

Glioma therapy

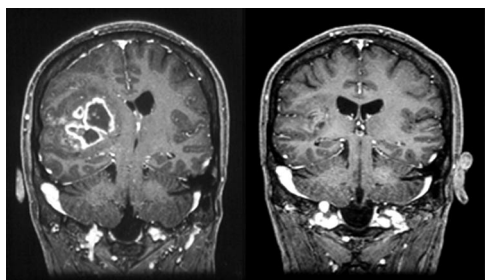
Gliomas are the most common primary intracranial tumours with an annual incidence of approximately 12/100000 persons. They are graded according to their morphological features and range from WHO Grade I (pilocytic astrocytomas) through to the most malignant WHO Grade IV (glioblastoma multiforme GBM). Grade I tumours are usually curable by surgery and will not be considered any further. The median survival for Grade II tumours (diffuse astrocytoma, oligodendroglioma and mixed oligoastrocytoma) is typically between five to seven years, for Grade III tumours (anaplastic astrocytoma) two years and for GBM one year. Treatment of gliomas is limited by their diffusely infiltrative behaviour, the involvement of eloquent brain structures and their tendency to recur at the primary site. The prognosis has improved little over the last thirty years and so we are constantly on the look out for new management strategies.

Surgery

Brain tumour surgery has come of age. Open craniotomy with direct visualisation and reliance on angiography with the associated high morbidity and mortality is no longer practised. In their place, surgeons have high quality pre-operative and, in some centres, peri-operative MRI, functional imaging with PET/SPECT or fMRI and stereotactic systems that allow precise computer aided navigation to avoid eloquent areas and blood vessels. This has led to dramatic changes in the risks associated with surgery but whether these advances have been translated into improvements in prognosis is not known. We still need prospective randomised controlled studies to determine if surgery has any role at all in improving outcome. Studies showing a relationship between extent of resection and prognosis are all retrospective and suffer from the natural bias of surgeons who select the best preoperative cases to operate on. A recent meta-analysis of surgery for low-grade gliomas concluded that the only management standard based on high-quality evidence was tissue diagnosis. All other treatment methods are "practice options" supported by evidence that is inconclusive or conflicting. Similarly a meta-analysis of surgery in malignant gliomas found only 4 out of 20 studies reporting a relationship between extent of resection and survival. In two of these, it followed age, performance status and histological findings in importance suggesting that any benefit from the surgical resection is modest. Therefore the crucial question as to whether resection can be recommended over biopsy to prolong survival has yet to be answered.

Radiotherapy

Unlike the situation with surgery, radiotherapy has been shown in two separate trials to prolong survival in patients with malignant gliomas. The situation with low-grade gliomas is less clear-cut. One dose-response study found no difference in median survival between a low dose (45 Gy) and a high dose (54.9 Gy) protocol. A subsequent study, comparing radiotherapy at diagnosis versus radiotherapy at progression found no difference in overall survival after a median follow-up of 4.6 years although there was a tendency for a longer progression-free survival in the irradiated group. Because of this and because radiotherapy is associated with a significant incidence of CNS toxicity, especially over the long term when treatment fields are large, my



Coronal T1W MRI scans with gadolinium enhancement before and after 4 cycles of PCV showing right frontal anaplastic oligodendroglioma presenting with subacute left hemiparesis. The symptoms and signs resolved completely after the first cycle. The scans show disappearance of mass effect and contrast enhancement with shrinkage of both the cystic and solid elements of the tumour.

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practice is only to recommend treatment when there is clinical and radiological evidence of malignant transformation or in medically-intractable epilepsy.

There have been many attempts to increase the radiation dose to the tumour while minimising the dose to surrounding normal tissue but none have proven more successful than a standard course of external beam radiation delivered to the tumour plus a 2-3 cm margin of normal tissue. Examples include interstitial radiotherapy (brachytherapy), stereotactic boosts, radiation sensitisers and hyperfractionation regimens.

Chemotherapy

In general, the use of chemotherapy for the treatment of gliomas has been disappointing, partly because of intrinsic chemoresistance and partly because of problems of drug delivery across the blood-brain-barrier. Adjuvant chemotherapy i.e. used in addition to radiotherapy does not provide a significant survival benefit although it is used routinely in the United States.

The most significant advance in recent years for chemotherapy of gliomas has been the realisation that anaplastic oligodendrogliomas with loss of chromosome 1p and 19q are exquisitely chemosensitive. Such tumours, previously regarded as highly malignant with a poor prognosis, show prolonged and reliable responses to a standard chemotherapy regime incorporating procarbazine, CCNU and vincristine (PCV). However these are rare tumours accounting for less than 5% of all primary brain tumours and the excellent results have not yet been translated to other more common glioma subtypes.

The other important advance in chemotherapy of gliomas has been the introduction into clinical practice of a new imidazotetrazine compound called temozolomide, an oral alkylating agent, which has recently been approved by NICE for the second line treatment of recurrent malignant gliomas. A phase III MRC sponsored trial is due to begin this year which will determine whether temozolomide, for all its hype, is better than conventional first line treatment with PCV for recurrent disease. Unfortunately, patients with recurrent malignant gliomas have a uniformly dismal prognosis and so interest is focusing on other potential applications of this new drug.

Because of the multiplicity of confounding factors which affect our ability to assess the true effectiveness of a drug in the setting of recurrent disease, further trials should examine promising new agents in primary treatment i.e. in newly diagnosed patients who have not received any other chemotherapy or radiotherapy and who have measurable disease. An example of such a study has been reported for temozolomide which, in preliminary results from an open label phase II study of 51 patients, produced a response rate of 39% (complete and partial responses). Furthermore the drug was well tolerated with only occasional severe myelosuppression, nausea and constipation.

In addition, a recently completed trial using temozolomide given on a daily basis during radiation therapy in newly diagnosed patients with glioblastoma multiforme followed by standard cycles after radiotherapy has shown early encouraging results with a twelve month survival estimate of 67%. A phase III trial is planned and hopefully results will be available next year.

New drugs are continuously being evaluated for efficacy in malignant gliomas because of the poor response rates from standard regimens. For example, preliminary data for the new drug irinotecan (CPT-11), a topoisomerase inhibitor has shown only modest activity.

Conclusions

Gliomas are still incurable tumours which has led to a considerable degree of therapeutic nihilism associated with their treatment. Surgery may be useful, radiotherapy prolongs survival but is not curative. Chemotherapy is being increasingly used in and new indications are emerging.