National Institute for Health and Clinical Excellence
Health Technology Appraisal

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

Response to Appraisal Consultation Document (ACD)

1 Introduction

The Appraisal Committee preliminary recommendations on Carmustine implants and Temozolomide for the treatment of newly diagnosed high grade glioma were arrived at without discussion and advice from invited experts and without taking into account all the relevant evidence. The analysis as presented is largely guided by health economic considerations with flawed interpretation of the clinical research data and using models with limited factual base. The provisional recommendations are not considered sound.

2 Corrections to ACD

2.1 Section 2.4
There is insufficient data to show that grade 3 mixed oligoastrocytomas have better prognosis than grade 3 astrocytomas.

2.2 Section 2.6
The description of management of malignant glioma is incorrect.

2.3 Section 3.1
Carmustine is not known to interact with RNA; as an alkylating agent it alkylates DNA.

2.4 Section 3.2
Marketing authorization does not equate with indication.

2.5 Section 3.5
Alkylation by MTIC results principally in DNA strand breaks and not cross links.

2.6 Section 4.1.5
Reanalysis of data is not available in peer reviewed publication and the timing and rationale are not known.

2.7 Section 4.1.12
The EORTC generated the data independent of the manufacturer.

2.8 Section 4.2.1
Independent health economic analysis has been performed by EORTC and their partners (also applies to section 4.2.5).

2.9 Section 4.2.7
The applicability of general population health-utility scoring to patients with uncommon brain tumours is questionable and not validated.

2.10 Sections 4.2.8 & 4.2.9
The analyses make unverified assumptions on the use (and cost) of treatment at recurrence, which are at variance with factual resource use data from the RCTs and this is likely to be a major determinant of the differences in cost effectiveness.

2.11 Section 4.3.1
It is not clear what the objective impact of such qualitative evidence is and the statement is largely misleading.

2.12 Section 4.3.3
This section requires considerable correction, as a balanced personal statement may have been misunderstood. The facts are as follows:
i) No single randomized trial has shown convincing survival benefit for nitrosourea containing adjuvant chemotherapy in newly diagnosed malignant glioma patients.
ii) A meta-analysis of all randomized trials of adjuvant nitrosourea containing chemotherapy showed a 5% improvement in survival.
iii) The consensus in UK oncology community is that the benefit seen in the metaanalysis is not of sufficient magnitude to recommend routine use of adjuvant nitrosourea containing chemotherapy for newly diagnosed patients with malignant glioma.
iv) The results reported for Carmustine implants and Temozolomide, which are both principally alkylating agents, are in the same direction as the results reported for nitrosoureas (also alkylating agents).
v) An unpublished comparison of the magnitude of benefit seen in the metaanalysis and in the EORTC trial shows that the confidence intervals of the two survival outcomes do not overlap (i.e. the magnitude of benefit is significantly larger in the recent RCT).

2.13 Section 4.3.3
While it is acknowledged that there are no trials comparing Carmustine implants or Temozolomide with adjuvant nitrosourea containing chemotherapy the recent RCTs used the correct controls and the implied criticism in the selection of the control group is not justified.

2.14 Section 4.3.5 line 4 (typo)
Temozolomide is substituted for Carmustine implant

2.15 Section 4.3.7
It is assumed (but not clearly specified) that the comments on RCT refer specifically to Carmustine implants.

2.16 Section 4.3.9
The confident statements about validity of the model used do not acknowledge the uncertainties and the theoretical nature of some of the estimates. The assertion of the committee on the superiority of the AG model is open to considerable discussion.

2.17 Section 4.3.11
While the committee acknowledges the impact of therapy at progression on the cost-effectiveness analysis, the absence of a serious data based analysis largely invalidates the calculations. The committee's opinion on the "use of NHS resources",

taken without consultation with the experts, is contrary to the factual approach taken and at variance with the real clinical situation.

Without a real calculation of resource use of second line treatment at the time of recurrence, which takes into account real data (to be obtained either from the RCT or from UK data collection) the present cost-effectiveness analysis is largely worthless.

2.18 Section 4.3.13
The committee failed to consider the potential impact of the therapies on subgroups of patients defined by known prognostic factors. The EORTC RCT prospectively stratified patients by performance status and the extent of surgery. Patients with WHO performance status 0 and patients aged < 50 years of age had a survival benefit of 4 months. Conversely, patients with WHO performance status 2 and patients following biopsy alone had little survival benefit.
The committee chose to select information on the potential future value of MGMT analysis which indeed requires validation.

2.19 Section 5.1
The comments need clarification. A randomized UK NCRI trial is currently testing PCV chemotherapy vs Temozolomide at the time of first recurrence with second randomization comparing conventional vs high dose Temozolomide. The trial design preceded information on MGMT status and patients are not prospectively stratified. RTOG/NCI (USA) and EORTC are planning a study of low dose vs high dose adjuvant Temozolomide in the initial therapy of patients with glioblastoma which has not yet been activated.
The information on MGMT status may be of value in the future which is likely to be additional to the information on the recognized prognostic factors.

2.20 Section 5.2
This section attests to the lack of consultation with the experts and with the research bodies involved in brain tumour trials. The suggestions presented lack understanding of the current evidence and the important issues in this field and seriously invalidate the APC.

2.21 Section 6
The serious flaws in the analysis (above) make the conclusion untenable and at variance with the views of the experts.

3 General comments
From a clinical and academic perspective the assessment of the technology should take into account: a) quality and reliability of the research data used in the assessment of efficacy of the technology, b) prospectively collected data on resource use with model based considerations used as supporting evidence and c) standard therapies in malignant glioma as practiced in UK.

Only one reasonably powered randomized study provides data on which the efficacy of Carmustine implants could be assessed. The results summarised in 4.1.2 – 4.1.6 of the ACD describe some of the difficulty in the assessment of the technology. In addition the study was conducted and analysed by the manufacturer with possible

consequences to the independence of the study analysis as already highlighted in the FDA and NICE assessment. The principal peer reviewed publication lacks robust statistical conclusions on survival benefit and a subsequent analysis (not generally permitted in trials run by independent trial organisations without clear rationale set by an independent committee) is not available as a peer reviewed publication. Hence the data, while intriguing is not fully validated. The outcome data is applicable only to the population of patients studied which is restricted to patients who undergo radical tumour resection.

The primary decision to be taken by the committee is on the validity of the data, based on the peer reviewed publications with inclusion of factual information on the use of second line treatment and stratification by prognostic factors.

The RCT assessing the value of Temozolomide was a robust, appropriately powered study (2nd largest study of primary therapy in malignant glioma and the largest in glioblastoma) conducted and analysed by an independent research organization albeit with industry sponsorship. Resource use and quality of life information were prospectively collected.

Notwithstanding the incorrect appraisal (summarised in Section 2) it seems inappropriate to assess the two technologies without taking into account the considerations outlined above.

4 Conclusions

Based on the above considerations the Appraisal Consultation Document is flawed and its conclusions unsound.

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