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Outcome of Pediatric Patients with Low-Grade Astrocytoma of the Brain and Spinal Cord

*Taneva M and Johnston DL**

Division of Pediatric Hematology/Oncology, Children's Hospital of Eastern Ontario, Canada

Abstract

Background: Low-grade astrocytomas are the most common pediatric central nervous system tumours. They can occur anywhere in the central nervous system and are often challenging to treat.

Methods: A retrospective review to compare the response to therapy for spinal cord astrocytomas to that of brain astrocytomas.

Results: Five patients had low-grade spinal cord astrocytoma and 43 had low-grade brain astrocytoma. One spinal cord and 16 brain patients underwent complete resection, and 2 and 20, respectively, partial resection. Of the 56% total patients with a partial resection, 31.8% and 4.5% received adjuvant chemotherapy and radiotherapy, respectively. 14% of all patients received chemotherapy, without resection.

Three patients with spinal cord tumours underwent subtotal resection/biopsy followed by chemotherapy. They showed a mean tumour decrease of 36.9%, and none relapsed. The remaining patients showed tumour progression which responded to chemotherapy.

Ten brain tumour patients received chemotherapy and 4 received radiation. Tumour size decreased by 44.5% with surgery/adjuvant therapy, and 27.1% with adjuvant therapy alone. Ten patients relapsed at a mean of 9.6 months. Those treated underwent resection (n=3) or adjuvant therapy (n=5) and 4 relapsed again.

Conclusions: All patients with low-grade spinal cord astrocytomas responded to chemotherapy and none received radiation while 81.8% of those with brain astrocytoma responded to adjuvant therapy including radiation.

Keywords: Low-grade astrocytoma; Chemotherapy; Therapy response

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Correspondence:
Donna Johnston, Division of Hematology/Oncology, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, Canada, Tel: 613-737-7600; Fax: 613-738-4828; E-mail: djohnston@cheo.on.ca

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Introduction

Low-grade astrocytomas (LGA) are the most common central nervous system tumors in the pediatric population [1]. They occur more frequently in the brain, representing 30-50% of newly diagnosed brain neoplasms in this population [2], and approximately 60% of spinal cord tumors [3,4]. The World Health Organization (WHO) classifies LGAs as Grade I or Grade II, and the most common include pilocytic astrocytoma (Grade I), pilomyxoid astrocytoma (Grade II) and diffuse astrocytoma (Grade II) [2].

Low-grade astrocytomas are often amenable to surgery. Gross total resection of LGAs has been reported to offer 10-year survival rates greater than 90% [5,6], and to be the most important prognostic factor for progression free survival [7-9]. Despite this, the management for LGAs in the spinal cord remains controversial. Complete resection is often difficult due to the infiltrative nature of these tumors [6], and may lead to increased morbidity due to pain, motor dysfunction and spinal deformity [10].

The role of chemotherapy and radiation therapy for LGAs is also unclear. Protocols for therapy of LGA include both Grade I and II astrocytomas so these were both examined for this study. Retrospective studies have offered conflicting evidence on the value of adjuvant radiation on overall survival and progression-free survival [6,11,12]. This, in addition to the known long-term neurologic sequelae, warrants the study of safer methods. Adjuvant chemotherapy has been shown to be of benefit in pediatric low-grade astrocytomas of the brain, with a response rate of 52-62% for both newly diagnosed and progressing tumors [6], and has replaced radiation as first-line therapy when resection is not possible. Based on this evidence, adjuvant chemotherapy has been hypothesized to have a similar effect in children with spinal cord low-grade astrocytomas as well. In this study,

Table 1: Treatment and outcome summary of all patients with low-grade astrocytoma of the brain and spinal cord.

	Spinal Cord		Brain	
	Grade I Astrocytoma (n=3)	Grade II Astrocytoma (n=2)	Grade I Astrocytoma (n=40)	Grade II Astrocytoma (n=3)
Initial Therapy, n(%)				
Complete Resection	1 (33%)	0 (0%)	13 (33%)	3 (100%)
Chemotherapy	2 (67%)	1 (50%)	10 (25%)	0 (0%)
Radiation Therapy	0 (0%)	0 (0%)	3 (8%)	1 (33%)
Relapsed, n(%)	1(33%)	1 (50%)	10 (25%)	1 (33%)
Additional Chemotherapy, n(%)	1(33%)	1 (50%)	4 (10%)	1 (33%)
Additional Radiation Therapy, n(%)	0 (0%)	0 (0%)	1 (3%)	1 (33%)
Additional Resection, n(%)	0 (0%)	0 (0%)	4 (10%)	0 (0%)
Alive at last follow-up, n(%)	3 (100%)	2 (100%)	39 (98%)	2 (67%)

we have reviewed the patients with low-grade brain and spinal cord astrocytoma to compare the response rate to therapy.

Materials and Methods

A retrospective chart review was performed of all patients diagnosed and treated for low-grade central nervous system astrocytoma from 2000 to 2013 at our institution. Any patient diagnosed with a grade I or II astrocytoma was included. Patients were classified as brain astrocytoma if they had a tumor of the cerebrum, cerebellum or brainstem. Patients were classified as spinal cord astrocytoma if the tumor was in the spinal cord. Data were collected from radiographic, pathological, operative and clinic reports. These were used to determine demographics, histological diagnosis, extent of resection, treatment received, and duration of follow-up and relapse and progression status. The Children's Hospital of Eastern Ontario Research Ethics Board approved this study.

Response to therapy was determined by evidence of an objective decrease in tumor size or a lesion becoming non-enhancing. Time to progression was defined as time from diagnosis to evidence of tumor growth or recurrence on magnetic resonance imaging (MRI). Following completion of therapy (either surgery, chemotherapy or radiation therapy), patients underwent routine follow up neurologic examination and imaging every 3 months for the first 24 months off therapy then every 6 months for the subsequent 24 months then yearly.

Results

A total of 48 patients were found to have a histological diagnosis of LGA, 5 with LGA of the spinal cord and 43 with LGA of the brain. Forty-two (87.5%) patients were diagnosed with WHO Grade I astrocytoma (41 pilocytic astrocytoma, 1 desmoplastic astrocytoma), 10% with WHO Grade II (1 fibrillary astrocytoma, 2 oligoastrocytoma, 2 pilomyxoid astrocytoma), and 1 patient with an unspecified low-grade astrocytoma. Of the patients with LGA of the spinal cord, there were 2 with pilocytic astrocytoma, and 1 each with fibrillary astrocytoma, oligoastrocytoma and unspecified low-grade astrocytoma. Two patients had metastatic disease: 1 with metastasis from the spinal cord to the brain, and the other, with metastasis from the brain to the spinal cord. The median age at diagnosis for all patients was 8.2 years (3.9 and 8.5 years for spine and brain patients, respectively), 52.1% being female.

Patients with LGA of the brain presented most commonly with headache (57.8%), vomiting (55.8%), gait disturbance (32.6%), head tilt and/or vision changes (30.2%) and hemiparesis (11.6%). Patients with LGA of the spinal cord presented with bowel or bladder dysfunction (60%), gait disturbance (40%), hemiparesis (40%) and foot drop or eversion (40%).

All patients had MRIs of the brain and spinal cord. The majority of patients (83.3%) had precise initial tumor measurements on MRI, and 46.5% of patients had precise tumor measurements after initial treatment. The tumor was located in the cervical spinal cord in 1 patient, the thoracic spinal cord in 2 patients, and both cervical and thoracic spinal cord in 2 patients. Of those with LGA of the brain, the tumor was supratentorial in 15 (34.8%) patients, infratentorial in 26 (60.5%) patients, and both infra- and supratentorial in 2 (4.7%) patients.

The treatment and outcome summary of all patients is shown in Table 1. Thirty-nine (81.3%) patients underwent surgical resection and 16.7% underwent biopsy only. Of all patients who underwent surgical resection, 89.7% (n=35) were diagnosed with pilocytic astrocytoma. One spinal cord patient and 16 brain patients underwent complete resection, and 2 and 20, respectively, underwent partial resection. Fourteen patients (82.4%) who underwent complete resection had a histological diagnosis of pilocytic astrocytoma, while the remaining were diagnosed with pilomyxoid astrocytoma (11.8%) or fibrillary astrocytoma (5.9%). Twenty-one patients who underwent partial resection were diagnosed with pilocytic astrocytoma (95.5%), and 1 with oligoastrocytoma. Of the 22 patients with a partial tumor resection (56.4%), 31.8% and 4.5 % received adjuvant chemotherapy and radiotherapy, respectively. Of all patients, five (13.2%) received chemotherapy, without surgical resection (Figure 1 and 2). Fourteen (82.4%) of those with complete resection remained progression free: 12 with pilocytic astrocytoma, 1 with fibrillary astrocytoma and 1 with pilomyxoid astrocytoma.

Of the 5 spinal cord tumor patients, 2 with partial resection and 1 with biopsy only received chemotherapy, and all responded to therapy. Tumor size decreased by a mean of 36.9%, and no patients

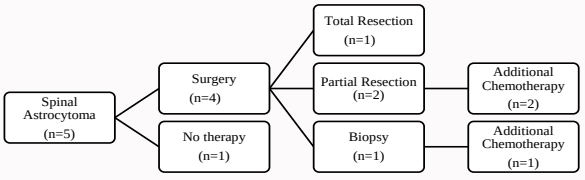

Figure 1: Distribution of patients with astrocytoma of the spinal cord by treatment.

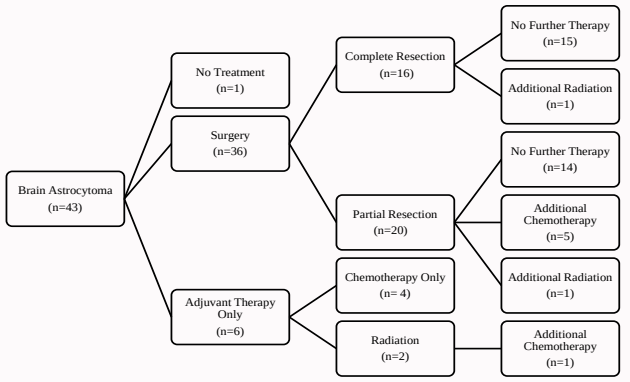

Figure 2: Distribution of patients with astrocytoma of the brain by treatment.

relapsed. All 3 received carboplatin/vincristine regimens. The 2 patients not treated with chemotherapy had initially undergone complete resection or biopsy with ventriculo-peritoneal shunt placement. They showed tumor progression at a mean of 29.5 months and subsequent chemotherapy resulted in either a decrease in tumor size or no evidence of remaining tumor at 7.5 years follow-up (mean). No spinal cord tumor patients received radiation therapy.

Ten (23.3%) brain tumor patients received chemotherapy, 6 of which were adjuvant treatment following partial resection (n=5) or radiation (n=1). Of these 6, 4 responded to treatment, 1 progressed, and 1 was transferred out of our institution. Seventy-five percent of those who only received chemotherapy responded to treatment. The chemotherapy regimens included carboplatin/vincristine (n=5), vinblastine (n=2), vinblastine/vinorelbine (n=1), temozolamide (n=1) and procarbazine/thioguanine/lomustine/vincristine (n=1). Four (9.3%) brain tumor patients received radiation, either following complete (n=1) or partial resection (n=1), prior to chemotherapy (n=1, mentioned above) or as sole treatment (n=1). The patient who underwent complete resection prior to radiation relapsed twice and died. The remaining patients responded to therapy and did not relapse at a mean of 5.5 years of follow-up (range 2.6-8.8 years). All 4patients received radiation at a dose of 54 Gray in 30 fractions. Of all brain tumor patients, tumor size decreased by a mean of 44.5% for those with surgery and adjuvant therapy, and 27.1% for those with adjuvant therapy alone.

Ten (23.3%) brain tumor patients relapsed at a mean of 9.6 months after diagnosis. Those treated underwent resection (n=3) or adjuvant therapy (n=5). Three (60%) of the latter and one (33.3%) of the former relapsed again. The one patient was treated with radiation, and remained progression-free at last follow-up. Of the 3 patients who relapsed after adjuvant therapy, 1 died, 1 was transferred to another institution, and 1 remained on chemotherapy at last follow-up.

There were 5 patients with WHO Grade II tumors: 1 fibrillary astrocytoma, 2 oligoastrocytoma, and 2 pilomyxoid astrocytoma. Three underwent a complete resection, of which one relapsed and 2 had a good outcome. One underwent partial resection and was treated with chemotherapy with good outcome, and 1 underwent biopsy with shunt, relapsed due to alternative therapy initially but then received chemotherapy and had a good outcome.

There were 17 (36.9%) patients who continued to have symptoms 3 months after initial therapy was completed. Of these, 58.8% had undergone partial resection with or without adjuvant treatment, 29.4% had undergone complete resection, and 11.8% had received only adjuvant treatment. The most common symptoms were headaches (41.2%), dysmetria (29.4%), hemiparesis (17.6%) and ataxia (9.3%). Twelve (26.1%) of these patients developed symptoms not present at diagnosis. Patients were followed for a mean of 5.4 years (range 3 months - 10.9 years).

Discussion

The management of low-grade spinal cord astrocytomas remains challenging. Surgical resection can be difficult due to the infiltrative nature of these tumors, and may result in long-term morbidity. While chemotherapy and radiation have been shown to be of benefit in LGA of the brain, their benefit in LGA of the spinal cord remains unclear. We have shown in this small study that chemotherapy may be of better benefit to patients with LGA of the spinal cord compared to those with LGA of the brain, as all 5 patients with spinal cord LGA responded to chemotherapy.

WHO Grade I and II pathologic classification of patients in this series found that 5 of 48 had Grade II and the remainder Grade I. The one patient who died had a Grade II astrocytoma in the brain. Of the relapsed patients, 2 were Grade II and 8 were Grade I, thus 20% of Grade II and 19% of Grade I patients relapsed, demonstrating no large difference among the two groups in terms of relapse rate, although numbers are too small to measure significance.

When feasible, gross total resection may be curative without adjuvant treatment [5]. Several studies have associated complete resection with decreased rates of tumor progression and survival rates of 90% or greater [11-14]. Among these, Fisher et al. [12], found that all children with low-grade gliomas who underwent gross total resection and 58% of those with a partial resection remained progression-free at a mean follow-up of 7.3 years [12]. In our study, of the 15 patients who only underwent gross total resection, 86.7% remained progression free at a mean follow-up of 5.6 years. Studies have reported an increased risk of neurological injury following total resection [15,16], and as such, it has been argued that resection should not sacrifice function [17,18]. We observed that the majority of patients who experienced symptoms post-operatively were those who underwent partial resections with or without adjuvant treatment (58.8%). By contrast, 29.4% of patients with complete resections experienced symptoms following surgery.

While some studies have found that adjuvant radiotherapy is of benefit to pediatric low-grade spinal cord astrocytomas [19-21], its effectiveness remains uncertain due to the lack of randomized trials. Possible adverse effects from radiotherapy include spinal deformities, myelitis, decreased fertility and an increased risk of second malignancy [6]. As such, it is often not considered as primary adjuvant therapy in children [6]. No patients in our study with LGA of the spine received radiation therapy, and all had good outcomes, demonstrating that it can be avoided in this tumor.

Chemotherapy has increasingly replaced radiotherapy as first-line adjuvant treatment for LGA [10]. Thirteen patients received chemotherapy, 3 of which had low-grade astrocytoma of the spinal cord. The latter are of interest as no large or randomized trials have documented its effect on low-grade spinal cord astrocytomas. However, several small-scale reviews have recorded a response to chemotherapy in pediatric patients with these tumors [3,4,6, 24-27]. Eight patients, including the 3 with spinal cord astrocytoma, received a carboplatin and vincristine regimen. All responded to treatment. One patient with astrocytoma of the spinal cord developed an allergic reaction

to carboplatin, and was substituted with actinomycin D. Carboplatin and vincristine have been shown to be effective in treating low-grade astrocytomas of the brain [22,23]. The Children's Oncology Group performed a randomized trial comparing the response to regimens of vincristine/carboplatin and thioguanine/procarbazine/lomustine/vincristine in young children with low-grade gliomas of the brain, and found these regimens to have similar 5-year event-free survival [23]. Regimens consisting of carboplatin and vincristine [4,27], or carboplatin alone [6,25], have been reported to be of benefit in other studies of pediatric patients with low-grade spinal cord astrocytoma. Lowis et al. [27], found a good response to carboplatin and vincristine in a 4-year-old child with spinal astrocytoma without radiation. Townsend et al. [4], also presented 4 spinal tumor patients treated with carboplatin and vincristine, after which disease stabilization or minor response was observed. Chamoun et al. [3], reported on two patients with progressive low-grade spinal cord astrocytomas initially treated with surgery and radiation. Both showed tumor stabilization following treatment with temozolamide.

Overall, our institutional experience shows that the use of chemotherapy in pediatric patients with low-grade astrocytomas in the spinal cord is of benefit to newly diagnosed and progressing tumours. As with other studies, our population is small and large-scale, national studies are warranted.

Conclusion

This study reviewed 48 pediatric patients diagnosed with low-grade astrocytomas of the brain and of the spinal cord, and compared their response to therapy. We found that all patients with low-grade astrocytomas of the spinal cord had a response to adjuvant chemotherapy and none received radiation therapy, while only 81.8% of those with astrocytomas of the brain had a response to adjuvant therapy including radiation therapy in 9%. Due to the rarity of these tumors occurring in the spinal cord, larger scale studies are necessary to confirm the effectiveness of adjuvant therapy.

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