Current Treatment Strategies for Malignant Gliomas

a report by
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Anaplastic astrocytomas, oligoastrocytomas and oligodendrogliomas (World Health Organization (WHO) grade III) and glioblastomas (WHO grade IV) are collectively referred to as malignant gliomas, whereas WHO grade I and II gliomas are designated low-grade gliomas.[1] For decades, neurosurgical resection – whenever possible – and post-operative radiotherapy have been the cornerstones of treatment for malignant gliomas. Most chemotherapeutic agents active in other types of cancer produced little benefit for glioma patients, with the possible exception of nitrosoureas. In contrast, recent years have seen significant advances in the fields of neurosurgical resection, radio-oncological treatment approaches and, most significantly, medical therapy (see *Table 1*), exemplified by the approval of temozolomide for newly diagnosed glioblastoma.[2]

Anaplastic Glioma

The classic treatment of anaplastic glioma included resection wherever feasible and radiotherapy of the tumour with a peri-tumoral safety margin of 2–3cm. Until a few years ago, gliomas of WHO grades III and IV were collectively considered malignant gliomas and enrolled into common clinical trials, which mostly evaluated the role of radiotherapy and adjuvant chemotherapy. However, it then became clear that WHO grade III anaplastic gliomas had a much better prognosis than glioblastomas, necessitating separate clinical trials for these tumour entities. For instance, in a recent large meta-analysis[3] the two-year survival rates were 9 and 13%, respectively, for glioblastoma patients treated initially with radiotherapy alone or radiotherapy plus chemotherapy, but 31 and 37%, respectively, for patients with anaplastic gliomas.[3]

Retrospective data suggest that anaplastic oligodendroglial tumours have a better prognosis than anaplastic pure astrocytic gliomas, with mixed oligoastrocytomas probably having an intermediate prognosis. In particular, it was felt that oligodendroglial tumours showed a more favourable response to chemotherapy. This led to an increased awareness of possible oligodendroglial components within malignant gliomas and an increase in their diagnosis, probably driven by the concern that a possibly effective treatment – such as procarbacine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), vincristin (PCV) chemotherapy – might be withheld from patients on the basis of the diagnosis of a pure astrocytoma. More recently, seminal studies by Cairncross and colleagues and many other groups revealed that the better prognosis of oligodendroglial tumours could largely be attributed to the subgroup of patients with tumours that exhibited a loss of genetic material on chromosomes 1p and 19q. These genetic changes are uncommon in anaplastic astrocytomas and glioblastomas.

Prospective data for the major prognostic role of these genetic losses come from two recent randomised clinical trials: Radiation Therapy Oncology Group (RTOG) 94-02 and the European Organization for Research and Treatment of Cancer (EORTC) 26951, which compared radiotherapy alone with radiotherapy plus PCV in anaplastic oligodendroglial tumours.[4,5] Further data have to mature from the RTOG 01-31 trial, which investigates the effect of pre-irradiation temozolomide. Both RTOG 94-02 and EORTC 26951 indicate that PCV added to radiotherapy increases progression-free survival, whereas there is no significant effect on overall survival. The failure of combined modality treatment as the first-line therapy to increase overall survival may result from the known efficacy of the treatment at recurrence – e.g. PCV when given as a salvage treatment at recurrence after radiotherapy. Interestingly, both trials also show, for the first time in a prospective setting, that the combined loss of heterozygosity on chromosomes 1p and 19q was an important predictor of longer progression-free survival and overall survival, but that this effect was independent of the initial treatment, whether radiotherapy alone or radiochemotherapy. It is important to note that both trials were designed to evaluate all anaplastic oligodendroglial tumours regardless of genotype, and any conclusions regarding the 1p/19q deleted/non-deleted subgroups have to be looked at with the limitations of a subgroup analysis. With these precautions in mind, 1p/19q status cannot be used to guide treatment decisions, but is solely a prognostic marker at present. Altogether, patients with 1p/19q-deleted oligodendroglial tumours may expect a median overall survival of six to seven years, whereas patients with 1p/19q-non-deleted tumours experience a median survival of two to three years, similar to the range expected for patients with anaplastic astrocytoma.

Further important information will be gained from the results of the German NOA-04, which enrolled 318 patients with all three types of anaplastic glioma and randomised them between radiotherapy alone and chemotherapy alone, using either the PCV regime or temozolomide (see *Figure 1*). Among others, this study will possibly identify a population of patients in whom radiotherapy can be safely deferred, and will also provide the first head-to-head comparison of PCV and temozolomide.

In the light of these data, it is important to design separate trials to optimise the treatment for 1p/19 intact and 1p/19q co-deleted tumours.

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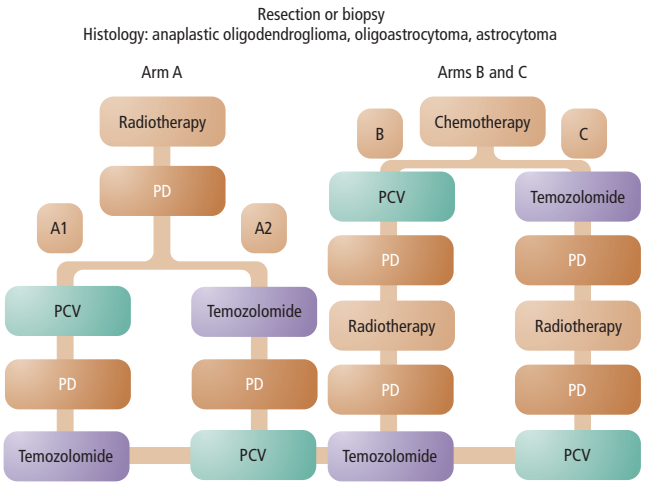
EORTC, the National Cancer Institute of Canada (NCIC), RTOG, the Medical Research Council (MRC) and High-priority Undertakings in Brain Tumors (HUB) have agreed on a concept for a multinational, four-armed trial termed CATNON for patients with anaplastic glioma without 1p/19q loss. CATNON will examine the role of chemotherapy, substituting PCV for temozolomide, in the concurrent or adjuvant setting. The study arms will include radiotherapy alone, radiotherapy plus concurrent temozolomide, radiotherapy plus adjuvant temozolomide and radiotherapy plus concomitant and adjuvant temozolomide. Chemotherapy will be administered for six months, but can be continued for up to 12 months for stable or responding patients. Patients will be stratified for O6-methylguanine DNA methyltransferase (MGMT) gene promoter methylation status. This study will be designed to identify the impact of concomitant and adjuvant temozolomide on overall survival in this patient cohort. A second companion protocol for 1p/19q-deleted tumours will probably compare radiotherapy alone, chemotherapy alone and radiochemotherapy using temozolomide. This trial will thus combine features of NOA-04 (see *Figure 1*) and the EORTC NCIC trial for glioblastoma.[2]

Figure 1: NOA-04 – Randomised Phase III Trial of Sequential Radiochemotherapy for Anaplastic Gliomas with Vincristin or Temozolomide



Glioblastoma

As with anaplastic glioma, the classic treatment of glioblastoma includes surgical resection when feasible and radiotherapy of the tumour with a peri-tumoral safety margin of 2–3cm. However, while the role of radiotherapy has not been questioned for decades,[6] the value of surgical resection was confirmed in a randomised trial only in 2006, by Stummer and colleagues.[7] Using the fluorescent marker 5-aminolevulinic acid to delineate the tumour area under the surgical microscope, they demonstrated an enhanced progression-free survival rate at six months in patients who had a complete resection defined by magnetic resonance imaging (MRI).

The approval in around 2005 of the novel alkylating agent temozolomide – which had previously been registered for recurrent anaplastic gliomas and glioblastomas – for use in newly diagnosed glioblastoma was probably the most encouraging step ahead in the medical management of malignant gliomas in the last few decades. The EORTC 26981-22981 NCIC CE.3 trial compared radiotherapy alone with concurrent and adjuvant temozolomide added to radiotherapy. It demonstrated an increase in median survival from 12.1 to 14.6 months and of the two-year survival rate from 10 to 26% in patients receiving temozolomide.[2] In particular, patients with tumours exhibiting methylation of the promoter region of the MGMT gene showed a striking benefit from temozolomide.[8] The encouraging results of the EORTC NCIC trial have led to intensified experimental and clinical efforts to improve the treatment of malignant gliomas. These efforts include the development of alternative dosing schedules of temozolomide, as realised in the ongoing RTOG EORTC trial for newly diagnosed glioblastoma (three weeks on, one week off) and the German NOA-08 trial for malignant astrocytomas (grades III and IV) in the elderly (one week on, one week off), as well as these and various other regimens for recurrent disease.[9]

Table 1: Current Treatment Options for Malignant Glioma

	Newly Diagnosed	Recurrence or Progression
Anaplastic astrocytoma WHO grade III	Resection (or biopsy) and radiotherapy (and chemotherapy)	Re-resection and chemotherapy (temozolomide or nitrosourea) or re-irradiation
Anaplastic oligodendroglioma and anaplastic oligoastrocytoma WHO grade III	Resection or biopsy and chemotherapy (PCV or temozolomide)[a] or radiotherapy[a] (or combined modality treatment)[b]	Re-resection and radiotherapy or chemotherapy (temozolomide or nitrosourea)
Glioblastoma WHO grade IV	Resection (or biopsy) and radiotherapy and chemotherapy (temozolomide)[c]	Re-resection and chemotherapy (nitrosourea) or re-irradiation

a. See NOA-04 trial; b. See EORTC 26951 and RTOG 94-02;[4,5] c. See EORTC 26981-22981 NCIC CE.3.[2]
WHO = World Health Organization.

Perspectives

The introduction of temozolomide for the treatment of malignant glioma has resulted in a renaissance of interest in clinical trials for patients with newly diagnosed or recurrent malignant gliomas. There is a great variety of novel concepts, including:

- various tyrosine kinase inhibitors with a focus on epidermal growth factor receptor (EGFR);
- angiogenesis using agents such as bevacuzimab, enzastaurin or cilengitide; and
- various approaches of locoregional treatment, such as adenovirally mediated suicide gene therapy or immunotoxin-based strategies.

Results from most of these trials are likely to be available within the next one or two years, and will hopefully enrich the currently limited repertoire of treatment options for malignant glioma patients. ■

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