Should patients with anaplastic oligodendroglial tumours receive adjuvant chemotherapy?

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Anaplastic oligodendrogliomas are sensitive to chemotherapy, but the role and timing of chemotherapy remain controversial, according to the findings of a recent study.

Oligodendrogliomas comprise roughly 10% of all gliomas and have a more favourable prognosis than astrocytic tumours of the same histologic grade. In addition, recurrent anaplastic oligodendrogliomas (AOs) are particularly sensitive to chemotherapy with procarbazine, lomustine and vincristine (PCV), as first reported almost 20 years ago.[1] To determine the efficacy of PCV as part of upfront therapy, the EORTC trial (see opposite) randomised patients to receive either radiotherapy alone (considered the standard of care when the trial opened in 1995) or radiotherapy followed by six cycles of adjuvant PCV. Although radiation plus PCV resulted in an improvement in median progression-free survival (PFS) relative to radiation alone (23.0 vs 13.2 months; P=0.0018), there was no significant difference in overall survival (OS; 40.3 vs 30.6 months; P=0.23).

The Radiation Therapy Oncology Group (RTOG) Trial 9402 also examined the addition of PCV to radiation.[2] In this trial, 289 patients were randomised to receive four cycles of 'intensive' PCV before radiation or radiation alone. Similarly to adjuvant PCV, neoadjuvant PCV improved median PFS relative to radiation alone (31 vs 20 months; P=0.004), but did not significantly affect OS (58 vs 56 months; P=0.26). More-liberal histologic criteria for anaplasia and the higher frequency of tumours with loss of heterozygosity of chromosomes 1p and 19q (1p 19q LOH; 46% vs 25%) might account for the longer PFS and OS in patients in the RTOG study.

In both trials, however, 80% of patients in the radiation-alone arm received chemotherapy at progression. The two trials, therefore, studied upfront versus delayed chemotherapy rather than chemotherapy versus no chemotherapy. In that light, the lack of a significant effect on OS is not surprising; the results of both trials suggest that chemotherapy at progression has as much of an effect on OS as chemotherapy at diagnosis.

It therefore remains an open question as to whether or not the prolongation of PFS following adjuvant or neoadjuvant PCV in concert with radiation is worth the potential toxicity of the chemotherapy regimen. In fact, the treatment of newly diagnosed AO has become even more controversial since both trials opened. A recent survey of brain tumour specialists demonstrated significant variability in practice patterns.[3] For example, temozolomide is less toxic than PCV, and many patients now receive temozolomide in place of PCV.[3] The efficacy of temozolomide relative to PCV in the management of AO remains unclear, however, as the two chemotherapy regimens have never been prospectively compared.

Finally, when the EORTC and RTOG trials opened, radiotherapy was considered the standard of care for newly diagnosed AO, and both trials were designed to address whether or not chemotherapy could improve outcome. They did not, however, address the issue of deferred radiotherapy.

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Chemotherapy alone might be advised for patients with AO because they can survive long enough to experience cognitive toxicity from brain radiotherapy, especially patients with tumours exhibiting 1p 19q LOH. Several phase II trials of chemotherapy with deferred radiotherapy are currently underway or completed, and large multicentre retrospective and prospective phase III trials will also address this issue.

The EORTC and RTOG trials were landmark studies in the management of newly diagnosed AO; however, both trials raised new issues in addition to answering important questions. Future trials will require large cohorts of patients followed for many years and the participation of multiple centres. Until then, optimal management of newly diagnosed AO remains controversial.

References

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Synopsis

MJ van den Bent, AF Carpentier, AA Brandes et al. (2006) **Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial.** *J Clin Oncol 24:2715–2722*

Background. Two-thirds of patients with oligodendroglial tumours respond to chemotherapy with procarbazine, lomustine and vincristine (PCV). Tumours with deletions of chromosomes 1p and 19q are particularly chemosensitive. However, it is not clear when chemotherapy should be administered.

Objectives. To examine the value of adjuvant PCV chemotherapy after radiotherapy in patients with anaplastic oligodendroglioma (AO) or anaplastic oligoastrocytoma (AOA), and to evaluate the relationship between loss of heterozygosity of chromosomes 1p and 19q (1p 19q LOH) and outcome.

Design and intervention. This multicentre, randomised, controlled phase III trial included 368 patients (aged 16–70 years) with a newly diagnosed AO or AOA (Eastern Cooperative Oncology Group [ECOG] performance status 0–2). Between August 1996 and March 2002, 185 patients were randomly assigned to receive 59.4 Gy of radiotherapy in 33 fractions followed by six cycles of standard PCV chemotherapy. The remaining 183 patients received only radiotherapy. Treatment at the time of progression (defined according to Macdonald's criteria) was at the discretion of the treating physician. Disease assessment was conducted at baseline and every 3 months thereafter, and included neurological examination and brain imaging (MRI or CT). The median follow-up time was 62.6 months in the radiotherapy plus PCV arm and 59 months in the radiotherapy-only arm. A Cox proportional hazard model was used to assess factors that might predict outcome, such as age, ECOG performance score, and 1p 19q status (evaluated in 311 patients by fluorescent in situ hybridisation).

Outcome measures. The primary outcome variable was overall survival (OS); secondary outcome variables were progression-free survival (PFS) and toxicity.

Results. Adjuvant chemotherapy had no impact on OS, with a median OS time of 30.6 months in the radiotherapy-only arm and of 40.3 months in the radiotherapy plus PCV arm (P=0.23). Median PFS time, however, was significantly prolonged in the radiotherapy plus PCV arm compared with the radiotherapy-only arm (23.0 vs 13.2 months; P=0.0018). Most of the patients (65%) in the radiotherapy-only arm who were diagnosed with disease progression received salvage PCV. The 5-year OS and PFS rates in both treatment arms were higher among patients with 1p 19q LOH (25.1% of evaluated patients) than among those with a different 1p 19q status. In fact, 1p 19q LOH was the most important predictor of survival, with a hazard ratio for death of 0.27 (95% CI 0.13–0.56; P<0.001). Adjuvant chemotherapy was only moderately well tolerated. Only 30% of patients completed the intended six cycles of adjuvant treatment. The most frequent reason for premature discontinuation was haematological toxicity (33%).

Conclusion. Adjuvant PCV chemotherapy in this patient population improved PFS, but not OS. As most patients received chemotherapy at relapse, this finding indicates that the timing of chemotherapy was of little relevance for survival. Patients harbouring tumours with 1p 19q LOH had the best prognosis.

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