Health Technology Appraisal

Carmustine implants and Temozolomide for the treatment of High Grade Glioma (HGG)

Personal Statement by Prof Garth Cruickshank for Society of British Neurosurgeons

1. I see 300 new patients a year with high grade gliomas. Of these most are de novo HGG with around 15% being HGG tumours arising from low grade glial tumours.
Most patients 70% have resective surgery as we believe that these patients require less steroid dosing and have an easier time through Radiation. We aim to resect better than 80% of the gadolinium positive tumour on preop MRI scans checked postoperatively with an overall new morbidity of below 10%[1]. Most patients with good performance after surgery will go for standard 60GY Radiation over six weeks commencing at four weeks from surgery. Drop out from radiation is negligible, but we accept 10% level 1 CTC toxicity as normal.15-20% patient undergo stereotactic biopsy and ¾ of these will go on to have radiation treatment. The rest are generally unsuitable for further aggressive treatment.

2. At six weeks post radiation patients have MRI imaging which is repeated at 8-12 week intervals looking for signs of regrowth of tumour. On detection where there is no indication for repeat surgery e.g. mass effect, and the performance level is good Karnovsky = or >60, patients are offered PCV chemotherapy. Where the tumour mass is large or threatening important structures patients are offered further surgery with either subsequent PCV or Gliadel wafers, where good resection is possible.

3. This is followed by further imaging monitoring as above. At further recurrence or treatment failure patients are offered treatment with Temozolomide. Further relapses are either offered carboplatin, irinotecan where available or access to clinical trials.

4. Clinical management, therapy decisions and reporting occur through a weekly Peer reviewed MDT involving surgeons, radiologists, radiotherapist/oncologists, pathologists and clinical nurse specialists. Specialist glioma clinics are easily accessible by patients once a week held adjacent to routine neuro-oncology clinics for integration of diagnostic, symptom and surveillance support. Access to palliative care, counselling and pathway liaison is achieved through nominated key workers at the MDT and who are known to the patients. Rapid access to radiation is facilitated by good referral contact with regional radiotherapists. 31/62 monitoring is tailored to patient pathway definition for all new referrals.

5. Currently Temozolomide is available for use in patients under NICE guidance for recurrent patients who have 'failed' PCV therapy. Current experience with over 100 patients shows that at current dosing level of 200mg/m^2 for 5/7 out of 30 days (one cycle), the major problems are related to cycle dependent bone marrow suppression, which is non-cumulative. Around 10% of patients have difficulty with nausea during the 5 day treatment period which needs careful management. A number of patients have received considerably more Temozolomide than the usual six monthly treatment cycles, some having received up to 40 cycles without problems with good tumour control. There is evidence of a number of patients developing progressive fatigue unrelated to bone marrow state. In general patients tolerate this treatment well and clinical response is often greater than tumour response as demonstrated by decreased tumour mass effect swelling without change in enhancing tumour dimensions.
6. Gliadel implants are available for patients who satisfy the criteria for the Brem study[2] and in whom good maximal resection is considered possible. Over 20 patients have undergone this process in the last year in Birmingham without complications but it is clear that the extent of resection is essential for best efficacy and watertight dural closure for least complications.

No bone marrow impact is seen despite the local concentration from wafer implantation in the brain being up to 1000 times that achievable by the systemic route (PCV or CCNU). Hence the need for regular blood tests is unnecessary. In addition after surgery patients rarely have other implant/local chemotherapy related problems if good resective decompression has been achieved.

Temozolomide Chemoradiation/Adjuvant treatment in de novo HGG patients.[3]

The evidence concerning efficacy and safety of this treatment will be presented by other parties and will not be repeated here. In this section certain practical and patient related issues will be highlighted.

6. In the context of the above patient pathway patients would be selected for treatment after surgery or biopsy if their performance level is good, and confirms pathology. In the Stupp study patients who did best with this therapy showed Hazard ratio benefits from maximal > 80% resection of their tumours in the context of a delay from surgery to radiation treatment of four weeks. In addition in this study such postoperative selection before randomisation enabled the control group to achieve a median survival better than any other reported clinical trial in this area. This implies that factors such as good surgery and early radiation are important factors in all groups but are important in optimising the effect of temozolomide given this way, i.e. the patient care conditions must be to a sufficient standard and careful patient selection made.

7. The survival benefits to patients from this therapy need to relate to the discomforts and disadvantages. Early treatment of patients offers the chance of controlling disease whilst the patient has a good performance level. 2.5 months improvement in median survival seems relatively little, but represents a 20% improvement for a patient with only twelve months median survival. This needs to be compared with equivalent results in other less rare tumour groups, eg lung, breast. More convincing is the improvement in longer term 2year survival from 10 to 26%. This is substantial benefit to patients, but has a cost in terms of patient follow- up support and performance level. The Stupp study showed a much greater drop out rate for radiation treatment and a reduced number of patients receiving the whole drug course. Recent evidence has confirmed that the useful QOL of surviving patients is prolonged as well. Hence the there is survival benefit and utility benefit for these patients but that there is a cost in terms of support provision.

8. There is evidence that patients that express reduced amounts of the repair enzyme MGMT derive most benefit from this treatment. If validated, this would help select patients for this treatment and protect those unlikely to respond from unnecessary exposure. This selection will require access to the testing procedures which will contribute to the individual cost, but may reduce overall costs by patient selection..

9. It is argued that this treatment now represents the gold standard for the treatment of newly diagnosed Glioblastoma. As such the capacity of the UK to contribute to phase III clinical trials will depend on this treatment becoming accepted as the standard arm. In addition there will increasing pressure on clinicians from patients to provide this treatment. At present it is available for patients in a limited way heterogeneously across the UK often without due regard for the service standards that should be in place. It is important that many of the issues to do with achieving the best result from this drug treatment (and Gliadel) depend on the provision of service quality and support. As such it would be important for this NICE Tech assessment to relate to the concomitant NICE guidance process ‘Improving the Outcomes for Brain and CNS Tumours’ due for publication in April 2006, which provides a framework for service provision which would underpin good practise in the management of this disease.

10. Who might benefit from this treatment and at what cost?

The current first operation rate for adult patients with HGG varies across the UK between 60 and 80% of cases. In the West Midlands (5.3 million, 3 Neurosurgical centres) and especially QEH, the largest referral centre in the UK we would estimate 240 patients per year and approximately 100 cases between UHCW and UHNS. We would estimate that the maximum benefit from early use Temozolomide would accrue to patients undergoing maximal surgical resection and who have the best performance levels. This would reduce the suitability of patients to around 50% of these figures i.e. 120 + 50 =170 patient per annum

11. The patients likely to obtain the maximum benefit from this treatment as described by the study would be those with good performance levels after surgery or biopsy before radiation treatment. Applying these criteria to the West Midlands population a few less patients might satisfy the criteria after surgery, but several more maybe a further 5-10% who have biopsy only, may be eligible i.e. 170 + 10% = 187. Patients under this regimen receive daily temozolomide at 75mg/m^2 throughout their radiation and then six cycles of monthly treatment at 200mg/m^2. This amounts to an expected cost of around £7,400 for the whole course (drug treatment only). The total number of eligible patients based on the RCT inclusion criteria is likely to be limited and fairly constant over the foreseeable future, e.g. a fraction of the 3500 patients presenting per annum in the UK, various estimates from consensus meetings have put this at around 20-30% of presenting patients

3500 x 30/100 x £7400 = £7,770,000 per annum across the UK
for Gliadel there would be fewer suitable patients (surgery vs biopsy)
thus
3500 x 20/100 x £6000 = £4,200,000 per annum across UK

Patients who have early Temozolomide treatment would in most cases absent themselves from subsequent consideration for this drug treatment at recurrence a treatment offset cost for these two mutually exclusive uses of Temozolomide should be considered in calculations

12. If one assumes the reported improvements in median survival are associated with a maintained quality of life or performance level, then the cost per Quality Adjusted Life Year for

. Temozolomide is 12/2.5 x £7400 = £35,520
Gliadel is 12/2 x £6000= £36,000

NICE boundaries are at £20,000 and £30,000
The Utilities level adjustment is yet to be decided for this group of tumours but is likely to be between 0.6 and 0.8.

Gliadel implantation at First Surgery

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13. The concept of early adjuvant drug treatment commencing with first definitive treatment (surgical excision) is appealing to surgeons who recognise that tumour volume control is the key to disease control. In addition there is some evidence that early chemotherapy may achieve suppression of tumour regrowth before the onset of radiation. The fact that for both the Temozolomide (Stupp study) and the Gliadel (Westphal study[4]) increased survival with these agents was best seen with those undergoing maximal resection, points to the value of effective safe surgical excision at improving survival in this context.

14. The one step process associated with the use of Gliadel offers significant benefits to the patient and prescribing centre with very few if any drawbacks. No blood monitoring is required and patient compliance and acceptability is guaranteed. There are few complications in experienced hands.
15. It is not yet known what if any the interaction in terms of benefit or deficit is for sequential use of Gliadel with Temozolomide. There is some evidence of safety but not of efficacy as yet.

General Comments

The introduction of these two drug technologies represents the first real advance in the treatment of high grade glioma since the introduction of steroids and radiation (30 years ago). There is now a National and Global recognition of this and that patients should have access to these treatments where clinicians can reasonably expect patients to derive the reported gains.

16. The issue that is most urgent and important is that there should be consistency in decision making for the funding of expensive drugs used in the treatment of patients with recurrent or newly diagnosed high grade brain tumours (gliomas). Funding should be comparable across the UK and by delivery centre. It should be no worse per head for this rarer cancer than for the more common cancers e.g. lung breast. It should not differ from policies adopted by the rest of the EC to avoid further inconsistencies as have been reported in the press, and used by patient groups to appeal to the European Court.

17. The use of these drugs for <u>new patients</u> has an equally justified if not stronger evidence basis than that for drug use in patients with recurrent tumours under the prescribing conditions existing now. This illogicality must be rectified and replaced with a generic mechanism that uses simple standards of cost and benefit to prevent patients particularly in these high risk groups being disadvantaged by the slow development of new prescribing guidance especially where time is of the essence..

18. To support this process a Decision Making process is needed with the clear intention that patients should only be recommended for these treatments

-where the patient satisfies the inclusion criteria for the original trial

-the service supplier can ensure that the conditions to effect the best outcome as described in the trial details are available e.g. surgical ability, access to radiation

-the patient is at the correctly identified stage of their disease to benefit.

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[1] Laws et al Glioma Outcome Project *J.Neurosurg* 99:467-473 2003

[2] Brem H et al. Lancet 1995;345:1008-1012.

[3] Stupp et al NEJM 2005

[4] Westphal M et al. Neuro-Oncol 2003;5:79-88