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Radiation Therapy Oncology Group 9802: Controversy or Consensus in the Treatment of Newly Diagnosed Low-Grade Glioma?

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Abstract

Treatment of newly diagnosed or suspected low-grade glioma (LGG) is one of the most controversial areas in neuro-oncology. The heterogeneity of these tumors, concern regarding morbidity of treatment, and absence of proven overall survival benefit from any known treatment have resulted in a lack of consensus regarding the timing and extent of surgery, timing of radiotherapy (RT), and role of chemotherapy. The long-term results of Radiation Therapy Oncology Group (RTOG) 9802, a phase III randomized trial comparing RT alone with RT and 6 cycles of adjuvant procarbazine, CCNU, vincristine (PCV), demonstrated an unprecedented 5.5-year improvement in median overall survival with the addition of PCV chemotherapy in high-risk patients with LGG. These results are practice changing and define a new standard of care for these patients. However, in the intervening decade since the trial was completed, novel molecular markers as well as newer chemotherapy agents such as temozolomide have been developed, which make these results difficult to incorporate into clinical practice. This review summarizes the evidence for and against the role of upfront RT and PCV in newly diagnosed patients with LGG.

Introduction

Treatment of newly diagnosed or suspected low-grade glioma (LGG) is one of the most controversial areas in neuro-oncology. Historically, this controversy was due in part to the variability in natural history, which is increasingly being identified as correlating with different molecular subtypes.[1-4] In addition, the potential toxicities of treatment in patients with extended survival potential but little hope of cure significantly contributed to this debate. The heterogeneity of these tumors, concern regarding morbidity of treatment, and absence of proven overall survival (OS) benefit from any known treatment have resulted in a lack of consensus regarding the timing and extent of surgery, timing of radiotherapy (RT), and role and timing of chemotherapy.

When comparing the current landscape to the era of the early radiation dose escalation trials, it is clear that the LGG treatment paradigm has shifted from aggressively pursuing treatment

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in hopes of improved survival to minimizing treatment morbidity and prolonging quality of life (QOL) and cognitive function for as long as possible.[5] Although Radiation Therapy Oncology Group (RTOG) 9802 was designed to intensify treatment with the addition of chemotherapy to “high-risk” patients after RT, now chemotherapy commonly is used as a method to delay RT and the potential cognitive effects associated with RT. Favorable responses seen with the combination of procarbazine, CCNU, and vincristine (PCV) in anaplastic oligodendrogliomas led to the evaluation of this combination in low-grade oligodendrogliomas and oligoastro-cytomas and eventually all histologies of diffuse low-grade gliomas, as was included in RTOG 9802.[6,7] The oral alkylating agent temozolomide (TMZ), which has demonstrated efficacy in glioblastoma[8] and has a superior tolerability profile to PCV, has been increasingly evaluated in LGG. Multiple reports demonstrated objective shrinkage in 31%-62% of LGGs with TMZ,[9,10] and median duration of tumor response or stabilization ranges from 10-31 months for recurrent LGGs and may exceed 3 years in patients previously untreated with RT.[9]

With no concerns of a resulting detriment to OS, neuro-oncology providers have based treatment decisions primarily on the goal of minimizing morbidity—pursuing treatment for patients whose tumor was expected to cause imminent morbidity, or delaying treatments expected to have more toxicity than progressive tumor. The eligibility of the currently open RTOG 0925, an observational study for patients with “low-risk” LGG reflects this modern treatment paradigm. Patients of any age with residual T2 abnormality < 2 cm in greatest dimension, patients younger than 40 years with any extent of resection, and patients younger than 50 years with tumor size < 4 cm before resection are all eligible for observation based on a predicted median survival of greater than 10 years. With the recent report of the results of RTOG 9802, a breakthrough in LGG treatment has been reported: improved OS based on the study intervention, the addition of PCV chemotherapy to RT. Should the outcomes of RTOG 9802 result in a paradigm shift once again?

PCV Chemotherapy in Gliomas

Foreshadowing of this tectonic shift began with the final reports of the efficacy of PCV chemotherapy in anaplastic oligodendrogliomas and oligoastrocytomas. The RTOG and European Organization for Research and Treatment of Cancer (EORTC) both reported long-term outcomes of prospective, randomized trials showing evidence that PCV and RT improved survival compared with RT alone in patients with isocitrate dehydrogenase (IDH) mutations, with or without 1p/19q codeletion.[13,14] Both trials began before genetic features o these tumors was completely understood, but tumor tissue was obtained for future genetic analyses. The addition of PCV chemotherapy to RT improved progression-free survival (PFS) but not OS in the initial report of RTOG 9402. In long-term follow-up, again there was no difference in survival with the addition of PCV to the group overall. However, in patients with both 1pand 19q gene deletions,the addition of PCV improved survival from 7.3 to 14.7 years ($P = 0.03$). Although this difference in survival was marginally statistically significant in the EORTC study ($P = 0.0594$), the hazard ratio (HR) for the risk of death was reduced by a similar effect in both studies. These results must be interpreted with caution as neither study was powered for subgroup analysis and stratification by codeletion was an unplanned retrospective analysis. Nevertheless, this unprecedented improvement in OS and

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understanding that 1p/19q codeletion and IDH mutation status are not only prognostic factors but molecular factors that inform treatment[15] renewed interest in the long-term results of RTOG 9802.

Before our current understanding of molecular heterogeneity in these tumor types, diffuse low-grade gliomas were risk classified based on results of the initial dose-finding studies performed by both North American and European cooperative group trials.[16, 18] Although risk classification differs slightly between the reports, the most important clinical variables with prognostic significance for poor OS are age (>40 years), tumor diameter (> 6 cm), tumor crossing midline (which also correlates with resectability), presence of neurologic deficit, and astrocytic histology.[11,19] Although not as well established during this time period, evidence was emerging that 1p/19q codeletion, often seen in oligodendroglial tumors, was associated with improved OS in patients with LGG regardless of treatment suggesting a different natural history in this molecular subtype.[1,3]

With this background, RTOG 9802 was designed with 2 cohorts, a high-risk group randomized to adjuvant chemotherapy or no adjuvant therapy after conventional RT and a low-risk group that was observed without radiation or chemotherapy. The high-risk group in this study was defined as patients with diffuse gliomas (regardless of histology) who were 40 years or older with any extent of resection and patients who were 18 years or older whose tumors were less than completely resected. The radiation dose was 54 Gy in 30 fractions. Patients assigned to receive chemotherapy were treated with 6 cycles of procarbazine (60 mg/m^2 orally per day on days 8 through 21 of each cycle), lomustine (110 mg/ m^2 orally on day 1 of each cycle), and vincristine (1.4 mg/m^2 [maximum 2 mg]) intravenously on days 8 and 29 of each cycle. The cycle length was 8 weeks.

Initial results of RTOG 9802 were published in the Journal of Clinical Oncology in 2012.[20] With a median follow-up of 5.9 years, PCV chemotherapy was found to have significantly prolonged PFS compared with patients assigned to radiation alone. However, OS was not significantly prolonged in the prespecified initial analysis. The rates of grade 3 and grade 4 hematologic toxicities were 8% and 3% with RT alone compared with 51% and 15% with RT and PCV ($P < 0.001$). Although the investigators report that 95% of patients completed their study regimen with “acceptable” variations, previous studies using PCV including RTOG 9402 suggest that it is poorly tolerated. In RTOG 9402, only 48% of patients randomized to PCV completed all 4 cycles as designed in the study. Because of the toxicity of treatment and lack of OS benefit, PCV was not routinely adopted as standard adjuvant therapy in these patients. In addition, TMZ had largely replaced PCV when chemotherapy was given.

The recently reported updated results now have a median follow-up of 11.9 years, and 55% of patients have died (Table).[21] The HR (0.5) for progression-free survival is now significantly in favor of RT and PCV, similar to the effect size in anaplastic oligodendrogliomas and oligoastrocytomas in the RTOG and EORTC trials. The median PFS for combined modality treatment is 10.4 years compared with 4 years if they received radiation alone. As opposed to many studies in which PFS differences stabilize over time, the differences between arms widen over time with an absolute difference at 5 years of 17%

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increasing to nearly 30% at 10 years. The long-term results also demonstrate that the difference in OS between the 2 arms is now statistically significant (HR = 0.59, $P = 0.03$). Patients treated with radiation therapy and PCV had a median OS of 13.3 years compared with 7.8 years for radiation alone, again strikingly similar to the results seen in the anaplastic studies. OS differences also widened over time with an absolute difference at 5 years of approximately 10%, increasing to 20% by 10 years.

Currently, it is not clear why the separation of the PFS and OS distributions widens over time. Evaluation by histologic type and genetic alterations is still pending, but there may be a subset of patients with a favorable genetic profile that is chemosensitive. Similar survival distributions were seen in patients with anaplastic oligodendroglial tumors treated with radiation therapy alone or radiation therapy plus PCV in protocol RTOG 9402. The survival benefit associated with the addition of chemotherapy was limited to those patients with 1p/19q codeletions and IDH mutations.[13] Alternatively, the results also may suggest that salvage treatment is not as effective as upfront adjuvant treatment in controlling this disease. Radiation oncologists are very familiar with this pattern. Although it took 15 years of follow-up to demonstrate, radiation therapy as a part of breast conservation is now known to result in an improvement in OS in addition to reducing the risk of local recurrence.[22] In diseases that have effective salvage regimens such as breast cancer and now LGG, differences in progression may not manifest as differences in OS for many years. Although in breast cancer the eventual improvement in OS is likely owing to prevention of local recurrences that eventually result in metastatic disease, the mechanism by which the addition of PCV after RT results in improvement in OS is less clear. However, it is well known throughout oncology that both radiation and chemotherapy have the highest likelihood of eradicating nonhematopoietic malignancies when used in the setting of minimal-residual disease. Either by way of alterations in blood-brain barrier or by addition of PCV to tumors that have been injured immediately before RT, chemotherapy may be more effective in the adjuvant setting than when salvaging growing, radioresistant tumors. This hypothesis is unsettling in a population in which aggressive treatment has not been the treatment paradigm for nearly a generation.

Modern Treatment of LGG: The Role of TMZ

Although the results from this trial demonstrate conclusively that RT and PCV dramatically improve OS in historically high-risk patients as compared with radiation alone, the trial raises more questions than it answers. In the intervening decade since the trial's inception, radiation alone is not often the “standard” treatment, and instead chemotherapy alone is considered, especially for tumors with 1p/19q deletion or IDH mutations or both. One may hypothesize that as there is not a survival advantage associated with RT,[18] the real question is whether adjuvant rather than salvage radiation adds benefit to PCV for these patients. In addition, in the intervening decade since the trial was completed, TMZ has largely replaced PCV as standard first-line chemotherapy for most gliomas.

Although TMZ has not been compared with PCV in a prospective trial in LGG, the German Cancer Society Neuro-oncology Working Group reported on the results of a comparison study for anaplastic oligodendroglial tumors. NOA-04 randomized patients to either RT or

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chemotherapy with either PCV or TMZ, with a planned salvage crossover design, and failure was defined as failure of both treatments. The results have been reported with a maximal follow-up of 54 months, which is too premature to base any definitive conclusions. As expected, TMZ was better tolerated with less frequent and shorter treatment interruptions. Hematologic toxicity delayed 18% of cycles in PCV arm and 6% of cycles in TMZ arm. The median number of completed cycles was 4 (range: 1-5 cycles) for PCV and 8 (range: 0-12 cycles) for TMZ. The most common treatment-limiting nonhematologic toxicity was polyneuropathy, which occurred in 10% of patients treated with vincristine and led to discontinuation in 7% of patients. Prolonged PFS was seen in both RT and chemotherapy arms for patients with IDH1 mutations and MGMT promoter hypermethylation. The initial report revealed no difference in time to failure or survival between the study arms, but all patients received combined treatment as “salvage,” and there is no “adjuvant” arm for comparison. The RTOG also performed a single-arm phase II trial of TMZ in anaplastic oligodendroglial tumors evaluating the role of preirradiation and concurrent TMZ compared with historical patients treated on RTOG 0424 with RT-PCV. Patients received up to 6 cycles of dose-dense TMZ (150 mg/m2 body surface area for days 1-7 and days 15-21 of 28 days), followed by concurrent RT-TMZ for those without a complete response. Updated results of this trial demonstrated the 6-year OS for codeleted patients was greater following TMZ ± RT than RT + PCV in RTOG 9402 (82% vs 67%), although the results were not significant. Although it may appear that TMZ may have similar effects in codeleted patients with anaplastic oligodendroglial, the RTOG phase II study was small, with 40 patients enrolled, of which only 23 were codeleted, so caution should be used when drawing comparisons between these results as RTOG 9402 demonstrated no evidence of benefit of PCV in patients with neither 1p/19q codeletion nor IDH mutations.

Preliminary results of RTOG 0424, a single-arm phase II study evaluating concurrent and adjuvant TMZ with 54 Gy of RT in patients with LGG suggest TMZ may improve survival in high-risk patients compared with historical controls receiving RT alone. High-risk patients in this study had 3 or more of the EORTC-established risk factors. With a median follow-up time of 4.1 years, median survival was not yet reached. The 3-year OS rate was 73.1% (95% CI: 65.3%-80.8%), which was significantly improved compared with historical controls ($P <$ 0.0001). Although the definition of “high risk” is different between the trials and it is likely that RTOG 9802 included more lower risk patients, 3-year OS on the both the RT-alone arm and RT-PCV arm of was nearly 80%. Further statistical analysis may be able to match risk factors for improved comparisons; however, it is well established that OS in LGG has improved over time,[27,28] likely owing to a combination of earlier diagnosis, safer and more aggressive surgical intervention, and more effective salvage regimens highlighting that care must be taken when comparing more modern results with historical patients. Thus the efficacy of TMZ in this group, especially compared with PCV, has not yet been established.

Future Directions

Although the results of RTOG 9802 should be practice changing, will they be? With increased understanding of the molecular subtypes and dense penetration of TMZ in the clinical armamentarium, there is still resistance to this practice-changing “consensus” for newly diagnosed LGG. The identification of molecular markers such as 1p/19q deletion and

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IDH mutations that identify subgroups of patients with median survival exceeding 10 years has also resulted in reclassification of patients previously considered “high risk” to patients in whom aggressive treatment is often deferred. For example, should a gross-totally resected, 1p/19q deleted, IDH mutated oligodendroglioma in a patient 4age 40 years receive immediate RT and PCV? This patient would have been considered high risk by RTOG 9802 criteria. What is an appropriate balance between an improvement in the number of years gained compared with the quality of those years? Although RT is often quoted as a concern for decreased cognitive function and reduced QOL in patients with brain tumor, patients with LGG receiving focal RT with modern techniques have very mild cognitive changes over time that are not detectable by formal neuropsychiatric evaluation until greater than 12 years from treatment.[29,30] With the addition of PCV, many patients are living more than 12 years and thus are at risk of developing cognitive changes. The importance of tumor progression on cognition is poorly understood and is under investigation in the currently open RTOG “low-risk” observational study, RTOG 0925. Information on this study will be critical in helping weigh the risks of observation in this cohort. Unfortunately, neither RTOG 9802, RTOG 9804, nor the EORTC studies included formal neurocognitive assessment (other than Mini-Mental State Examination) as a part of the trial. Thus, we will never have robust neurocognitive data (which requires baseline evaluations) from these prospective studies with long-term follow-up to help weigh these risks and benefits for modern patients who are now often observed in attempt to delay treatment-related morbidity.

Analysis of RTOG 9802 by histologic subtype is still pending. Preliminary results of the exploratory subgroup analysis have been presented in abstract form and suggest that although all patients treated with PCV had apparent improvement in OS and PFS, the effect appears to be greatest in patients with oligodendroglioma, and least in those with astrocytoma, in whom the differences were not statistically significant (7.7 vs 4.4 years [P=.31] for OS and 3.7 vs 1.8 years [P=.06] for PFS).[21] The final analysis of both the RTOG and EORTC studies in grade III patients revealed that a statistically significant survival advantage was limited only to patients with 1p/19q or IDH gene deletions. In a 45-year-old individual with a 1p19q noncodeleted grade II astrocytoma, do the benefits of PCV outweigh the toxicities in comparison with TMZ? Until we have further understanding of the influence of molecular markers on outcomes, these and other questions remain unanswered. Further study comparing adjuvant TMZ with adjuvant PCV after RT as well as evaluating the additional benefit of RT in addition to these chemotherapy agents in light of our new understanding of molecular markers is needed. CODEL, a randomized phase III trial of radiation therapy plus either TMZ or PCV for patients with newly diagnosed 1p/19q codeleted anaplastic gliomas, is ongoing and will likely be modified to include patients with 1p/19q codeleted grade 2 gliomas to answer the question of the optimal chemotherapy regimen.

Although we rejoice in the prolonged survival we see in the treatment of LGG in the modern era, studies requiring more than a decade to determine results are no longer fashionable, both owing to the current funding environment and in consideration of advancing the science in the best interest of our patients. Moving forward, investigators should focus on developing valid surrogates of OS to hasten the time for obtaining definitive results. PFS may be valid in some disease setting; however, PFS did not correlate with OS in radiation alone studies, but

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PFS and OS were very similar in R9402, EORTC 26951, and R9802. Advanced imaging techniques, such as PET or novel MRI sequences that can be correlated with outcomes, may provide guidance. Finally, robust neuro-cognitive assessment and quality-of-life evaluation must be included in LGG trials to help weigh the benefits and risks of treatment in this population.

In the meantime, we now have level I evidence that the addition of PCV to RT improves OS by greater than 5 years in patients with LGG. These results are practice changing. Patients meeting RTOG 9802 eligibility criteria should be treated with RT and PCV, unless there are clear contraindications or patient preferences to proceed otherwise. Until compelling data are available demonstrating either superior outcomes, equivalent outcomes with less toxicity, or subsets of patients who do not benefit from the treatment, this is the new standard of care. For patients and providers who are resistant to these recommendations, the only way to answer the remaining questions is by enrollment on prospective clinical trials. Patients and providers who feel observation after surgery is appropriate for modern “low-risk” patients who would have been eligible for RTOG 9802 should enroll their patients on the currently open observational study RTOG evaluating the consequences of observation on neurocognitive outcomes as well as survival. The CODEL trial is expected to be modified to allow 1p/19q deleted grade 2 patients and is evaluating TMZ as an alternative to PCV. Only by participation in well-designed clinical trials can we develop new evidence-based treatment strategies. The reason we practice evidence-based medicine is that we are truly not smart enough to predict the efficacy and toxicity of therapies without it.

Conclusions

RTOG 9802 is the first prospective trial in LGG to demonstrate a treatment-related increase in survival. Patients with high-risk LGG, defined as age > 40 years or subtotal resection in an adult, have an unprecedented 5.5-year median improvement in OS. Although these results are practice changing, incorporation of these results into clinical practice has not been straightforward for all patients. In the decade since the trial was completed, significant advances have occurred in the understanding of molecular subtypes in LGG as well as development of effective and more easily tolerated chemotherapy, TMZ, has occurred. Further study comparing adjuvant TMZ with adjuvant PCV after RT, such as the CODEL trial, as well as evaluating the role of RT in addition to these chemotherapy agents, is needed. Future efforts should also include neurocognitive assessment, QOL, and development of surrogates for OS to allow for earlier evaluation of results in this group of patients with prolonged OS. However, until compelling data are available demonstrating either superior outcomes, equivalent outcomes with less toxicity, or subsets of patients who do not benefit from this treatment, RT and adjuvant PCV is the new standard of care in high-risk LGG.

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Table

Prospective Trials of Chemotherapy and Radiation for Newly Diagnosed Grade 2 and Grade 3 Gliomas

Trial	*n* (% 1p/19q Codeleted*)	(*P* Value) Median PFS (y)	(*P* Value)_Median OS (y)	Eligibility
RTOG 9802[21]	251 (not reported)	(*P* = 0.002)	(*P* = 0.0)	Grade 2
RT	128	4	7.8	>18 if STR
RT/PCV	126	10.4	13.3	≥40 any resection
RTOG 9402[13]	291 (48)	(*P* = 0.003)	(NS)	Grade 3 AO and AOA
RT	143	1.7	4.7	≥18 any resection
PCV/RT	148	2.6	4.6	
		(*P* < 0.001)	(*P* = 0.03)	
RT (codeleted)	52	2.6	7.3	
PCV/RT (codeleted)	44	>10 (From graph)	14.7	
EORTC 26951[14]	368 (25)	(*P* < 0.001)	(*P* = 0.018)	Grade 3 AO and AOA
RT	183	1.1	2.6	≥18 any resection
PCV/RT	185	2.0	3.5	
		(*P* = 0.002)	(*P* = 0.059)	
RT (codeleted)	37	4.2	9.3	
PCV/RT (codeleted)	43	13.1	Not reached 10 y, 58% (est)	
NOA-04[23]	318 (41)	(NS)	(NS) not reached	Grade 3
RT+(TMZ or PCV)	160	2.6	4 y, 72.6%	
(TMZ or PCV) + RT	107	2.7	4 y, 64.6%	
RTOG 0424[26]			Not reached	Grade 2
(RT/TMZ) +TMZ	136 (Not reported)	4.5	3 y, 73.1%	>3 high-risk factors
RTOG BR0131[25]			Not reached	Grade 3 AO and AOA
TMZ+(RT/TMZ)	40 (56)	5.8	3 y, 73% (est)	≥18 any resection

Abbreviations: AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; est, estimated from survival curves, NOA, Neuro-oncology Working Group of the German Cancer; OS, overall survival; PFS, progression-free survival; STR, subtotal resection.

*Percentage based on patients with evaluable tissue.