Response of Brain Tumour UK to the ACD for glioma ('Carmustine implants and temozolamide for the treatment of newly-diagnosed high-grade glioma')

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Conflict of Interest: None

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Gliomas are the most common type of brain tumour. Whereas brain tumours represent a small percentage of all primary cancers, their impact on the patients and family is profound. Gliomas have a poor prognosis, with high-grade gliomas being rapidly fatal. Conventional treatment for high-grade gliomas consists of surgical resection to the extent possible, followed by adjuvant radiotherapy. The outlook for these patients remains, however, very bleak, with few patients surviving more than one year. There is therefore a huge need for treatments that can improve and prolong their life, even when it is not possible to cure their underlying disease. Adjuvant chemotherapy has been evaluated since the 1970's, but only the recent introduction of particularly temozolamide and carmustine implants has given any real hope to these patients. Recent studies have shown that particularly the addition of temozolomide to radiotherapy for newly-diagnosed glioblastoma, the most malignant type, resulted in a clinically meaningful and statistically significant survival benefit with minimal toxicity. Other studies have shown that these agents can also prolong the disease-free interval and quality of life in patients with a relapse following earlier conventional treatment. The clinical specialists that were consulted were unanimously in favour of allowing these drugs. However, NICE did not acknowledge this, but seems to have based its recommendations upon an economic, financial model, which we believe is flawed. Brain Tumour UK therefore does not agree with the NICE preliminary advice not to recommend these agents for the management of newly-diagnosed high-grade gliomas, except in well-designed clinical studies.

1. Preliminary recommendations

These preliminary recommendations are not acceptable to us for the following reasons:

- The quality of life has already been assessed (see Taphood et al)
- The MGMT trial is up and running, which was not acknowledged
- The subgroups that are incorporated into current studies have been partially done in the temozolamide study, which was not acknowledged
- Recommending that future research should be conducted to compare temozolomide or carmustine implants with other chemotherapy regimens suggests these treatments have already been accepted as the standard or care. This is counterintuitive since NICE have not recommended the use of these agents for the treatment of newly diagnosed high-grade glioma.

2. Clinical need and practice

There is a great clinical need to help patients with high-grade glioma, because under the present circumstances their life expectancy and quality of life are so dire, and the impact on their families is massive. Time is not on their side. The NICE recommendations make no comment about these factors, and especially the number of person-years lost. There is furthermore a number of studies showing that the addition of temozolomide to radiotherapy for newly-diagnosed glioblastoma (the most malignant form of high-grade glioma) significantly improved survival with minimal toxicity and without a negative effect on the health-related quality of life (Stupp et al, Taphoorn et al). In a large multi-centre study, the two-year survival rate of patients that had was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone.
The two-year survival rate of patients who had treatment was 26.5 per cent with radiotherapy plus temozolomide, and 10.4 per cent with radiotherapy alone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 haematological toxic effects in 7 percent of patients.

4. Evidence and interpretation

4.1.4 The median survival time that was used to evaluate the results is not necessarily the most accurate way to assess these data. The actual data show that there is a marked improvement in the long-term (2-year survival) when compared with radiotherapy alone, which was most marked for the temozolamide group, but also evident for those with carmustine implants. Patients that had surgery followed by radiotherapy and temozolamide treatment had a 16.5% higher survival rate at 2 years, whereas this was 8.3% for the carmustine group. This longer-term survival is of immense benefit to patients and families.

4.1.11 A MGMT trial to assess response to therapy and prognosis of patients with high-grade glioma is currently ongoing. However, even though it is possible that MGMT may be a predictor of benefit from treatment with temozolamide, this trial has not yet been validated. Such data are still preliminary.

4.1.12 The ACD reports that subgroup analysis showed increased benefit and survival following temozolamide treatment in patients that had a complete rather than a partial resection. But, these subgroup data were not included in the evaluation of the potential benefits of this drug. The Assessment Group should have conducted an analysis to assess the cost-effectiveness of temozolamide in this patient group. Temozolamide might have major benefits for such subgroups.

4.3.1 Committee have commented that they considered the clinical evidence and comments from the patient groups, but seem to have based their decision purely on the AG economic model. However, the AG model acknowledges their model is sensitive to certain data and the assumptions they have used. As the economic model appears pivotal to the success/failure of this assessment, we need to establish whether the model has been properly validated, and if so how and by whom.

4.3.2 Available evidence suggests that temozolomide/carmustine implants do <u>not</u> have a detrimental effect on quality of life. Rather, they improve it by increasing progression-free and overall survival without causing appreciable toxicity, thus providing a major benefit to both patients and their families.

4.3.3 We do not understand why the number of patients treated with radiotherapy plus temozolamide is considered too small to draw conclusions about the effectiveness of temozolamide in increasing survival. To date, three large, international, multi-centre, placebo-controlled, randomised and controlled trials have been conducted to evaluate the effects of post-operative radiotherapy alone versus radiotherapy with concomitant and adjuvant temozolomide chemotherapy (Stupp et al, Taphoorn et al, van den Bent et al). These studies totalled over 1700 patients, half of whom were treated with radiotherapy plus temozolamide, the other half with radiotherapy alone. This is a very large number of patients. Surely, these must be relevant and significant data. Furthermore, all these studies showed that addition of temozolomide during and after radiotherapy significantly improved survival, especially at 2-years, whereas it was also shown not to have negative effects on health-related quality of life.

4.3.4 Post-operative radiotherapy, with or without adjuvant chemotherapy, is considered to be more effective when started before or around 6 weeks post surgery. Concerns about access to radiotherapy in some units should, however, not be used as an argument not to recommend temozolamide/carmustine. It is evident that clinicians would not treat with either temozolomide and/or carmustine if radiotherapy was not available – this would be a waste of resource.

4.3.9 QALY analysis may not be appropriate in this case, since it can only give poor results in a disease that has such a bleak prognosis. A 50% increase in life expectancy but fewer overall years does not carry much weight in this model, even though it would have huge positive implications for both patients and their families. Furthermore, quality of life data was assessed in the temozolomide trial using a disease specific instrument. There is no validated methodology for estimating utilities based on this instrument. The NICE model is also sensitive to median survival and does not take into consideration that survival might be disproportionately greater in certain subgroups. Median survival time is not necessarily the most accurate way to assess these data. The actual data show that there is a marked improvement in the long-term (2-year survival) when compared with radiotherapy alone, which was most marked for the temozolamide group, but also evident for those with carmustine implants. In the light of these factors, cost utility analysis was not feasible.

4.3.11– ‘The Committee concluded on the balance of the economic evidence that the use of carmustine implants and temozolamide for the treatment of newly diagnosed gliomas would not be a cost-effective use of NHS resources.’ However, we have been given to understand that temozolamide may have a major indication in the second line treatment of relapsing glioma, and this would obviously be affected by this decision.

4.3.13– No specific mention is made of subgroup analysis for temozolomide, although this has been examined in a number of the submissions. When done, subgroup analysis highlighted increased benefits in specific groups. E.g. Stupp’s study showed that adjuvant temozolamide had the greatest benefits in patients that were fittest at the beginning and had the greatest degree of tumour resection, and similar data were also presented in the manufacturer’s submission.

5. Proposed recommendations for further research

Europe, the USA and Australia currently use these treatments as the standard care based on the trials conducted to date.

Trials are ongoing for these treatments for e.g. temozolomide and MGMT. If temozolamide and carmustine are not recommended in the UK, research here would be pulled. This would include the study that Edinburgh are currently participating in. The UK will then fall behind the rest of the world in treating patients with gliomas.

ACD preliminary recommendation is restricted use to well designed RCTs. Since about 1800 patients a year are diagnosed with high-grade-glioma in the UK, the vast majority of these patients will be denied treatment.

4 Proposed date for review on guidance

Research based charities would be discouraged from funding research if the next technology review is not until 2009. The overall outcome wold be a tremendous setback for glioma patients in the UK.

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