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Neuro-Oncology Clinical Debate: PCV or temozolomide in combination with radiation for newly diagnosed high-grade oligodendroglioma

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Abstract

The treatment of newly diagnosed oligodendroglioma has been revolutionized in the past decade by multiple studies demonstrating that the addition of chemotherapy to radiation therapy results in a significant survival benefit. While the most direct evidence comes from clinical trials that utilized PCV, a chemotherapy regimen consisting of procarbazine, CCNU (lomustine), and vincristine, there is circumstantial evidence suggesting that the oral agent temozolomide (TMZ), which is both better tolerated and logistically simpler than PCV, may also be effective. The lack of currently available direct comparative data for PCV vs TMZ results in a diversity of practice. In this article, Ruff and Buckner argue for PCV as part of the standard-of-care regimen for newly diagnosed anaplastic oligodendroglioma, while Geurts and van den Bent defend the use of TMZ.

Keywords

glioblastoma | glioma | lomustine | oligodendroglioma | PCV | temozolomide

Clinical Scenario

A previously healthy 35-year-old woman presents with a recent diagnosis of anaplastic oligodendroglioma, isocitrate dehydrogenase (*IDH*)-mutant and 1p/19q codeleted, status postgross total resection. Her Eastern Cooperative Oncology Group performance status is 0, and her blood work is within normal limits. Would you recommend procarbazine, lomustine, and vincristine (PCV) or temozolomide, in combination with radiation therapy, as the optimal initial treatment for this patient?

Pro-PCV View: PCV, the data-driven choice, Michael W. Ruff and Jan C. Buckner

The treatment paradigm for oligodendroglioma, now defined by the presence of whole-arm codeletion of chromosomal arms 1p/19q, has shifted, owing to new diagnostic criteria[1] and phase III clinical trial evidence.[2–4] Patients with oligodendroglioma benefit more from treatment with radiation therapy plus chemotherapy with procarbazine,

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lomustine, and vincristine (PCV) than radiation alone.[2–4] This combined treatment results in prolongation of both progression-free (PFS) and overall survival (OS) compared to radiation monotherapy. The patient presented in this vignette should be treated with radiotherapy (RT) followed by PCV chemotherapy to maximize potential OS. The available data support this treatment approach.

Most relevant to this discussion are the Radiation Therapy Oncology Group (RTOG) 9402 and The European Organization for Research and Treatment of Cancer (EORTC) 26951 studies.[3,4] Both were phase III studies examining the benefit of PCV chemotherapy in addition to RT compared to RT alone in patients with anaplastic oligodendroglioma (per histological diagnosis).

In the RTOG 9402 study, for the entire cohort there was no difference in median OS by treatment (4.6 years PCV/RT vs 4.7 RT). However, in those patients with 1p/19q-codeleted tumors, treatment with RT plus PCV doubled median OS (14.7 years vs 7.3 years, hazard ratio [HR] 0.59, with 95% CI 0.37 to 0.95, $P = .03$). Thus, for patients with 1p/19q-codeleted tumors, PCV plus RT may be an especially effective treatment, though the observation was derived from an unplanned analysis for which it was underpowered.

EORTC 26951, a phase III clinical trial in patients with newly diagnosed anaplastic oligodendroglioma, randomized 368 patients to receive either radiation therapy alone (59.4 Gy) or the same RT followed by 6 cycles of adjuvant PCV. Results demonstrated a significantly longer OS in the RT/PCV arm vs RT-alone arm (42.3 vs 30.6 months, HR 0.75; 95% CI 0.60 to 0.95). In the 80 patients with 1p/19q codeletion, OS was increased, with a trend toward more benefit from adjuvant PCV (OS not reached in the RT/PCV group vs 112 months in the RT group; HR 0.56; 95% CI 0.31 to 1.03). The authors concluded that the addition of 6 cycles of PCV after 59.4 Gy of RT increases OS in anaplastic oligodendroglial tumors and that 1p/19q-codeleted tumors derived more benefit from adjuvant PCV compared with non-1p/19q-deleted tumors.[4]

Results of the RTOG 9802[2] and the NOA-04[5] studies reinforce the benefit of adjuvant PCV. RTOG 9802 was a phase III trial in adults with low-grade glioma. Median PFS was 4.0 vs 10.4 years for radiation therapy alone vs chemoradiation, with a 10-year PFS of 21% and 51%, respectively. OS was also superior in the chemoradiation group. Median survival was 7.8 years vs 13.3 years for radiation therapy alone vs chemoradiation, and 10-year survival was 40% vs 60%, respectively. The HRs in favor of chemoradiation were 0.43 for patients with histologically diagnosed oligodendroglioma. Retrospectively, the patient data for the RTOG 9802 study were examined: Ninety-seven patients had sufficient DNA for profiling. Of these, 33 (34%) were *IDH* mutant, 1p/19q-codeleted patients. This subgroup had superior PFS with PCV + RT compared with those treated with RT alone (1p/19q-codeleted HR = 0.16, 95% CI 0.05 to 0.058, $P = .002$). These data further bolster the benefit of adjuvant PCV in oligodendroglioma, albeit in a lower grade than the presented case.

In the NOA-04 study, patients with newly diagnosed anaplastic gliomas were randomized to upfront RT or upfront chemotherapy (PCV or TMZ). At progression those randomized to RT were treated with chemotherapy, and those randomized initially to chemotherapy were treated with RT. Patients with 1p/19q-codeleted tumors treated with TMZ had a worse outcome: Patients treated with TMZ had a shorter PFS (4.46 years) than PCV (9.4 years) and RT (8.67 years) ($P = .02$). Median OS in the TMZ initial therapy group was 8.09 years, while median OS was not reached in either the PCV as initial monotherapy group or the RT as initial monotherapy group after follow-up of 9.5 years. NOA-04 demonstrated that primary monotherapy with chemotherapy is not superior to primary RT; additionally, the authors concluded that this trial does support the use of primary chemoradiotherapy with PCV.[5]

A startling hypothesis for the inferiority of TMZ as a monotherapy is the concern that TMZ may contribute to an aggressive hypermutated phenotype. Johnson et al performed genome sequence analysis of initial and recurrent human gliomas with and without exposure to TMZ (notably, there was no PCV arm).[6] Tumors treated with TMZ were hypermutated at recurrence in a greater proportion of TMZ-exposed patients. The resulting genetic alterations resembled those found in glioblastoma (disruption of the retinoblastoma-associated protein tumor suppressor pathway and activation of the Akt–mammalian target of rapamycin [mTOR pathway]), raising the possibility that TMZ monotherapy could accelerate tumor transformation to a more aggressive phenotype. If this phenomenon is unique to TMZ, it could by extension be an inferior agent when combined with RT as compared to PCV.

Lassman and colleagues provided retrospective evidence for the superior efficacy of PCV when compared to TMZ in an analysis of 1013 patients with histologically diagnosed anaplastic oligodendroglioma treated from 1981 to 2007.[7] Patients variably received RT alone, chemotherapy alone or chemoradiotherapy as an upfront strategy. Forty-nine percent of patients with 1p/19q codeletion who received RT/PCV were alive at 10 years (95% CI 34 to 68), compared to 15% (95% CI 1 to 48) of patients who were treated with RT/TMZ.

Though the final answer to this question will come only with the completion of the CODEL trial, which comprises randomized patients with 1p/19q-codeleted tumors only, both grade II and grade III to RT followed by PCV to RT plus TMZ followed by adjuvant TMZ to determine whether TMZ is noninferior to PCV, several signals are already present in the literature.

In the original CODEL trial design, there was an RT-alone arm and a TMZ-alone arm; however; randomization was halted by the Data Safety Monitoring Committee owing to more frequent tumor progression in the TMZ-alone group after a median follow-up of 3.4 years (n = 6/12; 50%) than in the RT-containing arms (n = 2/24; 8%; $P = .002$). Additionally, 3 of the 6 patients with disease progression on TMZ-alone arm died, whereas 1 of 2 patients with progression in the RT-alone arm died.[8,9] The RT-alone arm was discontinued after the publication of the EORTC 26951 and RTOG 9402 studies.

As we await the results of the CODEL study, which may be many years down the line, we strongly recommend the use of RT with adjuvant PCV in high-risk patients such as the one presented in this article. It is currently our practice, however, to use TMZ if the patient is unable to tolerate adjuvant PCV.

Pro-Temozolomide View: Temozolomide in combination with radiotherapy—the most reasonable treatment for patients with newly diagnosed oligodendroglioma, Martin J. van den Bent and Marjolein Geurts

Oligodendrogliomas (*IDH* mutant and 1p19q codeleted) are very chemosensitive brain tumors with a relatively favorable prognosis. Patients with newly diagnosed oligodendroglioma have a median OS of more than 10 years after treatment with the combination of chemotherapy and RT, regardless of tumor grade. The optimal chemotherapy regimen for patients with newly diagnosed oligodendroglioma, however, remains controversial. We state that TMZ chemotherapy, rather than PCV chemotherapy, in combination with RT is a reasonable treatment option for patients with newly diagnosed oligodendrogliomas.

The chemosensitivity of oligodendrogliomas was initially demonstrated with treatment using PCV in patients who had recurrence or progression after initial treatment with RT.[10,11] Later, it was demonstrated that recurrent oligodendrogliomas can also effectively be treated with TMZ chemotherapy, with 1p/19q-codeleted tumors being particularly responsive.[12–15] Subsequently, large randomized trials in newly diagnosed oligodendroglioma patients demonstrated a survival benefit if PCV was added to radiation therapy both in anaplastic[4,16] and low-grade gliomas including oligodendrogliomas.[2] However, by the time the phase III trials on adjuvant PCV chemotherapy revealed clinical benefits, many (neuro)-oncologists had replaced the PCV chemotherapy regimen with TMZ because of concerns about the significant toxicity associated with PCV. Lomustine causes a cumulative bone marrow suppression, which may result in a persistent bone marrow dysfunction. In addition, procarbazine causes a protracted nausea and anorexia that is difficult to control, as well as frequent skin reactions requiring procarbazine discontinuation. Vincristine induces peripheral neurotoxicity and does not readily cross the blood-brain barrier, and may therefore be of limited use.[17] Taken together, the use of PCV is usually complicated by dose delays and reductions, and premature discontinuation of drugs.

The 3 randomized trials comparing the combination of PCV and RT to RT alone provide a clear understanding of the toxicity of PCV. Buckner and colleagues reported occurrence of a blood or bone marrow disorder in 76% of patients treated with PCV and RT, compared to 4% of patients treated with RT only. Nausea occurred in 62% of patients treated with PCV and RT, compared to 21% of patients treated with RT only.[2] In the RTOG 9402 study, 148 patients were treated with the combination of PCV and RT. Two patients died of PCV-induced neutropenia. No early deaths occurred in the 143 patients treated with RT only.[16] In the EORTC 26951 study, 161 patients were treated with the combination of PCV and RT, of whom 38% could not complete PCV treatment because of hematologic toxicity (33%) or nonhematologic toxicity (5%).[4]

The favorable safety profile of TMZ and the ease of its administration were well established by 2 studies that showed that this drug is an attractive alternative to PCV. In the NOA-04 trial, a German multiarm study also comparing TMZ to PCV in anaplastic glioma, chemotherapy was discontinued in 18 of 54 patients in the PCV monotherapy arm (because of procarbazine toxicity in 14 patients and for neuropathy in another 4 patients), as opposed to none of the 53 patients in the TMZ monotherapy arm.[18] Similarly, Chang et al compared TMZ to single-agent lomustine (or BCNU, a comparable chemotherapeutic agent) in anaplastic astrocytoma patients. Of the 99 patients treated with lomustine (or BCNU), 28% discontinued treatment for toxicity in contrast to none of the 97 TMZ-treated patients.[19]

Although the efficacy of TMZ compared to PCV for newly diagnosed oligodendroglioma has not been studied, the circumstantial evidence for efficacy of TMZ is convincing. First, the working mechanism of TMZ is comparable to that of PCV. The main effective drug of the PCV schedule is probably lomustine. Both lomustine and TMZ are DNA cross-linking alkylating agents that readily cross the intact blood-brain barrier. Second, TMZ monotherapy is highly effective in *recurrent* oligodendrogliomas. Two large phase II studies showed excellent response rates. In the EORTC 26971 study, 38 patients with recurrent or progressive oligodendroglioma after initial treatment with RT were treated with TMZ. Twenty (53%) of them (95% CI 36% to 69%) had a complete or partial response. At 12 months from the start of treatment, 40% of patients were still free from progression.[15] Brandes et al studied 67 patients with recurrent oligodendroglioma after initial treatment with RT, who were then treated with TMZ.[12] The overall response rate was 46%, which compares to previous reported response rates of PCV.[10,11] In *newly* diagnosed oligodendrogliomas, high response rates to initial therapy with TMZ have also been demonstrated, similar to the response reported for PCV.[20] Efficacy data should, however, be interpreted with caution, as many studies included oligodendrogliomas based on histopathological diagnosis, and it is likely that not all tumors harbored 1p19q codeletion, which is predictive of response to chemotherapy.[14,21–23] Larger phase II studies have confirmed the higher response rates in 1p/19q-codeleted oligodendroglioma, compared to histopathologically diagnosed oligodendroglioma without 1p/19q codeletion, which would be categorized as astrocytoma by current World Health Organization (WHO) diagnostic criteria.[12,15]

The optimal chemotherapy regimen for patients with newly diagnosed oligodendroglioma remains uncertain. So far, all randomized trials on adjuvant chemotherapy that enrolled oligodendroglioma studied PCV, but the recently reported CATNON trial on 1p/19q intact anaplastic glioma observed a survival benefit of adjuvant TMZ.[24] Until randomized trials prove otherwise, patients or physicians who prioritize convenience and avoidance of toxicity may reasonably choose TMZ over PCV.

Pro-PCV Reply, Michael W. Ruff and Jan C. Buckner

We appreciate Dr van den Bent and Dr Geurts' thoughtful reply. The overall argument for TMZ vs PCV can be summarized as convenience vs efficacy. We agree that the toxicity of PCV chemotherapy is indeed greater than that of TMZ, though notably, quality-of-life assessments performed

longitudinally in the RTOG 9402 study patients were similar to the RT-alone group. With careful attention to dose modifications based on interval toxicity, most patients have manageable toxicities well within the range of other oncologic therapies proven to have large treatment benefit. And while it is correct that premature discontinuation (prior to completion of 6 adjuvant cycles) was observed in the majority of patients in EORTC 26951, it is remarkable to note that the marked prolongation of survival was still observed with the addition to PCV to RT over RT alone, even with frequent discontinuation prior to completion of the 6 planned cycles. Accordingly, the higher grade 3 neutropenia observed during adjuvant PCV (32% in EORTC 26951) vs 7% in the Stupp trial utilizing RT with combinatorial and adjuvant TMZ is clearly less relevant as the addition of PCV essentially doubles life expectancy with the RT/PCV combination.

Currently, robust data support the use of PCV chemotherapy as an adjuvant to RT in high-risk patients such as the one presented in this article. In patients with codeleted tumors, receiving PCV plus RT in RTOG 9402, the HR was 0.36 (95% CI, 0.23 to 0.57, $P < .001$) and the median OS for chemoradiation was 14.7 vs 2.6 years in the RT alone; EORTC reported similar results. There is a dearth of comparable data to support TMZ in this scenario, and cross-study comparisons are unreliable.

Practically summarized, TMZ monotherapy is inferior to radiation monotherapy. Radiation monotherapy is inferior to combinatorial chemoradiotherapy with PCV. As TMZ adds less survival benefit as a monotherapy than RT, it is unlikely that the cumulative benefit of adding TMZ will be greater than that of PCV (which is more efficacious as a prospective monotherapy, and a retrospective combinatorial therapy), even in cases in which toxicity limits the number of cycles.

While we eagerly await the results of the CODEL study, in the interim we strongly recommend the use of RT with adjuvant PCV as the preferred upfront treatment strategy in high-risk patients.

Pro-Temozolomide Reply, Martin J. van den Bent and Marjolein Geurts

The definitive answer to the PCV vs TMZ question requires solid data, which are currently not available. The few comparisons that have been made between PCV and TMZ are retrospective and post hoc. The large review by Lassman and colleagues spanned many years, with the different regimens being used in different eras, and is subject to all types of bias that accompany retrospective studies.[7] The post hoc analysis presented as part of the German NOA-4 trial is based on only 33 codeleted patients, a small number that signals a risk for false-positive findings—this is why we conduct adequately powered trials.[5] Lastly, the rate of progression observed in the 12-patient TMZ monotherapy arm of the initial CODEL cohort is not in line with larger series on upfront TMZ treatment in oligodendroglioma, including the EORTC 22033 study, which did not see early dropout in 59 1p/19q-codeleted patients.[25] However, relatively early progression in patients with anaplastic oligodendrogliomas treated with TMZ has been reported in 2 retrospective series, but not in the prospective NOA-4 study. Taken together, these retrospective and uncontrolled data have to be weighed against the clear and substantial increase in clinically symptomatic toxicities induced by the PCV regimen, with some patients already coming off treatment after 1 or 2 cycles. Regarding the "TMZ-induced hypermutation," genome sequence analysis of recurrent gliomas after PCV has also been described,[26] but is probably less well studied since TMZ is now far more frequently used. It is at least premature to contribute any genetic alterations in recurrent gliomas to TMZ. Moreover, in the end what matters to the patients is the duration of initial response and OS, and the studies that describe the hypermutated recurrences have not addressed that.

Conclusion

Ultimately, the question of the optimal chemotherapeutic regimen for anaplastic oligodendroglioma is one that can be settled only by a properly conducted randomized, controlled trial. To that end, the "Phase III Intergroup Study of Radiotherapy With Concomitant and Adjuvant Temozolomide Versus Radiotherapy with Adjuvant PCV Chemotherapy in Patients with 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma" is currently ongoing, with a target enrollment of 360 patients. This study is also known by other names, including CODEL, N0577, NCI-2011-01915, and EORTC-26081-22086. First opened in 2009 as a trial of radiation alone vs TMZ alone vs radiation in combination with TMZ in patients with anaplastic WHO grade III codeleted tumors, the structure of the trial was revised in light of interval developments, as previously discussed. In its current form, CODEL is a noninferiority comparison of the 2 arms, powered for PFS. In addition to PFS, the study will evaluate differences in OS, toxicity, quality of life, and cognitive sequelae between regimens. While this study should provide a definitive answer to the question of TMZ vs PCV in patients with codeleted glioma, mature data will not be available for many years, and the debate summarized herein will undoubtedly continue in clinical practice.

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