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Does intensification of chemotherapy in anaplastic oligodendrogliomas still have a role?

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See the article by Thomas et al. on pages 1380-1390.

Recent phase III trials have confirmed that 1p/19q codeletion in anaplastic oligodendrogliomas and oligoastrocytomas is significantly associated with increased chemosensitivity to alkylating agents, and this translates into improved outcome.[1,2] Given the potential longer survival of these patients compared with high-grade astrocytoma patients, a treatment approach of initial chemotherapy with dose-intensification strategies and delayed radiation therapy (RT) at tumor progression to prevent the risk of cognitive defects could be attractive. In this regard, high-dose myeloablative chemotherapy followed by autologous stem cell transplant is an approach whose main objective is to achieve higher CNS drug concentrations to maximize the chemoresponsiveness with an acceptable degree of systemic and neurologic toxicity.

In this issue of *Neuro-Oncology*, Thomas and colleagues[3] report the results of a multicenter phase II study of temozolomide (TMZ) and myeloablative chemotherapy with autologous stem cell transplant in a cohort of newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas whose diagnosis was based on the World Health Organization (WHO) 2000 classification. Induction chemotherapy consisted of 6 cycles of standard TMZ. Patients achieving a response or stable disease of the enhancing tumor on MRI were eligible for high-dose thiotepa and busulfan with autologous stem cell support. Forty-one patients were enrolled over a 7-year period. By the end of induction chemotherapy, 9 patients experienced disease progression, and another 11 withdrew for several reasons, so that 21 patients only were transplanted. Twenty of these patients had 1p/19q codeletion and in 1 patient 1p/19q status was unknown.

The first question that now arises is whether high-dose chemotherapy using TMZ in the induction phase is superior to standard treatment or dose dense TMZ as an upfront treatment in 1p/19q codeleted patients; however, available data for comparison are scarce and do not allow definitive conclusions. In fact, in the study by Thomas et al,[3] the transplanted patients (n = 21) had a 5-year progression-free survival (PFS) of 60.4% and a 5-year overall survival (OS) of 100% (with a median follow-up of 65.7 months), while in the recent multicenter single arm phase II trial of Ahluwalia and colleagues[4] using dose dense TMZ (1 wk on/1 wk off) in 20 patients, 5-year PFS was 55% and 5-year OS was ~90%.

A second, more general question is whether upfront chemotherapy with RT delayed until tumor progression in 1p/19q codeleted patients can yield similar survival results compared with an early combination of radiation and chemotherapy. The 2 phase III trials[1,2] that reported a significant superiority of RT followed by procarbazine/lomustine/vincristine (PCV) over RT alone in terms of PFS and OS have established the benchmark for future comparisons. In particular, in the European Organisation for Research and Treatment of Cancer (EORTC) trial,[2] 1p/19q codeleted patients who received RT + PCV (n = 43) had a 5-year PFS of 71.4% and a 5-year OS of 76.2%. The long-term results of NOA-04 suggest that chemotherapy alone may have a worse outcome,[5] while a large retrospective analysis[6] showed no difference in the median OS of patients with 1p/19q codeleted anaplastic oligodendrogliomas who had initially received chemotherapy alone (median 10.5 y) versus those receiving chemoradiotherapy (median 8.4 y).

Overall, some issues are critical in this debate. It is unknown whether salvage RT is as efficacious as early RT, and even more important, it is unknown whether a potential shorter survival following upfront chemotherapy alone compared with RT followed by chemotherapy is balanced by a better preservation of cognitive functions and quality of life.

Data are lacking, but a small retrospective study on long-term survivors of anaplastic oligodendroglioma in the EORTC study, receiving either RT alone or associated with PCV, has suggested that a substantial proportion of patients suffered from cognitive impairment while being health-related quality of life stable.[7] Future studies need to incorporate serial monitoring of cognitive functions over many years of follow-up to better clarify this issue, and this is not an easy task.

There are still conflicting data regarding a possible differential efficacy of PCV and TMZ. Both the retrospective study by Lassman et al[6] in 1p/19q codeleted patients and the study by Wick et al[5] of the NOA-04 study of cytosine-phosphate-guanine island methylated phenotype codeleted patients have reported a superior efficacy of PCV over TMZ.

The current phase III CODEL trial is being conducted under the assumption that chemoradiotherapy using TMZ or PCV will have similar efficacy with a better tolerability profile favoring TMZ: This has been recently suggested by a large retrospective study by Speirs et al.[8] Interestingly, two studies comparing TMZ versus PCV as induction regimen before higher-dose chemotherapy with autologous stem cell transplantation[3,9] have shown that patients enrolled in the PCV cohort had shorter median OS than those enrolled on TMZ.

In conclusion, it remains to be demonstrated whether a proportion of patients with anaplastic oligodendrogliomas, who according to the WHO 2016 Classification[10] have by definition 1p/19q codeletion, derive additional survival benefit from a transplantation procedure compared with some standard options. Future studies should better define the characteristics of those patients who are candidates for this aggressive procedure, patterns of response to salvage treatments, and last but not least, cognitive status and quality of life.

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