Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma

Brief Personal Statement of Dr Jeremy Rees

Introduction

The outlook for patients with malignant gliomas is so bleak (median survival of glioblastoma less than one year) that any new technologies, which offer the hope of improvement over current treatment modalities, are to be welcomed. As a neurologist with a special interest in oncology, I am involved in the diagnosis and decision making process for patients with gliomas although I do not personally carry out radiotherapy planning or prescribe chemotherapy.

Current treatment of malignant glioma

The standard treatment for malignant glioma is a maximal surgical resection where possible followed by adjuvant radiotherapy usually given at a dose of 60Gy in 30 fractions over six weeks. This leads to a median progression free survival of about five months for Grade IV gliomas and eighteen months for Grade III gliomas. More neurosurgeons are pursuing an aggressive surgical policy on patients with malignant glioma as they believe that there are quality of life benefits in terms of reduction of mass effect and steroid dependence even if a survival benefit cannot be easily proved.

Until recently, the role of chemotherapy in newly-diagnosed malignant glioma was limited. A large meta-analysis of chemotherapy trials combining individual patient data from 12 Randomised Controlled Trials of more than 3000 patients demonstrated that 'classical' adjuvant chemotherapy improved median survival at one year from 10 – 12 months and increased the proportion of patients surviving one year from 40% to 46% and surviving two years from 15% to 20%.**(1)** This modest benefit has limited the widespread use of adjuvant chemotherapy in the UK to progressive disease after radiotherapy alone.

Temozolomide

EORTC 26981, recently published in the New England Journal of Medicine, has shown that the use of concomitant temozolomide with radical radiotherapy followed by 6 cycles of adjuvant temozolomide offered a significant survival advantage over radiotherapy alone with minimal additional toxicity. Although the increase in median survival from **12.1 months** with radiotherapy alone to **14.6 months** in the concomitant temozolomide group was relatively modest, **the two-year survival rate increased from 10.4% to 26.5%. (2)**

In my opinion, the results of EORTC 26981 represent the first significant improvement in the outlook of patients with malignant gliomas since the early 80s when the radiotherapy trials were first published. This study will be regarded as definitive as the sample size was large (573 patients from 85 centres), prognostic factors were well matched between the two groups and 85% of patients in the concomitant arm completed both radiotherapy and temozolomide as planned. Furthermore an exploratory subgroup analysis defined

according to known prognostic factors demonstrated a survival benefit in nearly all subgroups.

In a parallel study on the same patient group investigating the role of genetic silencing of the *MGMT* (O^6-methylguanine–DNA methyltransferase) DNA-repair gene by promoter methylation, there was a striking survival benefit in those patients who received temozolomide and whose tumours contained a methylated *MGMT* promoter as compared to those who did not have a methylated *MGMT* promoter. **(3)** It is therefore likely that response to temozolomide in addition to radiotherapy will only be seen in about half of the patients treated and it would seem sensible to recommend the adoption of a rapid diagnostic test for the *MGMT* methylation status before deciding on the use of adjuvant chemotherapy. Other than that, the additional resource implications in terms of clinic time, blood tests etc are minimal.

Carmustine Implants (Gliadel Wafers)

The data on carmustine implants for newly diagnosed high-grade gliomas is based on two phase 3 randomized control trials, the first being a small study of only 32 patients (16 in each treatment group) which had to be terminated prematurely because the drug had become unobtainable **(4)** and the second, a larger phase 3 trial of 244 patients randomized to the carmustine implants or placebo wafers at the time of primary surgical resection. Both groups were matched for age, sex, performance status and tumour histology. The analysis was based on intention to treat and median survival was **13.9 months** for the carmustine implant group compared to **11.6 months** for the placebo treated group.

Adverse events were again comparable between the two groups except for CSF leak and raised intracranial pressure which were both more common in the active treatment group. **(5)**

In my opinion, the data for carmustine implants is not as persuasive as the temozolomide data, particularly as 2 year follow-up data are not available. Furthermore as carmustine implants can only be used in patients having complete resections and in whom watertight dural closure is possible, I suspect that only about 25% of patients would be eligible whereas any patient under the age of 70 with a malignant glioma who is in sufficiently good physical and mental condition could receive temozolomide.

Summary

There is now high quality randomized phase 3 trial data for both technologies and both produce a modest improvement in survival of patients with malignant glioma. This is comparable to previous studies of adjuvant chemotherapy. The most impressive result is the two year survival benefit seen in the concomitant temozolomide group which is almost certainly only applicable to a subgroup of patients. The temozolomide treatment could be potentially prescribed to all patients with Grade IV gliomas under the age of 70 with a reasonable performance status but in practice would probably only benefit patients with a specific tumour genetic profile. In contrast, carmustine implants would only be used in those patients who were deemed suitable for large tumour resections. This group represents only about a quarter of all patients with malignant gliomas.

References:

1. Glioma Meta-analysis trialist group chemotherapy for High-Grade Glioma. Cochrane Database Syst Rev 2002; 4: CD003913
2. Stupp R, Mason WP, Van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England Journal of Medicine 2005; 352: 987-996
3. Hegi M, Diserens A-C, Gorlia T et al. *MGMT* silencing and benefit from temozolomide in glioblastoma. New England Journal of Medicine 2005; 352: 997-1003.
4. Valtonen S, Timonen U, Toivanen P, et al Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: A randomized double-blind study Neurosurgery 1997; 41: 44 –49
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-oncology 2003; 5: 79-88