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Early results from the CODEL trial for anaplastic oligodendrogliomas: is temozolomide futile?

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See the article by Jaeckle et al. in this issue pp. 457–467.

Optimal incorporation of chemotherapy (CT) into the initial management strategy for patients with 1p19q codeleted anaplastic oligodendroglial tumors (AOTs) has intrigued our field for decades, particularly after Radiation Therapy Oncology Group 9402 and European Organisation for Research and Treatment Center (EORTC) 26951 showed survival was doubled by adding procarbazine, lomustine (CCNU), and vincristine (PCV) to radiotherapy (RT).[1,2] However, since those trials launched in the 1990s, the CT regimen of choice shifted from PCV to temozolomide (TMZ),[3] extrapolating from favorable results with combined TMZ and RT in glioblastoma,[4] particularly in light of the better tolerability and simpler schedule with than PCV.[5] Perhaps more importantly, relatively long survival is common, with the median exceeding 10 years in both RTOG 9402 and EORTC 26951.[1,2] Accordingly, late neurocognitive injury from early RT can be a serious concern,[6] and deferring RT altogether in favor of CT (usually with TMZ), became a common first-line approach by the mid-2000s.[3]

In that setting, the "CODEL" (Codeleted Anaplastic Glioma or Low-Grade Glioma) phase III trial (NCT00887146; North Central Cancer Treatment Group/Alliance for Clinical Trials in Oncology N0577, EORTC 26081-22086, NRG 1071, Canadian Cancer Trials Group CEC.6) was conceived and initially randomized patients with newly diagnosed codeleted AOTs to TMZ alone (originally arm C), or to RT without (arm B) or with (arm A) TMZ. In this issue of the journal, Jaeckle et al. report initial results from that study design, with strikingly poor progression-free survival (PFS) associated with TMZ alone in comparison to the combined results of the other two arms (median 2.9 years vs not reached, HR 3.12, 95% CI 1.26-7.69, log-rank $P < .01$).[7] While disappointing and worse than hoped, Jaeckle et al. noted the median was within the range (2.3-5.7) reported by others,[8–15] suggesting their results are not an outlier (Table 1).

However, before the utility of TMZ monotherapy is dismissed entirely, it is possible that noise from unexpectedly early disease progression among very few cases (particularly without central imaging review) could have clouded the efficacy signal in such a small cohort (n = 12 in arm C). For example, the 1-year PFS rate with TMZ alone in CODEL was approximately 60%,[7] whereas others reported rates as high as 100% (Table 1).[8–15] Therefore, such early failure to control the disease by TMZ seems unusual to us. Were there uncommon or uniquely negative prognostic factors among the few early progressors? Along these lines, 3/12 patients randomized to TMZ alone had tumors classified as isocitrate dehydrogenase (IDH) wild-type.[7] We agree with the authors' hypothesis that the *IDH* results could have been falsely negative for mutation. However, is it also plausible that 1p19q test results could have been falsely positive for codeletion in one or more of these 3 cases, despite central pathology review, explaining at least in part the unexpectedly poor outcome? Or, does codeletion alone (without *IDH* mutation), if a true result, have different biologic implications for prognosis or chemosensitivity than in tumors that also harbor *IDH* mutations? Similarly, could *CDKN2* loss or other unfavorable prognostic factors resulted in imbalance across the arms? Nonetheless, and despite the limitations of sample size and survival immaturity, we do agree that superior outcome with TMZ alone to the other arms was statistically impossible (and non-inferiority was exceedingly unlikely) based on these early results, and discontinuing enrollment to arm C was reasonable and appropriate.

What, then, is the optimal approach to treatment for codeleted AOTs. In our view, there is a spectrum of reasonable options. Clearly, RT alone is inadequate, but everything else remains on

Table 1 Studies of Temozolomide as First-Line Therapy for Anaplastic Oligodendroglial Tumors

First Author (Studies Alphabetized)	Temozolomide Regimen	n (With 1p19q Codeletion)	Median PFS/TTP (y)	0.5-y PFS/ TTP Rate	1-y PFS/ TTP Rate
Ahluwalia[8]	150 mg/m^2 BSA days 1-7 and 15-21 of 28	20	5.2	~90%	~85%
Gan[9]	150-200 mg/m^2 BSA, days 1-5 of 28	18	~2.3	~90%	~70%
Jaeckle (CODEL)[7]	150-200 mg/m^2 BSA, days 1-5 of 28	12	2.9	~80%	~60%
Lassman (retrospective)[10]	Various	68	3.3	~95%	88%
Mikkelsen[11]	150-200 mg/m^2 BSA, days 1-5 of 28	36	2.4	94%	77%
Taliansky-Aronov[12]	200 mg/m^2 BSA days 1-5 of 28	7[a]	Not reached	100%[b]	100%[b]
Thomas[13]	200 mg/m^2 BSA days 1-5 of 28	33	Impacted by other therapy[c]	~90%	Impacted by other therapy[c]
Vogelbaum (RTOG 0131, long-term results)[14]	150 mg/m^2 BSA days 1-7 and 15-21 of 28	18	Impacted by other therapy[d]	100%	Impacted by other therapy[d]
Wick (NOA-04, long-term results)[15]	200 mg/m^2 BSA days 1-5 of 28	16	4.5	~100%[e]	~95%[e]

PFS, progression-free survival; TTP, time to progression; RT, radiotherapy; mg/m^2 BSA, milligrams per square meter of body surface area; y, years; ~, estimated from published Kaplan-Meier survival curve.
[a]Included 1 patient each treated previously with RT or PCV for low-grade oligodendroglioma.
[b]PFS landmarks inferred from 100% rate at 2 years.
[c]High-dose chemotherapy with autologous stem cell transplant was planned following 6 cycles of temozolomide for patients without progressive disease; thus, median and 1-year PFS rate not attributable exclusively to temozolomide.
[d]RT was planned following 6 cycles of temozolomide for patients without a complete response by central review; thus, median and 1-year PFS rate not attributable exclusively to temozolomide.
[e]Among cases characterized as "Glioma CpG Island Methylator Phenotype-Codel" molecular subtype which closely aligns with 1p19q codeletion.

the table. PCV with (before or after) RT is best supported by the available data when prioritizing efficacy.[1,2] Combined RT and TMZ is also reasonable and will be compared against combined RT and PCV in the current CODEL schema, although maturity will require many years.[16] Unfortunately, concerns about late toxicity from proscribed RT as part of both of the current arms is a barrier to accrual: anecdotally, one of us (A.B.L.) was unable to accrue any patients to CODEL over a 2.5-year window, leading to closure by institutional monitoring committees. With regard to deferring RT, one ongoing trial in France (POLCA, NCT02444000) remains incomplete, randomizing patients to PCV alone or with RT, and will compare survival without neurocognitive deterioration. Pending results, another approach is to initiate PCV first and decide whether to initiate or defer RT depending on both response and the concern about safety. Recent expert guidelines also provide support for deferring RT (or both RT and CT), in select patients.[17]

Although treatment with PCV alone was not among the CODEL arms, the early PFS results from CODEL[7] reinforce the opinion we previously offered in this journal[18] that PCV rather than TMZ should be recommended as the regimen of choice if RT is deferred when disease control as the goal is prioritized over tolerability. As Jaeckle et al. noted, long-term results of the German NOA-04 phase III trial[15] and our retrospective study[10] also suggest that PFS is significantly longer with PCV than TMZ. Moreover, and although cross-trial comparisons are fraught with risk of overinterpretation, radiographic responses of codeleted AOTs are more frequent and durable with PCV (93%-100%) than TMZ (35%-82%), as reviewed elsewhere.[5]

However, since our prior writings,[5,18] a post-hoc analysis of one study surprisingly suggested the efficacy of TMZ is superior to PCV.[13] When taking into account the small sample size and immaturity of survival results in CODEL,[7] we admit that a reasonable argument can be made to support TMZ monotherapy for some patients, particularly when concerns about tolerability or compliance outweigh efficacy as the primary goal.

Open questions include the number of PCV cycles required for full effect, the relative contribution of vincristine to the regimen, the relative benefit (or harm) of TMZ dose intensification (Table 1), the potential to reduce toxicity by substituting proton for photon-based RT (or reduced RT in patients with highly favorable prognostic factors), and the impact on treatment recommendations of *MGMT* promoter methylation as well as other emerging biomarkers.

Perhaps most importantly, RT, TMZ, and PCV are now old treatments. New and better approaches are needed and would be welcomed by patients and providers. Many are under active investigation, and we eagerly await the results of ongoing studies.

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