Neuro-Oncology Advances

8(1), vdag025, 2026 | https://doi.org/10.1093/noajnl/vdag025 | Advance Access publication February 12, 2026

Long-term outcome of nimustine-based chemotherapy for oligodendroglioma

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Abstract

Background. Combination chemotherapy of procarbazine, lomustine (CCNU), and vincristine (PCV), a standard treatment for oligodendroglioma, is associated with frequent adverse events. In Japan, only nimustine (ACNU), an analog of CCNU, is approved. This study aimed to evaluate the long-term outcomes of ACNU-based chemotherapy after maximal safe resection with deferred radiation therapy (RT) for oligodendrogliomas.

Methods. This retrospective study included 50 patients diagnosed with IDH-mutant 1p/19q-codeleted oligodendroglioma of grades 2 (n = 27) or 3 (n = 23) between 2002 and 2022. Progression-free survival (PFS), overall survival (OS), and time to decline in performance status (deterioration-free survival [DFS]) were analyzed using the Kaplan-Meier method.

Results. Postoperative chemotherapy was administered to 94% of patients (procarbazine, ACNU, and vincristine [PAV], n = 24; ACNU, n = 22; temozolomide [TMZ], n = 1; excluded). Median follow-ups were 142.9 and 50.6 months for PAV and ACNU groups, respectively. Ten-year PFS rates were 54.2% and 30.0% for grades 2 and 3 tumors, respectively ($P = .0870$), and 10-year OS rates were 91.5% and 78.8% for grades 2 and 3, respectively ($P = .5098$), with comparable DFS ($P = .6922$). Comparing regimens, the 10-year OS rate was 82.3% for PAV, while all patients in the ACNU group remained alive. Five-year PFS were almost identical: 58.9% (PAV) versus 56.8% (ACNU), $P = .9996$. Treatment completion rates were 75% and 91% for PAV and ACNU, respectively.

Conclusions. ACNU monotherapy has a similar efficacy to PAV and tolerability to TMZ, suggesting that it is the most favorable chemotherapeutic option currently available in Japan, considering its risk-benefit profile.

Key Points

- Long-term outcomes of ACNU-based chemotherapy for oligodendrogliomas were evaluated.
- The 10-year OS rates were 91.5% and 78.5% for grades 2 and 3, respectively.
- ACNU monotherapy showed a similar efficacy to PAV and tolerability to TMZ.

Oligodendrogliomas have a relatively favorable prognosis, as their postoperative treatment has higher efficacy, compared with other adult diffuse gliomas. Since the 1990s, clinical trials have evaluated the efficacy of chemotherapy, and in the 2010s, phase 3 clinical trials RTOG 9402 and EORTC 26951 demonstrated for the first time that combination chemotherapy of procarbazine, lomustine (CCNU), and vincristine (PCV) improved long-term survival in anaplastic oligodendrogliomas.[1,2] Subsequently, RTOG 9802 revealed that PCV has also been shown to be effective for grade 2 tumors[3]; however, PCV itself has not been established as a standard treatment in clinical practice because of the complexity of the regimen and adverse events. The PCV regimen primarily consists of alkylating agents, with CCNU as the key agent. The CCNU has several analog

Received July 2, 2025; accepted January 30, 2026.

Importance of the Study

This retrospective study assessed long-term outcomes of ACNU-based chemotherapy following maximal safe resection with deferred radiation therapy in 50 patients diagnosed with IDH-mutant, 1p/19q-codeleted oligodendrogliomas (grades 2 or 3) between 2002 and 2022. The 10-year overall survival (OS) rates were 91.5% for grade 2 and 78.8% for grade 3, demonstrating that the chemotherapy-first approach yields survival outcomes comparable with or better than phase 3 trials of PCV with radiotherapy. Notably, complete remission was observed in some cases where residual tumors disappeared after chemotherapy. About half of the cohort remained recurrence-free beyond 10 years. During the study, the treatment protocol was shifted from PAV (procarbazine, ACNU, vincristine) to ACNU monotherapy. The switch maintained stable outcomes while improving treatment tolerability, with completion rates of 75% for PAV and 91% for ACNU. These findings suggest that ACNU monotherapy provides similar efficacy to PAV and tolerability comparable with temozolomide (TMZ), supporting its use in long-term management of oligodendroglioma.

formulations, including carmustine (BCNU), which is commercially sold as Gliadel wafers.[4] In Japan, because CCNU has not yet been approved, its analog nimustine (ACNU) has been utilized for a long time. The ACNU is a nitrosourea compound developed in Japan. Compared with other alkylating agents, it features both lipophilicity and superior hydrophilicity, making it suitable for intravenous administration. Furthermore, its lipophilicity ensures effective passage through the blood-brain barrier in vivo.[5] Based on RCTs in the 1980s showing that radiation therapy plus ACNU yielded better outcomes for malignant gliomas than radiation therapy alone, it was positioned as the standard treatment drug in Japan untilTMZ was approved.[6] A meta-analysis comparing the efficacy of ACNU with BCNU and CCNU also reported the noninferiority of ACNU.[7] Even after the 2010s, when the efficacy of PCV for oligodendroglioma had been established, CCNU remained unapproved in Japan, and ACNU continued to be used as an alternative. We have been using combination chemotherapy of procarbazine, ACNU, and vincristine (PAV), as an alternative to PCV therapy in patients with lower-grade gliomas. Due to these circumstances, PCV + RT—which should be positioned as the standard treatment—is practically impossible to implement, resulting in ambiguous treatment guidelines in Japan. Consequently, the current situation where actual clinical practice in Japan deviates from the global consensus remains an unsolved issue.

After favorable results for PCV/RT over RT alone were confirmed in 2013, the superiority of PCV + RT over PCV is currently being evaluated in the POLCA trial.[8] However, results have not yet been reported, leaving the matter undetermined. Since the 2000s, large retrospective studies have accumulated reports showing that the proportions of chemotherapy alone versus chemoradiation for anaplastic oligodendroglioma in general clinical practice have been nearly equal, or that outcomes with chemotherapy alone have been favorable.[9,10] In our previous study, the early treatment outcomes of a chemotherapy-first approach with PAV showed that the 75% OS was 133.5 months for both grade 2 and 3 tumors. These outcomes were comparable with those of PCV with radiotherapy (PCV/RT) in studies such as RTOG 9402, EORTC 26951, and RTOG 9802;[1–3] however, the relatively short observation period and low completion rates of the full regimen due to toxicity remain problematic.[11] The widespread adoption ofTMZ for malignant gliomas during this period, due to its mild adverse events, also fostered a trend of avoiding PCV regimens because of their toxicity. This trend led to a global movement exploring the efficacy of regimens with lower toxicity than PCV, such as those using fewer drugs.[12,13] Subsequently, we switched to ACNU monotherapy and accumulated the long-term treatment outcomes. In this study, we conducted a retrospective analysis to evaluate the effects of our treatment strategy over the past 20 years.

Methods

Patients

We extracted information on 67 patients who were newly diagnosed with oligodendroglioma from our database between 2002 and 2022. Of these, 17 patients who did not meet the molecular diagnostic criteria (IDH wild type: n = 8, IDH mutant without 1p19q co-deletion: n = 9) were excluded, leaving 50 eligible patients. The molecular diagnosis of these patients was confirmed using frozen tissue samples obtained during surgery. DNA extraction and genetic analysis were performed as previously described.[14] All tumors were diagnosed according to the 5th edition of the WHO classification of central nervous system tumors, revised in 2021. In this study cohort, 26 and 24 cases of grade 2 and grade 3 tumors, respectively, were identified. This study was conducted with the approval of Kyushu University Clinical Research Ethics Review Committee (approval number: 848-01) and was in accordance with the 1964 Declaration of Helsinki (revised in Fortaleza, Brazil in October 2013).

PAV Regimen

All patients received PAV therapy until 2015. The PAV therapy regimen was as follows: ACNU, 75 mg/body; procarbazine, 100 mg/body/day administered on days 8-21; and vincristine, 2.0 mg/body administered on days 8 and 29 in a 6-week cycle (The ACNU dose being/body is not an error. While it should be the/m^2 dosage, this setting was established at our facility in the 1990s, and its origin is unknown). A maximum of 6 cycles were administered, but the dosing interval was

adjusted at the discretion of the physician based on side effects.

ACNU-Alone Regimen

In 2016, the chemotherapy regimen changed from PAV to ACNU monotherapy. The ACNU was administered in cycles of 80 mg/m^2 every 8 weeks. The standard treatment consisted of 6 cycles, but up to 12 cycles were permitted if tolerated. Three cases with grade 2 tumors undergoing gross total removal entered follow-up after only 3 cycles. The actual number of cycles administered were as follows: 2 cycles in 1 case (discontinued due to myelosuppression), 3 cycles in 3 cases, 5 cycles in 1 case (discontinued due to delusions), 6 cycles in 14 cases, 8 cycles in 2 cases, and 12 cycles in 1 case.

Statistical Analyses

The purpose of this study was to evaluate overall survival (OS), progression-free survival (PFS), and deterioration-free survival (DFS) on a monthly basis in accordance with the methods of previous studies[11] and to set the date of the last follow-up for survivors as the censoring date. As previously described, "progression" was defined according to the RANO criteria,[15] and "deterioration" was defined as a decrease of 10 or more points in the Karnofsky performance score associated with disease progression or treatment-related events, including neurocognitive dysfunction, radiation necrosis, or severe polyneuropathy related to vincristine. Kaplan-Meier analysis was used to evaluate OS, PFS, and DFS, and log-rank tests were used to compare survival distributions. Clinical and molecular characteristics were evaluated using the χ^2 test, Mann-Whitney *U* test, and Fisher exact test. All *P* values were 2-sided, and a 0.05 level was considered statistically significant. Statistical analyses were performed using JMP Pro v. 18.1.1 (SAS Institute Inc, NC).

Results

Patient Characteristics and Treatments

Of the 50 patients enrolled in this study, chemotherapy was administered to 47 (94%), with PAV administered to 24 patients; ACNU to 22 patients; and TMZ to 1 patient, who was excluded. Of the 46 patients, 24 were diagnosed with grade 2 tumor, of whom 13 were treated with PAV and 11 with ACNU, and 22 were diagnosed with grade 3, of whom 11 were treated with PAV and 11 with ACNU. There was no difference regarding the administration of different chemotherapy regimens between patients with grades 2 and 3 tumors (P=1.0000). The median age of patients was 47 years and 23 (50%) were women. Surgical resection included gross total resection in 19 (41.3%) patients, subtotal resection (with a resection rate of 90% or more) in 10 (21.7%), and partial removal in 14 (30.4%), and 3 (6.5%) patients underwent biopsy. We compared clinical factors after stratifying the cohort by tumor grades and treatment regimens. Significant differences in tumor size (P=0.0185) and contrast enhancement (P=0.0097) were observed between tumor grades; however, no other differences were observed between grades (Table 1). There was no significant difference in the analysis by treatment groups (Table 2).

Survival Analyses

The median follow-up period after surgery was 64.3 months for grade 2 and 78.3 months for grade 3 tumors. A total of 19 patients (41.3%) experienced recurrence, of whom 7 died (15.2%). Of the 19 patients with recurrence, surgical resection was performed in 12. After the surgeries, 8 patients underwent concurrent TMZ and RT (TMZ/RT), and chemotherapy alone was administered to 3 patients (TMZ, n=1; ACNU, n=2). Of the 7 patients who did not undergo surgical removal of recurrent lesions, 2 underwent TMZ/RT, and chemotherapy alone was administered to 4 patients (bevacizumab, n=1; ACNU, n=3). In summary, the secondary treatments for the 19 patients with recurrence were surgical removal (n=12) and chemotherapy, including ACNU (n=5), bevacizumab (n=1), TMZ (n=1), and TMZ/RT (n=10). The 10-year PFS rate in the entire cohort was 57.4% for grade 2 and 30.0% for grade 3; however, the difference did not exceed the significance level (P=.0870, Figure 1). In contrast, the 10-year OS rates were favorable, with 91.5% for grade 2 and 78.8% for grade 3, and no significant differences were observed between grades (P=.4591, Figure 1).

Table 1. Clinical and molecular features (n=46)

Variable assessed	All (n=46)	Grade 2 (n=24)	Grade 3 (n=22)	P value
Age (years), median (range)	47 (20–78)	45 (20–66)	48 (27–78)	0.6030
≤ 40 (%)	15 (32.6)	7 (29.2)	8 (36.4)	
≥40 (%)	31 (67.4)	17 (70.8)	14 (63.6)	
Male sex (%)	23 (50.0)	13 (54.2)	10 (45.5)	0.7683
Tumor size (mm) median (range)	50 (26–100)	45 (26–75)	56 (31–100)	0.0185
Contrast enhanced lesion (%)	24 (52.2)	8 (33.3)	16 (72.7)	0.0097
KPS median (range)	90 (60–100)	100 (80–100)	90 (60–100)	0.3364
>80 (%)	42 (91.3)	23 (95.8)	19 (86.4)	
≤80 (%)	4 (8.7)	1 (4.2)	3 (13.6)	
Resection rate				0.5520
GTR or STR (%)	29 (63.0)	14 (58.3)	15 (68.2)	
PR or biopsy (%)	17 (37.0)	10 (41.7)	7 (31.8)	
Chemotherapy				1.0000
PAV (%)	24 (52.2)	13 (54.2)	11 (50.0)	
ACNU alone (%)	22 (47.8)	11 (45.8)	11 (50.0)	

Abbreviations: ACNU, nimustine; GTR, gross total resection; KPS, Karnofsky performance score; PAV, procarbazine, ACNU, and vincristine; STR, subtotal resection.

The 10-year DFS rates were also favorable when compared with PFS rates, with 72.3% and 69.1% DFS rates for grade 2 and grade 3 tumors, respectively, and no significant differences were observed between grades (P=.6560, Figure 1).

Table 2. Clinical and molecular background of the PAV and ACNU alone groups

Variable assessed	PAV (n=24)	ACNU alone (n=22)	P value
Age (years), median (range)	45 (20–73)	47 (35–78)	0.4598
≤40 (%)	9 (37.5)	6 (27.3)	
≥40 (%)	15 (62.5)	16 (72.7)	
Male sex (%)	11 (45.8)	12 (54.5)	0.7683
Tumor size (mm), median (range)	55 (28–92)	46 (26–100)	0.3220
Contrast enhanced lesion (%)	15 (62.5)	9 (40.9)	0.2371
KPS median (range)	90 (70–100)	90 (60–100)	1.0000
>80 (%)	22 (91.7)	20 (90.9)	
≤80 (%)	2 (8.3)	2 (9.1)	
EOR			0.2329
>90% (%)	13 (54.2)	16 (72.7)	
≤90% (%)	11 (45.8)	6 (27.3)	
WHO grade 2	13 (54.2)	11 (50)	1.0000
WHO grade 3	11 (45.8)	11 (50)	
Chemotherapy completion (%)	18 (75.0)	20 (90.9)	0.2470

Abbreviations: ACNU, nimustine; EOR, extent of resection; KPS, Karnofsky performance score; PAV, procarbazine, ACNU, and vincristine.

The 5-year PFS rates when compared according to treatment regimens were almost identical: 58.9% in the PAV group and 56.8% in the ACNU group (P=.9996; Figure 2). While the 10-year OS rate was 82.3% in the PAV group, all patients in the ACNU group were alive (P=.1866; Figure 2). The 5-year DFS rates were also similar, at 91.5% in the PAV group and 94.4% in the ACNU group (P=.8486, Figure 2). Treatment completion rates were 75.0% and 90.9% for PAV and ACNU treatments, respectively (P=.1550). The adverse events that led to treatment discontinuation are summarized in Table S1.

As an illustrative case, treatment was switched to ACNU monotherapy in a patient due to adverse events after 2 courses of PAV therapy. Complete remission of the lesion was achieved after the switch (Figure 3). In this study, this case was considered a nontreatment completion case in the PAV group. Additionally, in the ACNU group, we experienced a case where FLAIR high-intensity areas appeared at the resection site after treatment initiation, raising the suspicion of recurrence. However, the subsequent course showed a necrotic lesion radiographically, leading to the conclusion of pseudoprogression (Figure 4). This case was considered to have no recurrence at the time of analysis.

Discussion

In our cohort spanning over 20 years, the 10-year OS rates were 91.5% and 78.8% for grades 2 and 3, respectively. In the latest large-scale report, the French national prospective cohort *Prise en charge des OLigodendrogliomes Anaplasiques* (POLA), which aims to continuously collect real clinical data, showed a 10-year OS rate of 72% for grade 3 following PCV/RT treatment.[16] Also, joint final report of RTOG9402 and EORTC 26951 showed 10-year OS rates of

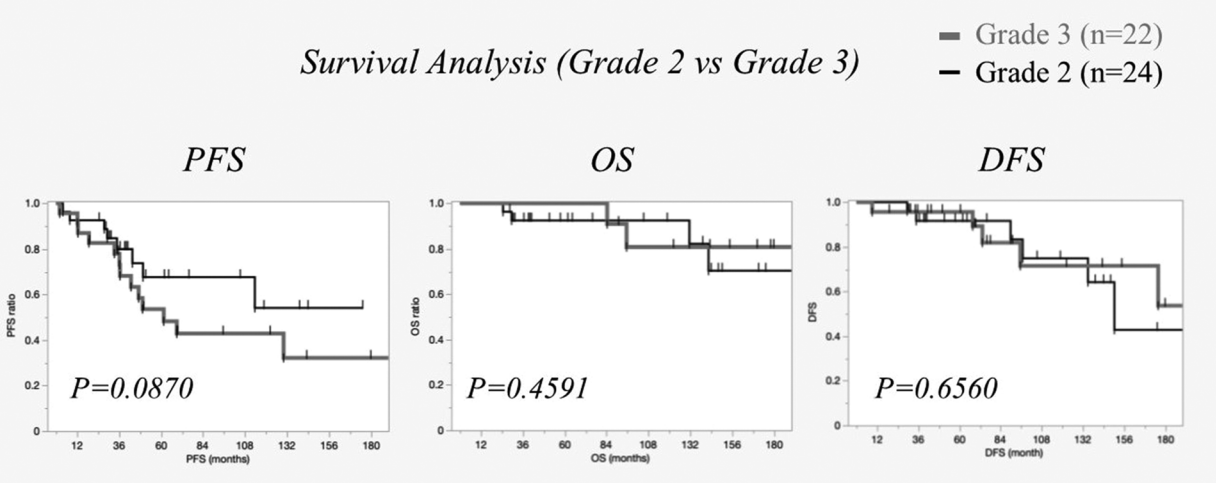

Figure 1. Kaplan-Meier analyses for PFS, OS, and DFS of the 46 patients diagnosed according to WHO classification. Red and blue lines indicate the survival curves of grade 2 (n=24) and 3 (n=22) oligodendrogliomas are indicated with black and gray lines, respectively. PFA (left) was shown to be unfavorable in patients with grade 3 tumors compared to patients with grade 2 tumors; however, the difference was not significant. Favorable OS (center) and DFS (right) in patients with grade 3 as well as grade 2 tumors were observed. Abbreviations: DFS, deterioration-free survival; OS, overall survival; PFA, progression-free survival.

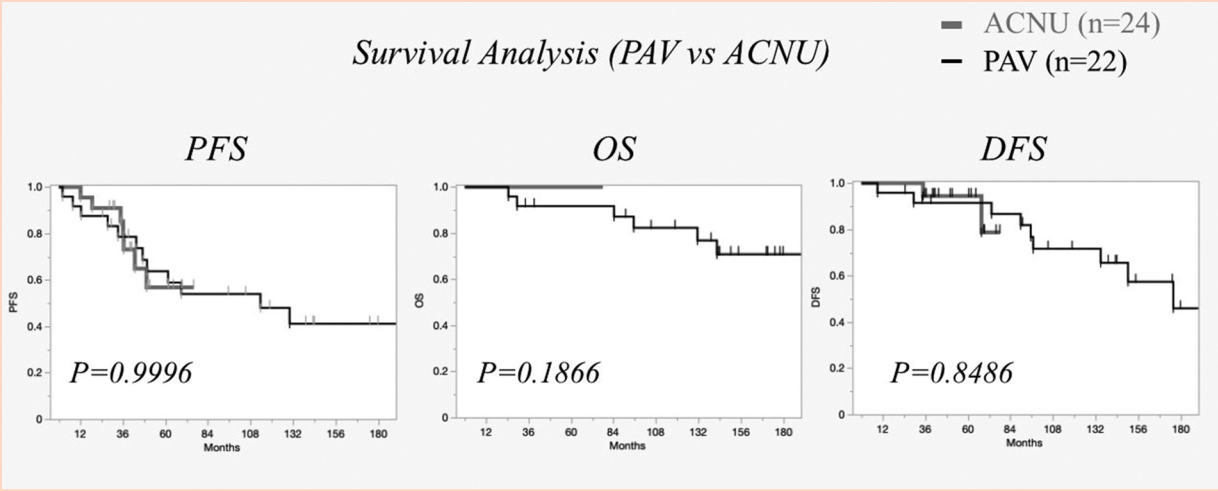

Figure 2. Kaplan-Meier analyses for PFS, OS, and DFS of the 46 patients according to chemotherapy regimen. Black and gray lines indicate the survival curves of oligodendrogliomas treated with PAV (n = 22) and ACNU (n = 24), respectively. PFS and DFS (left and right) of PAV and ACNU groups were observed to be almost identical. The 10-year overall survival rate for the PAV group was 82.3%, while all patients in the ACNU group were alive at the time of analysis (center). Abbreviations: ACNU, nimustine; DFS, deterioration-free survival; OS, overall survival; PAV, procarbazine, ACNU, and vincristine; PFA, progression-free survival.

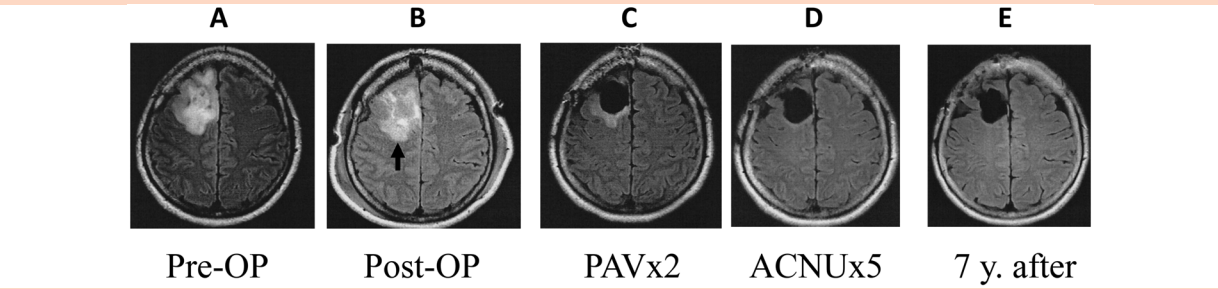

Figure 3. FLAIR images of an illustrative case with successfully chemotherapy-treated oligodendroglioma. A 49-year-old female patient underwent subtotal removal of the right frontal oligodendroglioma, grade 3 under the monitoring of motor evoked potential. (A and B: preoperative and post-operative images). PAV regimen was selected for postsurgical treatment and partial remission of the residual tumor beneath the primary motor area was observed. (C: After two cycles of PAV). As the patient developed dermatitis and neuropathy, we switched the treatment regimen to ACNU alone after two cycles of PAV. As complete remission of the residual tumor was achieved after five cycles of ACNU (D), chemotherapy was finalized. Currently, seven years have passed since the surgery. The patient has not developed any neurological deficit and follow-up MRI show complete remission (E). Abbreviations: ACNU, nimustine; FLAIR, fluid-attenuated inversion recovery; PAV, procarbazine, ACNU, and vincristine.

56% for grade 3.[17] Considering that we deferred RT, our results appear to be favorable (Table S2). The 10-year PFS rates were 57.4% and 30.0% for grades 2 and 3, respectively. Considering that the 10-year PFS rate in the PCV/RT group of the POLA cohort was 67%, outcomes of our cohort cannot be considered favorable (Table S2). This finding supports the interpretation that early consolidation with RT is an appropriate treatment strategy to prevent early recurrence, particularly for grade 3 tumors. However, considering the favorable OS results, we speculate that the survival benefit of administering RT at an early stage is offset by administering it at the time of recurrence or later, indicating the presence of a crossover effect. This situation is similar to that observed in phase 3 trials that evaluated the add-on effect of bevacizumab in patients with primary glioblastoma.[18,19] The finding that the 10-year DFS rates were favorable also supports our speculation. Considering the small difference in treatment outcomes including OS and DFS, between grades 2 and 3, it can be concluded that first-line treatment intensity stratification based on grade was not essential. In other words, our results suggest that if we chose a chemotherapy-first strategy, early recurrences might be more common; however, most of these recurrent lesions would be well controlled by subsequent secondary treatment options, inhibiting further progression and avoiding serious outcomes such as deterioration of the patient's

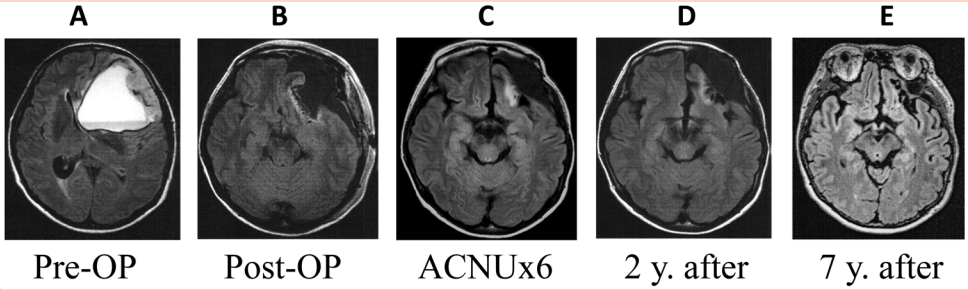

Figure 4. FLAIR images of an illustrative case demonstrating chemotherapy-induced transient radiographic change mimicking tumor recurrence. A 47-year-old female patient underwent awake surgery for left frontal oligodendroglioma, grade 3, and gross total removal of the tumor was achieved (A and B: preoperative and postoperative images). ACNU regimen was selected for postsurgical treatment and six cycles of treatment were completed; however, FLAIR hyperintense lesion developed around the resection cavity (C: After six cycles of ACNU). As the patient did not develop any neurological deficit, we selected short-term follow-up of MRI with no additional treatment. Thereafter, the lesion gradually disappeared within two years (D). Presently, follow-up MRI shows complete remission during seven years after surgery (E). Abbreviation: ACNU, nimustine; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

condition or early death. Secondary options include RT, surgical resection, and chemotherapy rechallenge, as shown in our cohort. We believe that our treatment strategy for deferral radiation therapy for grade 3 tumors seems to be acceptable; however, considering that secondary treatment is necessary in more than half of the cases, it is important to select an appropriate secondary treatment option according to each situation.

Radiation therapy can affect cognitive function in the long term. Considering that oligodendroglioma progresses over decades, the decision to delay RT as long as possible is reasonable. In our entire cohort, approximately half of the patients remained recurrence-free for more than 10 years, indicating that the benefits of avoiding RT are significant. Traditionally, low-grade gliomas have been considered to have low proliferative capacity and, therefore, low radiosensitivity, leading to the widespread belief that RT should be delayed until the tumor progresses to a more malignant stage. Clinical trial results indicate that early RT only prolongs PFS without extending OS, further supporting this approach for low-grade gliomas.[20] As a result, treatment strategies aimed at avoiding early RT, whenever possible, were widely adopted beginning in the 2000s. Owing to the favorable long-term prognosis of oligodendrogliomas, the risk of late complications associated with early RT should be considered.[21] Therefore, especially in cases classified as low risk, there is a motivation to adopt a treatment strategy that defers RT to a later stage. It has been analyzed that PCV monotherapy does not lead to long-term cognitive decline in patients,[22] and that radiation necrosis occurs at a higher rate in oligodendrogliomas.[23] Considering these issues, the rate of selecting a chemotherapy-first strategy for oligodendrogliomas is high in clinical practice, and its efficacy has been demonstrated through retrospective analyses.[9,10] The PCV/RT versus PCV is currently being evaluated in the ongoing POLCA trial.[8] Considering the potential efficacy of chemotherapy, it is essential to establish a treatment strategy that adequately balances the tradeoff between the prevention of early recurrence and late radiation-related complications. Future analyses should incorporate assessments of neurocognitive function to deepen our understanding of DFS.

Prior to the establishment of the molecular classification, it was difficult to clearly distinguish between astrocytomas and oligodendrogliomas and to develop treatment strategies accordingly. Therefore, the prevailing approach was to treat oligodendrogliomas using treatment options similar to those for astrocytomas. However, recent reports based on molecular classification have suggested that small residual tumors after resection in oligodendrogliomas have a low impact on outcomes,[24,25] leading to an era in which the choice of surgery and subsequent multidisciplinary treatment are considered independent of astrocytomas.[26] In our cohort, we observed cases in which the residual tumors disappeared after chemotherapy, resulting in complete remission. In oligodendrogliomas, we believe that the strategy of first assessing the response to chemotherapy postoperatively, even if residual tumors are present, is more feasible than moving on to additional resection or early radiation. In such cases, as we have also noted, chemotherapy alone may follow a course equivalent to pseudoprogression[27] so careful judgment should be made regarding recurrence when radiographic changes occur.

Switching from PAV to ACNU monotherapy resulted in favorable outcomes. In Europe and the United States, chemotherapy regimens for oligodendrogliomas have fluctuated over time. Two phase 3 trials published in 2013 demonstrated that a multimodal treatment regimen combining RT with PCV achieved high levels of efficacy for oligodendroglioma.[1,2] However, at the time of their initial interim reports in the 2000s, neither trial demonstrated an additional benefit of PCV,[28,29] leading to temporary skepticism about its efficacy and a shift to TMZ, which became available around the same time. The TMZ was originally approved for glioblastoma under the Stupp regimen[30]; however, since it is an oral medication with mild adverse effects, if assuming equivalent efficacy, it is quite natural to choose TMZ over PCV.[31] The rate of TMZ use in clinical practice has remained high, since 2013.[32] However, clinical trials evaluating the efficacy of TMZ in low-grade gliomas have not yet

been completed and their final reports have not yet been published. Therefore, the lack of evidence regarding the benefits of TMZ remains an unresolved issue. The CODEL trial is currently comparing PCV/RT and TMZ/RT, but the results are not expected to be announced for some time.[33] In oligodendrogliomas, analysis results have indicated that TMZ monotherapy achieves treatment efficacy equivalent to that of RT alone.[34] However, a large retrospective study reported that TMZ was less effective than PCV.[35] Additionally, an interim analysis of the CODEL trial reported early deaths in the TMZ group,[33] and recent studies have accumulated negative evidence regarding TMZ.[36] The latest report from the POLA cohort also showed that PCV/RT as first-line therapy was associated with better OS than TMZ/RT.[16] Concerns have been raised that TMZ may induce a hypermutant phenotype, a condition prone to poor outcomes such as dissemination, over the long term.[37] However, PCV itself is associated with a high incidence of adverse events and low completion rates; therefore, there may be situations in which selecting TMZ and aiming for completion would be more beneficial. The ASCO-SNO guidelines also list TMZ as a reasonable alternative therapy for patients who cannot tolerate PCV; however, there is no significant evidence supporting the use of TMZ as first-line therapy in this setting.[38] Grade 3 or higher toxicity with TMZ was approximately 15% in the CATNON study.[39] In POLA cohort, 36% of patients were unable to continue the 6 cycles of PCV regimen, and the group stated that TMZ may be a safer regimen, despite its inferior efficacy.[16] Considering patient conditions and other factors, it may be practical to evaluate the regimen to be selected. In this context, the equivalent outcome of the ACNU monotherapy to PAV, as shown here, provides important insights.

The ACNU was used as an alternative to CCNU because CCNU has not yet been approved in Japan. The ACNU has been reported to have higher efficacy than other alkylating agents[7] and is considered to have efficacy that is at least equivalent to that of CCNU. In Japan, the PAV regimen has been widely used as a domestic alternative to PCV for a long time. We previously reported favorable results for PAV therapy in oligodendrogliomas,[11] and similar reports have been published by other institutions in Japan.[40] We switched to ACNU monotherapy after 2015, considering concerns about peripheral neuropathy caused by the neurotoxicity of vincristine and reports indicating that ACNU plus procarbazine (PA) and ACNU alone had equivalent therapeutic effects.[41] We showed that the completion rate of chemotherapy increased after the switch, and treatment outcomes were maintained. Therefore, in situations where TMZ is traditionally selected, ACNU may emerge as a treatment option, offering a more favorable risk-benefit profile.

Although chemotherapy-based approaches seem promising, future treatment strategies may undergo a paradigm shift owing to the development of IDH inhibitors. The first IDH inhibitor to receive approval demonstrated efficacy in the INDIGO trial42; however, there is concern regarding the extent to which long-term administration of IDH inhibitors that require prolonged use is beneficial for patients with a favorable long-term prognosis.[43] In this context, future developments will be closely monitored to determine the positioning of our approach, especially for grade 2 tumors.

The limitations of our study include a single-center retrospective design, small number of cases, and short observation period of the ACNU monotherapy group. The heterogeneity of clinical variables, including tumor grade (WHO grade 2 vs 3), surgical approach (biopsy vs resection), and adjuvant treatment (PAV vs ACNU), limits the statistical power and interpretability of the results. Furthermore, the impact of CDKN2A loss, which has become a popular topic in recent years, was not evaluated due to the small number of relevant cases, as described in our previous report.[44] There is no detailed data presented that enables us to discuss toxicity in the overall study cohort. The classification of various clinically possible events, such as radiation necrosis or vincristine-induced neuropathy, as deterioration within the concept of DFS used in this study remains controversial. The most significant limitation is the lack of theoretical background regarding the long-term use of an unestablished treatment strategy, rather than radiation plus chemotherapy. Fundamentally, when favorable results from phase 3 clinical trials emerged in 2013, Japan should have promptly approved CCNU to create an environment enabling PCV/RT introduction. This would have enabled the benefits of treatment aligned with worldwide consensus and might provide insights from comparative clinical evaluations between ACNU and CCNU. Japan is expected to mature its healthcare system to swiftly adopt newly developed, globally standard treatments.

In conclusion, our chemotherapy-first approach for oligodendroglioma achieved a long-term OS equivalent to or better than that reported in phase 3 clinical trials of PCV/RT. In addition, we switched to a treatment regimen using ACNU alone, and the outcomes remained stable. Nonetheless, it is worth noting that delaying radiotherapy in grade 3 cases should be interpreted with caution, as current evidence supports early radiotherapy in combination with chemotherapy, and modern techniques have significantly reduced long-term toxicity. Oligodendroglioma is a tumor with a long clinical course; therefore, it is important to continue long-term follow-up of its clinical course at our facility, which remains a future challenge.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

1p19q codeletion | ACNU | oligodendroglioma | PCV

Author Contributions

Conceived and designed the study: N.H., R.O., M.M., and K.Y. Acquired funding: N.H., R.O., M.F., and K.Y. Provided study materials: R.O., N.H., D.K., Y.F., Y.S., R.H., HF, YM, MM, and KY. Collected the data: R.O. and N.H. Performed statistical analysis: R.O. First draft of the manuscript: N.H. All authors reviewed and edited the manuscript and approved the final manuscript.

Conflict of Interest Statement

None declared.

Funding

This work was supported by JSPS KAKENHI (grant numbers 23K08545, 23K27712, 25K19906) and the Fukuoka Public Health Promotion Organization Cancer Research Fund.

Acknowledgments

The authors thank Ms Aki Sako for technical assistance.

Ethical Approval

This study was conducted with the approval of Kyushu University Clinical Research Ethics Review Committee (approval number: 848-01) and was in accordance with the 1964 Declaration of Helsinki (revised in Fortaleza, Brazil in October 2013).

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the privacy of research participants.

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References

1. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol*. 2013;31:337-343. https://doi.org/10.1200/JCO.2012.43.2674
2. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol*. 2013;31:344-350. https://doi.org/10.1200/JCO.2012.43.2229
3. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med*. 2016;374:1344-1355. https://doi.org/10.1056/NEJMoa1500925
4. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol*. 2003;5:79-88. https://doi.org/10.1093/neuonc/5.2.79
5. Hori T, Muraoka K, Saito Y, et al. Influence of modes of ACNU administration on tissue and blood drug concentration in malignant brain tumors. *J Neurosurg*. 1987;66:372-378. https://doi.org/10.1215/15228517-5-2-79
6. Takakura K, Abe H, Tanaka R, et al. Effects of ACNU and radiotherapy on malignant glioma. *J Neurosurg*. 1986;64:53-57. https://doi.org/10.3171/jns.1986.64.1.0053
7. Wolff JEA, Berrak S, Koontz Webb SE, Zhang M. Nitrosourea efficacy in high-grade glioma: a survival gain analysis summarizing 504 cohorts with 24193 patients. *J Neurooncol*. 2008;88:57-63. https://doi.org/10.1007/s11060-008-9533-5
8. Penas-Prado M, Wu J, Cahill DP, et al. Proceedings of the comprehensive oncology network evaluating rare CNS tumors (NCI-CONNECT) oligodendroglioma workshop. *Neurooncol Adv*. 2020;2:vdz048. https://doi.org/10.1093/noajnl/vdz048
9. Lassman AB, Iwamoto FM, Cloughesy TF, et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. *Neuro Oncol*. 2011;13:649-659. https://doi.org/10.1093/neuonc/nor040
10. Panageas KS, Iwamoto FM, Cloughesy TF, et al. Initial treatment patterns over time for anaplastic oligodendroglial tumors. *Neuro Oncol*. 2012;14:761-767. https://doi.org/10.1093/neuonc/nos065
11. Hata N, Yoshimoto K, Hatae R, et al. Deferred radiotherapy and upfront procarbazine-ACNU-vincristine administration for 1p19q codeleted oligodendroglial tumors are associated with favorable outcome without compromising patient performance, regardless of WHO grade. *Onco Targets Ther*. 2016;9:7123-7131. https://doi.org/10.2147/OTT.S115911
12. Tabouret E, Reyes-Botero G, Dehais C, et al. Relationships between dose intensity, toxicity, and outcome in patients with oligodendroglial tumors treated with the PCV regimen. *Anticancer Res*. 2015;35:2901-2908. https://doi.org/10.1093/neuonc/nou243.18
13. Webre C, Shonka N, Smith L, et al. PC or PCV, that is the question: primary anaplastic oligodendroglial tumors treated with procarbazine and CCNU with and without vincristine. *Anticancer Res*. 2015;35:5467-5472. https://doi.org/10.1200/jco.2014.32.15_suppl.2046
14. Hata N, Fujioka Y, Otsuji R, et al. In-house molecular diagnosis of diffuse glioma updating the revised WHO classification by a platform of the advanced medical care system, Senshin-Iryo. *Neuropathology*. 2024;44:344-350. https://doi.org/10.1111/neup.12970
15. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28:1963-1972. https://doi.org/10.1200/JCO.2009.26.3541
16. Kacimi SEO, Dehais C, Feuvret L, et al. Survival outcomes associated with first-line procarbazine, CCNU, and vincristine or temozolomide in combination with radiotherapy in IDH-Mutant 1p/19q-codeleted grade 3 oligodendroglioma. *J Clin Oncol*. 2025;43:329-338. https://doi.org/10.1200/JCO.24.00049
17. Lassman AB, Hoang-Xuan K, Polley MC, et al. Joint final report of EORTC 26951 and RTOG 9402: phase III trials with procarbazine, lomustine, and vincristine chemotherapy for anaplastic oligodendroglial tumors. *J Clin Oncol*. 2022;40:2539-2545. https://doi.org/10.1200/JCO.24.00049
18. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:709-722. https://doi.org/10.1056/NEJMoa1308345
19. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:699-708. https://doi.org/10.1056/NEJMoa1308573

20. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet*. 2005;366:985-990. https://doi.org/10.1016/S0140-6736(05)67070-5
21. Cayuela N, Jaramillo-Jiménez E, Càmara E, et al. Cognitive and brain structural changes in long-term oligodendroglial tumor survivors. *Neuro Oncol*. 2019;21:1470-1479. https://doi.org/10.1093/neuonc/noz130
22. Habets EJ, Taphoorn MJ, Nederend S, et al. Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. *J Neurooncol*. 2014;116:161-168. https://doi.org/10.1007/s11060-013-1278-0
23. Ahmad H, Martin D, Patel SH, et al. Oligodendroglioma confers higher risk of radiation necrosis. *J Neurooncol*. 2019;145:309-319. https://doi.org/10.1007/s11060-019-03297-7
24. Kavouridis VK, Boaro A, Dorr J, et al. Contemporary assessment of extent of resection in molecularly defined categories of diffuse low-grade glioma: a volumetric analysis. *J Neurosurg*. 2020;133:1291-1301. https://doi.org/10.3171/2019.6.JNS19972
25. Wijnenga MMJ, French PJ, Dubbink HJ, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. *Neuro Oncol*. 2018;20:103-112. https://doi.org/10.1093/neuonc/nox176
26. Hou Z, Hu J, Liu X, et al. Decision system for extent of resection in WHO grade 3 gliomas: a Chinese glioma genome atlas database analysis. *J Neurooncol*. 2023;164:461-471. https://doi.org/10.1007/s11060-023-04420-5
27. Esparragosa Vazquez I, Ndiaye M, Di Stefano AL, et al. T2-fluid-attenuated inversion recovery (FLAIR) pseudoprogression in patients with anaplastic oligodendrogliomas treated with procarbazine, lomustine and vincristine (PCV) chemotherapy alone. *Eur J Neurol*. 2023;30:2879-2883. https://doi.org/10.1111/ene.15873
28. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: intergroup radiation therapy oncology group trial 9402. *J Clin Oncol*. 2006;24:2707-2714. https://doi.org/10.1200/JCO.2005.04.3414
29. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol*. 2006;24:2715-2722. https://doi.org/10.1200/JCO.2005.04.6078
30. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996. https://doi.org/10.1056/NEJMoa043330
31. van der Meulen M, Mason WP. First-line chemotherapeutic treatment for oligodendroglioma, WHO grade 3-PCV or temozolomide? *Neurooncol Pract*. 2022;9:163-164. https://doi.org/10.1093/nop/npac023
32. Lin AJ, Kane LT, Molitoris JK, et al. A multi-institutional analysis of clinical outcomes and patterns of care of 1p/19q codeleted oligodendrogliomas treated with adjuvant or salvage radiation therapy. *J Neurooncol*. 2020;146:121-130. https://doi.org/10.1007/s11060-019-03344-3
33. Jaeckle KA, Ballman KV, van den Bent M, et al. CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design. *Neuro Oncol*. 2021;23:457-467. https://doi.org/10.1093/neuonc/noaa168
34. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. 2016;17:1521-1532. https://doi.org/10.1016/S1470-2045(16)30313-8
35. Wick W, Roth P, Hartmann C, et al. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. *Neuro Oncol*. 2016;18:1529-1537. https://doi.org/10.1093/neuonc/now133
36. Weller J, Katzendobler S, Karschnia P, et al. PCV chemotherapy alone for WHO grade 2 oligodendroglioma: prolonged disease control with low risk of malignant progression. *J Neurooncol*. 2021;153:283-291. https://doi.org/10.1007/s11060-021-03765-z
37. Yu Y, Villanueva-Meyer J, Grimmer MR, et al. Temozolomide-induced hypermutation is associated with distant recurrence and reduced survival after high-grade transformation of low-grade IDH-mutant gliomas. *Neuro Oncol*. 2021;23:1872-1884. https://doi.org/10.1093/neuonc/noab081
38. Mohile NA, Messersmith H, Gatson NT, et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. *J Clin Oncol*. 2022;40:403-426. https://doi.org/10.1200/JCO.21.02036
39. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22:813-823. https://doi.org/10.1016/S1470-2045(21)00090-5
40. Iwadate Y, Matsutani T, Shinozaki N, Saeki N. Anaplastic oligodendroglial tumors harboring 1p/19q deletion can be successfully treated without radiotherapy. *Anticancer Res*. 2011;31:4475-4479.
41. Shibui S, Narita Y, Mizusawa J, et al. Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305). *Cancer Chemother Pharmacol*. 2013;71:511-521. https://doi.org/10.1007/s00280-012-2041-5
42. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med*. 2023;389:589-601. https://doi.org/10.1056/NEJMoa2304194
43. Mohile NA, Lassman AB, Schiff D, Blakeley J. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline rapid recommendation update clinical insights. *JCO Oncol Pract*. 22:16-18. https://doi.org/10.1200/OP-25-00185
44. Otsuji R, Hata N, Yamamoto H, et al. Hemizygous deletion of cyclin-dependent kinase inhibitor 2A/B with p16 immuno-negative and methylthioadenosine phosphorylase retention predicts poor prognosis in IDH-mutant adult glioma. *Neurooncol Adv*. 6:vdae069.https://10.1093/noajnl/vdae069