

Glioblastoma: If this is the “Temozolomide Era” Where is the Evidence?

Can J Neurol Sci. 2014; 41: 301-302

Every day 27 Canadians are diagnosed with a brain tumour.¹ Glioblastoma is the most common primary brain tumour in adults and the incidence of this dreaded type of cancer is increasing. In the past decade we have witnessed an explosion of knowledge on the molecular genetic features of glioblastoma, thanks in large part due to strides made by the inclusion of glioblastoma early in the Cancer Genome Project. While we understand many more of the genetic mechanisms controlling protein expression and the connections of multiple pathways controlling glioma growth, invasion, and angiogenesis, these findings have translated into only modest gains in the clinic.

Investment by the Terry Fox Research Institute and strong molecular oncology programs in Vancouver and Calgary, to name just two, provide hope that future molecular discoveries will translate into therapeutic targets for testing in Canadian patients enrolled into clinical trials. Groups such as the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) and the Canadian Brain Tumour Consortium (CBTC, www.cbtc.ca) are poised to bring novel therapies to as many Canadian brain tumour centres as possible. This all said, the sobering reality is that studies of population-based outcomes from the treatment of glioblastoma, in Canada and around the world, show that much work is to be done before tomorrow's treatments will be discovered.

In this issue of the Journal, Coate *et al* present a retrospective analysis of patients with glioblastoma treated at the Princess Margaret Cancer Centre between 2004-2008.² These few years represent a landmark as the beginning of the “temozolomide era” due to the publication of the pivotal NCIC-CTG/EORTC clinical trial demonstrating improved survival in patients treated with temozolomide (TMZ) given in combination with radiotherapy and then used for up to six months in monthly maintenance cycles. Notwithstanding this important advance, it is notable that in the ‘real world’ setting of a regional cancer centre, less than half of the newly diagnosed patients received this treatment, while others received supportive care alone or radiotherapy alone. In patients older than 70 less than 1% received temozolomide with radiotherapy, only 5% received adjuvant (maintenance) temozolomide and only 8% received temozolomide at the time of disease progression. So, in this so-called ‘temozolomide era’, very little temozolomide was actually used!

So, what might be the reasons that, despite being treated in one of Canada's most advanced cancer centres, the majority of patients appear not to have received standard of care therapy?

Might it be that these patients were enrolled in clinical trials testing newer novel therapies? It appears not as only 5/421

patients in the reported series were in clinical trials; a sure sign that we have much work to do to improve clinical trial availability and access for brain tumour patients in Canada.

Might it be that the benefits of temozolomide therapy apply only to a restricted populations of patients? In the pivotal trial, the benefit of concurrent and adjuvant chemotherapy was largely restricted to the 40% of newly diagnosed glioblastoma patients who harbor the genetic biomarker represented by methylation of the O6-methylguanine-methyltransferase gene promoter (MGMT methylation). Patients with MGMT methylation who received radiotherapy and TMZ had a remarkable two year survival rate of 46%, but this benefit appeared to decrease with increasing age. In a subgroup analysis from the pivotal trial benefit appears maintained from 60-65 years (HR = 0.64, 0.43-0.94, $p = 0.02$ however it is reduced between ages 65-70 (HR = 0.78, 0.50-1.24, $p = 0.29$).³ These data need to be interpreted cautiously since these results may be explained in whole or in part by low statistical power in the older subgroup. For this reason the NCIC-CTG designed and powered a new clinical trial specifically testing the role of concomitant and adjuvant temozolomide in addition to radiotherapy versus radiotherapy alone in patients over the age of 65.⁴ This global phase III trial has completed accrual and survival results with MGMT analysis are expected in the near future.

Might it be that very few of the newly diagnosed patients assessed in a ‘real world’ practice are candidates for aggressive treatment? Unlike specialized referral centres typical of American practice, Canadian cancer centres are organized on a population basis. It is likely that there is very little selection of patients with brain tumours for referral into regional cancer centres; virtually all patients who have surgery for glioblastoma are assessed for possible radiation and chemotherapy. The experience of Coate *et al* reflects outcomes typical of other Canadian cancer centres.^{5,6} Brain tumour professionals in these clinics are challenged daily with a myriad of patient-specific issues including their neurological condition, cognitive state, goals and preferences for care, and logistical concerns regarding the delivery of care. Of the 421 patients described in this series, median survival for the entire cohort was 9.8 months, which is roughly half of the typical median survival reported in clinical trials in recent years. Pre-treatment prognostic variables such as patient age, performance status, and tumour biology account for more of the variance in survival than treatment itself; a sobering reflection of the very modest efficacy of modern therapy that is highlighted in series such as this one.

What does the road forward look like?

Data from two recent randomized controlled trials, the Nordic study, and the NOA-08 study help us and are new data, not reflected in the outcomes of this series of patients from 2004-2008.^{7,8} Both studies, NOA-08 in particular, found the MGMT biomarker to be predictive of improved survival with temozolomide treatment. In fact, the MGMT-methylated group of patients who received temozolomide chemotherapy had longer survival than patients (methylated or unmethylated) treated with radiation therapy. Both studies confirmed prior Canadian randomized data that a hypofractionated or 'short-course' radiation schedule is associated with similar survival to the 60Gy in six weeks standard from the NCIC-CTG/EORTC trial. In fact, elderly patients treated with six weeks of radiotherapy may do worse than those treated with shorter hypofractionated schedules. The data from Coate *et al* cannot address this question since the 40Gy/15 fraction schedule has long been adopted in Toronto centres as the standard of care.

These newer randomized data help Canadian patients and their families make better treatment decisions. For the elderly, 30 trips for radiation are no longer required, reducing the logistic burden of treatment and likely shortening the length of hospital admission for patients unable to be treated in an outpatient fashion (for example due to distance from the treatment centre, or mobility issues). Moreover, temozolomide alone, rather than radiotherapy can be reasonably offered to elderly patients with MGMT methylation. This will be a significant advantage for patients unable to tolerate radiation therapy, unable to attend due to distance or disability, and for whom radiation volumes might confer increased toxicity such as somnolence and progressive neurological symptoms. MGMT analysis should be standard of care for elderly patients with glioblastoma to leverage the knowledge from these new clinical trials. Considerable resource savings might be found if only MGMT methylated patients are given temozolomide and if these patients are spared radiation therapy. I suspect a similar retrospective review done ten years from now, from 2014-2018 will look very different than the series reported here. As far as glioblastoma in older patients is concerned it may be that the "temozolomide era" is just beginning.

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