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CLINICAL – PATIENT STUDIES

Effectiveness of novel combination chemotherapy, consisting of 5-fluorouracil, vincristine, cyclophosphamide and etoposide, in the treatment of low-grade gliomas in children

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Abstract Low-grade gliomas (LGG), which account for about 30% of brain tumors in children, are usually treated with surgical excision and/or radiotherapy. For patients who have significant residual tumor after resection or relapse after radiation, the proper chemotherapy regimen has not yet been identified. Thirteen children diagnosed with LGG outside the cerebellum between January 1999 and December 2004, all of whom had significant residual tumor after surgical resection, relapsed after radiation or showed visual deterioration, were treated for 18 months with a multidrug regimen of vincristine, etoposide, cyclophosphamide and 5-fluorouracil. Of the 7 patients who completed chemotherapy, 1 showed complete response (CR), 5 showed partial response (PR), and 1 had stable disease (SD). In 5 patients, chemotherapy was prematurely discontinued; 4 of these patients showed tumor progression and 1 had SD. One patient is still undergoing treatment. The side effects of chemotherapy were manageable. The median time to tumor response was 34 months (range, 2–82 months). The progression free survival was 67.3%. Pediatric LGG patients with residual tumor after surgery or who undergo relapse(s) may be successfully treated using our combination chemotherapy regimen.

Keywords Brain tumor · Chemotherapy · Children · Low-grade glioma

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Introduction

In children, about half of all brain tumors originate from glial cells [1]. Of these, 70–80% are low-grade gliomas (LGGs), which account for 30% of all pediatric brain tumors [2]. Although surgical resection is usually used to treat LGG [3], the location of the tumor may cause serious neurologic and cognitive side effects [4]. Relapse may occur, however, if complete resection is not performed. While radiotherapy may be effective, it can cause neurologic damage, developmental retardation, hormonal imbalances and secondary cancer in younger children [5, 6]. These drawbacks of surgical treatment and radiotherapy have led to the need for effective chemotherapy to reduce the size of residual tumors and to avoid or delay radiation therapy. We have developed a novel combination chemotherapy regimen, consisting of vincristine, etoposide (VP-16), cyclophosphamide, and 5-fluorouracil. We report here the results of this regimen in 13 pediatric patients with LGG who had significant residual tumor after surgical intervention, relapsed after radiation or showed visual deterioration.

Materials and methods

We performed a prospective study in patients under 20 years of age who were diagnosed with LGG at Asan Medical Center (Seoul, Korea) between January 1999 and December 2004. All tumors were located outside the cerebellum. The patient cohort included those who had one or more relapses, a progressive clinical course or significant residual tumor after surgical resection, as well as patients under age 3 years with residual tumor.

All patients had brain magnetic resonance imaging (MRI) prior to the start of chemotherapy. Spine MRIs and CSF cytology were checked to assess the state of leptomeningeal dissemination. During the course of treatment, brain MRIs or computerized tomography (CT) scans were taken every 3 months to assess the response to treatment.

Treatment protocol

The chemotherapy regimen consisted of vincristine (1.5 mg/m^2; maximum dose, 2 mg) and VP-16 (180 mg/m^2) on day 1 and cyclophosphamide (255 mg/m^2) and 5-fluorouracil (300 mg/m^2) on days 1–4 of each 21-day treatment cycle for 18 months (Fig. 1). Each cycle was started only when absolute neutrophil counts were above 1,000/μL, platelet counts were above 100,000/μL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were each below 200 U/L, and bilirubin levels were below 1.4 mg/dL. If these conditions were not met, treatment was postponed for 1 week. If absolute neutrophil and platelet counts remained low after 2 weeks, cyclophosphamide dose was reduced for the next cycle. If jaundice or paralytic ileus occurred, vincristine dose was reduced.

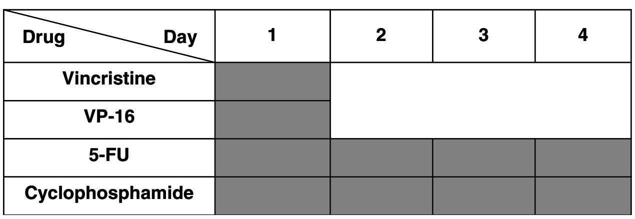

Fig. 1 Chemotherapy protocol schema. Vincristine (1.5 mg/m^2, maximum dose, 2 mg) and VP-16 (180 mg/m^2) were administered on day 1, and cyclophosphamide (255 mg/m^2) and 5-fluorouracil (300 mg/m^2) were administered on days 1–4 of each 21-day treatment cycle

The study protocol was approved by the Asan Medical Center Institutional Review Board and written informed consent was obtained from the patients and/or their guardians.

Evaluation and response

For each patient, brain MRI taken prior to treatment was used as a baseline. Response to chemotherapy was assessed from a brain CT or MRI scan taken every 3 months. After the completion of chemotherapy, routine brain MRI/CT scans were taken every 4 months or when clinical or neurological symptoms appeared. Patients were classified as having complete response (CR) if no residual tumor was present, partial response (PR) for a reduction of at least 50% in tumor size, minor response (MR) for a reduction in tumor size greater than 25% but less than 50%, stable disease (SD) if there was a less than 25% decrease in tumor size, or progressive disease (PD) if there was an increase in tumor size. Chemotherapy was discontinued in patients with PD or who manifested deteriorating clinical symptoms or signs, and these patients were treated with surgery, radiation therapy or a different chemotherapy regimen.

Results

A total of 13 patients (4 females, 9 males) were entered in the study, with median age at the time of diagnosis of 5 years 9 months (range, 5 months to 12 years 11 months). Of the 13 patients, 5 had experienced at least one previous relapse. Nine patients had tumors in the optic pathway. In the remaining 4 patients, the tumors were located in the right thalamus, midbrain, pineal gland, and cervicomedullary junction respectively. Histologically, 12 of the tumors were pilocytic astrocytomas, and the one remaining had a diffuse pilomyxoid astrocytoma. None of the patients had accompanying neurofibromatosis (Table 1).

Table 1 Patient characteristics

No.	Age at diagnosis	Sex	Tumor location	Histology	Prior therapy	No. of prior recurrence	Time to recurrence from diagnosis
1	7 mo	M	optic chiasm, hypothalamus	pilocytic astrocytoma	STR	0	
2	5 yr 9 mo	M	Right thalamic, intraventricular invasion	pilocytic astrocytoma	STR	0	
3	2 yr	F	optic chiasm, hypothalamus	pilocytic astrocytoma	Bx, NTR	1	5 mo
4	6 yr 10 mo	M	optic chiasm	pilocytic astrocytoma	STR	0	
5	1 yr 6 mo	M	optic chiasm, hypothalamus	pilocytic astrocytoma	STR	1	10 mo
6	12 yr 11 mo	F	opticothalamus	pilocytic astrocytoma	STR	0	
7	7 yr 9 mo	F	optic chiasm	pilocytic astrocytoma	STR, STR, STR	2	7 mo, 4 yr 6 mo
8	5 yr 10 mo	M	optic chiasm, hypothalamus	Diffuse pilomyxoid astrocytoma	STR	0	
9	11 yr 8 mo	M	midbrain, pons	pilocytic astrocytoma	STR	1	2 yr 9 mo
10	2 yr 4 mo	M	Pineal gland	pilocytic astrocytoma	STR	0	
11	5 mo	F	optic chiasm	pilocytic astrocytoma	STR	1	6 yr 9 mo
12	11 yr 11 mo	M	optic chiasm	pilocytic astrocytoma	STR	0	
13	3 yr 5 mo	M	cervico-medullary junction	pilocytic astrocytoma	STR	0	

Abbreviations: Bx—biopsy; STR—subtotal resection; NTR—near total resection

Response to treatment

The median age at the start of chemotherapy was 6 years 6 months (range, 9 months to 16 years 1 month). Seven patients completed treatment and one was still undergoing treatment. Of the 7 who completed treatment, 1 achieved CR, 5 achieved PR, and 1 had SD (Fig. 2). The patient who is still undergoing

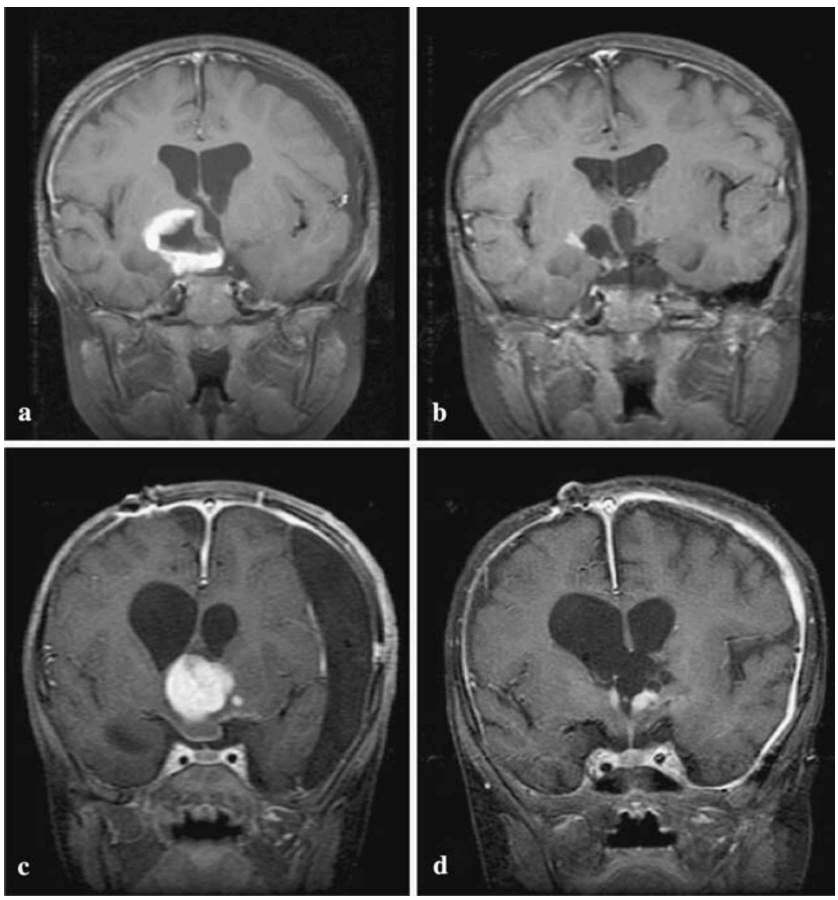

Fig. 2 Brain MRIs of patients showing partial responses. Brain MRIs of case 5 before (**a**) and 18 months after 24 courses of chemotherapy (**b**). Brain MRIs of case 8 before (**c**) and 26 months after 24 courses of chemotherapy (**d**)

treatment is showing SD. For completers, the mean number of chemotherapy cycles was 22 (range, 18–25).

Of the 5 patients who were unable to complete the treatment course, 4 showed progressive disease (PD), whereas 1 had SD. This patient was suspected of having residual tumor on postoperative MRI, but follow up MRI showed no evidence of residual tumor, leading to discontinuation of chemotherapy. Two patients showed SD initially, but follow up MRI revealed PD. One of these patients received adjuvant radiotherapy, whereas the other was treated with another chemotherapy regimen which was composed of vinblastine and carboplatin as per COG A9952. The median number of chemotherapy cycles for these 5 patients was 6 (range, 3–20) (Table 2).

Toxicity of treatment

Overall, there was no incidence of severe toxicity. A reduction in dosage was required for only one subject, due to decreased absolute neutrophil and platelet counts, the latter of which required platelet transfusion. Due to repeated episodes of syndrome of inappropriate antidiuretic hormone (SIADH), mild paralytic ileus and jaundice, the vincristine dose was reduced in this patient and subsequently discontinued for the final 3 months of treatment. In addition, 4 patients showed 4th degree hematologic and liver toxicity. Two of these patients had absolute neutrophil counts below 500/μL, and one had elevated AST and ALT (each above 200 U/L). The other patients recovered completely and did not require any modification of drug dosage. The mean cumulative dose of VP-16 for patients who completed the treatments was 3,960 mg/m^2 (range, 3,240–4,500 mg/m^2). During the time of observation, none of these patients developed secondary leukemia.

Survival

Over a median time of observation of 65 months (range, 13–107 months), all patient is alive, resulting in an overall survival rate of 100%. Aside from the two patients who developed PD, the median response time was 34 months (range, 2–82 months). Six-year progression free survival was 67.3% (Fig. 3).

Discussion

According to the WHO classification system, LGGs can be histologically categorized as pilocytic astrocytomas, low-grade astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas [7]. LGGs can also be classified according to their location: in the cerebellum (12–18%), cerebral hemisphere (8–20%), hypothalamic/optic pathway (3–5%), brain stem (3–6%) and thalamus [7, 8].

Although wide or radical surgical resection is important in the treatment of LGG [3], significant neurologic and cognitive side effects can result from surgery, depending on the location of the tumor [4]. If there is considerable residual tumor, however, relapse may jeopardize survival and quality of life, despite the slow clinical course of these tumors [2]. Radiotherapy can damage neuropsychological, developmental and hormonal functions of the patient, with damage to cognitive function more severe in patients under age

Table 2 Clinical features and responses to chemotherapy

No.	Age at start of Chemotherapy	Total no. of chemotherapy courses	Tumor response chemotherapy	Additional therapy to after chemotherapy	Response duration (months)	Follow-up (months) from diagnosis
1	9 mo	18	PR	No	82+	83+
2	6 yr 6 mo	4	PD	STR, RT	NA	76+
3	2 yr 5 mo	18	PR	No	61+	67+
4	7 yr	18	SD	No	51+	53+
5	2 yr 6 mo	24	PR	RT	19	54+
6	13 yr 1 mo	25	CR	No	40+	42+
7	11 yr 8 mo	22	PR	No	39+	86+
8	6 yr 1 mo	22	PR	No	34+	37+
9	16 yr 1 mo	8	PD	RT	NA	85+
10	5 yr 2 mo	6	SD	RT	4	65+
11	7 yr 3 mo	3	SD-> PD	RT, STR	2	107+
12	12 yr 1 mo	20	SD-> PD	Other chemotherapy	14	18+
13	3 yr 6 mo	20	SD	on going	12+	13+

Abbreviations: CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease; NA—not applicable; RT—radiotherapy; STR—subtotal resection

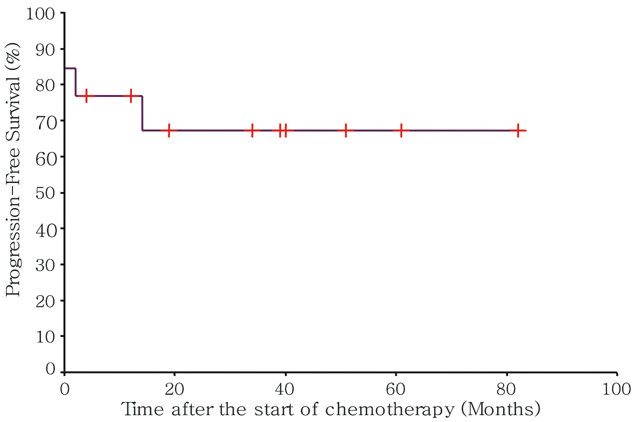

Fig. 3 Kaplan-Meier analysis of 13 patients showing 6 year progression-free survival after the start of chemotherapy

3 years. These drawbacks of surgery and radiotherapy have made it necessary to find an effective chemotherapy regimen that can be used to treat young patients, thus delaying or avoiding radiotherapy.

Beginning in the 1960s, many chemotherapy regimens have been tested for their ability to control the progression of recurrent brain tumors. These regimens primarily involve agents that can cross the blood–brain barrier (BBB), such as alkylating agents and low molecular weight or platinum based drugs [9, 10]. Vincristine was found to have a positive effect on recurrent brain tumors, leading to trials with other single agents [11, 12], and administration of high dose cyclophosphamide (1.2 gm/m^2/cycle) to 14 glioma patients resulted in CR in 1 and SD in 8 [13]. Cyclophosphamide treatment, however, resulted in low platelet counts, leading to bleeding within the tumors and the death of one patient [9]. Cyclophosphamide, carboplatin and VP-16 were each shown to have efficacy against astrocytomas, although the efficacy of low dose cyclophosphamide was ambiguous [14–16, 18].

A combination of vincristine and VP-16 was shown to be effective against low grade astrocytomas; of 20 patients, 15 showed PR, MR or SD [18]. A combination of carboplatin and vincristine resulted in progression-free-survival rates of 75% over 2 years and 68% over 3 years [19], making it one of the most effective regimens used to date. However, 5–10% of patients had allergic reactions to carboplatin. Other chemotherapeutic agents used include 6-thioguanine, procarbazine, lomustine (CCNU) and vincristine [20], and 5-fluorouracil has been tested in pilot studies against brain stem gliomas [21]. While co-administration of 5-fluorouracil had no effect on survival rates in malignant glioma patients receiving intra-arterial injections of carmustine (BCNU) [22], it had a positive effect when used in combination with external radiation. Recently, microsphere insertion of 5-fluorouracil had been used in the treatment of brain tumors [23], and temozolomide and/or thalidomide has been used to treat patients with glioma [24].

Weekly injections of vinblastine (6 mg/m^2) for 52 weeks was found to result in at least SD in 15/20 (75%) patients who showed no initial response or whose cancer recurred, suggesting that vinblastine might be a useful drug in the treatment of LGG [25], and an additional study reported the effectiveness of vinblastine in treating LGG [26]. A summary of previous reports of chemotherapy regimens for LGG is shown in Table 3.

In our study, because of parents' refusal of radiation therapy, chemotherapy was started first in two patients (#6, #7) despite the fact that the patients were within the age group to receive radiotherapy. They showed complete remission and partial remission respectively. One patient (#9) also refused radiotherapy at first. After 8 cycles of chemotherapy, the patient had PD eventually necessitating radiation therapy. This patient is still alive. The patient (#12) who showed PD after 20 cycles of chemotherapy had also refused radiotherapy. This patient was put on chemotherapy protocol containing vinblastine and carboplatin similar to COG A9952 regimen.

The side effects of this regimen were negligible, and there was no need for dose adjustment in 12 of the 13 patients. One patient, however, developed severe jaundice and paralytic ileus, necessitating the discontinuation of vincristine. This patient later relapsed, suggesting that vincristine may be a very important component of this chemotherapeutic regimen. In most combined cancer treatments, hematologic toxicity is common, but it often resolves without any major event, although death due to myelodysplastic syndrome (MDS) had been reported during MOPP chemotherapy [10]. In the current study, the cumulative dose of VP-16 in patients completing treatment was 3,960 mg/m^2 (range, 3,240–4,500 mg/m^2), but there were no incidents of secondary leukemia during follow-up.

Results presented here show that the combination regimen of vincristine, low dose cyclophosphamide, VP-16 and 5-fluorouracil resulted in favorable responses for patients with LGG. An overall survival rate of 100%, and 6 year progression free survival rate of 67.3% are quite encouraging. Especially, 2 of the 5 patients who had experienced one or more recurrence previously showed PR at 61 months and 39 months respectively. And one patient (#6) even showed CR.

Chemotherapeutic agents that are lipophilic and have a small molecule may easily overcome the BBB. On the other hand, it is also well recognized that the

Table 3 Summary of previous reports of chemotherapy for low-grade glioma

Reference	Drugs	Number of patients	Histology (Number of patients)	Objective responses (Number of patients)					
				CR	PR	MR	SD	PD	
[10]	MOPP, VCR/CPM, CDDP/VP- 16, Ifosfamide	13	Astrocytoma (9), mixed glioma (1), oligodendroglioma (1), optic pathway neoplasm (2)	1	6		3	3	Progression free interval of PR responders, 17–29 months. All patients received RT after then.
[13]	CPM	14	Pilocytic astrocytoma (8), astrocytoma NOS (2), optic pathway neoplasm (4)	1	0		8	5	Early closure due to excessive number of children with PD
[17]	Carboplatin	12	optic pathway neoplasm	0		4	6	2	Median duration of f/u, 38.6 months. Overall progression free survival, 83 ± 11%
[18]	VCR/VP-16	20	LGA (13), LGA/fibrillary (3), LGA/pilocytic (2), LGA/oligodendroglioma (1), optic pathway neoplasm (1)	0	1	3	11	5	
[19]	Carboplatin/ VCR	78	Fibrillary (32), pilocytic (17), mixed/ganglia (3), not determined(26)	4	22	18	29	5	Progression free survival, 75 ± 6% at 2 years; 68 ± 7% at 3 years
[20]	6TG/CCNU/PCB/DBD/VCR	42	JPA (23), astrocytoma (11), ganglioglioma (1), oligodendroglioma(1), not determined (6)	0		15	25	2	5-year survival rate, 78%
[24]	Temozolomide	13	JPA (7), fibrillary astrocytoma (1), ganglioglioma (1), optic pathway glioma (3), not determined (1)	0	3	1	5	4	Unresectable location
[25]	Vinblastine	20	Pilocytic astrocytoma (8), LGG NOS (8), ganglioglioma (3), pilomyxoid tumor (1)	0	4	3	8	5	Overall response rate was 35% and 75% patients remaining at least SD
[26]	Vinblastine	9	oligoastrocytoma	1	1	5	2	0	Median f/u, 22 months (range, 6.0–45.9 months)

Abbreviations: CR—complete response; PR—partial response; MR—minor response; SD—stable disease; PD—progressive disease; MOPP—nitrogen mustard; oncovine, procarbazine, prednisone; VCR—vincristine, CPM, cyclophosphamide; CDDP—cisplatin; VP- 16—etoposide; TG—thioguanine; CCNU—lomustine, PCB: procarbazine; DBD—dibromodulcitol; LGG—low grade gloma; NOS—not otherwise specified; LGA—low grade astrocytoma; JPA—juvenile pilocytic astrocytoma; f/u—follow up

BBB is only partially intact in many CNS tumors. This might be the reason why our regimen had brought reasonably good response rate. Chemotherapeutic agents that are known to have large water-soluble molecules such as platinum agents have even shown effectiveness in the many brain tumors [27].

Although our chemotherapy regimen has originally been formulated for the treatment of all the low grade gliomas in children, the pathology of the tumors in the patients accrued and enrolled are mostly pilocytic astrocytomas. Therefore, the therapeutic result we have seen here are more relevant to the patient with pilocytic histology.

This protocol is composed of 4 drugs, but there were no incidents of ototoxicity or nephrotoxicity that may be seen in the regimens containing platinum compound. And low dose cyclophosphamide led to very little risk of hemorrhagic cystitis. Moreover, the combination regimen was administered mostly on an outpatient basis, resulting in significant cost savings.

The combination regimen used here was quite effective, with 6 of 13 patients achieving PR or better. Of the 5 patients who had at least 1 relapse prior to treatment, 3 finished their treatments and achieved PR. More remarkable is that 1 patient achieved CR.

Conclusion

We have shown here that, of 13 children with LGG who were given a combination regimen of 5-fluororacil, cyclophosphamide, vincristine, and VP-16, 6 achieved a response of PR or better, with 1 achieving CR. These findings suggest that the chemotherapy regimen reported here is effective and safe in the management of recurrent or residual LGG and may be used to avoid or postpone radiotherapy in the very young.

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