1983.
6. Austin EJ, Alvord EC Jr: Recurrences of cerebellar astrocytomas: a violation of Collins' law. J Neurosurg 68:41–47, 1988.
7. Duffner PK, Cohen ME, Thomas PR, Lansky SB: The long-term effects of cranial irradiation on the central nervous system. Cancer 56:1841–1846, 1985.
8. Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, Prados M, Jakacki R, Reaman G, Needle MN, et al: Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 11:850–856, 1993.
9. Cohen ME, Mahoney DH Jr, Duffner PK, Gemer L, James HE, Langston JW, Fontanesi J, Friedman HS: Evaluation of optic pathway tumors: natural history and treatment. Pediatric Oncology Group (POG). Neurology 36:505, 1994.
10. Moghrabi A, Feidmen HS, Burger PC, Tien R, Oakes WJ: Carboplatin treatment of progressive optic pathway gliomas to delay radiotherapy. J Neurosurg 79:223–227, 1993.
11. Pollack IF, Hurtt M, Pang D, Albright AL: Dissemination of low grade intracranial astrocytomas in children. Cancer 73:2869–2878, 1994.
12. Prados M, Mamelak AN: Metastasizing low grade gliomas in children. Redefining an old disease [editorial]. Cancer 73:2671–2673, 1994.
13. Mishima K, Nakamura M, Nakamura H, Nakamura O, Funata N, Shitara N: Leptomeningeal dissemination of cerebellar pilocytic astrocytoma. J Neurosurg 77:788–791, 1992.
14. Auer RN, Rice GP, Hinton GG, Amacher AL, Gilbert JJ: Cerebellar astrocytoma with benign histology and malignant clinical course. J Neurosurg 54:128–132, 1981.
15. McLaughlin JE: Juvenile astrocytomas with subarachnoid spread. J Pathol 118:101–107, 1976.
16. Shapiro K, Shulman K: Spinal cord seeding from cerebellar astrocytomas. Childs Brain 2:177–186, 1976.
17. Bruggers CS, Friedman HS, Phillips PC, Wiener MD, Hockenberger B, Oakes WJ, Buckley EG: Leptomeningeal dissemination of optic pathway gliomas in three children. Am J Ophthalmol 111:719–723, 1991.
18. Kocks W, Kalff R, Reinhardt V, Grote W, Hilke J: Spinal metastasis of pilocytic astrocytoma of the chiasma opticum. Childs Nerv Syst 5:118–120, 1989.
19. Obana WG, Cogen PH, Davis RL, Edwards MS: Metastatic juvenile pilocytic astrocytoma. Case report. J Neurosurg 75:972–975, 1991.
20. Trigg ME, Swanson JD, Letellier MA: Metastasis of an optic glioma through a ventriculoperitoneal shunt. Cancer 52:599–601, 1983.
21. Civitello LA, Packer RJ, Rorke LB, Siegel K, Sutton LN, Schut L: Leptomeningeal dissemination of low-grade gliomas in childhood. Neurology 38:562–566, 1988.
22. Kepes JJ, Lewis RC, Vergara GG: Cerebellar astrocytoma invading the musculature and soft tissues of the neck. Case report. J Neurosurg 52:414–418, 1980.
23. Brown MT, Friedman HS, Oakes WJ, Boyko OB, Hockenberger B, Schold SC Jr: Chemotherapy for pilocytic astrocytomas. Cancer 71:3165–3172, 1993.
24. Packer RJ, Sutton LN, Bilaniuk LT, Radcliffe J, Rosenstock JG, Siegel KR, Bunin GR, Savino PJ, Bruce DA, Schut L: Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. Ann Neurol 23:79–85, 1988.
25. Petronio J, Edwards MS, Prados M, Freyberger S, Rabbitt J, Silver P, Levin VA: Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy. J Neurosurg 74:701–708, 1991.

26. van Eys J, Cangir A, Coody D, Smith B: MOPP regimen as primary chemotherapy for brain tumors in infants. J Neurooncol 3:237–243, 1985.
27. Friedman HS, Krischer JP, Burger P, Oakes WJ, Hockenberger B, Weiner MD, Falletta JM, Norris D, Ragab AH, Mahoney DH Jr, 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.
28. Longee DC, Friedman HS, Albright RE Jr, Burger PC, Oakes WJ, Moore JO, Schold SC Jr: Treatment of patients with recurrent gliomas with cyclophosphamide and vincristine. J Neurosurg 72: 583–588, 1990.