Progress in glioma diagnosis, classification and treatment

Patrick Y. Wen and David A. Reardon

Gliomas are the most common form of malignant primary brain tumour. In the past year, substantial progress has been made in the classification and treatment of lower-grade gliomas (WHO grades II and III), and the FDA has approved a new therapy for newly diagnosed glioblastomas.

Gliomas account for 80% of all malignant primary brain tumours, with an annual incidence of approximately 6 per 100,000 in the USA1. Under the current WHO classification, gliomas are divided into four histological grades2. Grade I gliomas, such as pilocytic astrocytomas, are very slow-growing tumours that are potentially curable if completely resected. Grade II gliomas (astrocytomas, oligodendrogliomas and oligoastrocytomas) and the more aggressive grade III gliomas (including anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas) have an intermediate clinical course, whereas grade IV gliomas (glioblastoma) have the most aggressive clinical course (median survival between 14.5 and 16.6 months3-4).

Clear classification of the different types of glioma is crucial to ensure that they are diagnosed accurately and treated with the appropriate therapy. Such classification is particularly important for grade II and III gliomas (lower-grade gliomas). The diagnosis and surgical removal of these tumours is hindered by their diffuse nature, and they generally progress to higher-grade tumours over time5. Despite its widespread use, the WHO histopathological classification is limited by substantial interobserver variability and poor correlation with clinical outcome. Three studies published in 2015 clarified the classification of lower-grade gliomas, thereby potentially improving the prediction of tumour outcome, and guiding therapeutic strategies to treat gliomas3-7.

In addition to histopathological characteristics, a number of molecular alterations have been identified in lower-grade gliomas over the past two decades. Such genomic modifications correlate with prognosis and, in some cases, predict response to therapy. Codeletion of chromosome arms 1p and 19q is associated with oligodendrogliomas and with sensitivity to chemotherapy8. Mutations in the isocitrate dehydrogenase 1 and 2 genes (IDH1 and IDH2) are present in the majority of lower-grade gliomas and predict an improved outcome5. TP53 and ATRX mutations are present in astrocytomas, and mutations in the promoter of TERT, a gene that encodes a subunit of the telomerase enzyme, are seen in a subset of oligodendrogliomas and glioblastomas8.

Using unsupervised clustering of mutations and various whole-genome molecular analyses (including exome and RNA sequencing, and DNA copy number and DNA methylation profiling), the Cancer Genome Atlas Research Network1 and a group from Japan9 classified lower-grade gliomas into three non-overlapping and prognostically relevant subtypes (types I–III) (Fig. 1), according to the presence or absence of IDH mutations and 1p/19q codeletions. 80% of lower-grade gliomas had IDH mutations, which were associated with improved prognosis. The 30% of patients who had lower-grade gliomas with an IDH mutation and 1p/19q codeletion (type I) had the most favourable clinical outcome. Most of these tumours were oligodendrogliomas and harboured mutations in CIC, FUBP1, NOTCH1 and/or the TERT promoter. 50% of lower-grade gliomas harboured IDH mutations but no 1p/19q codeletion (type II), were usually classified histologically as astrocytomas, and had mutations in TP53 (94%) and/or ATRX (86%). The 20%...
of lower-grade gliomas without IDH mutations (type III) had genomic aberrations and a clinical course that closely resembled that of glioblastoma. It is interesting to note that oligoastrocytomas, which have histopathological features of both astrocytomas and oligodendrogliomas, were found among all three subtypes and did not exhibit a specific molecular signature, thereby providing support for the eventual elimination of oligoastrocytoma as a diagnostic entity.

The third study classified lower-grade gliomas on the basis of IDH and TERT promoter mutations and codelletion of chromosome arms 1p and 19q. The authors categorized these tumors into five molecular subgroups and, importantly, they confirmed the three main subgroups found by the other two studies. These three studies have important implications for patients with lower-grade gliomas. Division of lower-grade gliomas into three robust subgroups (Fig. 1) will allow more-accurate determination of diagnosis and prognosis, and assignment of patients to the most appropriate therapies. For example, the 20% of patients with gliomas that have no IDH mutations would probably benefit from more-aggressive therapies, as their tumors exhibit molecular features and behaviour that closely resemble those of glioblastoma.

In addition to the progress made in the classification of lower-grade gliomas, 2015 has seen an important advance in the treatment of grade II gliomas. The Radiation Therapy Oncology Group conducted a study (RTOG 98-02) involving patients with grade II gliomas who were considered to be at high risk of recurrence (age ≥240 years or age <40 years with subtotal resection). These patients were randomly assigned to radiotherapy alone or radiotherapy followed by up to six cycles of PCV (procarbazine, lomustine and vincristine) chemotherapy. The patients treated with radiotherapy and PCV had a significantly longer median survival time (13.3 versus 7.8 years) and a longer median progression-free survival time (10.4 versus 4.0 years) than those treated with the radiotherapy alone. The benefits of the combined treatment were most prominent in patients with oligodendrogliomas and oligoastrocytomas, although some efficacy was also observed in patients with astrocytomas. These results suggest a new approach to the treatment of high-risk lower-grade gliomas, with chemotherapy being introduced earlier in the course of treatment, after initial resection. Given the toxicity of PCV chemotherapy, some debate remains as to whether the better tolerated temozolomide is preferable to PCV.

The past year has also seen progress in the treatment of glioblastoma. Since 2005, the standard therapy for glioblastoma has consisted of radiotherapy with temozolomide chemotherapy, and all attempts to develop more-effective therapies have been unsuccessful. In October 2015, the FDA approved the use of low-intensity, intermediate-frequency alternating electric fields (tumour treating fields, or TTF), in conjunction with standard chemoradiotherapy to treat patients newly diagnosed with glioblastoma. This electromagnetic therapy is believed to disrupt cell division in glioblastoma cells. In a phase III trial in patients newly diagnosed with glioblastoma, the addition of TTF to standard chemoradiation improved progression-free survival to 7.1 months, compared with 4.2 months for the chemoradiation-only control group. Most importantly, the use of TTF increased the overall survival time to 19.4 months compared with 16.6 months for the control group. TTF treatment was well tolerated with no significant added toxicity except for scalp rash related to the electrodes. Quality of life and gross cognitive function were also comparable in the two arms of the trial. However, some controversy persists regarding this therapy, and its role in the standard treatment of patients with glioblastoma and in clinical trials remain to be determined.

In a field where progress has been unacceptably slow, the past year has seen important advances in the classification and treatment of gliomas which, hopefully, will translate into improved outcomes for patients. Future challenges include establishment of strategies to overcome the extensive spatial and temporal heterogeneity of molecular alterations in gliomas, and development of agents that cross the blood–brain barrier effectively.

Patrick Y. Wen and David A. Reardon are at the Centre for Neuro-Oncology, Dana Farber/Brigham and Women's Cancer Centre, 450 Brookline Avenue, Boston, Massachusetts 02215, USA. Correspondence to P.Y.W. pwen@partners.org doi:10.1038/nrneurol.2015.242

Published online 18 Jan 2016