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Clinical Article

Temozolomide Salvage Chemotherapy for Recurrent Anaplastic Oligodendroglioma and Oligo-Astrocytoma

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Objective : To evaluate the efficacy of temozolomide (TMZ) chemotherapy for recurrent anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA).

Methods : A multi-center retrospective trial enrolled seventy-two patients with histologically proven AO/AOA who underwent TMZ chemotherapy for their recurrent tumors from 2006 to 2010. TMZ was administered orally (150 to 200 mg/m^2/day) for 5 days per 28 days until unacceptable toxicity occurred or tumor progression was observed.

Results : TMZ chemotherapy cycles administered was median 5.3 (range, 1-41). The objective response rate was 24% including 8 cases (11%) of complete response and another 23 patients (32%) were remained as stable disease. Severe side effects (≥grade 3) occurred only in 9 patients (13%). Progression-free survival (PFS) of all patients was a median 8.0 months (95% confidence interval, 6.0-10.0). The time to recurrence of a year or after was a favorable prognostic factor for PFS (p<0.05). Overall survival (OS) was apparently differed by the patient's histology, as AOA patients survived a median OS of 18.0 months while AO patients did not reach median OS at median follow-up of 11.5 months (range 2.7-65 months). Good performance status of Eastern Cooperative Oncology Group 0 and 1 showed prolonged OS (p<0.01).

Conclusion : For recurrent AO/AOA after surgery followed by radiation therapy, TMZ could be recommended as a salvage therapy at the estimated efficacy equal to procarbazine, lomustine, and vincristine (PCV) chemotherapy at first relapse. For patients previously treated with PCV, TMZ is a favorable therapeutic option as 2nd line salvage chemotherapy with an acceptable toxicity rate.

Key Words : Anaplastic oligodendroglioma · Anaplastic oligoastrocytoma · Chemotherapy · Recurrence · Temozolomide.

INTRODUCTION

Anaplastic oligodendroglioma (AO) is a relatively rare tumor comprising 5-25% of malignant gliomas and having a variable clinical course[22,23]. Appearance of a mixed astrocytic component on pathological examination confers a histologic diagnosis of anaplastic oligo-astrocytoma (AOA) but these two tumors have similar molecular profiles and are frequently categorized together in clinical treatment settings[14,20,31].

Although recent clinical trial results found benefits from adjuvant procarbazine, lomustine, and vincristine (PCV) chemotherapy, standard therapy for newly diagnosed AO/AOA is still surgical resection with adjuvant radiation therapy, but recurrence is inevitable as with other malignant gliomas[5,7,26].

AO/AOA is expected to show a high response rate to chemotherapy among malignant gliomas, especially in subgroup with 1p-19q co-deletion. Reported results of PCV chemotherapy for newly diagnosed AO/AOA are fairly high, up to 75% although with significant occurrence of hematologic toxicity[5,6,19]. Thus, availability of salvage chemotherapy for recurrent AO/AOA has been limited by clinical parameters such as chemo-experience and old age, and reports of response rates are rare and vary by regimen in a range of 23-77%[1,3,4,9-11,28,32].

Among those experiences, temozolomide (TMZ) is high-

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lighted for salvage treatment as it possesses good bioavailability although orally administered, and low cumulative toxicity such as myelosuppresion[19]. For recurrent malignant gliomas, TMZ chemotherapy showed improved progression-free survival (PFS) in patients with recurrent glioblastoma compared to PCV and revealed significant objective response rate of 35% in recurrent anaplastic astrocytoma and AOA at an acceptable, low rate of adverse events[33,34].

However, a prospective clinical trial for evaluating the efficacy of TMZ salvage chemotherapy for this relatively rare AO/AOA has not been opened yet and several retrospective reports from single institutional experiences are not conclusive. Thus, our Korean Society for Neuro-Oncology (KSNO) group cooperated with Korean Health Insurance Review and Assessment (HIRA) to perform a multi-center, retrospective study to evaluate the efficacy and safety of TMZ salvage chemotherapy for recurrent AO/AOA.

MATERIALS AND METHODS

Eligibility criteria

Patients with histologically proven WHO grade 3 AO/AOA, who underwent TMZ chemotherapy for their recurrent tumors treated at the medical centers having Institutional Review Board qualified for multi-disciplinary study, had been asked for selective permission of HIRA for medical insurance coverage. The patients registered at HIRA database as who underwent TMZ salvage chemotherapy were considered to be enrolled in our study. Pathological diagnosis is confirmed by submission of the signed pathology report from each institution. After careful screening of case report form with pathology report of 95 patients from 19 medical centers, 23 patients who were lost without follow-up images after TMZ chemotherapy, or no evidence of recurrence between the initial treatment and TMZ chemotherapy, or whose recurrence was from WHO grade 2 tumors were eliminated from the study. All patients were screened to receive TMZ chemotherapy about the following criteria : 1) surgically proven histopathology for initial WHO grade 3 AO/AOA; 2) Eastern Cooperative Oncology Group (ECOG) performance status 3 or lower; 3) bone marrow function compatible to undergo chemotherapy on complete blood count (CBC) profile (hemoglobin over 10 g/dL, leukocyte over 4000/μL, platelet over 100000/μL); 4) normal hepatic and renal function.

Temozolomide chemotherapy protocol

TMZ was administered at 150 mg/m^2/day for 5 days every 28 days for the first cycle, with doses increased to 200 mg/m^2/day for 5 days every 28 days for subsequent cycles if no grade 3/4 toxicity was observed. Corticosteroids were not limited and administered at a dose determined by attending physician. Patients were allowed to continue on this regimen until unacceptable toxicity or clinical/radiological disease progression. CBC and liver function test was done in the end of every cycle to monitor the toxicities. All the toxicities relevant to TMZ chemotherapy were recorded and evaluated in reference to Common Terminology Criteria for Adverse Effect (CTCAE, version 3.0). For patients who experienced equal or more than grade 2 toxicities at the 1st cycle, the dose was not elevated to the next level (i.e., 200 mg/m^2/day). We did not reduce or modify the TMZ dose except the above grading and delayed the next cycle until patient completely recovered from the toxicities.

Response and evaluation

The tumor response was evaluated by MRI taken at 3 or 6 months after completion of 3 or 6 cycles of chemotherapy and at the time of suspicion of progression as compared to the baseline MRI, which was taken at the time of recurrence. Macdonald et al.[15] for malignant glioma was adopted as the product of the maximal cross-sectional enhancing diameters are used to access tumor response. The PFS was defined as the time when the patients showed clinical deterioration with the evidence of radiological recurrence.

Statistical methods

The primary end point was the PFS, obtained by the Kaplan-Meier method (SPSS software version 12.0, SPSS Inc., Chicago, IL, USA). We also calculated the radiological response rate and OS as the secondary end point. For the analysis of factors affecting the PFS and OS, the Cox proportional hazard model was used to estimate the hazard ratio and corresponding 95% confidence interval (CI) on univariable analysis. Multivariable analysis included all the variables considered in the univariable analysis, and forward variable selection with selection criteria of 0.05 was performed to determine the final model. Various factors related to radiological response were also verified by using Student's t-test and chi-square or Fisher's exact test as appropriate.

RESULTS

Patient characteristics

Seventy-two patients from 19 medical centers, who had histologically proven AO/AOA and underwent salvage TMZ chemotherapy for their recurrent tumors between June 2006 and April 2010, were collected for retrospective analysis. The clinical characteristics of the patients are summarized in Table 1. Their mean age was 47.8 years (range, 11-76). The number of male patients was 40 and the female was 32. Most patients (86%) were ambulatory and capable of self-care and had ECOG performance score of 2 or less (29% with ECOG 0, 44% with ECOG 1 and 13% with ECOG 2). Only 10 patients (14%) had ECOG scores of 3. In fifty seven patients, AO/AOA was an initial diagnosis of their tumor (*de novo*). At the time of diagnosis of WHO grade 3, 15 patients (21%) had a previous history WHO grade 2 gliomas. Median time to recurrence from the initial diagnosis of AO/AOA was 9.0 months (range, 1-123). Forty patients (56%) had received surgical resection followed by radiation therapy,

then chemotherapy with either PCV (70%) or other chemotherapy (TMZ in 5 patients, avastin-irinotecan in 4 patients, ACNU-CDDP in 2 patents, and BCNU-CDDP in one patient). Three patients, for whom conventional radiation therapy was performed at the time of low-grade diagnosis, underwent debulking surgery and received PCV chemotherapy only without radiation therapy. These forty-three patients were defined to chemo-experienced group.

Other 26 patients received surgical resection and conventional radiation therapy without adjuvant chemotherapy. Another three patients receiving debulking surgery underwent stereotactic radiosurgery for their residual tumors. These 29 patients (40%) were chemo-naive before the enrollment to TMZ chemotherapy.

Response to temozolomide

A median of TMZ chemotherapy cycles administered was 5.3 (range, 1-41) and all the patients were evaluated to TMZ response as we excluded the patients without follow-up MR image (Table 2). There were 8 patients (11%) who achieved complete response and 9 patients (13%) who achieved partial response. Thus, objective response rate of TMZ salvage chemotherapy was 24%. Another 23 patients (32%) remained in the range of stable disease and the tumors progressed in 32 patients (44%). Thus, tumor stabilization rate was 56% in the patients. The response rates according to the histologic subtype were summarized in Table 2. The different histology of AO vs. AOA failed to show statistically significant difference in response rate although the response rate of 28% in AO patients was apparently higher than that of 14% in AOA patients. Gender, origin of tumor (*de novo* vs. secondary), previous chemotherapy experience, and other demographic variables categorized (i.e., age of <40 vs. ≥40, ECOG of 0-1 vs. 2-3, and time to recurrence after the initial treatment for AO/AOA of <1 year vs. ≥1 year) were evaluated for effect on the response rate. Among tested variables, the origin of tumor (*de novo* vs. secondary) was statistically significant as the secondary tumors showed a 53% response rate compared to the de novo tumors at 16% (p<0.01).

Toxicities

All toxicities recorded were graded according to the CTCAE version 3.0 and listed in Table 3. Hematologic side effects were observed in 16 patents (22%) but severe side effects (grade 3 or 4) that caused delay of the next cycle occurred only in 6 patients (8%). Nausea and vomiting were recorded in 5 patients (7%) and one grade 4 nausea patient dropped out after one cycle by his wishes. Hepatotoxicity was only AST/ALT elevation (CTCAE grade 1 or 2) without other hepatobiliary symptoms in five patients but a grade 3 elevation up to 200/713 IU/L in one patient. All these abnormalities of hepatic enzymes returned to normal after either delay or termination of the TMZ therapy.

Progression-free survival and overall survival

Over the median image follow-up of 6.0 months (1 to 36

Table 1. Clinical characteristics of patients

Characteristics	n
Histology (%)	
AO	51 (71)
AOA	21 (29)
Mean age (range)	47.8 (11-76)
Gender (%)	
Male	40 (56)
Female	32 (44)
ECOG scale (%)	
0	21 (29)
1	32 (44)
2	9 (13)
3	10 (14)
Origin (%)	
De novo	57 (79)
Secondary	15 (21)
Median time to recurrence (range)	9.0 months (1-123)
Previous treatment (%)	
Surgery+SRS	3 (4)
Surgery+chemotherapy	3 (4)
Surgery+radiation	26 (36)
Surgery+radiation+chemotherapy	40 (56)
Median cycles of TMZ administered	5.3 (1-41)

AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma, SRS : stereotactic radiosurgery, TMZ : temozolomide, ECOG : Eastern Cooperative Oncology Group

Table 2. Response rate in patients with recurrent AO or AOA after salvage TMZ chemotherapy

Response	AO (n=51)	AOA (n=21)	Total (n=72)
Complete response	7 (14%)	1 (4.8%)	8 (11%)
Partial response	7 (14%)	2 (9.5%)	9 (13%)
Stable disease	17 (33%)	6 (29%)	23 (32%)
Progressive disease	20 (39%)	12 (57%)	32 (44%)

AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma

Table 3. Toxicities in patients with recurrent AO or AOA after salvage TMZ chemotherapy

Side effects	AO (n=51)	AOA (n=21)	Total (n=73)
Hematologic			
Grade 1 or 2	7	3	10 (14%)
Grade 3 or 4	6	-	6 (8%)
Nausea/vomiting			
Grade 1 or 2	2	1	3 (4%)
Grade 3 or 4*	2		2 (3%)
Hepatotoxicity			
Grade 1 or 2	4	1	5 (7%)
Grade 3 or 4	-	1	1 (1%)

*One grade 4 nausea lead to discontinuation. AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma, TMZ : temozolomide

months), 49 patients showed progression. PFS of all patients was a median 8.0 months (95% CI, 6.0-10.0). Actuarial 6 months PFS rate was 52% and 1-year PFS 27%. Various clinical factors were evaluated to see if they can affect PFS (Table 4). By histology, AO patients showed a median PFS of 8.0 months while AOA patients had a median PFS of 10.0 months but this apparent difference did not reach the statistical significance (Fig. 1A). Among tested clinical factors, only the time to recurrence had significant influence on PFS as the patients recurred within a year showed a median PFS of 5.0 months, which was significantly shorter than that of 11. 0 months in patients recurred at one year or after (p=0.04) (Fig. 1B) in univarable analysis but became insignificant in multivariable analysis (p=0.07).

Patients were followed for a median of 11.5 months (range, 2-66). As only 20 out of 72 patients died during the observation period, a median overall survival was not reached. The estimated 1-year survival rate was 81% and 2-year 63%. Clinical factors were also tested to see if they significantly affect the OS (Table 5). AOA patients had a median OS of 18.0 months and 1-year OS rate of 76% while AO patients did not reach median OS and 1-year OS rate was 83% but this apparent difference did not show statistical significance (Fig. 2A). Among various clinical factors, ECOG status of completely ambulatory or better (0 and 1) significantly prolonged patients survival in both univariate and multivariate analysis (p=0.004 and 0.006, respectively) (Fig. 2B). 'Time-to-recurrence after the initial treatment for AO/AOA' less than a year showed a tendency of negative influence on patients survival in univariate analysis (p=0.058) but failed to show statistical significance in multivariate analysis (p=0.079).

DISCUSSION

Treatment options for recurrent AO/AOA

Early studies of PCV chemotherapy for newly diagnosed or recurrent AO/AOA showed favorable response rate[4,6,16,18]. Based on those results, two phase 3 clinical trials (RTOG 9402 and EORTC 26951) of PCV adjuvant chemotherapy to surgery with radiation were launched[5,27]. Up-to-date reports of long-term follow up from both studies prove long-term OS benefit and increased long-term survival[7,26]. Thus, it can be expected for PCV chemotherapy to be adopted as one arm of standard therapy for AO/AOA. Hence, we need an effective salvage therapy for recurrent AO/AOA other than PCV chemotherapy[21,24,29]. However, to date, non-alkylating chemotherapy tried for chemo-experienced AO/AOA is not satisfactory. Chamberlain and Johnston[9], analyzed data of bevacizumab for recurrent alkylator-refractory 1p19q co-deleted AO patients. Similar to other bevacizumab-based trials, initial response rate was fairly high (68%) but a me-

Table 4. Cox-proportional hazard model analysis of factors affecting patient's progression-free survival after TMZ salvage chemotherapy

Factors	Univariable analysis			Multivariable analysis		
	p value	Hazard ratio	95% CI	p value	Hazard ratio	95% CI
Histopathology (AO vs. AOA)	0.52	1.23	0.65-2.33	0.35	1.38	0.70-2.71
Age (<40 vs. ≥40)	0.16	1.56	0.84-2.91	0.56	1.23	0.61-2.49
Gender (male vs. female)	0.27	1.37	0.78-2.41	0.17	1.49	0.84-2.66
ECOG (0-1 vs. 2-3)	0.97	1.01	0.52-1.99	0.88	1.06	0.52-2.13
Origin (*de novo* vs. secondary)	0.44	0.77	0.40-1.48	0.37	0.72	0.35-1.48
Time to recur (<1 year vs. ≥1 year)	0.04	0.53	0.29-0.99	0.07	0.52	0.26-1.05
Previous chemotherapy (naïve vs. experienced)	0.93	1.03	0.57-1.84	0.62	1.18	0.61-2.24

CI : confidence interval, ECOG : Eastern Cooperative Oncology Group, TMZ : temozolomide, AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma

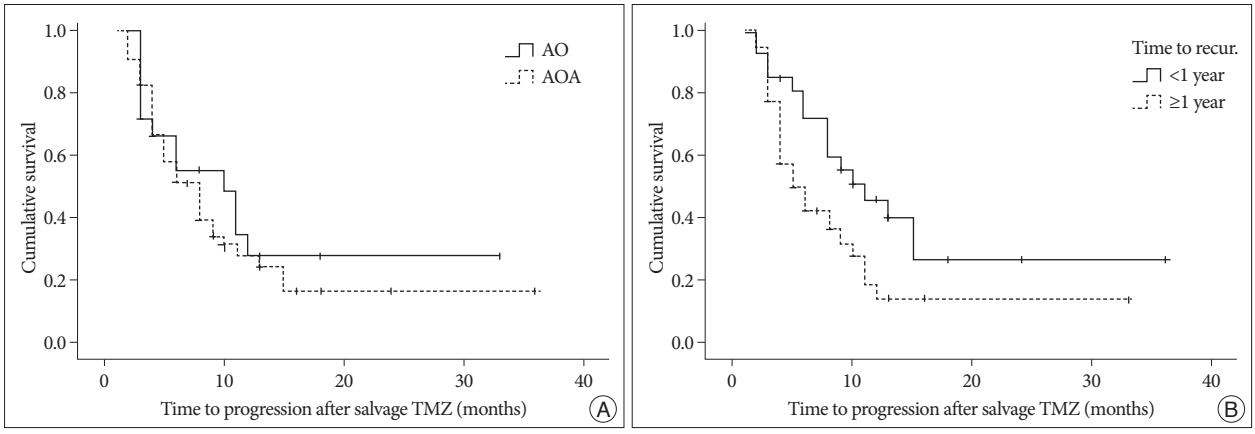

Fig. 1. Kaplan-Meier progression-free survival in patients with recurrent AO or AOA after salvage TMZ chemotherapy (A) according to histopathology (AO vs. SOA, p>0.05) and (B) time to recurrence after the initial treatment for AO/AOA (<1 year vs. ≥1 year, p=0.04). AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma, TMZ : temozolomide.

Table 5. Cox-proportional hazard model analysis of factors affecting patient's overall survival after TMZ salvage chemotherapy

Factors	Univariable analysis			Multivariable analysis		
	p value	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI
Histopathology (AO vs. AOA)	0.24	1.70	0.69-4.18	0.64	1.26	0.48-3.31
Age (<40 vs. ≥40)	0.75	0.85	0.31-2.34	0.84	0.89	0.27-2.88
Gender (male vs. female)	0.87	1.08	0.45-2.60	0.99	1.00	0.38-2.61
ECOG (0-1 vs. 2-3)	0.007	3.34	1.38-8.06	0.006	3.73	1.47-9.49
Origin (*de novo* vs. secondary)	0.41	1.86	0.43-8.09	0.34	2.14	0.45-10.24
Time to recur (<1 year vs. ≥1 year)	0.068	0.38	0.13-1.07	0.079	0.36	0.11-1.12
Previous chemotherapy (naive vs. experienced)	0.34	1.54	0.63-3.74	0.18	1.98	0.73-5.42

TMZ : temozolomide, CI : confidence interval, AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma, ECOG : Eastern Cooperative Oncology Group

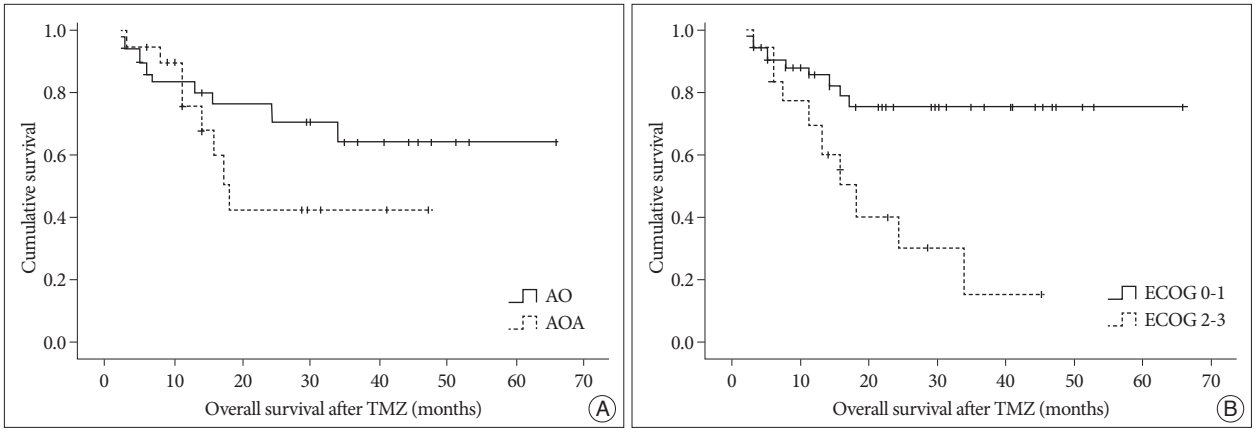

Fig. 2. Kaplan-Meier overall survival in patients with recurrent AO or AOA after salvage TMZ chemotherapy (A) according to histopathology (AO vs. AOA, $p>0.05$) and (B) ECOG performance status (0-1 vs. 2-3, $p=0.007$). AO : anaplastic oligodendroglioma, AOA : anaplastic oligo-astrocytoma, TMZ : temozolomide.

dian PFS was only 6.8 months. The efficacy of irinotecan (CPT-11) for recurrent chemo-experienced (TMZ or BCNU) AO patients was evaluated in phase 2 prospective trial, but only modest effect was observed (28% of response rate, and median PFS of 4.5 months)[8].

Safety of TMZ in AO/AOA

The virtues of TMZ for the treatment of malignant gliomas are good bioavailability in spite of per os administration, fairly high CNS penetration and most of all, good tolerance with a low rate of serious adverse events (SAE)[14]. Although TMZ itself is an alkylator carrying a high risk of cumulative hematotoxicity, the reported rate of SAE is fairly acceptable even in a salvage treatment setting[1,2,10,12,17,25,34]. In our study, only one patient discontinued due to grade 4 nausea/vomiting and 6 patients (8%) delayed the next cycle for leucopenia/thrombocytopenia. Reported SAE rate of TMZ ranged 6-31% according to dose schedule or demographic factors[1,2,12,13,17,25]. Against the prejudication of more SAE in chemo-experienced patients than chemo-naïve patients, TMZ seemed to provoke equal or paradoxically less hematotoxicity in chemo-experienced settings compared with chemo-naïve one. Chinot et al.[10] used the standard 5 days per 28 days schedule for recurrent PCV-experienced AO/AOA, but dose modification scheme down to 50% were applied. They reported 6.4% of grade 3 or 4 thrombocytopenia and dose-reduction was required only in 1.2% of total cycles. Two studies treated chemo-naïve recurrent oligodendrial tumors with TMZ with standard 5 days schedule[3,30]. van den Bent et al.[28,30] observed grade 3/4 hematotoxicity in 10 out of 38 patients (26%) and dose reduced and delayed in 11% and 15% of patients with oligodendroglioma or oligoastrocytoma, respectively. Brandes et al.[3] reported the occurrence of grade 3/4 hematotoxicity in 13% of patients with AO/AOA and needed dose reduction and delays in 15% and 22% of patients, respectively. Although patients number was small (n=29), Yang et al.[32] observed no significant toxicity with TMZ in Korean patients with malignant gliomas. However, these occurrences of SAE from TMZ should be presented with MGMT methylation status and need to be re-evaluated in future prospective study[13].

Response rate of TMZ in AO/AOA

The response rate of TMZ as 1st line salvage for (chemo-naïve) recurrent oligodendrial tumors was fairly high and similar to that of up-front or adjuvant TMZ therapy ranging 53-75%[13,17,25]. A prospective, phase 2 trial by van den Bent et al.[30] revealed response rate of 53% including a half of CR among responders in patients with recurrent oligodendroglioma or oligoastrocytoma. Brandes et al.[3] reported an overall response rate of 46% in-

cluding a higher response in AO histology than AOA (62% vs. 25%), and in 1p/19q loss (59% vs. 34%). In our study, secondary AO/AOA showed a higher response rate than *de novo* AO/AOA (53% vs. 16%, $p<0.01$). But histologic type (AO vs. AOA) showed no difference of radiological response. We have a provision of gathering molecular profiles including 1p/19 co-deletion and MGMT methylation status of these 'clinically validated' 72 recurrent AO/AOA patients as a second-term plan of the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family Affairs, Republic of Korea.

The response rate of PCV as 1st line salvage chemotherapy for recurrent AO/AOA was 59% and the result was comparable to TMZ salvage therapy but incurred a high risk of persistent toxicity[4]. Although grade 3/4 hematotoxicity occurred only in 6.9% of total cycles given, sixteen of their 37 patients discontinued chemotherapy due to incomplete recovery within 2 weeks of treatment delay at a mean 3.5 cycles per patient.

Reports evaluating the efficacy of 2nd line TMZ salvage chemotherapy for AO/AOA are rare, but only one study is available. Chinot et al.[10] reported an objective response rate of 43.8% and median PFS of 6.7 months. The PFS was relatively short compared to the high response rate, but their response measurement was not a Mcdonald criteria but a volumetric analysis. In our study, chemo-naive patients showed apparently higher response rate (8 of 29 patients, 28%) than chemo-experienced patients (9 of 43 patients, 21%), but the difference failed to reach statistical significance.

Based on these relatively high response rate with acceptable low incidence of SAE, TMZ has been adopted as up-front chemotherapy or adjuvant chemotherapy in AO/AOA and reported fairly good clinical results[12,13,17,18,25]. And also, our study group (KSNO) launched TMZ concomitant chemo-radiation in AO/AOA patients without 1p19q co-deletion in 2012 (KNOG-1201). However, introducing TMZ as CCRT and/or adjuvant setting in newly diagnosed AO/AOA has not been accepted as a standard therapy, yet.

CONCLUSION

Although the response rate of 24% in our study is apparently lower than those from other studies of TMZ salvage therapy, both PFS and OS of our study are comparable with other TMZ salvage therapy and seem better than those studies using non-alkylating agents at a low rate of SAE. Thus, we recommend standard 5 days TMZ chemotherapy for recurrent AO/AOA at an equally expected efficacy to PCV chemotherapy as 1st line salvage therapy. For PCV experienced patients or patients at a risk of prolonged hematotoxicity, we expect TMZ salvage would be a choice with expectation of superior tolerability than other chemotherapy.

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