Neuro-oncology, a decade of temozolomide and beyond

Roger Stupp
Author for correspondence: Department of Neurosurgery, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland roger.stupp@chuv.ch

Monika Hegi
Laboratory of Brain Tumor Biology and Genetics, Department of Neurosurgery, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland

Michael Weller
Department of Neurology, University Hospital Zürich, Frauenklinikstrasse 26, 8091 Zürich, Switzerland

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It has been a decade since the regulatory approval of temozolomide, the first drug specifically developed for the treatment of malignant glioma. Initially, only a conditional approval was granted by the US FDA based on a high radiological response rate in recurrent anaplastic astrocytoma, while in glioblastoma the observed responses in two pivotal studies were only 5 and 8%, respectively [1–3]. Nevertheless, the clinical observation that disease stabilization may be clinically relevant in this disease setting led clinical investigators to pursue this agent further. In addition, the absence of better alternatives, its excellent tolerability and favorable toxicity profile have facilitated its use and investigation in a disease setting where quality of life has been a particular concern [4].

The contribution of temozolomide to the development of neuro-oncology has been far beyond its direct anti-tumor activity. The availability of a drug with (modest) single-agent activity was an important factor in stimulating research. Patients who previously had no active treatment options and who were often quickly transferred to a palliative care unit would now be seen by disease specialists. Specialized oncological care includes not only the administration of chemotherapy and regular follow-up, but also optimization of supportive measures, and revisiting the indication for steroid and antiseizure medication. Importantly, the awareness of neuro-oncology led to the creation of specialized multidisciplinary teams and clinics. Subsequent systematic academic clinical research allowed the establishment of combined chemoradiotherapy as the standard of care and backbone of therapy in glioblastoma [5,6].

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Several randomized studies in lower grade glioma are ongoing or have recently been completed. In the randomized German Neuro-Oncological Working Party (NOA)-04 trial in anaplastic glioma, the treatment sequence of primary chemotherapy with radiotherapy given as salvage therapy at disease progression was compared with primary standard radiotherapy with salvage chemotherapy [7]. Both treatment strategies appear comparable. The important comparison of concomitant chemoradiotherapy versus sequential therapies is the subject of the ongoing international European Organisation for Research and Treatment of Cancer (EORTC)-Intergroup trial

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(Concomitant and Adjuvant Temozolomide for Non-Deleted Anaplastic Glioma [CATNON] trial [101]). This trial should allow us to identify the relative contribution of concomitant temozolomide chemoradiotherapy and the adjuvant (maintenance) administration of this alkylating agent. While combined treatment strategies with little consideration for late toxicities are justified for malignant glioma, which still generally has a short survival, management of low-grade gliomas is more complex. The high variability in natural history, a median survival of over 5–7 years (or even >10 years for oligodendroglioma), and the availability of only a few clinical or radiological prognostic markers are additional challenges. Watchful waiting remains indicated for many younger patients with smaller tumors. A randomized EORTC–National Cancer Institute of Canada (NCIC) trial comparing primary temozolomide chemotherapy versus standard radiotherapy has recently completed accrual for patients requiring therapy (EORTC trial #22033–26033, NCIC CE.5). Correlative science (tissue submission was mandatory for central pathology review and loss of heterozygosity 1p determination) should allow the subsequent identification of some molecular markers or profiles, helping to prognosticate outcome and individualize treatment strategy.

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Translational research allowed for new insights into molecular genetics and tumorigenesis. Aberrant methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter has been identified as a predictive marker for benefit from temozolomide chemotherapy in glioblastoma [8,9]. Ongoing studies aim at validating its assay, the optimal cut-off and its predictive value for clinical use. Molecular markers, including MGMT, often also carry inherent prognostic value, adding to the complexity of interpretation and clinical use. Of course, one does not want to withhold a potentially effective therapy from a patient; however, at the same time treatment with ineffective, possibly toxic therapies is of no benefit. Furthermore, persisting with the use of temozolomide for all patients may prevent adequate development of more effective tailored therapies.

The financial success of temozolomide prompted further investment into research for brain tumors. An unprecedented number of new agents are currently in clinical trials for malignant glioma. Strategies for inhibiting VEGF-mediated signaling have attracted a lot of interest and promise in malignant glioma. Impressive radiological responses and temporary clinical improvement has been demonstrated with the anti-VEGF monoclonal antibody bevacizumab in recurrent glioma [10,11]. Based on uncontrolled Phase II trials, the FDA granted provisional approval for recurrent glioblastoma, while the EMEA rejected the application. Most recently, cediranib, a promising VEGF receptor tyrosine kinase inhibitor has failed to meet its primary end point in a proper and well-designed Phase III trial in recurrent glioblastoma. Despite persistent doubts regarding the quality of the anti-tumor effect of single-agent bevacizumab, it may be a useful agent in selected patients with large tumors and important peritumoral edema. Two large ongoing trials are evaluating the benefit of bevacizumab in addition to standard chemoradiotherapy in newly diagnosed glioblastoma (AvaGlio [102]; Radiation Therapy Oncology Group [RTOG]0825 [103]).

Cilengitide is a first-in-class integrin inhibitor that is currently being developed for treatment of glioblastoma in a randomized Phase III trial (Cilengitide in Combination with Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Phase III Randomized Clinical Trial [CENTRIC] [104]). Based on theoretical considerations and results of a pilot Phase II trial, only patients with a methylated MGMT gene promoter are eligible for randomization and cilengitide therapy [12]. Despite the substantial additional challenges of upfront centralized molecular marker testing, this trial is accruing well and completion of recruitment is expected in the first quarter of 2011.

While upfront chemoradiotherapy has become the standard of care for newly diagnosed glioblastoma, there is no established standard of care in recurrent disease. Enzastaurin, a PKC inhibitor, has failed to demonstrate significant single-agent activity when compared with lomustine in recurrent glioblastoma [13]. Similarly, the EGFR tyrosine kinase inhibitor erlotinib has not shown meaningful single-agent activity in a randomized Phase II trial [14]. Nevertheless, there remains a great need for better salvage treatments.

Progress in understanding tumor biology has allowed us to identify a number of key signaling pathways and processes of tumorigenesis. However, owing to the redundancy of pathways and alternative signaling, inhibition at only one level may be insufficient to substantially inhibit tumor growth, and a combination of several agents may be needed. However, regulatory hurdles prohibiting investigation of several nonapproved agents in combination, and fierce competition among pharmaceutical companies limit the development of rational combination therapies.

“The change in the field and the increased research interest is also reflected in the success of ... dedicated neuro-oncology meetings...”

Over the last decade the focus in clinical research has been on malignant glioma. The network of expert treatment centers and cooperative groups now available should allow the focus to fall on other rare CNS malignancies, as recently demonstrated again by the German network that included over 500 patients with primary CNS lymphoma in a trial investigating the relative benefit of the addition of whole-brain radiotherapy [15]. Basic research and understanding paired with early clinical observations led to exploratory clinical trials in patients with recurrent primitive neuroectodermal tumors/medulloblastoma using a Hedgehog inhibitor [16]. The larger cooperative group networks may want to explore this strategy in prospective randomized trials in newly diagnosed patients in combination with chemo- and radiotherapy.
The change in the field and the increased research interest is also reflected in the success of the dedicated neuro-oncology meetings by the Society of Neuro-Oncology in the USA and the European Association of Neuro-Oncology, where several hundred participants are expected at their respective meetings in Montreal (Canada) in November 2010 and Maastricht (The Netherlands) in September 2010. We can expect more exciting news during these meetings.

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