Efficacy and Feasibility of Procarbazine, Ranimustine and Vincristine Chemotherapy, and the Role of Surgical Resection in Anaplastic Oligodendroglioma

MASAAKI YAMAMOTO, MITSUTOSHI IWAASA, MASANI NONAKA, HITOSHI TSUGU, KAZUKI NABESHIMA and TAKEO FUKUSHIMA

Departments of Neurosurgery and Pathology, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan

Abstract. The safety, tolerance and preliminary efficacy of a chemotherapy regimen consisting of procarbazine (PCB), ranimustine (MCNU) and vincristine (VCR) were assessed for patients with newly diagnosed supratentorial anaplastic oligodendroglioma. Materials and Methods: Between October 1999 and September 2003, 5 patients were enrolled. The initial regimens were prescribed as adjuvant therapy in conjunction with radiotherapy following standard surgical treatment. All patients received a chemotherapy comprising ranimustine (100 mg/m²) intravenously on Day 1, procarbazine (60 mg/m²) on Days 8 to 21, and vincristine (1.4 mg/m², maximum total 2 mg) on Days 8 and 29. The cycles were repeated every 8 weeks until tumor progression was evident, or for a total of 6 cycles over a 1-year period. The primary end-points were safety and tolerability, while the secondary end-point was overall survival. Results: Five consecutive eligible patients were treated. Of the 4 evaluable patients, 3 partially responded to the treatment (PR), while 1 had a complete response (CR): all patients are still alive. However, 3 of the 5 patients showed relapse, with a time to tumor progression (TTP) of 50, 143 and 241 weeks, respectively. Two of these patients received combined treatment with carboplatin, etoposide and recombinant human mutant tumor necrosis factor-alpha at the first relapse. This regimen appeared to be safe and neither neurological toxicity, severe or life-threatening hematological toxicity, nor fatal toxicity (WHO Grade 4) were experienced. Conclusion: These results suggest that a chemotherapy regimen consisting of PCB, MCNU and VCR in this patient population seems to be safe and tolerable, and the response rate was high. Thus, wide resection with a risk of major neurological morbidity due to nearby functionally critical areas can be avoided. However, since the relapse rate was high, a second-line chemotherapy should be developed for anaplastic oligodendroglioma to improve the long-term control of the disease.

Oligodendroglioma is a rare, although increasingly more common, primary brain tumor (1), which represents 4 to 15% of primary glial tumors (2-6). Significant attention has been focused on oligodendrogliomas because of their unique chemosensitivity compared with astrocytomas (7, 8). Many patients with new or recurrent anaplastic oligodendroglioma have responded well to PCV (procarbazine, lomustine and vincristine) chemotherapy (1, 9, 10). Oligodendrogliomas have a high incidence of allelic loss of 1p and 19q chromosomal arms (11), which is associated with chemosensitivity (12, 13). While most newly diagnosed patients with oligodendrogliomas frequently respond well to PCV, with some responses being durable (14), most show disease progression after the initial treatment (15, 16). The median survival may be greater than 10 years in well-differentiated oligodendroglioma, whereas patients with anaplastic oligodendrogliomas have a median survival time of less than 5 years (4, 17-19) and ultimately die of their disease (20).

Many neurosurgeons recommend that gliomas should be resected as extensively as possible, which is associated with longer survival, especially in patients with glioblastoma (21, 22). The extent of resection of the tumor has been considered a favorable prognostic factor even in oligodendroglioma (23). However, it is still difficult to resect gliomas completely because of their diffuse, infiltrative and destructive nature (24), especially if they are near functionally critical areas.

In this study, we reviewed our results of anaplastic oligodendroglioma treated by surgical removal and radiation therapy concomitant with a chemotherapy regimen of PCB, MCNU and VCR.
regimen consisting of PCB, MCNU and VCR, a modified PCV regimen using drugs available in Japan, and determined the efficacy and role of this initial treatment for anaplastic oligodendroglioma.

Materials and Methods

Patient selection. Five patients met the following inclusion criteria for enrollment onto the study. The patients were adults (>18 years and <70 years old) with malignant oligodendroglioma. The histological diagnosis was anaplastic oligodendroglioma (grade III) (human brain tumors were classified according to the revised WHO criteria for tumors of the central nervous system) (25); no previous treatment with chemotherapy or immunotherapy; Karnofsky performance status (KPS) >60%; and life expectancy >8 weeks. The patients were required to have adequate liver, bone marrow, renal and cardiovascular function, granulocyte count >1,500/mg, platelet count >10x10^9/mg, hemoglobin >10 mg/ml, SGTP and alkaline phosphatase <2 times normal, bilirubin <1.5 mg% and BN or creatinine <1.5 times normal prior to starting therapy. They were candidates for this study within 3 weeks after the primary surgical treatment, while patients with any immediately life-threatening operative or postoperative complications were excluded. Written informed consent was obtained from each patient.

Surgery. All of the patients underwent extensive resection, depending upon the tumor location. Tumors near functionally critical areas were left in subtotal or partial removal when it was determined that further removal of the tumor could cause major neurological morbidity. Intraoperative pathological diagnosis was made by either frozen section or squash smear. The extent of the resection was evaluated by postoperative magnetic resonance imaging (MRI); i.e., grossly total; subtotal (50% to 99%); partial (<50%); or biopsy only.

Radiation therapy. Radiation therapy, given prior to chemotherapy, was provided at 60 Gy, administered 1.5 Gy per day, 5 times a week. In all cases, postsurgical CT or MR imaging was used to delineate the irradiation field and volumes.

Chemotherapy. MCNU was administered intravenously at 100 mg/m^2 on Day 1 followed by 1.4 mg/m^2 VCR intravenously on Day 8 and Day 29. Between Days 8 and 21, PCB was administered orally at 60 mg/m^2, usually in conjunction with antiemetic medications, as modified from a previous report (8). Chemotherapy was given with this regimen each 8-week cycle until tumor progression was evident, or for a total of 6 cycles over a 1-year period. Evaluations consisted of a hemogram and liver function studies obtained on Days 1, 8 and 22.

Data collection and statistical analyses. All medical records were reviewed and entered into a database. Common toxicities were defined using the WHO criteria (26). The parameters that were monitored to determine the response to therapy included neurological status and tumor size, as measured on MRI before and after each treatment and at 3-month intervals. The tumor size was estimated as the volume of abnormal enhanced lesion on MRI studies. The response was classified into 1 of 4 categories: CR, complete response, defined as complete disappearance of the tumor for a period of at least 4 weeks; PR, partial response, defined as a reduction of 50% or more in tumor size for at least 4 weeks; NC, no change, defined as either a decrease of less than 50% or an increase of less than 25% in tumor size for at least 4 weeks; and PD, progressive disease, defined as an increase of 25% or more in tumor size. The duration of survival was defined as the period from the start of treatment to death or the most recent evaluation.

Results

Clinical outcome. The 5 patients received this regimen for up to 6 cycles (Table I). Of 4 evaluable patients, 3 partially responded to the treatment (PR), and 1 showed a complete response (CR). Three patients subsequently relapsed with a time to tumor progression (TTP) of 50, 241 and 143 weeks, respectively. Case 1 underwent surgical resection of the tumor at the time of tumor recurrence. All of the patients are still alive (range 67 – 265 weeks) and the median overall survival has not been reached.

Toxicity of treatment. Treatment toxicity was assessed in accordance with the WHO criteria (26). All the patients experienced toxicity as the result of radiation therapy, in the form of alopecia and mild skin reactions to radiation. One patient (Case 1) stopped this chemotherapy regimen due to a skin reaction to PCB and MCNU of Grade 3 severity. Transient elevation of serum transaminases (ALT, AST) occurred in 2 patients (< grade 2). Neither neurological

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Surgery</th>
<th>PCV</th>
<th>Response</th>
<th>TTP (Wks)</th>
<th>Survival (Wks)</th>
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TTP, time to progression; D/A, dead or alive.

Table I. Patient characteristics and treatment.

5 M 49 partial 6 PR - 67 A
3 M 39 partial 6 CR - 204 A
1 M 33 total 2 - 50 265 A
2 F 42 partial 6 PR 241 253 A
1 M 33 total 2 - 50 265 A
4 M 35 partial 6 PR 143 208 A
5 M 49 partial 6 PR - 67 A

F: female; M: male; Wks: weeks.
toxicity, severe or life-threatening hematological toxicity, nor fatal toxicity (WHO Grade 4) was experienced. None of the patients experienced delayed treatment due to treatment-related toxicities.

Representative cases. Case 2, a 42-year-old female, presented with dizziness. T1-weighted MRI showed a partially enhanced mass lesion at the right frontal lobe, which involved the contralateral frontal lobe via the corpus callosum (Figure 1). She was initially treated with surgery (partial resection) and diagnosed with anaplastic oligodendroglioma in January 2000 (Figure 2). There was remnant tumor on postoperative MRI (Figure 3, A and B). After 6 courses of PCB, MCNU and VCR, MR images in May 2001 showed a decrease in tumor volume of more than 50% (Figure 3, C and D). Follow-up MRI in August 2004, 241 weeks from the beginning of her initial treatment, showed a well-enhanced mass lesion at the right frontal lobe (Figure 4, A, B and C). The T/N ratio of this lesion on TI-SPECT was more than 4.0, which was interpreted as tumor recurrence. The patient underwent another operation with partial resection, and histopathological examination of the surgical specimen revealed recurrent anaplastic oligodendroglioma (Figure 5). She subsequently received adjuvant chemotherapy with carboplatin and etoposide.

Case 5 was a 49-year-old male who presented with recent memory disturbance and personality change. MRI in July 2003 showed a right frontal mass lesion with extension into the contralateral frontal lobe (Figure 6). Intraoperative histopathological diagnosis with squash smear (Figure 7 A) and frozen section revealed anaplastic oligodendroglioma, which confirmed the postoperative histopathological examination of a surgical specimen (Figure 7 B). He underwent resection of a right frontal tumor (partial removal), and the remnant tumor was evident on postoperative MRI in July 2003 (Figure 8, A and B). After 6 courses of PCB, MCNU and VCR, MR images in
September 2004 showed a decrease in tumor volume of more than 50% (Figure 8, C and D), and this patient has remained clinically stable for more than 6 months.

**Discussion**

There are still many unanswered questions regarding the best treatment for patients with oligodendroglioma, although the biochemical basis of oligodendroglioma chemosensitivity has been clarified over the past decade (12, 15, 27, 28). Currently, PCV plays an important role (29-31), but we still do not know if there are better or less toxic regimens, or whether PCV therapy can provide a curative response in patients with anaplastic oligodendrogliomas.

In this study, a clear benefit was observed in the response rate with a chemotherapy regimen consisting of PCB, MCNU and VCR concurrent with radiotherapy. Of the 4 evaluable patients, 3 (75.0%) partially responded to treatment and 1 (25.0%) had a complete response: all of the patients are still alive. Although this chemotherapy often induced mild hematological toxicity and skin rashes, these were transient and quickly responded to medication. Grade 4 hematological
Figure 4. MR images showing a regrowth of residual tumor at the right frontal parenchyma (A, B and C). TI-SPECT showing a hot-spot at the right frontal lobe with a T/N ratio of more than 4.0 (D) in Case 2.

Figure 5. Case 2, recurrent tumor. The tumor shows increased cellularity, nuclear atypia and high mitotic activity. Original magnification, x 100.
toxicities were not experienced in this study. None of the patients experienced a treatment delay due to toxicities.

There is still some controversy regarding the extent of surgical resection to be performed for malignant gliomas. Many neurosurgeons recommend that gliomas should be resected as extensively as possible, which is associated with longer survival, especially in patients with glioblastoma (21, 22). The extent of resection of the tumor has been considered a favorable prognostic factor even in anaplastic oligodendroglioma (23, 32). However, it is sometimes impossible to resect gliomas completely without major neurological morbidity when they are near functionally critical areas. In 3 of our cases, the tumor invaded the contralateral frontal lobe via the corpus callosum, so that total removal of the tumor was virtually impossible, even using new technologies such as a surgical navigation system. Our results suggest that surgical resection of the tumor can be limited to subtotal or partial removal in oligodendroglioma tumors when the tumor is located near a critical area and if it is thought that surgical removal of the tumor could cause major neurological morbidity. Adjuvant therapy with PCV chemotherapy is effective for remnant malignant oligodendroglioma (14). It is also important to accurately select and identify patients with oligodendrogial tumors during the operation who will respond well to adjuvant chemotherapy with PCV. A simple intraoperative diagnostic

Figure 6. Case 5. T2-weighted MRI demonstrating a high-intensity mass lesion spreading into the contralateral frontal lobe (A, B), which was enhanced heterogeneously by Gd-T1-weighted MRI (C, D).
Figure 7. Case 5. A) Smear cytology shows tumor cells that spread readily with little cellular cohesion and no glial fibrillary matrix. The cells have rounded but larger and hyperchromatic nuclei. Binucleation is also seen. B) Histology shows tumor cells with pronounced nuclear atypia and mitotic figures. Original magnification, x 200 (A, B).

Figure 8. Serial MR images obtained before chemotherapy with evident remnant tumor (A, B), and after 6 courses of procarbazine (PCB), ranimustine (MCNU) and vincristine (VCR), showing a decrease in tumor volume of more than 50% (C, D) in Case 5.
marker should be developed for malignant glioma to detect oligodendrogial components, since it is time-consuming to detect LOH in 1p and 19q in tumor tissues (33).

However, the results of this study showed that the long-term relapse rate was high. In 2 of 4 cases, the tumor subsequently recurred after 1-year of chemotherapy with PCB, MCNU and VCR. Furthermore, the second-line chemotherapy with carboplatin and etoposide failed to provide a durable response in one case. Little is known about what agents may be effective as salvage therapy for tumor progression in patients who have been previously treated with PCV or other chemotherapy (34). Further treatment with PCV after the prior administration of PCV seemed to be ineffective (35). A variety of multimodal salvage therapies for tumor progression in patients who have been previously treated with PCV or other chemotherapy have been developed, including cisplatin plus etoposide (35), carboplatin (34, 36) and temozolomide (37, 38). The second-generation oral alkylating agent, temozolomide, has recently been shown to be safe and effective in patients with malignant gliomas, and has been approved in the United States for the treatment of adult patients with refractory anaplastic astrocytoma (39-42). Temozolomide might also be considered as the preferred second-line treatment for oligodendrogial tumors after the failure of PCV chemotherapy (20, 43). A novel chemotherapeutic agent should be developed to achieve a long-term response or cure for malignant oligodendrogial tumors, since the present second-line chemotherapy for patients with recurrent or progressive oligodendrogial tumors has limited efficacy (36, 44).

In conclusion, combined therapy with procarbazine, ranimustine and vincristine concurrent with radiotherapy was effective as an initial treatment for malignant oligodendroglioma, although the long-term relapse rate was high. A more effective regimen, combination and improved drug-to-tumor delivery should be developed for this type of tumor.

References


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