Treatment Recommendations for Anaplastic Oligodendrogliomas That Are Codeleted

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Although important questions still remain regarding chemotherapy choice, sequence, and dosing, the answers to which will require additional large phase III trials, radiotherapy alone is no longer appropriate therapy for 1p/19q codeleted anaplastic oligodendrogliomas.

Introduction

Anaplastic oligodendroglioma (AO) is a rare malignant tumor with features of oligodendrogliarial lineage and histological features corresponding to World Health Organization (WHO) grade III.[1] The reported annual incidence rates of AO ranges from 0.07 to 0.18 per 100,000 person-years and comprise only 0.5% to 1.2% of all primary brain tumors.[2,3] Only about 30% of oligodendroglial tumors have anaplastic features. The peak incidence of AO is between 45 and 50 years of age; patients on average are approximately 7 to 8 years older than those with grade II oligodendroglioma. Although not proven, this age difference may correspond to the mean time to progression from a grade II oligodendroglioma (6 to 7 years).[1] Similar to low-grade (WHO grade II) oligodendroglioma, AO tends to preferentially occur in the frontal lobe, with the temporal lobe the next most common location. Seizures are the main presenting symptom, both in patients who develop de novo AO and in patients with a prior longstanding history of oligodendroglioma who undergo transformation to AO. Although recent study results show impressive survival statistics, historically, the median overall survival for all patients with AO has been reported to be between 2 and 6 years with treatment.[4-6] Several studies have established certain clinical features as favorable prognostic factors: younger age, higher Karnofsky performance status (KPS), larger extent of resection, presenting symptom of seizure, and progression from a prior low-grade oligodendroglioma.[6-9] There is no known environmental factor that increases the risk of development of an oligodendroglial tumor. A single nucleotide polymorphism on chromosome 8q24.21 has now been described that is associated with an odds ratio of 6.5 (95% confidence interval [CI], 4.2–10; \( P = 9.5 \times 10^{-18} \)) for development of oligodendroglial tumors.[10] The standard therapy for anaplastic gliomas (including both astrocytic and oligodendrogliarial tumors) has been radiotherapy, since clinical trials encompassing all anaplastic gliomas and evaluating treatment with chemotherapy alone or in combination with radiotherapy failed to show significantly different overall survival yet demonstrated additional toxicity.[4,5,11] However, because of early data demonstrating chemosensitivity of oligodendroglial tumors to combined treatment with PCV (procarbazine [Matulane], lomustine [CeeNU], and vincristine), there has remained interest in the early use of chemotherapy for these specific tumors, particularly to delay radiation therapy.[12,13] Clinical trends over the last 30 years have demonstrated an increased prevalence of the use of chemotherapy alone or chemotherapy in addition to radiation, despite the absence of Level 1 evidence.[14]

Histopathology and Imaging

AOs have a heterogeneous appearance on MRI, consisting of mixed areas of nonenhancing and enhancing tumor, cystic and solid portions, and frequently calcifications and intratumoral hemorrhage.[1] There is not usually significant surrounding mass effect or edema. Histologically, AO is characterized by mitotically active cells with significant cellular atypia, and can have microvascular proliferation and pseudopalisading necrosis. Classical morphology includes a fixation artifact that gives a “fried egg” appearance.[1] Frequently, abnormal or reactive astrocytes are found within the tumor, a finding that often results in misdiagnosis as an anaplastic oligoastrocytoma or glioblastoma with oligodendrogial features, and that can lead to a lack of consensus even among
Molecular Characteristics

Molecular changes in AO that impact patient outcomes were first described beginning in the late 1990s. One significant finding associated with tumors of oligodendroglial lineage was codeletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). Frequently, deletion of 1p or 19q was found in anaplastic oligodendrogliomas, but only when both were deleted was there a significant improvement in sensitivity of these patients to treatment and improved survival. It has since been shown that the majority of 1p/19q codeletions are mediated by a translocation of 1p and 19q. In some of these cases, there is an accompanying mutation of either the CIC (capicua) gene and/or the FUBP1 (far upstream element-binding protein 1) gene in the remaining allele. The 1p/19q codeletion can be tested routinely using fluorescent in situ hybridization (FISH) analysis. However, patients identified as having a relative 1p/19q codeletion due to aneuploidy may have a significantly worse prognosis and a clinical course more suggestive of anaplastic astrocytoma, and must be differentiated from those with true codeletion.

Another recently discovered prognostic genetic change is the mutation in the genes encoding for the isocitrate dehydrogenase 1 and 2 enzymes (IDH1 and IDH2) in glioma cells. The IDH mutations result in the accumulation of 2-hydroxyglutarate, which is thought to be involved in oncogenesis. The IDH mutations also result in a hypermethylated phenotype that has a better prognosis than that of patients with wild-type IDH. Of note, nearly all patients with the 1p/19q codeletion tend to have either an IDH1 or an IDH2 mutation. However, there is a separate cohort of tumors that do not have the 1p/19q codeletion but that do have an IDH mutation. This latter group has a worse prognosis than the 1p/19q codeleted subpopulation, but a better prognosis than the IDH wild-type group.

Rarely, other molecular features are found in AO, such as PI3K mutations, PTEN loss, EGFR amplification, 10q loss, or high VEGF expression. These findings tend to be associated with a poorer prognosis. A molecular feature that distinguishes AO from other anaplastic gliomas is the absence of mutant p53. The Ki-67 (MIB-1) index may play a prognostic role, with values higher than a cutoff of around 23% representing worse progression-free and overall survival in AO.

Long-Term Follow-Up Alters Trial Results

Chemotherapy Used in (A) EORTC 26951[31], (B) RTOG 9402[29], (C) RTOG 0131[35], and (D) NOA-04[11]

The recognition in the early 1990s that some patients with AO demonstrated dramatic responses to either radiation or chemotherapy led to the development of two complementary clinical trials. The Radiation Therapy Oncology Group (RTOG) 9402 trial looked at dose-intense PCV therapy followed by radiotherapy, and the European Organisation for Research and Treatment of Cancer (EORTC) 26951 trial looked at radiotherapy followed by PCV therapy. Neither trial incorporated 1p/19q deletion status or IDH mutation status (neither marker had been described at the time), but both...
trials retrospectively tested tissue samples once those data had been shown to be important. When these data were initially presented in 2006, there was no significant difference in overall survival between the combination arms and the radiotherapy alone arms, but it was noteworthy that the median survival in the combination arms had not yet been reached in those with 1p/19q codeletion.[4,5] While there had been a clear improvement in progression-free survival in the patients with 1p/19q codeletion, in the correlative quality-of-life study done in conjunction with RTOG 9402, there was no significant difference in quality-of-life measures associated with the improvement in progression-free survival.[4,29,30]

Over the next several years, not only did additional follow-up data become available, but significant efforts were made to complete testing for many patients regarding their 1p/19q status and the presence of IDH mutations.[29,31] The long-term data from RTOG 9402 and EORTC 26951, with median follow-ups of 11.3 and 11.7 years, respectively, now show a significant improvement in overall survival in the patients with 1p/19q codeletion, with median overall survivals (mOS) of 14.7 years and NR (not reached) in the patients receiving combination therapy, compared with 7.3 years and 9.3 years in those receiving radiation alone (hazard ratio [HR] = 0.47; 95% CI, 0.30 to 0.72; \( P < .001 \) — and HR = 0.56; 95% CI, 0.31 to 1.03; \( P = .0594 \)).[29,31] TABLE 1

**Long-Term Outcomes From EORTC 26951[31] and RTOG 9402[29]**

RTOG 9402 had a longer median overall survival than EORTC 26951 for all patients in both the radiation/PCV arm and the radiation-alone arm (Table 1). This is likely related to the RTOG 9402 study having a higher percentage of 1p/19q codeleted patients (48% vs 25%) and a younger median age. Both studies had similar proportions of biopsies and subjects with poor performance status, as well as similar protocols for radiation treatment and follow-up. However, the difference in outcomes in the 1p/19q codeleted patients favoring EORTC 26951 over RTOG 9402 cannot be easily explained; EORTC 26951 has longer median progression-free survival in both the PCV/radiation and radiation-alone arms, and even has a longer median overall survival in the radiation-alone arm. Judging from the Kaplan-Meier curve, the median overall survival in the PCV/radiation arm in the EORTC study may be longer as well, once it is reached. A difference in just the PCV/radiation arm might be explained by the differences between the protocols with regard to the delivery of chemotherapy (adjuvant standard dose vs neoadjuvant dose-intensive chemotherapy). However, the difference with radiation alone is difficult to interpret, and would caution against drawing conclusions regarding chemotherapy in patients with 1p/19q codeletion when comparing the results of the two trials.

There was also a trend of improved outcome for those receiving combination therapy in some of the AO patients without 1p/19q codeletion; this is thought to have been influenced by the proportion of patients without 1p/19q codeletion but with IDH mutations, as these patients represent a distinct subtype of AO that may also respond to combination therapy.[26,29] There was no benefit for the patients who were IDH wild-type and without the 1p/19q codeletion.[26] On the basis of these results, radiation alone is no longer considered adequate treatment for patients with AO containing 1p/19q codeletion. The RTOG 9402 and EORTC 26951 studies did not address the efficacy of chemotherapy alone, a treatment approach that has been widely used by the neuro-oncology community.[32] TABLE 2
Reported Toxicities With PCV, TMZ, and Dose-Dense TMZ

**Temozolomide**

After the initiation of both RTOG 9402 and EORTC 26951, temozolomide (Temodar) was tested in a series of clinical trials for recurrent glioblastoma and anaplastic glioma. These efforts resulted in approval of this agent in 1999 for recurrent, nitrosourea-refractory anaplastic glioma. Temozolomide is an oral DNA alkylating agent with a much better toxicity profile (Table 2) than either lomustine alone or the PCV regimen, and small studies demonstrated activity in recurrent AO. The RTOG evaluated the potential role of temozolomide as neoadjuvant treatment in patients with newly diagnosed AO. A single-arm phase II trial, RTOG 0131, used dose-dense temozolomide followed by radiation therapy with concurrent temozolomide in AO (see Figure 2). The study design required residual disease prior to radiotherapy, and the investigators have noted that in two patients who had complete responses, radiotherapy was delayed and those patients continue to have durable responses. In the 23 patients with 1p/19q codeletions, neither median overall survival nor median progression-free survival have been reached after a median follow-up of 7.4 years. The 6-year overall survival is 82%, compared with 67% in the RTOG 9402 codeleted cohort who received PCV and radiation therapy. While these recently presented results are similar to the results of RTOG 9402, direct comparisons are difficult.

The NOA-04 (Neuro-Oncology Working Group [German] 04) trial randomly assigned patients with newly diagnosed anaplastic gliomas, including some AOs, to receive either radiation therapy or chemotherapy (temozolomide or PCV therapy) as first-line treatment, with crossover between arms allowed (see Figure 2). There was no significant survival difference between the two groups of patients. However, there were not enough patients with AOs, or data regarding 1p/19q status, to draw conclusions about treatment with chemotherapy alone. Nonetheless, this trial did establish that there were fewer adverse events in the patients receiving temozolomide than in the patients receiving PCV, although overall, there were more adverse events in either of the chemotherapy arms than in the radiation therapy arm. Of note, patients receiving PCV in this trial had fewer hematologic side effects than did patients in the prior trials with PCV; this difference is possibly related to the fact that patients in NOA-04 received a PCV regimen that was less intense than the one used in either RTOG 9402 or EORTC 26951.

**Discussion and Recommendations**

The National Comprehensive Cancer Network (NCCN) guidelines for adult anaplastic oligodendroglioma with 1p/19q codeletion, version 1.2013, begin with maximal safe feasible resection with a goal of gross total resection, verified by MRI 24 to 72 hours following surgery. While not all studies of oligodendrogial tumors have validated maximal surgery as a prognostic feature, an effort to obtain the largest safe resection possible is still recommended. Patients with AOs with 1p/19q codeletion have now been shown to clearly benefit from frontline use of radiation therapy and chemotherapy. Therefore, 1p/19q status is a predictive marker that has an impact on treatment decisions, and the NCCN guidelines mandate that all AOs be tested for 1p/19q codeletion. The predictive utility of IDH mutations is less clear; however, there are recent studies suggesting that patients with tumors that are without the 1p/19q codeletion but that are IDH-mutated may benefit from radiation and chemotherapy. Although strong evidence now exists for the use of radiation and chemotherapy in AO with 1p/19q codeletion, important questions remain. Given the significant toxicity associated with PCV—and the lesser toxicity of temozolomide compared with PCV—many clinicians would prefer to substitute...
temozolomide; however, there is not clear evidence of equivalent efficacy. A retrospective study involving a total of over 1,000 patients with AO suggests that when used alone, PCV (n = 21) may be superior to temozolomide (n = 68) in time to progression (7.6 years [95% CI, 4.2–9.3] vs 3.3 years [95% CI, 2.6–4.2]; \( P = .0186 \)) and in median overall survival (10.5 years vs 7.2 years; \( P = .16 \)) in patients with the 1p/19q codeletion.[36] However, there were no significant differences between 1p/19q codeleted patients who received radiation therapy and either temozolomide or PCV therapy. There are caveats to interpretation of these findings, such as the small sample size in this subgroup, changes in the diagnostic criteria for AO and for detection of disease progression over time, and differences in follow-up between these groups that obviate final conclusions.[36] The CODEL study, originally designed to compare radiation to combined radiation and temozolomide and to temozolomide alone for codeleted AO, is being reconfigured in light of the recent RTOG and EORTC results. The new protocol will likely compare combined radiation and PCV to combined radiation and temozolomide. However, this study will likely take years to complete accrual and several more years for efficacy data to emerge. Additionally, the optimal sequence of radiation and chemotherapy has not been established. The RTOG studies (9402 and 0131) used preradiation dose-intense chemotherapy, whereas the EORTC trial administered standard-dose PCV after radiation. Further complicating the issue, the RTOG 0131 study used a dose-dense temozolomide schedule, raising questions regarding the optimal temozolomide schedule as well. Also, vincristine has been shown to have limited blood-brain barrier penetration, leading some to omit vincristine, using PC instead of PCV.[37] In conclusion, we believe, based on the current data, the postoperative standard-of-care treatment for patients with 1p/19q codeleted AO should be a combination of radiation and chemotherapy. There are no studies for which Level I evidence exists that have directly compared PCV with temozolomide (data are limited to phase II studies). The issue of PCV vs temozolomide will likely be addressed in the reformulated international CODEL trial, but it will be many years before results are forthcoming. In the meantime, the optimal chemotherapy regimen (PCV or temozolomide) remains uncertain, and formal recommendations would be speculative. It is likely that many practices will continue to use temozolomide because of the toxicity issues associated with PCV, whereas others will change to PCV, prompted by the compelling results from two randomized clinical trials.

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