PCV for oligodendroglioma

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- Unlocking new horizons: advances in treating IDH-mutant, 1p/19q-codeleted oligodendrogliomas
- Oligodendroglioma of the Hippocampus: A Case Report and Systematic Review on Therapeutic Approaches of Oligodendroglioma After WHO 2021 Classification
- APPROACH: Analysis of Proton versus Photon Radiotherapy in Oligodendroglioma and Assessment of Cognitive Health - study protocol paper for a phase III multicentre, open-label randomised controlled trial
- Trends in the Management of Oligodendrogliomas: A Multinational and Multidisciplinary Survey Study
- Congress of Neurological Surgeons systematic review and evidence-based guidelines for the role of chemotherapy in newly diagnosed WHO Grade II diffuse glioma in adults: update
- The Role of Systemic Therapies in the Treatment of Grades 1-4 Gliomas
- Congress of Neurological Surgeons systematic review and evidence-based guidelines on the management of recurrent diffuse low-grade glioma: update
- Impact of upfront adjuvant chemoradiation on survival in patients with molecularly defined oligodendroglioma: the benefits of PCV over TMZ

The PCV regimen (Procarbazine, Lomustine, and Vincristine) has been an important therapeutic approach for oligodendroglioma treatment, particularly for patients with tumors that have the 1p/19q codeletion and an IDH mutation, which are molecular markers associated with a better prognosis and increased responsiveness to therapy.

Efficacy

The PCV regimen has been shown to be particularly effective in oligodendrogliomas with the 1p/19q codeletion, especially when used in conjunction with radiotherapy. Numerous studies have demonstrated that this combination therapy leads to prolonged progression-free survival (PFS) and in some cases, overall survival (OS), when compared to alternative treatments like temozolomide (TMZ).

Key Findings in Studies

Grade 2 and Grade 3 Oligodendrogliomas: Patients with grade 3 oligodendrogliomas who received PCV in combination with radiation therapy had significantly longer PFS compared to those treated with TMZ or no adjuvant chemotherapy. The benefits of PCV were particularly evident in the higher-grade tumors.

Superior Outcomes Compared to TMZ: In several trials, patients treated with PCV had better long-term outcomes than those treated with TMZ, which is often preferred for its easier administration and lower toxicity profile. PCV, despite its side effects, has demonstrated superior efficacy in delaying disease progression.

Long-term Benefit

In landmark trials like the RTOG 9402 and EORTC 26951, the combination of PCV and radiation improved overall survival in patients with 1p/19q codeleted oligodendrogliomas, with benefits observed even after many years of follow-up.

Side Effects

The PCV regimen is known for its toxicity, particularly:

Bone marrow suppression (leading to anemia, neutropenia, and thrombocytopenia)

Gastrointestinal issues (nausea, vomiting)

Neurotoxicity (from vincristine, causing peripheral neuropathy) These side effects can limit the use of PCV in some patients, particularly those who are older or have comorbidities. However, despite these challenges, the significant PFS and OS benefits often justify the use of PCV in appropriate patients.

Current Clinical Relevance

PCV continues to be recommended in the treatment guidelines for oligodendroglioma, particularly for patients with grade 3 tumors and the 1p/19q codeletion, as it offers superior outcomes compared to other regimens like TMZ. As research advances, further refinements in treatment strategies are being explored, but PCV remains a cornerstone of therapy for molecularly defined oligodendrogliomas.

Adults with IDH-mutant, 1p/19q codeleted oligodendroglioma (WHO grade 2 or 3) who underwent surgery between 2005 and 2021 were identified. Clinical data, disease characteristics, treatment, and outcomes were collected.

A total of 207 patients with grade 2 and 70 with grade 3 oligodendrogliomas were identified. Median (IQR) follow-up was 57 (87) months. Patients with grade 3 tumors who received adjuvant radiation and PCV had longer median PFS (> 110 months) than patients who received radiation and TMZ (52 months, p = 0.008) or no adjuvant chemoradiation (83 months, p = 0.03), which was not seen in grade 2 tumors (p = 0.8). In multivariate analysis, patients who received PCV chemotherapy (Relative Risk [95% CI] = 0.24[0.05-1.08] and radiotherapy (0.46[0.21-1.02]) trended towards longer PFS, independently of grade.

Adjuvant radiation and PCV are associated with improved PFS over radiation with TMZ in patients with grade 3 molecularly defined oligodendrogliomas, and all-grade patients treated with PCV trended

towards decreased risk of recurrence and progression. These results highlight the importance of ongoing clinical trials investigating these treatments [1)].

The objective was to assess the overall survival (OS) and progression-free survival (PFS) associated with first-line PCV/RT versus TMZ/RT in patients newly diagnosed with O3IDHmt/Codel. We included patients with histologically proven O3IDHmt/Codel (according to WHO criteria) from the French national prospective cohort Prise en charge des OLigodendrogliomes Anaplasiques (POLA). All tumors underwent central pathological review. OS and PFS from surgery were estimated using the Kaplan-Meier method and Cox regression model.

Results: 305 newly diagnosed patients with O3IDHmt/Codel treated with RT and chemotherapy between 2008 and 2022 were included, of which 67.9% of patients (n = 207) were treated with PCV/RT and 32.1% with TMZ/RT (n = 98). The median follow-up was 78.4 months (IQR, 44.3-102.7). The median OS was not reached (95% CI, Not reached [NR] to NR) in the PCV/RT group and was 140 months (95% CI, 110 to NR) in the TMZ/RT group (log-rank P = .0033). On univariable analysis, there was a significant difference in favor of PCV/RT in both 5-year (PCV/RT: 89%, 95% CI, 85 to 94; TMZ/RT: 75%, 95% CI, 66 to 84) and 10-year OS (PCV/RT: 72%, 95% CI, 61 to 85; TMZ/RT: 60%, 95% CI, 49 to 73), which was confirmed using the multivariable Cox model adjusted for age, type of surgery, gender, Eastern Cooperative Oncology Group performance status, and CDKN2A homozygous deletion (hazard ratio, 0.53 for PCV/RT, 95% CI, 0.30 to 0.92, P = .025).

In patients with newly diagnosed O3IDHmt/Codel from the POLA cohort, first-line PCV/RT was associated with better OS outcomes compared with TMZ/RT. Our data suggest that the improved safety profile associated with TMZ comes at the cost of inferior efficacy in this population. Further investigation using prospective randomized studies is warranted [2)].

The standard postsurgical options for low-grade gliomas include watchful waiting or radiotherapy depending on the risk factors for recurrence. The use of chemotherapy for the treatment of this disease is generally controversial, although the published results of the first of two large randomized phase III clinical trials (RTOG 9802 a EORTC 22033-26033), focusing on the evaluation of chemotherapy for the upfront treatment of newly diagnosed low-grade gliomas, are reassuring in this respect. The long-term results of a RTOG 9802 comparing radiotherapy alone with radiotherapy and six cycles of adjuvant PCV chemotherapy (procarbazine, lomustine, vincristine) in patients with high-risk low-grade gliomas will probably have an impact on daily clinical practice. The increase in median overall survival from 7.8 years to 13.3 years, mainly for patients with oligodendrogliomas, is unprecedented, but the toxicity of PCV is too high and molecular marker analysis remains inadequate. It is still unclear whether less toxic temozolomide can replace PCV and whether temozolomide can be used upfront alone instead of with radiotherapy. This question is addressed by the ongoing EORTC 22033-26033 study. The preliminary results show no significant difference in progression-free survival between patients receiving radiotherapy and those receiving temozolomide alone. Treatment with temozolomide was not associated with an improvement in cognitive function compared with treatment with radiotherapy. Despite limited follow-up, the study clearly confirmed the importance of molecular characterization of low-grade gliomas, as currently defined in the new 2016 WHO Classification of Tumors of the Central Nervous System [3)].

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