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Anaplastic Glioma: Treatment Approaches in the Era of Molecular Diagnostics

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Opinion statement

The treatment paradigm for anaplastic glioma has shifted, owing to new diagnostic criteria and new phase III clinical trial evidence. In 2016, the WHO classification of brain tumors including diffuse gliomas was redefined to include molecular criteria, often supplanting the morphological appearance of the tumor cells. This was necessary as prognosis is more closely associated with molecular diagnosis than with morphology and grade. Recently, the benefit of adjuvant chemotherapy in addition to radiotherapy has been demonstrated in both anaplastic oligodendroglioma and anaplastic astrocytoma, as well as lower grade gliomas with the most marked benefit evident in IDH-mutated (astrocytoma) and 1p/19q co-deleted (oligodendroglial) tumors. The defining principle of recent breakthroughs has been the benefit of combinatorial therapy (chemo-radiation) as opposed to treatment in series or treatment of either modality after a period of observation upon evidence of progression.

Introduction

In the current models of gliomagenesis, a mutation in the isocitrate dehydrogenase (IDH) gene appears to be an early proximal event, following which there is a branch point, with subsequent whole-arm co-deletion of 1p and 19q lead to oligodendrogliomas, whereas loss of alpha-thalassemia/mental retardation syndrome X-linked gene (ATRX) expression leads to astrocytoma lineage [1, 2••]. Astrocytomas may also develop without IDH mutation (or loss of ATRX) and typically have loss of p53. Telomerase reverse transcriptase (TERT) mutations may be found in either oligodendroglioma or astrocytoma [2••, 3•].

Patients with anaplastic oligodendroglioma and anaplastic astrocytoma benefit more from chemoradiation

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than radiation alone. Specifically, in patients with oligodendroglioma, treatment with radiation therapy plus chemotherapy with procarbazine, lomustine, and vincristine (PCV) results in a tremendous prolongation of survival and progression free survival [4, 5]. Additionally, the significant survival benefit of adjuvant temozolomide chemotherapy in patients with anaplastic astrocytoma was recently reported in the interim results of the CATNON trial [6••] (ClinicalTrials.gov, number NCT00626990).

We will first discuss the updates in anaplastic oligodendroglioma.

Anaplastic oligodendroglioma

The Radiation Therapy Oncology Group (RTOG) 9402 study (initiated in 1994) [4, 7] and the European Organization for Research and Treatment of Cancer (EORTC) 26,951 studies [5] were both phase III studies examining the benefit of PCV chemotherapy in addition to radiotherapy, compared to radiotherapy alone in patients with anaplastic oligodendroglioma (pre WHO 2016 revision histological diagnosis).

In the RTOG 9402 study, 291 patients with histologically defined anaplastic oligodendroglioma, or histologically defined anaplastic oligoastrocytoma (an entity which was omitted from the WHO 2016 revision) were randomized to PCV followed by RT ($n = 148$) versus RT alone ($n = 143$), with the primary endpoint of overall survival. For the entire cohort, there was no difference in median overall survival by treatment (4.6 years PCV/RT versus 4.7 RT). When initial results were reported in 2006, concurrently with results of the EORTC 26951 study, neither study found an overall survival difference between the treatment arms [7].

With the genetic data available, a pattern emerged. Genetic alterations (1p/ 19q co-deletion and IDH mutation) were not identified until well after these studies had been initiated, but fortunately due to the foresight of the RTOG and EORTC study teams, archival tumor tissue from study participants could be located and assessed for these key genetic determinants, which yielded practice-altering results. A doubling of survival in the subset of patients with 1p/19q co-deletion eventually became clear as the data matured. This marked benefit was not detectable in 2006, when the median survival was 5 years. The implication that combinatorial chemoradiotherapy was superior to RT emerged only with mature follow-up.

In 2014, further analysis of the RTOG 9402 patient data [4] demonstrated that in the 210 (of the 291 on study) patients who were able to be evaluated for IDH mutation status, 154 (74%) had IDH mutations. In patients with IDH wild type tumors, combinatorial therapy did not prolong median survival (1.3 versus 1.8 years, HR 1.14, 95% CI 0.63–2.04, $P = 0.67$) or 10-year survival (6% in the combinatorial group, 4% in the RT only group). In contrast, patients with IDH mutant tumors did live longer after combinatorial therapy than with RT alone (5.5 years versus 3.3 years, HR 0.56, 95% CI 0.32–0.99, $P < 0.5$). An even more remarkable improvement in survival was seen in those patients with 1p/19q co-deleted tumors, in which treatment with RT plus PCV *doubled* median overall survival (14.7 years versus 7.3 years, HR 0.59, with 95% confidence interval 0.37 to 0.95, $P = 0.03$). Thus, for patients with 1p/19q co-deleted tumors, PCV plus RT may be an especially effective treatment, though the observation was derived from an unplanned analysis. The authors concluded that 1p/19q co-deletion and IDH mutational status identified patients with histologically diagnosed oligodendroglial tumors that benefited from

combinatorial chemo-radiotherapy.

Additionally, the authors of the RTOG study noted that the histologic criteria were not reliable in determining which patients would harbor the 1p/19q co-deletion, as 29% of anaplastic oligodendrogliomas had preservation of 1p and 19q (i.e., were not oligodendrogliomas per WHO 2016 revision), whereas 24% of anaplastic oligoastrocytomas did harbor 1p/19q co-deletion (i.e., were actually oligodendrogliomas per WHO 2016 revision). Notably, in the absence of 1p/ 19q co-deletion, the presence of a mutation in the IDH gene was also predictive of survival benefit from PCV therapy (this is of particular interest, as these tumors would now be classified as IDH-mutated astrocytomas, rather than oligodendrogliomas, though were histologically diagnosed as oligodendroglioma).

EORTC 26951, in-kind with RTOG 9402, was a phase III clinical trial in patients with newly diagnosed anaplastic oligodendroglioma, which randomized 368 patients to receive either radiation therapy alone (59.4 Gy) or the same RT followed by six cycles of adjuvant PCV (the RTOG 9402 evaluated PCV followed by RT). Results demonstrated a significantly longer OS in the RT/PCV arm vs RT alone arm (42.3 v 30.6 months, HR 0.75; 95% CI, 0.60–0.95). In the 80 patients with a 1p/19q co-deletion, 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, 0.31–1.03). The authors concluded that the addition of six 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. IDH mutation again was also prognostically significant [5].

Summary paragraph

The RTOG and EORTC studies demonstrate the clear benefit of PCV chemotherapy in addition to radiation in the treatment of patients with anaplastic oligodendroglioma. Both the RTOG 9402 and EORTC 26951 studies reported essentially the same findings of the addition of chemotherapy doubled survival from approximately 8 years (RT alone) to 15 years or longer. The greatest benefit was in patients with 1p/19 q co-deletion, though there was also benefit in patients with IDH mutations. Following the WHO update for glioma classification [2••], IDH-mutated gliomas negative for 1p/19q co-deletion would now be classified as IDH mutant astrocytomas, as the current diagnostic criteria for oligodendroglioma requires 1p/19q co-deletion.

Anaplastic astrocytoma

The "Concurrent and/or Adjuvant TMZ for 1p19q Non-deleted Tumors" (CATNON) is a phase III open-label study which randomized patients with newly diagnosed non-co-deleted anaplastic glioma to 1 of 4 treatment arms (1:1:1:1) involving combinations of RT (59.4 Gy in 33 fractions of 1.8 Gy) alone or with adjuvant temozolomide (TMZ) (12 4-week cycles of 150–200 mg/m^2 given on days 1–5), or to receive RT with daily temozolomide (75 mg/m^2) with or without adjuvant temozolomide. Interim results were published in August 2017 [6••]. The primary endpoint was overall survival,

Table 1. Summary of trials

Study	Treatment	N patients	mOS	mOS 1p/19q	mOS IDH mutant	mOS IDH wild-type
RTOG 9402	RT	143	4.6 y ($n = 143$)	7.3 y. ($n = 67$)	5.7 y ($n = 76$)	1.8 y ($n = 23$)
RTOG 9402	RT + PCV	148	4.7 y ($n = 148$) $P = 0.1$ HR 0.79 95% CI 0.60 to 1.04	14.7 y ($n = 59$) $P = 0.03$ HR 0.59 95% CI 0.37 to 0.95	9.4 y ($n = 80$) $P = 0.006$ HR, 0.59; 95% 95% CI 0.40 to 0.86	1.3 y ($n = 31$) $P = 0.67$ HR, 1.14; 95% CI 0.63 to 2.04
EORTC 26951	RT	183	30.6 m	112 m ($n = 37$)	64.8 m ($n = 36$)	14.7 m ($n = 50$)
EORTC 26951	RT + PCV	185	42.3 m	NR* ($n = 43$) HR = 0.56 95% CI 0.31 to 1.03	NR* ($n = 45$) HR = 0.53 95% CI 0.30 to 0.95 NR	19.0 m ($n = 47$) HR = 0.78 95% CI 0.52 to 1.18
CATNON	RT*	372**	41·1 m 5-y survival 44·1% 95% CI 36·3–51·6	NA	***	***
CATNON	RT + TMZ*	373**	NR* 5-y survival 55·9% 95% CI 47·2–63·8	NA	***	***

Median overall survival measurements vary by study, mOS was reported in years in RTOG 9402, reported in months in EORTC 26951 and CATNON. EORTC 26951 and CATNON did not report *p* values, instead using confidence intervals. CATNON patients did not have 1p/19q co-deletion, per the inclusion criteria. While mOS was not yet reached in the intervention arm of CATNON, the 5-year survival was superior

NA not applicable

*mOS not yet reached

**patients in intention to treat interim analysis

***data not yet released

analyzed for intention to treat. At publication of the interim analysis, 745 patients had been enrolled. The hazard ratio for overall survival with use of adjuvant temozolomide was 0.65 (99.145% CI 0·45–0·93). Overall survival at 5 years with adjuvant temozolomide was 55·9% (95% CI 47·2–63·8), and 44·1% (36·3–51·6) without adjuvant temozolomide. As such, the preliminary results of the CATNON study conclusively demonstrated the benefit of adjuvant temozolomide; the study is still ongoing to determine whether temozolomide administered during radiation adds further benefit and we are still awaiting the results in terms of the impact of genetic alterations (e.g., IDH, MGMT methylation) on patient outcome.

How does the benefit of temozolomide compare to the benefit of PCV?

Both of the aforementioned pivotal studies (RTOG 9402 and EORTC 26951) were initiated in the mid-1990s, prior to identification of molecular alterations (such as IDH, 1p/19q deletion, TERT promoter, etc.) which ultimately led to the

2016 WHO revised classification of gliomas. With the emergence of data in 2000 showing benefit of temozolomide in the context of recurrent glioma [8] and the landmark publication of the "Stupp regimen" in 2005 that showed the benefit of temozolomide in the context of newly diagnosed glioblastoma [9], the neuro-oncology field subsequently shifted almost exclusively toward temozolomide. However, the 2013 publications highlighting the mature results of RTOG 9402 and EORTC 26951 brought PCV back into the limelight, raising the important question as to which of the alkylator regimens—temzolomide or PCV—is superior or if they are equivalent. As previously noted in this review, PCV chemotherapy as an adjuvant therapy has clear benefit in grade II and III oligodendroglioma and also benefit in patients with IDH-mutated astrocytoma. The benefit of adjuvant PCV chemotherapy is equivocal in patients with non-IDH-mutated astrocytoma [4, 5, 10] and has been demonstrated to be ineffective in treating glioblastoma [11].

Whereas, per the CATNON results [6••], temozolomide clearly has benefit in astrocytoma, it remains unresolved as to whether the degree of benefit of temozolomide is similar to that of PCV in IDH-mutated anaplastic astrocytoma. The potential impact of IDH mutation on patient outcome in the CATNON study population is not yet known, though we may infer that indeed, there may be benefit as TMZ is modestly beneficial in glioblastoma, the vast majority of which are IDH wild type. Whether TMZ is non-inferior to PCV in oligodendroglioma also remains unclear at present time, but the ongoing trial, CODEL, (ClinicalTrials.gov, number NCT00887146) that compares TMZ vs PCV in oligodendrogliomas will hopefully resolve this [12] Table 1.

The "Codeleted Tumors" (CODEL) trial randomizes patients with oligodendroglioma (1p/19q co-deleted tumors only, both grade II and grade III) to RT followed by PCV versus RT plus TMZ followed by adjuvant TMZ. Additionally, this trial will compare quality of life and neurologic function following initial treatment regimens. Importantly, tissue collection will permit detailed genomic analyses to determine variability in outcomes based on differences in genetic alterations [12].

Questions remain as to why oligodendrogliomas, now defined by 1p/19q co-deletion (and almost always positive for IDH mutation), and IDH mutant astrocytomas are chemosensitive. An interesting theory as to the chemosensitivity conferred by the 1p/19q co-deletion was recently published [12]. The answer may, in part, stem from the impact of 1p/19 co-deletion on the formation of tumor microtubules. Astrocytoma cells have been demonstrated to extend ultra-long membrane protrusions termed tumor microtubules (TM) and use them as conduits that facilitate brain invasion, proliferation, and to interconnect tumor cells over long distances. In effect, tumor microtubules may help align astrocytoma cells into a functional syncytium, with the resultant routes for intercellular transport/communication constituting a mechanism that underlies resistance to chemo- and radiation therapy. In this regard, TM-connected astrocytoma cells in a mouse model demonstrate resistance to radiotherapy and chemotherapy mediated cell death by buffering calcium, and resupplying damaged cells with organelles such as mitochondria and nuclei. Conversely, 1p/19q co-deleted tumor cells (oligodendrogliomas) are relatively deficient for TMs and therefore lack the interconnected physical network (and the associated inter-cellular

buffering associated with TMs) and consequently are rendered more sensitive to chemotherapy [13•].

Conclusion

In just over a decade, the field of neuro-oncology has gone from one in which the role of chemotherapy remains unproved to one where tremendous advances have led to improved overall survival with alkylating agents. First came the Stupp regimen [9] that demonstrated the benefit of temozolomide in treatment of newly diagnosed glioblastoma patients with the concurrent identification of one of the first biomarkers, the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) in glioma biology [14]. Subsequent to that were consistent, almost yearly advances, with the emergence of the benefit of PCV in 1p/19q co-deleted anaplastic gliomas (oligodendrogliomas) [4, 5] and low grade gliomas [15•] and the benefit of temozolomide in anaplastic gliomas negative for 1p/19q co-deletion [6••]. Collectively, these advances have conclusively demonstrated that chemoradiation is superior to either radiation therapy alone or chemotherapy alone for patients with anaplastic oligodendroglioma and anaplastic astrocytoma [4, 5, 6••, 15•]. These advances have been facilitated by exciting advances in the identification of molecular genetic alterations of both prognostic and predictive value (e.g., IDH, 1p/19q deletion, MGMT, TERT to name a few) which have not only guide therapies but also have led to a complete revision of how gliomas are diagnosed [2••], with the premise that genetic alterations, not grade, are the pivotal determinants of diagnosis and therapy [3•]. With advances come more questions, including whether TMZ is non-inferior to PCV in co-deleted gliomas (subject of the ongoing CODEL study) and the molecular/cellular mechanisms that underlie treatment resistance or sensitivity based on molecular alterations. Indeed, the last decade has been exciting in fine-tuning our use of alkylator regimens in the treatment of anaplastic glioma patients but our growing knowledge of the molecular alterations in gliomas point us to therapies beyond alkylators, such as IDH-targeted small molecule inhibitors [16] and even IDH-targeted vaccines [17]. If the track record of our field in the last decade is any indication, then the next decade holds the promise of even more exciting advances.

Compliance with Ethical Standards

Conflict of Interest
Michael W. Ruff and Joon Uhm declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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