Carboplatin chemotherapy for progressive intramedullary spinal cord low-grade gliomas in children: Three case studies and a review of the literature

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Introduction

CNS tumors account for at least 20% of all childhood malignancies and are the second most common after leukemia (Cokgor et al., 1998; Lowis et al., 1998; Stiller and Nectoux, 1994). Only 2% to 10% of these tumors are intramedullary spinal cord tumors (Allen et al., 1998; Bouffet et al., 1997; Chun et al., 1990; Constantini et al., 1996; Lowis et al., 1998; Nadkarni and Rekate, 1999; Rossitch et al., 1990; Stiller and Nectoux, 1994). The overall incidence of CNS tumors is approximately 24 to 35 per million in both Australia and the United States (Cokgor et al., 1998; Stiller and Nectoux, 1994). For most pediatric neuro-oncology units, the diagnosis of a patient with an intramedullary spinal cord tumor is a relatively rare event. In particular, in children younger than 3 years old, there are only 10 to 20 new cases per year in the United States (Constantini et al., 1996). Most intramedullary spinal cord tumors (up to 90%) are low-grade gliomas (Baleriaux, 1999), arising most frequently in either the cervical or thoracic regions, but may also occur as holocord tumors (Lowis et al., 1998). The estimated frequencies of these tumors based on histology are astrocytomas 60% to 70%, ependymomas 10%, oligodendrogliomas and gangliogliomas 10%, and malignant gliomas 10% (Heideman et al., 1997; Nadkarni and Rekate, 1999). Three cases of progressive low-grade glioma intramedullary to the spinal cord and their responses to chemotherapy (carboplatin) are reported here.

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Case Studies

Case One

A 28-month-old girl presented with a 9-month history of gait disturbance and head tilt. She had become less active and increasingly irritable with nocturnal waking. She had a stooped posture with flexed knees and hunched shoulders. Her gait was wide-based. She was unable to extend her neck, which was held in flexion and tilted to the left. All 4 limbs had increased tone and brisk tendon reflexes. Right ankle clonus and a right Babinski's sign were also present.

An MRI of the spine revealed a large, lobulated, heterogeneously enhancing intramedullary tumor of the spinal cord extending from C5 to T4 with extramedullary intradural extension over the same levels. There were also extramedullary intradural deposits at T8 and L1. Cystic changes were present at both the cranial and caudal aspects of the tumor. Associated edema of the cord extended from C1 to T8. A C4-to-L5 laminoplasty was performed with partial resection of the tumor. Postoperatively, there was marked improvement in her gait and resolution of her upper limb hypertonicity. The histology of the tumor was ganglioglioma.

After 16 months of stable clinical and radiologic findings, she represented with increasing back pain, abnormal posture, and right hemiparesis. An MRI of the spine demonstrated progressive tumor in the primary site with

large syrinx cavities both cranially and caudally and numerous enhancing nodules at the conus and cauda equina. A C7-to-T6 laminoplasty was performed with drainage of the syrinx cavities and biopsy of the tumor. Histology once again demonstrated ganglioglioma. Residual right-leg paresis was present postoperatively.

Monthly, carboplatin (560 mg/m^2) was commenced on an outpatient basis. Toxicities experienced in the 11 completed cycles were anemia in 2 cycles necessitating a 25% dose reduction and neutropenia in 1 cycle requiring a 40% dose reduction. Imaging during treatment showed stable disease. In the 17 months since completing carboplatin therapy, she has remained neurologically and radiologically stable.

Case Two

A 41-month-old girl presented with a 2-year history of an abnormal gait. Initially, her gait had developed normally, but at 18 months of age, she began walking with flexed knees. Over the next 14 months her gait gradually deteriorated with further flexion deformity of both the hips and knees. She could run only slowly with valgus deformities of both legs. By the time of presentation, she was unable to run and fell frequently. Both ankle and knee reflexes were absent. MRI scans revealed an intramedullary mass with heterogeneous enhancement expanding the cord, extending from T7/8 to L2/3. A syrinx cranial to the mass extended to C7 level.

A T7-to-L3 laminoplasty was performed with subtotal excision of the tumor. Histology showed pilocytic astrocytoma. Postoperatively, she had improvement in lower limb function. Six months later, she had further deterioration with development of left-leg weakness. MRI confirmed progression of the tumor from T7 to L1. A second subtotal resection was performed. Postoperative MRI showed significant residual tumor. Due to the progressive behavior of the tumor, she was commenced on monthly carboplatin (560 mg/m^2). Chemotherapy was ceased after 10 cycles due to the development of a hypersensitivity reaction to carboplatin. One cycle was complicated by anemia requiring blood transfusion. A partial response of 50% reduction in the tumor mass was seen after 2 cycles. After 10 cycles of treatment, there was a further 20% reduction. Her mild diplegia remains stable, although her kyphoscoliosis has worsened over the past 12 months. In the 27 months since ceasing chemotherapy, the residual intramedullary tumor has remained stable.

Case Three

A 26-month-old girl presented with a 6-month history of abnormal gait, crouching, toe walking, and loss of normal lumbar lordosis. She was unable to run or jump. She had episodes of mid-thoracic pain and would often cry if she laughed or coughed. She had upper motor neuron signs in her left leg associated with mild weakness. MRI demonstrated a well-defined heterogeneously enhancing intramedullary tumor causing expansion of the cord from T1 to T6. A T1-to-T5 laminoplasty was performed with central debulking of the tumor. Residual tumor was left anteriorly and laterally. Histology of the tumor was pilocytic astrocytoma. Two weeks after her surgery, her Karnofsky performance score had improved to 90% with a normalization of her gait and resolution of the upper motor neuron signs in her left leg.

The postoperative MRI was performed at 3 weeks and showed progression of the tumor at the primary site. She was, therefore, commenced on monthly carboplatin (560 mg/m^2) 1 month after surgery. This was well tolerated over the 12-cycle course with no reported toxicity. Her disease remained stable on surveillance imaging for the first 3 cycles of therapy. After 6 cycles, there was a significant partial response, and after 9 cycles there was a complete response to treatment (Fig. 1). As the reduction in tumor did not occur until after 3 months of carboplatin chemotherapy, we believe this is evidence of a chemotherapy response rather than involution of the tumor after partial surgical resection. This complete response has been maintained in the 5 months since completing carboplatin therapy. Her gait and leg power remain normal.

Discussion

To fully understand the potential role of chemotherapy in the treatment of pediatric patients with intramedullary spinal cord low-grade gliomas, knowledge of the history of the management of these tumors is necessary. Intraspinal and intracranial low-grade gliomas share the same histologic features and have similar biologic behavior. Lessons learned from the management of intracranial low-grade gliomas over the last 20 years are, therefore, important and will also be briefly discussed.

The history of curative management of intramedullary spinal cord tumors began early last century with von Eiselsberg's successful resection in 1907 and Cushing's similar success in the same decade. Elsberg wrote a definitive guide to spinal cord surgery in 1925 (Brotchi et al., 1991; Rossitch et al., 1990). In 1940, Greenwood demonstrated the effectiveness of bipolar coagulating forceps (Reimer and Onofrio, 1985). Technical advances that led to great improvements in surgical technique were the use of the operating microscope by Yasargil (Reimer and Onofrio, 1985), the Cavitron ultrasonic surgical aspirator (Epstein and Epstein, 1982), the plated bayonet, the CO_2 laser, MRI, intraoperative ultrasonography, and intraoperative somatosensory-evoked potential and motor-evoked potential monitoring (Brotchi et al., 1991; Nadkarni and Rekate, 1999; Przybylski et al., 1997). However, not all the new technology has proven to enhance patient outcome (Albright, 1999).

Gross total resection is one of the most important prognostic factors in determining survival in patients with intracranial low-grade gliomas (Cokgor et al., 1998; Packer et al., 1993; Pollack, 1999; Strojan et al., 1999). Those patients who have a complete resection have an overall 5-year survival of 90% to 100% compared with a 62% 5-year survival in those who have a partial resection only. Low-grade gliomas of the hypothalamus/thalamus are often not fully resected due to the risk of severe neurologic sequelae if aggressive resection is attempted (Packer et al., 1997). Intracranial low-grade gliomas

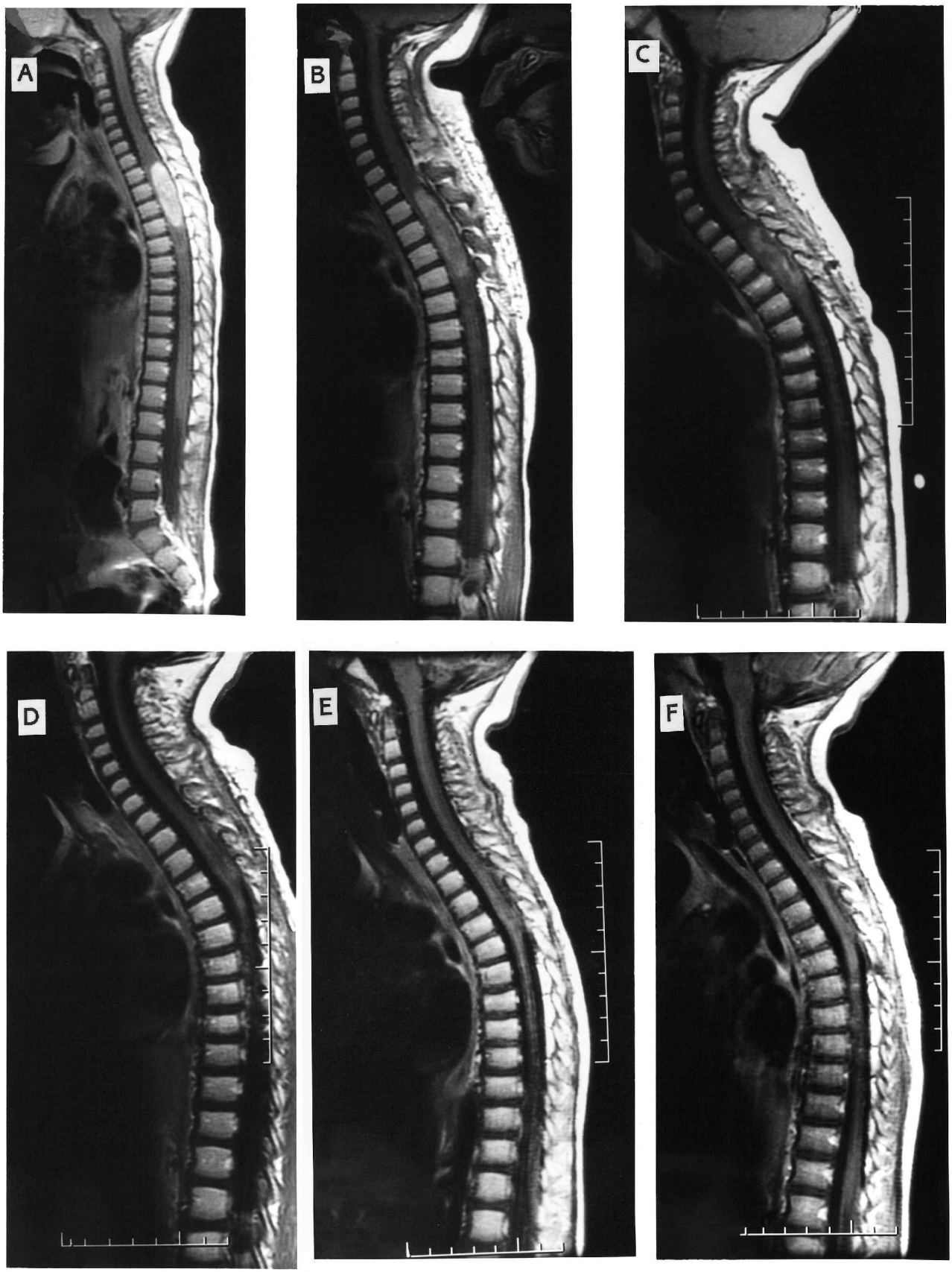

Fig. 1. MRIs of intramedullary pilocytic astrocytoma extending from T1 to T6 in a 26-month-old female. The sagittal T1-weighted images post-gadolinium were performed (A) at presentation; (B) at 3 weeks postoperatively, demonstrating progression; (C) after 3 cycles of carboplatin (stable disease); (D) after 6 cycles of carboplatin (partial response); (E) after 9 cycles of carboplatin (complete response); and (F) 5 months after completing carboplatin (complete response maintained).

have been observed to have an erratic, variable, and unpredictable history of growth and progression (Foreman et al., 1998; Packer et al., 1993). All of these considerations and principles apply to the surgical management of intramedullary spinal cord low-grade gliomas. It is important to note that a decision labeling a patient's tumor as "inoperable" based only on MR imaging is often presumptuous. All children should thus be considered for exploratory surgery at presentation (Baleriaux, 1999; Brotchi et al., 1991).

Epstein and Epstein (1982) presented one of the first series of pediatric patients with intramedullary spinal cord low-grade gliomas where aggressive surgical resection was the primary therapy, delaying the need for adjuvant therapy. Epstein and Epstein reported no deterioration, and often improvement, in their patients' postoperative neurologic state. When the follow-up series with an expanded patient group was reported in 1990, the overall survival was 95% (Constantini et al., 1996). However, some children did deteriorate postoperatively, possibly as a result of delayed presentation. Support for this approach has continued, with several authors (Cristante and Herrmann, 1994; Goh et al., 1997; Nadkarni and Rekate, 1999; Reimer and Onofrio, 1985) showing good survival data. However, there is the potential for increasing long-term neurologic dysfunction (Bouffet et al., 1998; Przybylski et al., 1997; Sandler et al., 1992), as the infiltrating nature of these tumors often results in adjacent normal neural tissue being disturbed during resection attempts (Bouffet et al., 1998; Nishio et al., 2000; O'Sullivan et al., 1994). Also, 25% to 40% of children suffer from postlaminectomy spinal deformities due mainly to mechanical destabilization, but also secondary to neurologic dysfunction and radiation effects (see next paragraph). Attempts at lessening this complication by performing osteoplastic laminotomies and reducing paraspinal muscle denervation have not been proven definitively successful. (Bouffet et al., 1998; Cristante and Herrmann, 1994; Epstein and Epstein, 1982; Goh et al., 1997; Heideman et al., 1997; Reimer and Onofrio, 1985).

The role of radiotherapy in pediatric patients with intramedullary spinal cord low-grade gliomas remains a vexed issue because the data that is available does not have sufficient statistical power (Bouffet et al., 1997; DeSousa et al., 1979; Lowis et al., 1998; Reimer and Onofrio, 1985). The threshold for spinal cord toxicity is approximately 45 to 50 Gy (Bouffet et al., 1997; Hopewell, 1998; Linstadt et al., 1989). This is based on the concept that the still developing spinal cords of children have a tolerance that is 10% to 15% lower than in adults, resulting in a greater susceptibility to radiation-induced myelopathy (Constantini et al., 1996; Reimer and Onofrio, 1985; Schultheiss et al., 1984). The tolerance of the spinal cord may be further diminished by the presence of infiltrating tumor (Linstadt et al., 1989). Above the cord threshold, significant radiotherapy's adverse effects include impaired vertebral body growth with loss of up to 15 cm (Rauhut et al., 1989), spinal deformities (up to 70%), and myelopathy (5%-10% risk) secondary either to acute radionecrosis or more chronic vasculopathies (Lowis et al., 1998; O'Sullivan et al., 1994). Other adverse sequelae attributed to radiotherapy include an increased risk (up to 20%) of second malignancy (e.g., malignant gliomas, meningiomas, and sarcomas) (Constantini et al., 1996; Doireau et al., 1999; Goh et al., 1997; O'Sullivan et al., 1994; Pollack, 1999; Przybylski et al., 1997), increased rate of wound complications (Przybylski et al., 1997), decreased fertility, and gastrointestinal problems (Shirato et al., 1995).

For many years, the use of radiotherapy as an adjuvant treatment has been accepted practice after either diagnostic biopsy or attempted resection in both pediatric and adult patients with intramedullary spinal cord low-grade gliomas (Chun et al., 1990; Constantini et al., 1996; Doireau et al., 1999; Epstein et al., 1992; Linstadt et al., 1989; Lowis et al., 1998; O'Sullivan et al., 1994; Rossitch et al., 1990; Shirato et al., 1995). The likelihood of local relapse is believed to be reduced by the addition of radiotherapy (Przybylski et al., 1997). Support for the efficacy of radiotherapy has come from a retrospective series of pediatric (O'Sullivan et al., 1994), adult (Shirato et al., 1995), or combined patient populations (Chun et al., 1990; Linstadt et al., 1989; Minehan et al., 1995), with long-term survival rates ranging from 40% to 71%. Conversely, there have been similar retrospective series where no survival advantage has been demonstrated with postoperative radiotherapy (Bouffet et al., 1998; DeSousa et al., 1979). Therefore, considering all the adverse effects and the possible benefits on long-term survival, it should be mandated that radiotherapy not be used as primary postoperative therapy in children (Bouffet et al., 1997; Brotchi et al., 1991; Epstein, 1995). It has been suggested that use of radiotherapy should be considered in intramedullary spinal cord low-grade gliomas only when recurrence/progression is definite (Nadkarni and Rekate, 1999). However, chemotherapy was not considered as a treatment option when this recommendation was made.

Over the last decade, numerous papers have supported the hypothesis that intracranial low-grade gliomas are chemosensitive tumors. The chemotherapy agents and the combinations that have shown efficacy include carboplatin, actinomycin-D/vincristine, carboplatin/vincristine, etoposide/vincristine, carboplatin/etoposide, lomustine/prednisolone/vincristine, and procarbazine/6-thioguanine/lomustine/vincristine (Brown et al., 1993; Castello et al., 1998; Cokgor et al., 1998; Heideman et al., 1997; Lowis et al., 1998; Mahoney et al., 2000; Moghrabi et al., 1993; Packer et al., 1993; Packer et al., 1997; Prados et al., 1997; Walter et al., 2000). Response rates in both newly diagnosed progressive and recurrent low-grade gliomas have ranged from 52% to 62% (Brown et al., 1993; Packer et al., 1993; Packer et al., 1997). Up to an additional 30% of patients can achieve prolonged stable disease (Packer, 1999). The subsequent 3-year progression-free survival rates are >60%, with the same disease control seen in both the responders and nonresponders (stable disease). The prolonged disease stabilization of an average of 2 years (Huncharek et al., 1999) is an advantage for these patients because it delays, or possibly avoids, the need for radiotherapy (Gropman et al., 1998; Packer et al., 1993; Packer et al., 1997; Prados et al., 1997). Interestingly, the benefit of adjuvant chemotherapy appears to be most clearly shown in children younger than 3 years, whose developing CNS is at most risk from damage of radiotherapy (Packer

Table 1. Published cases of chemotherapy responses in children with intramedullary spinal cord low-grade gliomas

Author	Patients (age)	Histology	Chemotherapy	Response	Follow-up (months)[a]
Lowis et al. (1998)	1 (4 yrs)	Astrocytoma (WHO grade II)	Carboplatin/VCR	CR	14
Fort et al. (1998)	5 (11–27 months)	JPA (3) LGA (2)	Carboplatin/VCR	CR(1), SD(2), PD(2)	1–43 (mean 22)
Doireau et al. (1999)	6 (1-11 yrs)	OA (3) JPA (2) Astrocytoma (1)	Carboplatin/PCBZ/VCR/ CPA/VP-16/CDDP	CR(2), PR(3), SD(1)	16–66 (mean 40.6) PD(2) at 16, 22
Merchant et al. (2000)	2 (10 mo–5 yrs)	LGA (2)	CDDP, VP-16 (1) Carboplatin (1)	SD(1), PD(1)	1–226
Present study (2001)	3 (26–41 months)	JPA (2) Ganglioglioma (1)	Carboplatin	CR(1), PR(1), SD(1)	17–37 (mean 27.3)

Abbreviations: WHO, World Health Organization; VCR, vincristine; CR, complete response; JPA, juvenile pilocytic astrocytoma; LGA, low-grade astrocytoma; SD, stable disease; PD, progressive disease; OA, oligoastrocytoma; PCBZ, procarbazine; CPA, cyclophosphamide; VP-16, etoposide; CDDP, cisplatin; PR, partial response.

[a] Follow-up duration calculated from commencement of chemotherapy.

et al., 1997; Prados et al., 1997). Thus, adjuvant chemotherapy is now considered standard therapy in patients with intracranial low-grade gliomas as a means of prolonging their progression-free interval. The chemotherapy use in these studies has been well tolerated with only mild myelosuppression. However, a small number of children will develop an allergy to carboplatin (often near the end of 12 months) (Brown et al., 1993; Packer et al., 1993; Packer et al., 1997). What is unknown are the possible late effects of chemotherapy, such as the development of a second malignancy (Prados et al., 1997).

Based on the experience in intracranial low-grade gliomas, the hypothesis that chemotherapy may be a treatment option in intramedullary spinal cord low-grade gliomas has begun to filter through the literature (Bouffet et al., 1998; Merchant et al., 2000; Nishio et al., 2000). However, as with radiotherapy, there have been no randomized trials performed, only anecdotal reports and reviews of small series. Lowis et al. (1998), Doireau et al. (1999), Fort et al. (1998), and Merchant et al. (2000) have presented evidence of response to chemotherapy in pediatric patients with progressive, intramedullary spinal cord low-grade gliomas (Table 1). The majority of the patients received carboplatin-based therapy. Overall survival rates and progression-free survival rates mirrored those described above for intracranial low-grade gliomas. There is, therefore, a need for large, multinational, cooperative trials to further explore this issue (Bouffet et al., 1998; Doireau et al., 1999).

In the 3 case reports above, each child presented with a long history of gait disturbance and other symptoms before being referred to our unit. A prolonged prodrome is typical of this condition and has been noted by other authors (DeSousa et al., 1979; Epstein and Epstein, 1982). The children's functional states had all deteriorated to McCormick grade II (McCormick et al., 1990) by the time surgery was performed as the primary attempt at curative treatment. Once the disease became progressive and surgical options were exhausted, carboplatin was commenced. This was given with the objective of obtaining a prolonged period of disease stabilization, thus delaying the need to consider radiotherapy in these young children. The 3 cases presented provide further anecdotal evidence of the efficacy of carboplatin therapy in intramedullary spinal cord low-grade gliomas, with either disease stabilization or improvement observed in each case. The chemotherapy was relatively easy to administer in an outpatient setting. It was well tolerated with minimal toxicity, including one episode of late carboplatin allergy.

Based on all evidence, an attempt at significant resection provides the most likely circumstance in which a child with an intramedullary spinal cord low-grade glioma will be a long-term survivor. However, the issue now is whether such surgery can be less aggressive based on the knowledge that chemotherapy also may lead to prolonged progression-free survival. The long-term morbidity suffered by a significant number of children as a result of aggressive surgery or radiotherapy may, therefore, be reduced. Although the small number of new patients per year precludes the establishment of a randomized study, there is a need to organize a multi-institutional study investigating the role of chemotherapy in the management of these tumors. This may be achieved by using current studies (e.g., CCG0052/A9952) to gather information on this important subgroup of CNS low-grade gliomas. The primary objective of a multi-institutional study will be to examine the efficacy of carboplatin in children with intramedullary spinal cord low-grade glioma who have progressive disease after an attempt at surgical resection. A secondary objective will be to observe whether long-term local disease control is improved by such therapy.

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