Successful Combination Chemotherapy (Vincristine, Procarbazine, Etoposide, and Prednisolone) in the Treatment of Inoperable, Radioresistant Low Grade Astrocytoma : A Case Report

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Abstract

A case of successful combination chemotherapy using vincristine, procarbazine, VP-16 and prednisolone to treat an inoperable low grade astrocytoma is presented. This patient, whose tumor was also resistant to radiotherapy, had well controlled symptoms after the initiation of chemotherapy. A brain CT scan demonstrated disappearance of the tumor mass after eight courses of a combination chemotherapy regimen. She is at present symptom-free 80 months after diagnosis. This result suggests that combination chemotherapy may offer treatment modalities for low grade astrocytoma.

Key word : Vincristine, Procarbazine, Etoposide, Prednisolone, Astrocytoma

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Chemotherapy has a restricted role in the treatment of low grade astrocytoma. Surgical intervention has been the first approach to any supratentorial hemispheric astrocytoma regardless of grade (1-3). Local radiotherapy has shown to be somewhat effective either as an adjuvant therapy to subtotal surgery or as an alternative in nonsurgical approachable cases(4-8). The result of combined treatment with surgery and radiation in low grade supratentorial astrocytoma is still not satisfactory, the 5 year survival rate ranges from 25-76 per cent, of which only as few as 14-28 per cent remained at 10 years(9,10). Chemotherapy is not widely used by majority of cancer centers due to its controversial outcome. We report here a patient who had an inoperable low grade astrocytoma whose tumor did not respond to radiotherapy but disappeared completely after 8 courses of combined chemotherapy.

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CASE REPORT

A 12 year old girl presented in February 1992 with a 4 month history of progressive headache and vomiting. Her physical examination was all within normal limits except bilateral papilledema. A brain CT scan demonstrated a large isodensity mass 9 x 5 x 4 cm. extending from the inferior and both lateral walls of the third ventricle down to obliterate the suprasellar cistern, a moderate degree of obstructive hydrocephalus was seen (Fig. 1). A ventriculo-peritoneal shunt placement was performed to reduce intracranial pressure produced by the obstructive hydrocephalus. A needle biopsy of the tumor was done under ultrasonic guidance through the inferior temporal gyrus, the pathological specimen was reported as astrocytoma, grade I (Fig. 2, 3). It was decided that the tumor was inoperable, her parents refused any further treatment on her and the patient was discharged. Two months later she then came back with signs of increased intracranial pressure namely drowsiness and spasticity. Cranial irradiation was initiated when her clinical symptoms and signs were improving with supportive care (hyperventilation and dexamethasone and decompression craniotomy). We were able to extubate her 5 days after the initiation of radiation therapy.

She had been well until six weeks after the completion of radiation therapy (total 5580 cGy), when she developed somnolence syndrome. A brain CT scan at this point was done and revealed no significant change in size of the mass compared to the previous studies (Fig. 4) at diagnosis and before

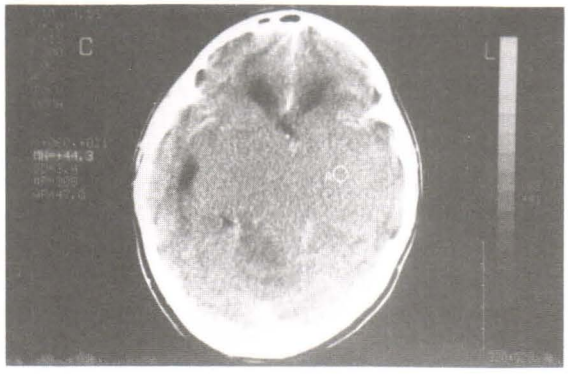

Fig. 1. At diagnosis a brain CT scan : showing a large isodensity mass 9 x 5 x 4 cm in size obliterates the suprasellar cistern.

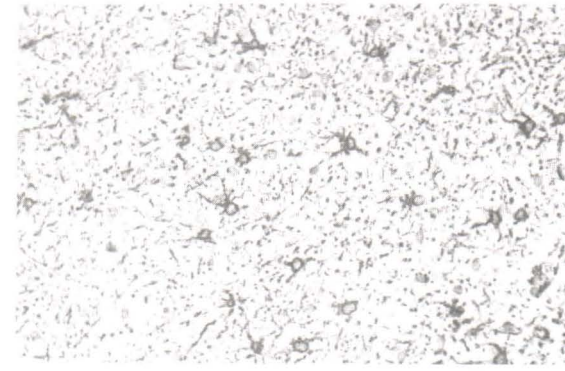

Fig. 3. Immunohistochemistry study using anti-GFA antibody confirms the mature of astrocytes (x 400).

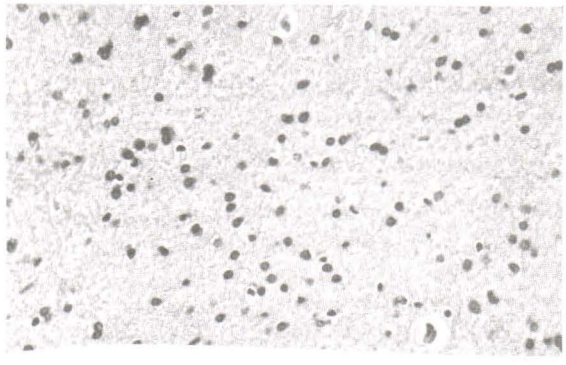

Fig. 2. The H and E section of the brain tumor tissue reveals numerous mature astrocytes (x 400).

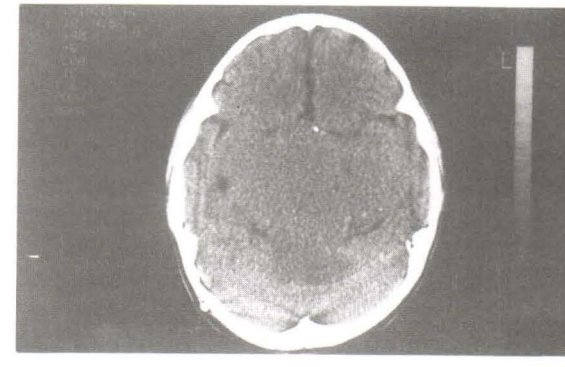

Fig. 4. 6 weeks after completion of radiotherapy : a brain CT scan demonstrating increased attenuation of mass as compared to previous study with no significant change in size.

initiation of radiotherapy. We then decided to start a combination chemotherapy regimen which consisted of vincristine 1.5 mg/m^2, day 1 and 8, procarbazine 100 mg/m^2, day 1-14 alternated every 4 weeks with etoposide (VP-16) 100 mg/m^2, day 1 and prednisolone 60 mg/m^2, day 1-5. At the end of the sixth chemotherapy course, a CT scan demonstrated a widening supra-sellar cistern as a result of tumor degeneration, no residual tumor was seen. Two more courses of the same regimen were continued as maintenance therapy. Repeated CT scans performed at the end of the treatment course and one year after completion of therapy showed no significant changes, no tumor recurrence was detected. She has been well and has come for regular follow-up visits. On her follow-up visit in March 1997, a brain MRI was done which showed no evidence of tumor. (Fig. 5)

Toxicities

During treatment, the degree of nausea and vomiting was well tolerated. No evidence of bone marrow suppression was detected even at the time chemotherapy was once interrupted when she developed pneumonia after the first course of chemotherapy. Her hair is sparse and thin (WHO grade II) which has had no significant change during these years. Growth and secondary sex characteristic development is severely delayed. At diagnosis she weighed 29.5 kgs and was 133 cms tall, although her weight has slightly fluctuated, she is at present 32.2 kgs. and her height is 135 cms. She has sexual maturity ratings 3 for both breast and pubic hair changes. The luteinizing hormone (LH) and the follicular stimulating hormone (FSH) increased significantly when the luteinizing hormone - releasing hormone (LHRH) test was performed. This sexual development retardation but still functionally reserved could either be the effect of treatment and/or the tumor itself.

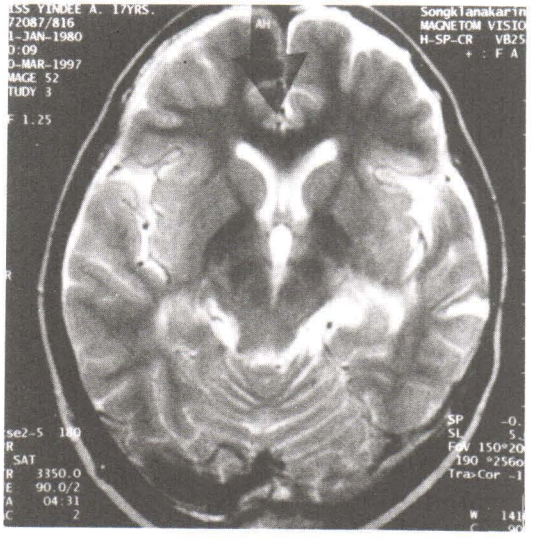

Fig. 5. A brain MRI on March 1997 : showing no evidence of tumor recurrence.

DISCUSSION

The only established role of chemotherapy in low grade astrocytoma is to delay radiotherapy in young children[11]. To our knowledge, the treatment results in older astrocytoma patients have been inconsistent, only a few patients have shown a complete response to chemotherapy and maintained free of disease. Shibamato found chemotherapy as a non-influence prognostic factor when it was added to the standard treatment regimen in his institute[12]. On the contrary, many authors have demonstrated certain benefits to different chemotherapeutic agents and regimens. Sumers, et al from Roswell Park Memorial Institute reported responses to combination chemotherapy consisting of BCNU, vincristine and intrathecal methotrexate in their low grade astrocytoma patients. They suggested that this trial of chemotherapy as adjuvant treatment to surgery and radiotherapy should be initiated since 1978[13]. Nitrosourea-based regimens have produced some activity as reported from the Royal Marsden Hospital[10]. Carboplatin-based regimens have also proved to be somewhat effective[14,15]. Recently, Packer sucessfully demonstrated objective responses in 56 per cent of newly diagnosed, progressive inoperable, low grade glioma patients by using carboplatin and vincristine. Etoposide either combined with carboplatin or other agents were shown to produce some responses[16-18]. Horowitz tried a MOPP regimen in 2 low grade astrocytoma patients with successful results[19]. Our regimen, although not carboplatin or nitrosourea based, consisted of known effective agents for brain tumors. Etoposide (VP-16) was used to replace mechlorethamine and the rest are the same as in the MOPP protocol. However, the disappearance of low grade astrocytoma in this patient might not have been totally the benefit of chemotherapy, radiotherapy might have played some role in inducing a tumor response.

The need to eradicate the tumor mass may be essential in low grade astrocytoma, although patients who carry residual stable tumors could be symptom-free for a period of time. Total tumor removal will result in a 5 year-survival of approximately 90 per cent[20,21]. Radiation therapy following subtotal removal of the tumor does improve the 5 year survival rate in low grade astrocytoma patients, however, long term survivals do not appear to be measurably influenced. The overall survival at 5 years and 10-years is 33 per cent and 16 per cent for grade I patients and 21 per cent and 6 per cent for grade II astrocytoma patients, respectively [10]. Capra reported a comparable result in combined grade I and II patients, 21 per cent were alive at 5 years and 13 per cent at 10 years[22]. In pediatric patients, although generally the prognosis is better than in adult patients, the 10-and-20 years survival was 74 per cent and 41 per cent respectively[21]. Fazekas found a 5-year survival of 41 per cent which had dropped to 20 per cent at 10 years[6]. The relatively poor prognosis in this low grade tumor is probably because of progression or transformation to a higher grade of malignancy as shown by Muller and Dirks,[23,24] who emphasized the time to anaplastic transformation varied between 2 and 10 years (mean 6.4 years). A complete disappearance of a tumor by any modality of treatment may have a major impact on the survivals, however, long term complications of chemotherapy must be considered against the benefit.

SUMMARY

Low grade astrocytoma can succesfully be treated with combination chemotherapy as demonstrated by our reported patient. At present, chemotherapy has not yet been included in the standard treatment for low grade astrocytoma. We would suggest that, in an inoperable case with no tumor response or with partial response evidenced following radiation therapy, adjunctive chemotherapy is worth initiating in order to increase chances for a long-term survivor. Further studies are required to determine the role of adjuvant chemotherapy in patients with partial response to post-operative radiation therapy.

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REFERENCES

1. Kadota RP, Allen JB, Hartman GA, Spruce WE. Brain tumors in children. J Pediatr 1989; 114: 511-9.
2. Walker RW, Allen JC. Pediatric brain tumors. Pediatr Ann 1983; 12: 383-94.
3. Duffner PK, Cohen ME, Freeman AI. Pediatric brain tumors : An overview. Cancer J Phys 1985; 35: 287-301.
4. Leibel SA, Sheline GE, Wara WM, et al. The role of radiation therapy in the treatment of astrocytomas. Cancer 1975; 3: 1551-7.
5. Sheline GE. Radiation therapy of brain tumors. Cancer 1977; 39: 873-89.
6. Fazekas JT. Treatment of grades I + II brain astrocytomas. The role of radiotherapy. Int J Radial Oncol Biol Phys 1977; 2: 661-6.
7. Medbery CA, Straus KL, Steinberg SM. Low-grade astrocytomas : Treatment results and prognostic variables. Int J Radiat Oncol Biol Phys 1988; 15: 837-41.
8. Shaw EG, Daumas Duport C, Scheithauer BW. Radiation therapy in the management of low-grade supratentorial astrocytomas. J Neurosurg 1989; 70: 853-61.
9. Heideman RL, Packer RJ, Albright LA, et al. Tumors of the central nervous system. In : Pizzo PA, Poplack DG (eds.). Principles and Practice of Pediatric Oncology 2nd ed. Philadelphia : J.B. Lippincott, 1993: 657-60.
10. Bloom HJG. Intracranial tumors : Response and resistance to therapeutic endeavors, 1970-1980. Int J Radiat Oncol Biol Phys 1982; 8: 1083-113.
11. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 1993; 11: 850-6.
12. Shibamoto Y, Kitakabu Y, Takahashi M, et al. Supratentorial low grade astrocytoma. Correlation

of computed tomography findings with effect of radiation therapy and prognostic variables. Cancer 1993; 72: 190-5.
13. Sumer T, Freeman AI, Cohen M, et al. Chemotherapy in recurrent noncystic low-grade astrocytomas of the cerebrum in children. J Surg Onc 1978; 10: 45-54.
14. Friedman HS, Krischer JP, Burger P. Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin : A pediatric oncology group randomized phase II study. J Clin Oncol 1992; 10: 249-56.
15. Zelzter PM, Epport K, Nelson Jr, et al. Prolonged response to carboplatin in an infant with brain stem glioma. Cancer 1991; 67: 43-7.
16. Packer RJ, After J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade glioma. J Neurosurg 1997; 86: 747-54.
17. Castello MA, Schiavetti A, Padula A, et al. Does chemotherapy have a role in low-grade astrocytroma management? A report of 13 cases. Med Pediatr Onc 1995; 25: 102-8.
18. Pons MA, Finlay JL, Walker RW, et al. Chemotherapy with vincristine (VCR) and etopside (VP-16) in children with low-grade astrocytoma. J Neurooncol 1992; 14: 151-8.
19. Horowitz ME, Mulhern RK, Kun LE, et al. Brain Tumors in the very young child. Cancer 1988; 61: 428-34.
20. Finlay JL, Goin SC. Brain tumors in children. II Advances in chemotherapy. Am J Pediatr Hematol Oncol 1987; 9: 264-71.
21. Wallner KE, Gonzales MF, Edwards MS, et al. Treatment results of juvenile pilocytic astrocytoma. J Neurosurg 1988; 69: 171-6.
22. Capra LG. Radiotherapy of cerebral Gliomas. In : DGT Thomas, DI Gragam (eds.). Brain Tumours. London : Butterworths 1980: 322-43.
23. Muller W, Afra D, Schroder R. Supratentorial recurrences of Gliomas : Morpholgical studies in relation to time intervals with astrocytomas. Acta Neurochirurg 1977; 37: 75-91.
24. Dirks PB, Jay V, Becker LE, et al. Development of anaplastic changes in low-grade astrocytomas of childhood. Neurosurgery 1994; 34: 68-78.

การรักษาผู้ป่วย low grade astrocytoma ที่ผ่าตัดไม่ได้ และไม่ตอบสนองต่อรังสีรักษาด้วยยาเคมีบำบัด

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รายงานผู้ป่วยเด็กหญิงไทยอายุ 12 ปี ได้รับการวินิจฉัยว่าเป็น low grade astrocytoma ของเนื้อสมองส่วน cerebral hemisphere เนื้องอกมีขนาดใหญ่มากจนไม่สามารถผ่าตัดออกได้ และไม่ตอบสนองต่อรังสีรักษา หลังจากให้การรักษาด้วยเคมีบำบัดประกอบด้วย vincristine, procarbazine, VP-16 และ prednisolone ก้อนเนื้องอกยุบหายไปหมด ปัจจุบันหลังจากวินิจฉัย 80 เดือน ผู้ป่วยยังมีชีวิตอยู่และปลอดโรค

ดังนั้นเคมีบำบัดน่าจะมีประโยชน์ในการรักษาผู้ป่วย low grade astrocytoma บางรายที่มีข้อบ่งชี้

คำสำคัญ : Low Grade Astrocytoma, ยาเคมีบำบัด

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