Understanding radiotherapy and its potential for use in novel combination trials

Glioma

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UK incidence

4,500 brain tumours per annum (approx. 7 per 100,000). Of these, approximately half are gliomas.

Grade distribution at presentation and indications for radiotherapy

Staging is not applicable to primary brain tumours. Treatment and prognosis is determined by grade and histological subtype (1).

Grade 1: (pilocytic astrocytoma) Predominantly affects children and young adults and is treated with surgical resection which is often curative. 10-year overall survival is around 95%.

Grade 2: Approximately 10–15% of gliomas. These are divided by histological subtype: astrocytoma (approx. 40%), oligoastrocytoma (approx. 10–15%) and oligodendroglioma (approx. 45%). 5-year survival rates are between 65% and 80%, 10-year survival between 30% and 50%. Oligodendrogliomas are associated with the best outcomes. Neurosurgical resection or debulking is performed where the risks of neurological deficit are low. Because of the high risk of late neurotoxicity, radiotherapy is generally deferred until necessary. Indications for radiotherapy include uncontrolled symptoms (including seizures) and clinical or radiological signs of disease progression or imminent transformation to higher grade. Optimum radiotherapy dose remains uncertain; recommended regimes vary between 50.4 Gy in 28 fractions (BR13/EORTC 22033 trial dose) and 55 Gy in 33 fractions. Chemotherapy (PCV [procarbazine, lomustine, vincristine] or temozolomide) may be used for disease control and to defer radiotherapy. Oligodendrogliomas are thought to be more chemosensitive than other subtypes. Up to 70% of grade 2 oligodendrogliomas exhibit 1p/19q chromosomal deletions; this genotype is associated with improved survival and is thought to further increase chemosensitivity, although this remains unproven.

Grade 3: Incidence has been difficult to document because of inconsistent histological classification; estimates vary between 6 and 30% of gliomas. Tumours are classified as anaplastic astrocytoma (AA, two-thirds of cases), anaplastic oligoastrocytoma (AOA, approx. 15%) and anaplastic

oligodendroglioma (AO, 15–20%). 60–70% of AO exhibit 1p/19q deletions and are associated with chemosensitivity and median survival rates of at least 6 years (2). Patients with these tumours are likely to benefit from first line chemotherapy and deferred radiotherapy; this hypothesis is being tested in the EORTC 'CODEL' study. Median survival for AA is 2–3 years and treatment remains controversial. Most centres treat these patients with radical radiotherapy (60 Gy in 30 fractions). The role of concomitant and/or adjuvant chemotherapy in these patients has not been defined and is being studied in the BR14/EORTC 26053 'CATNON' trial.

Grade 4: The commonest primary brain tumour, approximately 70% of gliomas. Glioblastoma (the previous term 'glioblastoma multiforme' is no longer recognised in the WHO classification) is the most common histological subtype. These may be primary (approx. 90%) or secondary, which arise from a pre-existing low grade glioma (approx. 10%). Patients with glioblastoma have a mean age of 60–65 years; prognosis and treatment is determined primarily by age and performance status. Patients aged over 70 years or with WHO performance status ≥2 are treated with short-course radiotherapy (typical dose 30 Gy in 6 fractions) and have an average life expectancy of around 6 months (3). Those aged under 70 years and with performance status 0–1 are eligible for radical radiotherapy (60 Gy in 30 fractions) with concomitant and adjuvant temozolomide chemotherapy and have 2- and 5-year survival rates of 25% and 10%, respectively (4). For radiotherapy planning, the gross tumour volume (GTV) is defined by the region of contrast-enhancing tumour and a 3 cm margin is usually added to generate the planning target volume (PTV). Because of the historical poor survival rates of these patients, it has not been deemed necessary to conform rigidly to dose constraints for critical normal tissues such as brain stem and optic chiasm. With improving survival rates for a subset of patients, more attention is being paid to these issues.

Chemotherapy

Concomitant and adjuvant temozolomide is now the standard of care for glioblastoma and is being tested for patients with grade 3 gliomas (excluding 1p/19q deleted AO). Intracavitary carmustine wafers are recommended as part of first-line therapy for patients with an intraoperative diagnosis of high grade glioma whose tumours are suitable for >90% resection (5). NICE guidance did not address the combined use of carmustine wafers and subsequent chemoradiation, but there is no evidence to suggest that this combination is unsafe. The BR12 trial demonstrated that PCV chemotherapy is equivalent to temozolomide in the treatment of recurrent glioblastoma in chemo-naïve patients. Because temozolomide is now used as first-line treatment, PCV is commonly prescribed at relapse. Response to temozolomide may be predicted by methylation status of the *MGMT* promoter; methylation correlates with increased survival and temozolomide sensitivity (6). 1p/19q chromosomal deletion also predicts chemosensitivity and increased survival as discussed previously.

Targeted therapies

From a clinical and molecular perspective, glioblastoma have traditionally been classified as primary or secondary, with primary glioblastoma occurring in older patients and exhibiting high levels of EGFR mutation or amplification and frequent PTEN deletion. Secondary glioblastoma arise from low grade glioma and exhibit high levels of p53 mutation.

More recent genome-wide studies indicate that mutations in three key signalling pathways are present in the majority of glioblastoma (7):

- **EGFR/Ras/PI3K**: EGFR mutation/amplification (45%), PTEN mutation/deletion (36%); PI3K mutation (15%); NF1 mutation/deletion (18%). The commonest EGFR mutation is EGFRvIII, which is constitutively activated.
- **p53:** p53 mutation/deletion (35%); CDKN2A deletion/mutation (49%).
- **Rb:** CDKN2A, CDKN2B deletion/mutation (approx. 50%); Rb1 deletion/mutation (11%)

Glioblastoma are also characterised by aberrant vasculature, hypoxia and necrosis.

Phase II bevacizumab studies generated promising data in recurrent glioblastoma (8), although response rates were probably exaggerated by using resolution of contrast enhancement as a response criterion. In the USA, bevacizumab +/- irinotecan is being widely used for recurrent disease whereas in Europe, bevacizumab is not approved for use in glioblastoma because the studies failed to show an improvement in overall survival. Radiological assessment of response to vascular targeting agents is difficult and new guidelines have been published (RANO criteria (9)). Oral anti-VEGF agents (e.g. cediranib) are also being tested in recurrent disease. The potential benefit of combining anti-VEGF agents with radiation remains unclear, particularly with regard to scheduling. A range of agents targeting the EGFR signalling pathway have been tested (gefitinib, erlotinib, cetuximab) but response rates have been low. Other agents being tested in combination with radiation +/- temozolomide are cilengitide (integrin inhibitor), temsirolimus (mTOR inhibitor), tipifarnib (Ras inhibitor) and enzastaurin (PKC inhibitor). Since tumours with unmethylated *MGMT* promoters are resistant to temozolomide, some studies of novel agents are focusing on this sub-group. Attempts to overcome temozolomide resistance by inhibiting MGMT, for example with O^6-benzylguanine, have been unsuccessful because they exacerbated toxicity.

PARP inhibitors sensitize glioma cells to both radiation and temozolomide and are extremely well tolerated. A number of PARP inhibitors are available and phase I/II studies of various agents in combination with radiation and/or temozolomide are under way. Recent evidence suggests that PTEN-mutated glioblastoma are deficient in homologous recombination repair and may be intrinsically sensitive to PARP inhibition, but this has not been confirmed in patients.

Therapeutic opportunities with radiotherapy in glioma

Evaluating novel radiotherapeutic approaches in the treatment of glioma is complicated by the relative inaccessibility of tumour tissue and the potentially devastating consequences of exacerbating late normal tissue toxicity. However, many opportunities exist to increase the effectiveness of radiotherapy in these patients.

Re-irradiation: With increasing numbers of patients surviving for more than 1 year after first-line radical radiotherapy, and accumulating data describing recovery of radiation tolerance in the CNS, re-irradiation protocols should be evaluated. Stereotactic radiation techniques are appealing,

although it is often difficult to accurately define tumour volumes and glioblastoma are by nature infiltrative.

Combining novel agents with radiation: Since temozolomide is part of standard therapy for good performance status patients with glioblastoma, novel agents must either be combined with radiation AND temozolomide in this patient group, or with radiation alone in patients who are ineligible for temozolomide. Short course radiotherapy regimens (e.g. 40 Gy in 15 fractions) are a potentially useful setting for testing novel agents. If *MGMT* promoter methylation is confirmed as a reliable predictive test for temozolomide sensitivity, patients with unmethylated *MGMT* promoters could be recruited to studies of novel agents plus radiation.

Specific agents of interest: Inhibitors of DNA damage response proteins, e.g. PARP, Chk1. Inhibitors of EGFR/Ras/PI3K signalling proteins, e.g. mTOR, PI3K, Ras. VEGF inhibitors, bearing in mind scheduling issues in combination with radiation.

Suitable patient populations

Phase I studies: Newly diagnosed glioblastoma ineligible for radical treatment or for concomitant chemotherapy; potentially patients with unmethylated *MGMT* promoters. Alternatively, combine novel agent with radiation/temozolomide if pre-clinical or phase I data predicts this will be safe.

Phase II studies: Should be randomised; patient populations as above.

Phase III studies: Newly diagnosed glioblastoma patients aged <70 years, WHO PS 0–1.

References

1. Louis DN, Ohgaki H, Wiestler OD*, et al.* The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007;114:97-109.
2. Cairncross G, Berkey B, Shaw E*, et al.* Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006;24:2707-14.
3. Brada M, Stenning SP. Radiotherapy for malignant gliomas in the elderly. *Semin Oncol* 2003;30:63-7.
4. Stupp R, Mason WP, van den Bent MJ*, et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-96.
5. Westphal M, Hilt DC, Bortey E*, et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003;5:79-88.
6. Hegi ME, Diserens AC, Gorlia T*, et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005;352:997-1003.
7. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008;455:1061-8.
8. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd*, et al.* Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722-9.
9. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010;28):1963–72.