Adjuvant chemotherapy is indicated in patients with lower-grade glioma

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The addition of chemotherapy to radiotherapy (RT) following surgery in patients with low grade glioma prolongs survival. In the recently published long-term follow-up of a randomised phase 3 trial, Buckner et. al reported 254 patients with high-risk WHO Grade II oligodendroglioma, oligoastrocytoma, or astrocytoma, randomised to either receive RT alone or RT followed by 12 months of procarbazine, vincristine and lomustine (PCV) chemotherapy [1]. In this study, high-risk was defined as patients aged 40 and over, or patients under 40 who had undergone subtotal resection or biopsy. Median follow up was 11.9 years by which time 67% had disease progression and 55% of patients had died. The addition of PCV to RT improved median overall survival (mOS) from 7.8 to 13.3 years (HR 0.59 p=0.003), and 10-year survival increased from 40% to 60%. Survival benefit was seen in all histological subtypes, although not statistically significant in astrocytomas (oligodendroglioma: HR 0.43 [95% CI 0.23-0.82] p=0.009; oligoastrocytoma: HR 0.56 [0.32-1.00] p=0.05; astrocytoma: HR 0.73 [0.40-1.34] p=0.31). Patients with isocitrate dehydrogenase 1 (IDH1) R132 mutation also had significant survival benefit from the addition of PCV (HR 0.42 [0.20-0.86] p=0.02), but conclusions were not made for patients with 1p19q co-deletion or with IDH wild-type tumours. Of note, patients who were randomised to RT alone were more likely to receive further treatment, but only 56% received chemotherapy, reasons for which are unclear.

This trial adds further evidence that adjuvant chemotherapy significantly improves survival in glioma. The EORTC26951 trial evaluated the addition of PCV to adjuvant RT in 368 patients with newly diagnosed anaplastic oligodendroglioma (WHO Grade III) and demonstrated an improvement in mOS with the addition of PCV from 30.6 to 42.3 months (HR 0.75 [0.60-0.95]) [2]. In the RTOG 9402 trial, mOS in patients with anaplastic glioma (WHO grade III) with 1p19q co-deleted tumours treated with RT plus PCV (n=148) was 14.7 years, compared with 7.3 years in those treated with RT (n=143) alone (HR 0.59 [0.37-0.95] p=0.03) [3]. Patients with IDH mutant tumours in this trial also derived benefit from the addition of PCV (mOS 9.4 versus 5.7 years, HR 0.59 [0.40-0.86] p=0.006) [4]. In patients with anaplastic glioma without 1p19q co-deletion, interim analysis from the CATNON trial has shown the addition of temozolomide to radiotherapy improves survival, although median overall survival has not yet been reached (HR for OS 0.65 [0.45-0.93] p=0.0014) [5]. In these trials, survival benefit was not observed until approximately 25% of patients had died, possibly reflecting the proportion of patients with chemoresistant disease. Thereafter, survival benefit increased with time.

Tumour biomarkers including IDH, 1p19q, and MGMT are associated with prognostic advantage and chemosensitivity [6, 7]. Lower grade gliomas which are IDH wild-type and without 1p19q co-deletions are considered morphologically and clinically similar to glioblastoma (WHO Grade IV) [6, 8]. RT with temozolomide chemotherapy is the established standard of care in glioblastoma. Universal adoption of this regimen followed the demonstration of a modest increase in mOS survival from 12.1 to 14.6 months (HR 0.63 [0.52-0.75] p<0.01) with addition of temozolomide to RT in the EORTC/NCIC randomised trial of 573 patients [9, 10].

In current practice, patients with glioblastoma are given adjuvant chemotherapy despite relatively limited benefit, whilst it is not routinely given to patients with low grade glioma who are more likely to benefit. Given the survival benefit demonstrated in clinical trials, we believe that all patients with grade IV, III, and high-risk grade II glioma and good performance status should be offered RT and chemotherapy after surgical resection. The potential for late toxicity is the primary negative sequelae of earlier chemotherapy and should be discussed with patients prior to commencing treatment. Possible late side effects of cytotoxic chemotherapy include neurocognitive decline, cardiovascular disease, reduced fertility, fatigue, and secondary neoplasms [11-14].

Whether patients with lower grade glioma should be given RT with concomitant and adjuvant temozolomide (the standard in glioblastoma) or RT followed by adjuvant PCV remains uncertain, and is under investigation in the CODEL Phase III clinical trial (NCT00887146). Future studies should aim to identify low-risk patients in whom it is safe to delay adjuvant therapy following surgery. Future patient stratification may occur with molecular signatures determined through analysis of ongoing studies of next generation sequencing of the tumour genome, transcriptome, and epigenome. These studies are aiming to establish a biomarker that is independently prognostic and predictive of response to therapy.

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