Cancer Research UK response to the National Institute for Health and Clinical Excellence's Appraisal Consultation Document: Glioma (newly diagnosed and high grade) – carmustine implants and temozolomide

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Background

Cancer Research UK is the world's largest independent organisation dedicated to cancer research, with an annual research spend of over £217 million. Cancer Research UK funds research into all aspects of cancer from exploratory biology to clinical trials of novel and existing drugs as well as population-based studies and prevention research.

Temozolomide was first synthesised by a Cancer Research UK funded scientist, Professor Malcolm Stevens, then at the University of Aston, Birmingham. It was taken into Phase I and early Phase II trials by Cancer Research UK, when activity in glioma and melanoma was identified. Based on this data, it was licensed by Cancer Research UK's then technology transfer company, CRC Technology, to Schering Plough who undertook pivotal Phase III studies.

Section 1: Appraisal Committee's preliminary recommendations

This NICE appraisal consultation has not recommended temozolomide in combination with radiotherapy for the treatment of newly diagnosed high grade glioma patients. Cancer Research UK does not support NICE's decision.

Temozolomide is a good example of the achievements of the enormous investment in cancer research in the UK. The use of temozolomide in combination with radiotherapy has received worldwide acclaim as the gold standard for the treatment of glioblastoma multiforme (GBM).

The development of temozolomide is an example of the UK leading the global fight against cancer. This recommendation would deny patients in England and Wales access to the benefits of this treatment which patients throughout Europe and the US are able to receive.

Section 4: Evidence and interpretation

The decision not to recommend this treatment relies heavily on the cost implications to the NHS, based on economic modelling. There is an implicit assumption in the Appraisal Committee's evaluation that all patients with newly diagnosed and high grade glioma would be prescribed temozolomide. However clinical practice is unlikely to reflect this.

Clinicians are more likely only to prescribe the drug to patients who are having full or partial resections or who have a performance status of one or better. This would be a much smaller subset of patients than included in the Institute's economic estimations. Thus the resulting cost implications to the NHS would likely be lower.

There is evidence[i] to demonstrate that temozolomide and radiotherapy combination therapy is particularly useful in subsets of patients with good performance status or who have a full or partial resection of their tumour. This research has reported clinical benefits in this subset of patients in median survival estimates superior to the overall study population. Looking at the median value across the whole patient population attenuates this benefit. We recommend that the Appraisal Committee reconsider re-running this model, looking at the cost per life year gained by this subset alone.

We therefore ask that, before making a final recommendation, the Appraisal Committee carry out a re-assessment of the cost-effectiveness of temozolomide in combination with radiotherapy in these sub-groups alone.

The economic model used in the appraisal relies on median survival values across the entire population. Long-term survival is more important than median survival in rare cancers, especially where side-effects are minimised. Temozolomide has shown an improvement in survival at two years from 10% to 26%. This is significant.

The special nature of brain cancer treatment makes patient access to temozolomide particularly important. Individually, none of the interventions that we use to treat brain cancer patients provide much difference in terms of prolonging life, but incrementally they provide big gains. A patient receiving no treatment would have a life expectancy of two to three months. Treating this patient with surgery might give them a prognosis of four to five months, and adding radiotherapy could take survival to a year. Giving temozolomide, in a small subset of patients as a first line therapy could extend this survival further still.

We also question whether QALYs are the most sensitive estimate in brain cancer patients, as these patients often have only a very few months, rather than years, to live. We suggest that the Appraisal Committee reconsider the appropriateness of QALYs in brain cancer patients. We refer the Committee to the validated economic evaluation instrument used in the EORTC trial of temozolomide as a more appropriate alternative to QALYs.

Section 5: Proposed recommendations for further research

The recommendations for further research in this Document require revision following consultation with the brain cancer research community. The Committee has noted that large trial comparing conventional to high dose temozolomide is planned. However, we understand that this trial does not include prospective stratification of patients by MGMT status.

Furthermore, this UK NCRI trial does compare temozolomide with the PCV regimen. It could be argued that research over and above this would be a duplication of effort, and unlikely to gain support from research funders. It is also worth bearing in mind that as temozolomide in combination with radiotherapy is widely accepted as the preferred treatment for GBM, it may be difficult to get ethical approval for a trial that uses less effective treatment options in its control arm.

Conclusion

This Document states that quality of life for patient's is paramount. However, the importance to many patients of the prolongation of life should not be underestimated. Temozolomide has been shown to be well tolerated and to have no detrimental effect on quality of life[ii]. We therefore ask the Appraisal Committee to reconsider its decision not to recommend temozolomide in combination with radiotherapy for the treatment of newly diagnosed high-grade glioma, except in well-designed clinical trials.

For more information please contact Hilary Jackson in the Policy and Public Affairs Team on 020 7061 8362 or email hilary.jackson@cancer.org.uk.

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[i] Stupp et al 2005 Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med. 352(10):987-96*

[ii] Taphoorn MJB et al 2005 Health-related quality of life in patients with glioblastoma: A randomised controlled trial. *Lancet Oncology. 6(12):937-44*