Anaplastic Oligodendroglial Tumors Harboring 1p/19q Deletion Can Be Successfully Treated without Radiotherapy

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Abstract. *Although anaplastic oligodendroglial tumors are known to be chemosensitive, patients under this diagnosis have been traditionally treated with radiotherapy. To avoid possible neurotoxicity, we prospectively treated patients with anaplastic oligodendroglial tumors harboring 1p/19q deletion, with exclusive procarbazine, ACNU, and vincristine chemotherapy without radiotherapy. Twenty-five patients were enrolled in the study (12 with 1p/19q co-deletion, 2 with 1p mono-deletion, 2 with 19q mono-deletion, and 9 without 1p/19q deletion). The median progression-free survival (PFS) was 50 months for all the patients, and those with tumors harboring 1p/19q deletion were progression free for a significantly longer period than those without the deletion (p=0.0391). The median overall survival (OS) time was not reached in both patient groups with and without 1p/19q deletion (p=0.230), and the 5-year OS rate was 62.2% for all patients. The excellent treatment results warrant a large-scale clinical study to confirm the efficacy of upfront chemotherapy omitting radiotherapy as initial therapy for anaplastic oligodendroglial tumors with 1p/19q deletion.*

Anaplastic oligodendroglial tumors are rare intracranial tumors that are conventionally treated with surgery and postoperative radiotherapy (1). Although many retrospective studies have suggested that the postoperative radiotherapy for anaplastic oligodendrogliomas has some benefit (2-6), radiation-induced cognitive impairment in long-term survivors leads to an increased need for replacing radiotherapy with other effective and less toxic therapies (7). Most low-grade oligodendrogliomas can be successfully controlled with exclusive chemotherapy using nitrosoureas, procarbazine, and vincristine (PCV or PAV) (8-11). Anaplastic oligodendroglial tumors are also reported to respond well to the nitrosourea-based chemotherapy or temozolomide (12, 13). Treatment strategies including radiotherapy are mostly established before the knowledge of the chemosensitive nature of the oligodendroglial tumors is gained. To avoid the potential neurotoxicity caused by radiotherapy, some researchers have started to try reserving radiotherapy until recurrence of anaplastic oligodendroglial tumors by increasing the intensity of chemotherapies (14-20).

Stratification or personalization of treatment strategy based on informative biomarkers is expected to maximize therapeutic effects while avoiding excessive and unnecessary therapy. It has been recently confirmed that anaplastic oligodendroglial tumors with chromosome 1p with or without 19q deletion are less aggressive and more responsive to chemotherapy (21-23). Furthermore, this genetic abnormality is known as a biomarker useful for the objective diagnosis of the oligodendroglial tumor component, which is otherwise a rather difficult characterization to be made regarding the histological diagnosis of high-grade tumors (24, 25). In the present study, we prospectively treated the patients with anaplastic oligodendroglial tumors confirmed to have 1p/19q deletion with exclusive PAV chemotherapy in a dose-down and cycle prolongation manner. Ultimately we discussed the clinical relevance of omitting radiotherapy for anaplastic oligodendroglial tumor.

Patients and Methods

We prospectively treated patients having anaplastic oligodendroglial tumors according to the following protocol: i) an upfront PAV chemotherapy in a dose-down and cycle prolongation manner without radiotherapy (nimustine (ACNU) at 75 mg/m^2 for day 1, vincristine at 1 mg/m^2 for days 8 and 29, procarbazine at 100 mg/day for days 8-21; four cycles a year for 2 years) for tumors with 1p/19q deletion (9); and ii) radiotherapy of 54 Gy with temozolomide chemotherapy in Stupp's regimen for the cases confirmed as not having 1p/19q deletion. We obtained Institutional

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Key Words: Glioma, oligodendroglioma, 1p19q, 1p, PAV, ACNU, procarbazine, vincristine, chemotherapy.

Review Board approval for the study protocol. The patients were required to provide informed consent before chemotherapy.

The patients were enrolled in this study only if their tumors had been histologically confirmed as newly diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma with at least 25% oligodendroglial elements. They had at least three out of five anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, and necrosis). The age, gender, original pathological diagnosis, initial symptoms, tumor location, imaging findings and extent of resection were recorded. A minimum of 6 months of clinical follow-up information was required.

The histological diagnosis was confirmed by a neuropathologist other than the one performing the initial diagnosis. The 1p/19q deletion analyses were carried out using standard fluorescence in situ hybridization (FISH) of standard cytogenetic preparation from fresh tumor tissues. FISH probes for 1p had a target region of 1p36 with a control region of 1q25, and those for 19q had a target region of 19q13 with a control region of 19p13. The total number of signals was counted, and a ratio of 1p:1q or 19q:19p less than 0.75 was diagnosed as indicating a deletion.

The primary endpoints of our study were indices for progression-free survival (PFS) and overall survival (OS). PFS was calculated from the date of surgery until the first sign of radiological progression, death, or last follow-up. OS was also calculated from the date of diagnosis until the date of death or last follow-up. The Kaplan-Meier method was used to estimate survival rates and the log-rank test was applied to compare the survival differences using StatView software (SAS Institute Inc., Cary, NC, USA).

Table I. *Patients characteristics*.

Age	
Mean	47
Range	32-83
>50	6 (30%)
Gender	
Male	15 (60%)
male	10 (40%)
Karnofski Performance Score	
≥70	13 (52%)
<70	12 (48%)
Contrast enhancement on MRI	
Yes	22 (88%)
No	3 (12%)
Surgery	
Gross total removal	12 (48%)
Partial removal	13 (52%)
Histology	
Anaplastic oligodendroglioma	15 (60%)
Anaplastic oligoastrocytoma	10 (40%)
MIB-1 labeling index	
≥20%	16 (64%)
<20%	9 (36%)
1p/19q Deletion	
Yes	16 (64%)
No	9 (36%)

Results

Twenty-five patients were treated and followed-up for a median period of 3 years. The patients' characteristics are summarized in Table I. Fifteen patients had anaplastic oligodendrogliomas (WHO grade III) and ten patients had anaplastic oligoastrocytoma (grade III). The study group consisted of 15 men and 10 women, and the mean age was 47 (range: 32-83) years. The initial presenting symptom was seizure in 14 patients (56%), consciousness disturbance in six (24%), and hemiparesis in four (16%). Magnetic resonance imaging (MRI) and computed tomography (CT) scans were obtained for all patients. Contrast enhancement was noted in 22 patients (88%). Twelve patients (48%) underwent total resection (postoperative MRI ensured a tumor-free margin), and thirteen patients (52%) underwent partial resection. Biopsy was not performed to obtain an accurate pathological diagnosis. Treatment-induced WHO class III myelosuppression was not observed in any of the patients, but discontinuation of chemotherapy was necessary for one patient because of alopecia.

1p/19q co-deletion was observed in 12 out of 25 cases (48%) analyzed with FISH. Isolated loss of 1p or 19q was observed in two patients (16%). These patients were treated in the same way as the patients whose tumors had co-deletion. The mean MIB-1 labeling index did not differ between the tumors with and without 1p/19q deletion (25.7% and 28.7%, respectively).

The median PFS was 50 months and the 5-year PFS rate was 45.3% for all the patients (Figure 1a). The median OS was not reached and the 5-year OS rate was 62.2% for all patients (Figure 2a). We then compared the survival periods by 1p/19q status. The median PFS was 14 months for the patients having tumors without 1p/19q deletion, whereas the median PFS was not reached and the 5-year PFS rate was 60.6% for those with tumors harboring 1p/19q deletion (Figure 1b). There is a significant statistical difference between the two patient groups (p=0.0391). The median OS was not reached for either patient group. The 5-year OS rate was 72% for the group with 1p/19q deletion, without significant difference compared to the group not having 1p/19q deletion (p=0.230) (Figure 2b).

Six months after completion of the initial therapy, 13 (81%) out of 16 patients with tumors harboring 1p/19q deletion returned to a pre-disease level of social activity, whereas only three (33%) out of nine patients with tumors lacking 1p/19q deletion who had received radiotherapy returned to a pre-disease level of activity (p=0.0166).

Discussion

There are few studies focusing on the role of exclusive chemotherapy without radiotherapy for newly-diagnosed anaplastic oligodendrogliomas (14-20). These studies employed the dose-intensive temozolomide or the intensive

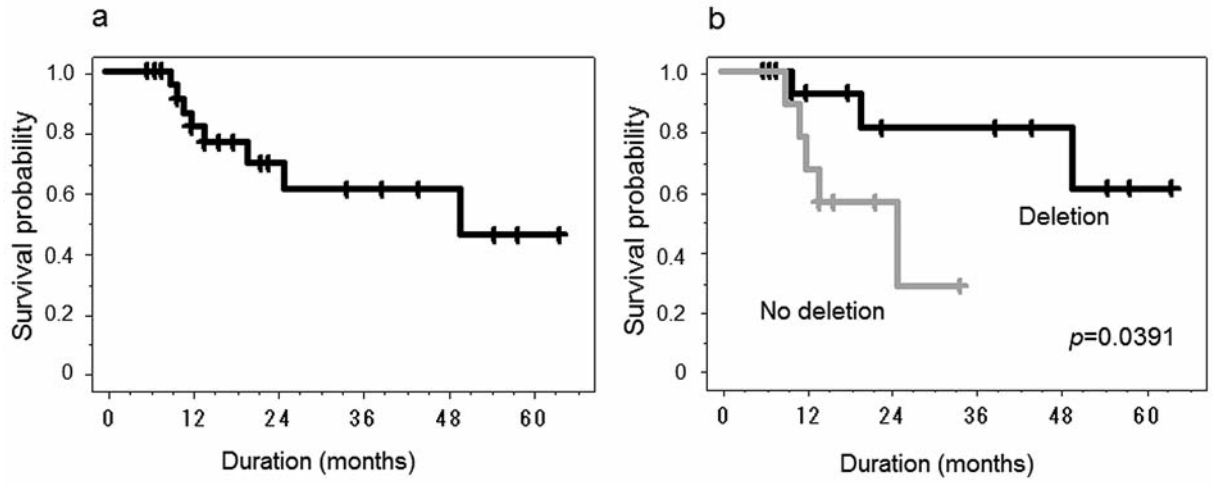

Figure 1. *Kaplan-Meier analyses of the progression-free survival for all the patients with anaplastic oligodendroglial tumors (a), and a comparison of the cases with and without 1p/19q deletion (b). Tick marks indicate last follow-up.*

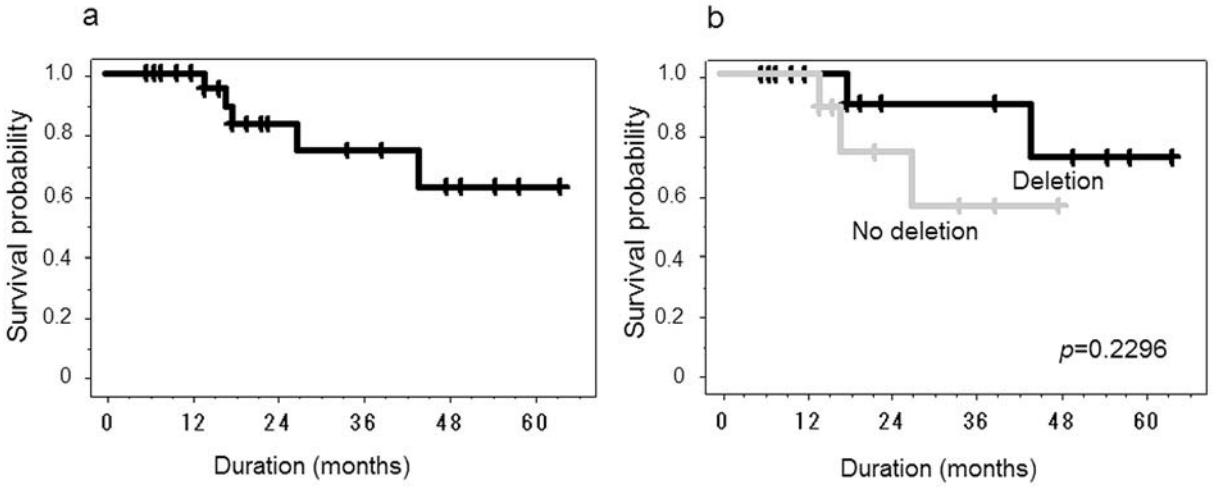

Figure 2. *Kaplan-Meier analyses of the overall survival for all the patients with anaplastic oligodendroglial tumors (a), and a comparison of the cases with and without 1p/19q deletion (b). Tick marks indicate last follow-up.*

PCV regimen using autologous stem cell rescue, which carries the risk of potentially lethal systemic side-effects (14-18). We reported here, for the first time, that anaplastic oligodendroglial tumors harboring 1p/19q deletion can be successfully controlled with standard-dose PAV chemotherapy while omitting radiotherapy. Although the median follow-up period of 3.0 years is not enough to support a definitive conclusion, the median survival time in our study can be favorably compared with those in previous reports (21-23). Treatment strategy featuring radiotherapy for grade III gliomas was established before the knowledge was gained of the chemosensitive nature of oligodendroglial tumors in retrospective studies including tumors of heterogeneous histology. Recent studies have shown that 1p/19q deletion can be used a prognostic and a predictive marker at least for grade III glioma (21-27). The present study shows that radiotherapy can be safely omitted from initial treatment, especially for anaplastic oligodendroglial tumors with 1p/19q deletion. This genetic abnormality can be used to stratify the treatment strategy for a 'minimally invasive therapy'. However, a large-scale prospective study is required to confirm the effectiveness of exclusive chemotherapy without radiotherapy in the treatment of anaplastic oligodendroglial tumors.

We have previously shown that low-grade oligodendrogliomas can be successfully treated with PAV chemotherapy alone without radiotherapy (9, 10). For anaplastic oligodendroglioma, two randomized phase III studies showed that early postoperative PCV chemotherapy improved PFS but did not affect OS (21,

22). In these studies, the absence of a benefit in OS is considered to be a result of the significant efficacy of PCV at the time of recurrence. Since oligodendroglial tumors are chemosensitive not only in low-grade but also in anaplastic subtypes, the histological discrimination of anaplastic oligodendrogliomas from other high-grade gliomas would be rather important. However, the agreement in this discrimination was only 50% among expert neuropathologists (24). 1p/19q deletion in combination with histological examination allows more reliable discrimination of anaplastic oligodendroglial tumors than does classical histology alone (25-27).

One of the reasons for the successful result of exclusive chemotherapy obtained in this study is the low rate of myelosuppression and the resultant high completion rate of PAV therapy. Since nitrosoureas usually cause severe myelosuppression lasting for a long period, we used it in a dose-down and cycle prolongation manner (9, 10). Other researchers also reported the need for modification in PCV therapy (28). However, the achieved cumulative dose-intensity in the present study was equivalent to the one achieved by the standard protocol of PCV. Because oligodendroglial tumors are usually much more indolent than high-grade astrocytomas such as glioblastoma, completion of the intended dose in a prolonged cycle period would be advantageous for effective control of tumor growth.

Patients with oligodendroglial tumors usually survive longer than those with other high-grade gliomas. The neurotoxic effects of radiotherapy, such as memory disturbance and cognitive dysfunctions, may frequently occur and spoil daily living, especially in long-term survivors (1). When radiotherapy is omitted from initial therapy, the risk of radiation-induced toxicity can be avoided at least until tumor recurrence. In the present study, a significantly larger proportion of the patients returned to their pre-disease level of social activity when treated with upfront chemotherapy, than those treated with the radiotherapy-included regimen. Obviously, such a performance status evaluation usually underestimates the pattern and severity of the cognitive impairments experienced by most patients with brain tumors. Severe decrements in memory and attention would exist beyond our estimation. Prospective neuropsychological assessments including cognitive functions should become an essential component of future clinical trials. However, preservation of the patients' daily activities at the pre-disease capacity is in our opinion more important in the treatment of gliomas instead of tumor disappearance or shrinkage at the cost of radiation-induced neurotoxicity.

The conclusions of this study are limited by the small sample size, the retrospective nature of the study design, and the short follow-up period. The clinically important information regarding therapeutic strategy for WHO grade III anaplastic oligodendroglial tumors obtained in the present study needs to be validated in a larger prospective trial with an independent cohort of patients.

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Received October 20, 2011
Revised November 17, 2011
Accepted November 18, 2011