National Institute for Health and Clinical Excellence

Health Technology Appraisal

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

Personal statement

Conventional treatment for malignant gliomas, anaplastic astrocytoma WHO grade III (AA) and glioblastoma multiforme WHO grade IV (GBM), consists of surgery followed by external beam radiotherapy. While the survival and quality of life benefit of surgery has not been tested in prospective randomised trials, the evidence for the benefit of external beam radiotherapy was demonstrated in three randomised trials (1, 2) (3). The role of adjuvant chemotherapy, particularly with nitrosoureas, has been under test since 1970's. While individual randomised trials showed marginal or no survival benefit, a meta-analysis of 12 trials of over 3000 patients demonstrated a 6% survival benefit at 1 year and 5% at 2 years and prolongation of median survival by approximately 2 months (4).

Despite many years of research, the reality of malignant glioma is that it represents an incurable malignancy with a median life expectancy in the region of 12 months and few, if any, long term survivors. The principal prognostic factors for survival are age, performance status and tumour histology. More favourable outcome is seen in younger patients with anaplastic astrocytoma and good performance status, and less favourable in older patients with glioblastoma histology and functional impairment.

The two new treatments under consideration, Carmustine implants (Gliadel) and Temozolomide, involve the use of alkylating agents given as intralesional or systemic treatment.

Carmustine (BCNU) impregnated polymer wafers (Gliadel) are a means of intralesional delivery of alkylating agent by insertion of wafers into the resection cavity at the time of surgical removal of malignant glioma. The efficacy of Gliadel was first examined at the time of recurrence. In patients with recurrent GBM treated with salvage surgery, the insertions of BCNU impregnated wafers compared to polymer wafers alone (controls), was shown to prolong median survival by 8 weeks (5).

Only one adequately powered randomised study tested Gliadel against placebo wafers as an adjuvant treatment to surgery and radiotherapy in newly diagnosed malignant glioma. In the study of 240 patients with GBM and AA, Gliadel was shown to prolong median survival by 2.3 months with approximately 10% survival benefit at 1 year and no demonstrable survival benefit at 18 months. In the principal subgroup of 207 patients with GBM the survival difference did not reach

statistical significance and no survival difference was seen beyond 18 months (6).

Temozolomide, an orally administered alkylating agent, was first tested at the time of recurrence. In a randomised phase II study in patients with recurrent GBM, median progression free survival was prolonged by one month when compared to Procarbazine and this did not translate into a significant survival benefit (7).

Temozolomide was tested in a randomised study of 573 newly diagnosed patients with GBM as an additional treatment to surgery and radiotherapy, given as concomitant treatment with radiation and as adjuvant chemotherapy for 6 months following completion of radiotherapy. The use of chemotherapy was associated with prolongation of median survival by 2 months and an improvement in 2 year survival of 15% (8).

In summary, the addition of Gliadel wafers at the time of surgery was shown to result in prolongation of median survival in a group of patients with GBM and AA. Although this is also likely to be the case for patients with GBM, the size of the study precluded the demonstration of a statistically significant survival benefit in this group. In the available peer review publication, the survival benefit is most pronounced at the median timepoint with no clear benefit seen beyond 16-18 months. Temozolomide given as concomitant and adjuvant treatment has shown survival benefit in patients with GBM, both at the median timepoint and persisting for the duration of the study with a persistent survival difference at 2 years. Nevertheless, all patients with GBM regardless of the use of Temozolomide, progress and no long term cures have been reported.

Both trials show encouraging results with survival benefit in a population of patients with poor prognosis not shown in individual trials carried out in the preceding decade. Nevertheless, the published results are in line with the existing knowledge of the effectiveness of systemic nitrosoureas in the treatment of malignant gliomas. Neither of the treatments under consideration have been compared to nitrosoureas (BCNU, CCNU or ACNU) and on the basis of the available data the magnitude of benefit of the new treatments is within the range seen for systemic nitrosoureas. A commonly held belief is that the toxicity of the new approaches is less that that seen previously with nitrosoureas but sound comparative data is lacking. Both randomised studies are the first demonstration of the survival benefit of the treatments under test and contain a relatively small number of patients. Despite a possible statistical desire to confirm the results in more robust studies, it is unlikely that the desperate plight of patients with malignant glioma would make repeat trials acceptable.

While both studies show a potential way ahead with prolongation of survival apparently without marked additional toxicity, they also leave a number of unanswered questions. The first question is a comparison to nitrosourea based chemotherapy. Realistically, a randomised study of Temozolomide against

nitrosoureas would be unlikely to accrue patients. A study comparing systemic and intralesional nitrosoureas is a marginally better prospect but in the current climate would have to allow for administration of Temozolomide and therefore only limited time for exposure to systemic nitrosoureas.

Further question is the applicability of the results demonstrated largely in patients with GBM to patients with AA. Based on the apparent equivalent benefit for AA and GBM shown in the meta-analysis (4) and on the apparently superior efficacy of Temozolomide in terms of response rate in patients with recurrent AA (9) compared in separate studies to recurrent GBM (7) (10) the treatment under test may be considered effective in AA. However, existing knowledge about the toxicity of concomitant chemotherapy and radiotherapy at other sites raises a concern about the potential damaging effect of combination of concomitant chemotherapy and brain irradiation and this is of particularly relevance for the best prognostic group of patients with malignant glioma who are young with AA and have a median life expectancy measured in years. One or more trials addressing the treatments under test in patients with AA should be encouraged. A trial addressing the role of concomitant Temozolomide in patients with AA is in advanced stage of preparation by the NCRI Brain Tumour Clinical Studies Group.

Another unanswered question is the potential relationship between the two treatments. On the basis of the available evidence, it is not possible to make a statement about the comparative efficacy of the two treatments under consideration unless a specific analysis of matched patients is performed. In this respect, a randomised trial comparing the individual treatments alone and in combination would be useful but in practice such a study would be difficult to organise. The reality of malignant glioma is that patients seek any treatment which may offer some benefit. If both treatments are approved, it is likely that patients who have Gliadel wafers inserted at initial surgery will be considered for additional treatment with Temozolomide, based on the unproven assumption of additive effect. Prospective collection of national and international outcome data on combined treatment would be of value.

One of the determinants of the efficacy of alkylating agents is the status of the DNA repair machinery. Studies of MGMT gene methylation status, used as a measure of the activity of the repair enzyme of alkylating agent induced damage, suggest that the benefit for adjuvant chemotherapy is seen predominantly in patients with impaired repair capacity (11). Further use of Gliadel and Temozolomide, both within and outside trials, should be accompanied by tests of repair enzyme status with the future aim of tailoring treatment to its predicted efficacy. Future studies of molecular predictors of treatment effectiveness should also lead to the development of strategies to overcome potential treatment resistance.

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