Anaplastic Oligodendroglial Tumors: A Tale of Two Trials

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The treatment of patients with anaplastic gliomas with an oligodendroglial component, either pure oligodendroglialoma or mixed oligoastrocytoma, remains controversial. In the early 1990s, it was recognized that some patients with these tumors demonstrated dramatic responses to systemic chemotherapy regimens, particularly the combination of procarbazine, lomustine, and vincristine (PCV), whereas patients with other types of glial malignancies within the same WHO grade 3 classification (ie, anaplastic astrocytoma) showed only modest and often short-lived treatment responses. This observation prompted two well-designed and complementary phase III trials for anaplastic oligodendrogial tumors, which are both reported in this issue.2,3

The Radiation Therapy Oncology Group (RTOG), in collaboration with four other North American–based cooperative groups, initiated RTOG 9402. Patients with histologically confirmed anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma were enrolled onto this clinical trial and were randomly assigned to receive either conventional external-beam radiation therapy or up to four cycles of the PCV combination chemotherapy regimen followed by external-beam radiation.2 Within 1 year of the initiation of the RTOG trial, the European Organisation for Research and Treatment of Cancer launched a study that randomly assigned patients with the same anaplastic oligodendrogial tumors to receive either external-beam radiation alone or external-beam radiation followed by six cycles of the combination PCV regimen.3 Both studies required central pathology review to standardize and confirm the histologic diagnosis. In addition, each study requested tumor tissue specimens be provided for future correlative studies. Both studies were successful in obtaining tissue samples from the majority of the enrolled patients, which proved to have a critical impact on the results from both trials.

Remarkably, both studies showed nearly identical results. They demonstrated no overall survival benefit when chemotherapy was added either before or after radiation in the initial treatment of anaplastic oligodendrogial tumors, despite the established chemotherapy sensitivity of these neoplasms. However, in both studies, the vast majority of patients who were randomly assigned to the radiation-only arm did receive chemotherapy off protocol at the time of tumor relapse. Therefore, a more accurate conclusion is that no survival benefit was noted with early chemotherapy compared with salvage regimens administered at the time of relapse or recurrence.

However, both studies did demonstrate a difference in the time to progression, which strongly favored the group receiving treatment with both chemotherapy and radiation. Does this mean that early chemotherapy is the better treatment approach? To answer this question, additional information is required that is currently not available. Specifically, these studies do not provide information regarding the impact of tumor progression on neurologic function and quality of life. If early chemotherapy, with the resultant prolongation of tumor control, delays neurologic worsening, then increasing time to progression has important clinical implications. However, the PCV regimen used by both studies was associated with a high rate of toxicity, particularly myelosuppression. Although we do not know the direct impact of chemotherapy-associated toxicities on neurologic function or quality of life, at least one patient had a treatment-associated death. Therefore, an analysis of the risk to benefit of the two approaches, early chemotherapy versus treatment at relapse, requires assessment of the functional status of the patients over the course of each trial. Without this analysis, it is difficult to decide whether delaying progression of disease with early chemotherapy is of any clinical benefit when the attendant risk of toxicity is considered. In this context, recent studies suggest that single-agent temozolomide may have similar activity as PCV in anaplastic oligodendrogial tumors but with a better toxicity profile.4 Therefore, the use of temozolomide would potentially alter the risk-to-benefit analysis of the early versus late use of chemotherapy. However, to date, a randomized clinical trial has not been reported that examines the efficacy of temozolomide plus radiation compared with radiation alone in this patient population.

The other critical component of these phase III trials is that they provide prospective validation of the predictive value of the allelic loss of heterozygosity (LOH) of the 1p and 19q chromosomes for oligodendrogial tumors. Previous reports in the literature examining this issue were either small trials or retrospective series that, although quite compelling, did not confirm the importance of this molecular finding.5-8 In both studies, patients with loss of 1p and 19q survived significantly longer than patients without the chromosomal changes. However, despite the reports of the association of 1p/19q LOH with response to chemotherapy, in these trials, the early addition of chemotherapy did not improve survival, although there was a significant impact on progression-free survival. This indicates that 1p/19q LOH is a marker for good prognosis and suggests that it may also predict response to treatment, either radiation or chemotherapy. In fact, this molecular profile with its profound association with outcome has stimulated
extensive investigations to find molecular changes of similar magnitude in other glial tumors.

These two well-performed phase III trials have not defined the standard of care for anaplastic oligodendrogliomas and anaplastic mixed oligoastrocytomas. Those who feel that prolonging disease control will positively impact neurologic function will likely use these findings to recommend the early use of chemotherapy along with radiation treatment. Others may recommend waiting for tumor recurrence to start chemotherapy, thereby delaying the toxicities associated with these treatment regimens. Given the available data, both approaches should be considered acceptable. However, what can be concluded from these studies is that histologic definitions of oligodendrogial tumors are no longer adequate. Determination of the presence or absence of 1p and 19q LOH should be mandatory because this finding has now been proven to have important prognostic and predictive power.

These clinical trials demonstrate the need for additional studies to define therapies for patients with grade 3 gliomas. Entry onto these trials must be based on a combination of histologic and chromosomal criteria. These studies should include serial and standardized measures of neurologic function,\(^9\) quality of life,\(^9,10,11\) and symptom assessment\(^12\) so that meaningful risk-to-benefit analyses, comparing the impact of treatment to that of tumor progression, can be carefully determined. These future studies, designed to establish the standard of care for grade 3 glial tumors, will require the accrual of a large number of patients onto randomized trials who are observed over long periods of time. Therefore, given the interest and expertise demonstrated by the two clinical trials under discussion, collaborative efforts between European and North American investigators should be encouraged.

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### References


### Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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