Clinical Discussion of the Management of Anaplastic Oligodendroglioma/Oligoastrocytoma (Both Codeleted and Nondeleted)

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Abstract
Anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA) are uncommon malignant tumors occurring in adults, but have garnered attention because of a high rate of response to chemotherapy in early studies. However, no clinical trial had demonstrated benefit with the addition of chemotherapy to radiotherapy alone until the long-term results of RTOG 9402 and EORTC 26951. These studies revealed prolonged survival in patients with anaplastic gliomas harboring the 1p/19q codeletion when treated with PCV (procarbazine, lomustine, and vincristine) and radiation therapy compared with radiation alone. These studies validated the use of 1p/19q codeletion status as a predictive biomarker in these tumors. Additional molecular characterization of these tumors may provide additional insight into treatment decisions, although these characterizations have yet to be fully elucidated. Even with the strength of the data advocating the use of combination therapy (PCV and radiotherapy), the incorporation of newer, less-toxic drugs such as temozolomide into many practices in the past decade raises important questions regarding the optimal chemotherapy regimen. Unfortunately, additional definitive phase III trials will take several years to answer remaining questions. Regardless, it is clear that patients with 1p/19q codeleted AO or AOA who can tolerate chemotherapy should not receive radiotherapy alone. (J Natl Compr Canc Netw 2014;12:665–672)

Molecularly driven therapy has become well established in the treatment of many subtypes of cancers. Despite efforts in the past decade to further refine glioma treatment according to molecular subtypes of malignancy, no significant progress in the development of predictive markers has been made. However, molecular patterns are now emerging that further define these tumors and their prognosis, and will potentially alter treatment recommendations. Currently, anaplastic oligodendroglioma (AO) is defined as a malignant tumor with features of oligodendrogial lineage and histologic characteristics, whereas anaplastic oligoastrocytoma (AOA) seem to have a mixture of oligodendrogial and astrocytic features; both correspond to WHO grade III.1,2 The reported annual incidence of AO ranges from 0.07 to 0.18 per 100,000, and it comprises only 0.5% to 1.2% of all primary brain tumors, whereas the exact incidence of AOA is not well established.2,4 This is complicated by the discordance even among expert reviewers, because the presence of abnormal astrocytes within an AO can lead to misdiagnosis as an AOA or anaplastic glioblastoma with oligodendroglial features, or an AOA might be misclassified as an AO if the astrocytic component is thought to be reactive.5 The peak incidence of these tumors is in the fifth decade and both tend to preferentially occur in the frontal lobe, followed by the temporal lobe.

Because prior results of clinical trials evaluating treatment of AO or AOA with chemotherapy, either alone or in combination with radiotherapy, showed no survival benefit and produced additional toxicity when compared with radiotherapy alone, standard therapy for these anaplastic gliomas was typically radiotherapy alone.6,8 However, crossover from patients undergoing radiation who receive chemotherapy after progression...
may have affected the ability to discern a survival difference. The growing evidence of the sensitivity of oligodendroglioma and oligoastrocytoma to combined treatment with procarbazine, lomustine, and vincristine (PCV) led to the consideration of the early use of chemotherapy for these specific tumors to delay or augment radiation therapy.9–11 Despite the absence of strong evidence in a randomized controlled study, an increased prevalence of the use of chemotherapy alone or with radiation has been seen in the past 3 decades.12

Even with therapy, the historical median overall survival for patients with AO has been reported to be between 2 and 6 years.6,7,13 In AOA, the average survival has been generally shorter, at around 3 years, although still improved compared with glioblastoma. Several studies have established the clinical features of younger age, higher Karnofsky performance status (KPS), and larger extent of resection as favorable prognostic features.13–17 Although no environmental factors are known to increase the risk of development of an oligodendrogial tumor, a single nucleotide germline polymorphism on chromosome 8q24.21 has recently been linked with this risk.18,19

Molecular Characteristics of AO and AOA

Inspired by the success of defining molecular subtypes of hematologic malignancies and other primary cancers, a molecular subtype of oligodendrogial tumors that was associated with differences in patient outcome was first described in the 1990s.20 The allelic loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) became associated with tumors of oligodendrogial lineage, revealing a new diagnostic marker, often termed 1p/19q codeletion.20 Additionally, when the 1p/19q codeletion was observed, a significant improvement in treatment response and improved survival were seen, further defining it as a prognostic marker.9 However, in contrast to the positive prognostic implications of the typical 1p19q codeletion, patients recognized to have a relative 1p19q codeletion because of aneuploidy may have a significantly worse prognosis and clinical course, and must be differentiated from those with a true 1p19q codeletion.21,22

More recently, further analysis revealed that most 1p/19q codeletions are produced by a translocation of 1p and 19q. Additionally, there is an accompanying mutation of either the homolog of Drosophila capicua (CIC) gene in most cases, and/or the far upstream binding protein 1 (FUBP1) gene in the remaining 20% of cases with 1p/19q codeletion.23,24 The TP53 mutation, which is most commonly observed in astrocytic lineage, is rarely described in AO, but is more frequently described in AOA, and are inversely related to the frequency of 1p/19q codeletion in AO and AOA.25 The 1p/19q codeletion can be tested routinely using fluorescent in situ hybridization (FISH) analysis, whereas the TP53 mutation can be evaluated with p53 immunohistochemistry (IHC), or with greater accuracy using mutational analysis.

O(6)-Methylguanine-DNA methyltransferase (MGMT) promoter methylation and the CpG island hypermethylation phenotype (CIMP) have also been identified in patients with AO and AOA.26 Both were prognostic markers for survival, but CIMP status had a stronger association, suggesting that MGMT promoter methylation status may be part of a methylation profile.26 The recently described mutation of the isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) enzymes in glioma cells is also strongly associated with a hypermethylated phenotype, leading to some speculation about a mechanistic association between IDH mutation and methylation.27 Patients with IDH mutations also have an improved prognosis over those with wild-type IDH, and these mutations may be a substitute for MGMT and CIMP status for evaluating methylation status.28 The mutation in the IDH enzymes results in the accumulation of 2-hydroxyglutarate (2HG), which is thought to be involved in glioma genesis.29 Notably, most tumors with 1p/19q codeletion have either an IDH1 or IDH2 mutation.30 Conversely, a separate cohort of tumors do not have the 1p19q codeletion but also have an IDH mutation. This latter group has a worse prognosis than the 1p19q-codeleted subpopulation, but an improved prognosis compared with the IDH wild-type group.25 Additionally, inactivating alterations in alpha thalassemia/mental retardation syndrome X-linked (ATRX) have been described in association with IDH mutations, and in most cases are mutually exclusive to the 1p/19q codeletion, suggesting they play a role in the development of glioma in patients with the IDH mutation but without the 1p/19q codeletion11,32 (Table 1).

PI3K mutations, PTEN loss, epidermal growth factor receptor (EGFR) amplification, 10q loss, CD-
KN2A loss, or high vascular endothelial growth factor (VEGF) expression are rare molecular features found in AO and AOA. These are generally associated with the IDH wild-type group, but even in rare patients who also have an IDH mutation, they are indicators of poor prognosis (Table 1). Ki-67 (MIB-1) index may play a prognostic role in AO, with one study suggesting that values higher than a cutoff of approximately 23% portend shorter progression-free and overall survivals.

### Table 1 Molecular Subtypes of AO/AOA

<table>
<thead>
<tr>
<th>Molecular Subtypes of AO/AOA</th>
<th>Composition of Subtypes</th>
<th>Prevalence in AO</th>
<th>Prevalence in AOA</th>
<th>Survival Independent of Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-CF</td>
<td>IDH mut and CIC-FUBP1 mut</td>
<td>77%</td>
<td>23%</td>
<td>8.0 y</td>
</tr>
<tr>
<td>I-A</td>
<td>IDH mut and ATRX mut</td>
<td>16%</td>
<td>65%</td>
<td>4.3 y</td>
</tr>
<tr>
<td>I-X</td>
<td>no CIC-FUBP1 or ATRX mut</td>
<td>7%</td>
<td>10%</td>
<td>1.1 y</td>
</tr>
<tr>
<td>IGS-9</td>
<td>1p19q codel ++, IDH ++, EGFR -</td>
<td>19%</td>
<td>26%</td>
<td>8.5 y</td>
</tr>
<tr>
<td>IGS-17</td>
<td>1p19q codel +, IDH ++, EGFR -</td>
<td>1%</td>
<td>1%</td>
<td>2.8 y</td>
</tr>
<tr>
<td>IGS-18</td>
<td>1p19q codel -, IDH -, EGFR +</td>
<td>IGS-18 (19%)</td>
<td>IGS-18 (19%)</td>
<td>1.2 y</td>
</tr>
<tr>
<td>IGS-23</td>
<td>1p19q codel -, IDH -, EGFR +</td>
<td>IGS-23 (19%)</td>
<td>IGS-23 (19%)</td>
<td>1.0 y</td>
</tr>
</tbody>
</table>

++ present in most samples; + present in some samples; – rarely present; – absent in all samples

Abbreviations: 1p19q codel, 1p/19q codeletion; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; ATRX, alpha thalassemia/mental retardation syndrome X-linked; CIC, homolog of Drosophila capicua; EGFR, epidermal growth factor receptor; FUBP1, far upstream binding protein 1; I-A, IDH1/ATRX group; I-CF, IDH1/CIC, FUBP1 group; I-X, neither I-A or I-CF; IDH, isocitrate dehydrogenase enzyme; IGS, intrinsic glioma subtype; mut, mutation present.

Combination Therapy for AO and AOA

RTOG 9402 and EORTC 26951 were complementary phase III clinical trials developed in the mid-1990s based on the early reports of high treatment response rates in patients with AO or AOA. RTOG 9402 compared dose-intense PCV therapy followed by radiotherapy and radiotherapy alone, whereas EORTC 26951 compared radiotherapy followed by PCV therapy and radiotherapy alone (Table 2). Although neither trial was initially designed to incorporate 1p/19q codeletion or IDH mutation status, because neither marker had been described at the time, both trials recognized the importance of prospective tissue collection, and were able to amend their protocols to retrospectively test tissue samples once those markers were established. For both studies, initial analyses in 2006 showed no significant difference in overall survival between the arms that combined therapies and the arms with radiotherapy alone. However, at the time of publication, the median survival in the combination arms had not yet been reached in patients with 1p/19q codeletion.

Although a clear improvement in progression-free survival was seen in the patients with 1p/19q codeletion, additional correlative quality-of-life studies performed by RTOG 9402 showed no significant difference in quality-of-life measures for the patients with 1p/19q codeletion.

Additional follow-up data over subsequent years coupled with extraordinary efforts to complete data regarding 1p/19q codeletion and IDH mutation status in both studies led to new long-term data. These data revealed significant improvements in overall survival among patients with 1p/19q codeletion, with median overall survivals of 14.7 years and NR (not yet reached) among those receiving combination therapy versus 7.3 years and 9.3 years in those receiving radiation alone in the RTOG and EORTC studies, respec-
tively (hazard ratio [HR], 0.47; 95% CI, 0.30–0.72; \(P<.001\) and HR, 0.56; 95% CI, 0.31–1.03; \(P=.0594\), respectively; Table 2). As the strongest available data, the studies indicate radiation alone should no longer be considered adequate treatment for patients with 1p19q codeleted AO tumors. However, these studies were not designed to address the efficacy of chemotherapy alone, which has been a widely used approach by the neurooncology community.

Additionally, combination therapy was also associated with a nonsignificant trend of improved outcome in some of the patients without 1p/19q codeletion in EORTC 26951 (Table 2). This finding highlights the fact that other molecular subtypes defined by markers other than 1p/19q codeletion exist that may benefit from combination therapy. The previously described group with both IDH and ATRX mutations may represent this additional subtype, because the trend of improvement with combination therapy is absent in the patients with IDH wild-type AO who are without the 1p/19q codeletion, but this has not yet been validated in a prospective clinical trial.

### Temozolomide in Anaplastic Glioma

Temozolomide is an oral DNA alkylating agent with a much better toxicity profile than either single-agent lomustine or the PCV regimen. After the initiation of both RTOG 9402 and EORTC 26951, temozolomide was tested in a series of clinical trials for recurrent glioblastoma and anaplastic glioma, and in 1999 this agent was approved for recurrent nitrosourea (ie, lomustine)–refractory anaplastic glioma. Small studies demonstrated the activity of temozolomide in recurrent AO and AOA. RTOG 0131 was a clinical trial designed to evaluate the role of temozolomide in the treatment of patients with newly diagnosed AO or AOA. This single-arm phase II trial administered temozolomide before radiation treatment, similar to RTOG 9402. In this trial, patients with AO were treated with dose-dense temozolomide followed by radiation therapy with concurrent temozolomide (Table 2). Results included 2 patients who experienced complete responses, and radiotherapy was deferred in those patients. Median overall survival has not been reached for the patients with 1p/19q codeletion, but a 6-year overall survival rate of 82% and 3-year progression-free survival rate of 77% were recently presented. Those without the 1p/19q codeletion had a median overall survival of 5.8 years and a median progression-free survival of 1.3 years. Given the small sample sizes, comparisons of results from RTOG 0131 and RTOG 9402 are difficult, although the results look similar (Table 2).

To evaluate the use of chemotherapy alone in anaplastic gliomas (including AOA and AO), the German Cancer Society Neuro-Oncology Working Group trial NOA-04 randomized patients to either radiation therapy alone or chemotherapy alone. Chemotherapy was either temozolomide or PCV, and crossover between arms was permitted (Table 2). No significant survival differences were found, even in light of the results from RTOG 9402 and EORTC 26951, and definitive conclusions about treatment with chemotherapy alone cannot be reached; there were not enough patients with AOA and AO or reported comparative outcomes stratified by 1p/19q codeletion. However, 1p/19q codeletion, MGMT methylation, and the IDH mutation were evaluated in these patients and were shown to be prognostic markers. As expected, this trial did confirm that patients receiving temozolomide experienced fewer adverse events than those receiving PCV. Although more adverse events occurred in the chemotherapy arms than in the radiation-only arm, fewer hematologic side effects were reported in this trial than in RTOG 9402 and EORTC 26951 (Table 2).

### Clinical Discussion and Recommendations

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for adult AO and AOA are currently stratified by 1p/19q codeletion status and KPS. The NCCN Guidelines state that all patients should undergo maximal resection, with an attempt at gross total resection, verified by MRI within 72 hours of the surgery. Most studies have validated extent of surgical resection as a prognostic feature, although these studies were performed in various types of malignant glioma. Additionally, obtaining tissue is important given the implications from molecular markers. Those with AO or AOA, KPS greater than or equal to 70, and 1p/19q codeletion are recommended to receive either combination radiation and chemotherapy or chemotherapy alone (as a category 2B option), whereas those without 1p/19q...
codeletion are grouped with anaplastic astrocytomas, and those with poor performance status (KPS<70) should receive less-aggressive care.

The inclusion of the 1p/19q codeletion status in the NCCN Guidelines is predicated on the benefit shown in RTOG 9402 and EORTC 26951 from frontline use of radiation therapy and chemotherapy, although RTOG 9402 included patients with a KPS of 60.36,38 Testing for it in all patients with AOA and AO is therefore mandated based on its utility as a predictive marker. The predictive utility of IDH mutations is less clear, although it is clearly a prognostic marker. However, recent studies suggest alternative molecular subgroups of AO and AOA, independent from the 1p/19q codeletion, that may benefit from combination therapy, associated with mutations in IDH and MGMT methylation.26,31,34 A small prospective study evaluating 107 patients with anaplastic glioma found that those with AOA and AO with 1p/19q codeletion and/or an IDH mutation had similar outcomes, also suggesting that molecular characteristics will provide a more accurate prognosis than histologic morphology.46

Despite the strong evidence for the use of radiation and chemotherapy in patients with AO with 1p/19q codeletion, important questions remain that were not addressed by prior studies. Given the significant toxicity associated with PCV, many clinicians prefer to use temozolomide, which has an overall better toxicity profile. Unfortunately, no prospective studies confirm the therapeutic equivalence of temozolomide. In a retrospective collection including 1000 patients with AO, data suggest that PCV may be superior to temozolomide when used without radiation therapy in patients with the 1p/19q codeletion, though the lack of prospective data precludes definitive conclusions.47 The CODEL study was originally a randomized phase III study designed to compare radiation with combined radiation and temozolomide versus temozolomide alone in patients with 1p/19q codeletion, but was halted because of the results of RTOG 9402 and EORTC 26951. The

### Table 2 Summary of the RTOG 9402, EORTC 26951, RTOG 0131, and NOA-04 Trials

<table>
<thead>
<tr>
<th>Comparison arm</th>
<th>RT alone</th>
<th>RT → PCV</th>
<th>TMZ → RT</th>
<th>CT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant results</td>
<td>mOS 4.7 vs 4.6 y</td>
<td>mOS 3.5 vs 2.6 y</td>
<td>mOS NR</td>
<td>mOS 6.9 vs 6.0 y</td>
</tr>
<tr>
<td>mPFS 8.4 vs 2.9 y</td>
<td>mPFS 13.0 vs 4.2 y</td>
<td>6-y OS: 82%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>mPFS 2.6 vs 2.7 y</td>
<td>mPFS 2.1 vs 1.8 y</td>
<td>mOS 5.8 y</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>mPFS 1.2 vs 1.0 y</td>
<td>mPFS 1.2 vs 0.7 y</td>
<td>mPFS 1.3 y</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

**Significant Toxicities From Chemotherapy**

| Hematologic | 56% | 46% | 38% | PCV 19%, TMZ 4% |
| Toxicity leading to abbreviated chemotherapy | 20% | 38% | 10% | PCV 16%, TMZ 6% |

**Abbreviations:** IV, intravenous; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; OS, overall survival; PCV, procarbazine, lomustine, vincristine; PFS, progression-free survival; RT, radiation therapy; TMZ, temozolomide.
revamped protocol will compare radiation with PCV and radiation with temozolomide, but will also provide some preliminary data regarding the frontline use of temozolomide alone, reserving radiation as a salvage regimen. For patients having an anaplastic glioma without the 1p/19q deletion, the ongoing CATNON study compares radiation alone; concurrent radiation and temozolomide; radiation followed by temozolomide; and concurrent radiation and temozolomide followed by temozolomide. In light of the experience of the prior clinical trials studying patients with AO, these studies will likely take years to complete, and several more years for efficacy data to mature. Additionally, final efficacy data may be difficult to interpret because of challenges from crossover when additional chemotherapy is used at progression.

Additionally, the optimal dosing of chemotherapy and sequence of radiation with chemotherapy has not been established, because both of the RTOG studies (9402 and 0131) used preradiation dose-intense chemotherapy, whereas EORTC 26951 administered radiation followed by standard-dose PCV. The RTOG 0131 study used a dose-intense temozolomide schedule, but no data comparing standard-dose temozolomide are available, leading to concerns regarding the optimal schedule for temozolomide use. Data suggesting decreased effectiveness of vincristine in primary brain tumors because of difficulty crossing the blood–brain barrier have also led some clinicians to drop the “V,” using a combination of procarbazine and lomustine (PC) in AO, instead of PCV, although the CODEL study will continue to use the full PCV regimen to avoid concerns about comparability with the prior RTOG and EORTC randomized trials.48

Conclusions

Based on the strongest data, the postoperative standard of care treatment for patients with 1p19q codeleted AO should be considered a combination of radiation and chemotherapy. Although no studies have evaluated comparative efficacy with PCV and temozolomide, the new CODEL trial should provide some answers, but in the short term, this pivotal question remains. Additionally, no study has compared the use of chemotherapy alone versus combined chemotherapy and radiotherapy in these patients, although CODEL will provide some preliminary data. Consequently, any formal recommendations regarding PCV or temozolomide schedule would be speculative and based on personal bias. Although no clear consensus exists, many physicians prescribe temozolomide as frontline treatment because of PCV toxicity. However, the results of RTOG 9402 and EORTC 26951 have resulted in a recent increase in the use of PCV for these patients. This uncertainty underscores the need for active recruitment and participation in the ongoing CODEL clinical trial. Conversely, the RTOG and EORTC studies provide support for using radiation therapy alone for patients without the 1p/19q codeletion, although some recent data suggest that grade III tumors with wild-type IDH may have tumor biology closer to grade IV gliomas, thereby requiring the chemoradiation treatment used for glioblastoma.31,34,49

Continued molecular studies and the development of agents, such as those targeting IDH mutation–related pathways, will likely impact future disease classification and lead to more refined treatment recommendations.50

References

7. van den Bent M, Carpenter AE, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic...


