HEALTH TECHNOLOGY APPRAISAL: Carmustine Implants and Temozolomide in the treatment of glioblastoma multeforme Comments on Appraisal Consultation Document (ACD)	
To: NICE	**FROM: NHS Quality Improvement Scotland**

Reviewer 1. Comments on the Carmustine and Temozolomide Consultation Document

I find the NICE ACD document unsatisfactory for the reasons listed below. I have expanded on these in the text where I concentrate on the technical issues. I leave it to others to expand on the impact that acceptance of the ACD conclusions will have on patients, service and research.

1. The endpoint chosen is inappropriate for this population of patients.
2. The endpoint has been developed by the investigators themselves, it has not been externally validated. There are likely flaws.
3. The economic model is complex, makes inaccurate assumptions, over-emphasises median survival and has not been convincingly validated in this group of patients.
4. The committee have accepted the economic model without providing criticism in the ACD and used it as the overwhelming criterion on which they base their recommendations.
5. The committee have concluded that the technologies should not be used outside of clinical trials without considering use limited to groups of patients (identified in the studies) who might particularly benefit and who, even on their economic model, may have a lower ICER.
6. The ACD has been written without direct input from an oncologist (and in particular no neuro-oncologist), and without input from a representative of brain tumour patients.
7. None of the NICE professional (neuro-oncology) experts, who advised the committee, accept the conclusions in the document.

8. The recommendations for further clinical study are of no value. These recommendations demonstrate the failure of the committee to understand the current state of research in this group of patients worldwide. This probably results from the lack of adequate neuro-oncology input to the document.

Introduction

I think it is unfortunate that the two technologies have been considered together. There are significant enough differences to make a joint assessment difficult. Gliadel (Carmustine) is a surgically applied treatment, restricted in application to those patients with tumours that are surgically removable in such a way as to leave favourable anatomy. The technology is applied to all high-grade gliomas fitting this description, including glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma.

Temozolomide is a treatment applicable to patients undergoing surgery or just biopsy and in whom a local pathologist has made a diagnosis of glioblastoma.

There were differences in study design and differences in study outcome for these two technologies. I am not convinced that the committee fully appreciated this. For example in paragraph 4.3.5 they write '*it considered concerns regarding the estimates of effectiveness of Temozolomide (including the length of survival in the placebo arm)'* Indeed there was no placebo arm used in this study!

1. Choice of endpoint

Whilst I appreciate the need for a parameter with which to compare different treatments in different diseases, I seriously question the use of QUALYs in this particular instance. It is questionable whether the QUALY model, which is based on members of the general public who are well assessing chronic, hypothetical health states, can apply to an explosive disease such as glioblastoma. Glioblastoma has virtually no chronic phase; its appearance is acute, and it is lethal in a short space of time. In such a situation, patients are much more likely to value an extension of survival, almost at any cost, and only secondarily value their 'symptomatic' health state. Further, this model takes no account of the value of extension of life to relatives. It is acknowledged that the use of QALY's in extreme health states is questionable and there are few more extreme states in oncology than glioblastoma. The economic group have not attempted to justify their choice of endpoint and this is difficult to accept.

2. Validity of endpoint

It was admitted by the Peninsula Group[1] (Assessment report page 95 section 5.5.2.1) that they did not find a validated source of utility values for patients with high grade glioma from which to calculate their QALY's . They therefore developed their own, using a set of scenarios based on the EORTC QLQ-30 questionnaire. For this, 36 members of an original group of 93 patients from a general population were used to generate the data, which would eventually be fed into the QUALY analysis. Do we know how this subgroup of 36 was chosen. It is a severely minority subgroup - were there biases? Is it valid at all to use so small a group? The approach was not validated in any acceptable way. In a very limited attempt to seek validity the Peninsula group report '*validity of the health state descriptions was sought using 3*

members of the expert advisory group'. This group concluded that '*standardising the impact of gliomas was difficult….*' It must be concluded from this that the methodology has not been internally validated and has certainly not been subject to any external review or validation process.

Summary

I would conclude that the chosen endpoint is of doubtful applicability in this group of patients and that the validity of the endpoint, even if it were appropriate, has not been established.

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3. Comments on the underlying model

The Peninsula Group have used a highly complex economic model and adapted it for brain tumour work[1]. A number of assumptions have been made which are at best approximations and at worst possibly wrong. For example, the model is based on an assumption that transition states are time dependent rather than state dependent. They admit that this is counter intuitive and I would argue that it is actually erroneous. The length of time a patient with glioma is likely to live is certainly most closely related to their state (whether in remission or has progressive disease) rather than their time from diagnosis, as assumed in this model. Though the two parameters may be related the relationship is not necessarily simple. A relapsed patient is likely to die sooner than one who has not relapsed. This discrepancy in the model is likely to be most apparent at longer lengths of survival, which is where the greatest benefit from Temozolomide occurs.

By their own admission, the model they have used is particularly sensitive to the median survival (Peninsula Group Assessment report page 5)[1]. When the more important parameter is survival at 2 years or later (as in the Temozolomide study) and when the median survival is less than 18 months, the model they have used may become particularly inappropriate and may underestimate the value of the technology.

A further criticism is that they appear to have calculated the costs of treatment at relapse based on an assumption that all patients receive PCV for relapsed disease. Certainly a significant number of patients who did not receive Temozolomide for their initial treatment will receive Temozolomide subsequently. (This has been recommended by NICE following a previous submission). This use of Temozolomide will increase costs in the radiotherapy only arm. It will act to decrease the cost differential and improve the ICER and the impact of this could be considerable.

4. Acceptance of the model

Once again the only assessment of this model appears to have been from the NICE Group themselves and the issues discussed above have not been acknowledged in the ACD. The group have spent the great majority of the document discussing economic issues without criticising the models on which they are based. They have not considered the broader picture of what patients and their relatives might want as outcome from treatment and what improvement they might consider valuable. They have not considered the quality of life data published by Taphoorn and colleagues[2] which uses *directly* the validated QLQ 30 instrument and not an unvalidated derivative of it as in the Peninsula model. Further, the report has been produced without input from a neuro-oncology clinician, which is very surprising. For these

various reasons I have considerable reservations as to whether this model (despite the detail) can be considered a valid instrument on which to judge this technology in this group of patients.

5. Consideration of use in subgroups

I am concerned that the Committee has failed to comment on the possible use of either technology in sub-groups of patients. In the original publication from Stupp et al,[3] it was clear that poor performance status patients and patients who did not receive a tumour resection, did not fair well either with or without chemotherapy. Conversely, those with the best performance status and the best resections had the greatest benefit from Temozolomide. If a further analysis had been done on this basis by the Peninsula group, it would undoubtedly have improved the ICER for patients in appropriate sub-groups. (Analysing a group of patients with a global 'better prognosis', as the Peninsula group does on their page 132 does not add to the debate and is a relative waste of time). Whilst I accept that numbers in the 'Stupp' sub-groups might be small, the differences never the less were strong (Data presented at numerous meetings inc ECCO 2005). I feel it is a mistake to fail to consider the evidence on sub-groups already available to the Committee and thereby to consider the possibility of limited prescribing on a selected basis.

6. Lack of specialist expertise on the appraisal committee

A list of the members of the appraisal committee is given in Appendix A.
I would express concern that although relevant clinicians have been used to advise the NICE Committee, no neuro-oncologist of any kind has been involved in the production of the ACD. Indeed I can see no evidence of an oncologist of any kind in the group. I find it difficult to understand how an adequate assessment can be made without such expert opinion. I believe this lack of expertise is demonstrated at many stages of the report, including the conclusions. Neither, as far as I can see, has a patient expert been involved at this stage. The only 'independent Patient Advocate' is Dr Ann Richardson. I would be keen to know what expertise this single individual brings with respect to the experience of patients with malignant glioma and their relatives.

7. Lack of support from specialist advisors.

I accept that the committee did take evidence from chosen experts and that these experts are indeed eminent in their fields and represent, reliably, opinion in the UK. However these experts were not involved in the writing of the ACD. I find it of grave concern that each of these advisors (Professors Brada, Cruickshank, Walker and Dr Rees) have each since felt it appropriate to criticise the conclusions of the report. I believe it true that none of these experts supports the conclusions. I would ask how the Committee can justify the production of a document that contradicts the opinion of their own chosen experts and opposes the great majority opinion of neuro-oncologists in the UK. Does the committee feel comfortable in producing such a report where there is such united opposition and particularly from amongst their own selected advisors?
I believe that similar remarks could be made with respect to the patient representatives advising the committee.

8. Recommendations for research

The recommendations on research made by the Committee show that they fail to understand the current situation with respect to this regimen, again demonstrating the lack of specialist input. The study itself has been viewed and reviewed by the international neuro-oncology and wider scientific community and has attracted very little criticism in its design, conduct or its conclusions. The regimen has been accepted as standard or care almost universally. The original study has been analysed in terms of quality of life and these data are available already[2]. Hence to recommend further research in this area without acknowledging what has been done is inappropriate and neglectful. Current randomised studies in this area do include a QOL aspect, if the committee had taken notice of their advisors they would know this.

A subsequent programme of research based on this regimen is already in place and includes an analysis of sub-groups, both clinical and chemical (including assessment of MGMT status). To suggest that we repeat this work in the United Kingdom based on a lesser regimen (radiotherapy alone), would attract no interest internationally and no funding nationally. I find it difficult to understand the recommendation to compare this regimen with other active chemotherapy treatments if this regimen is not accepted as 'standard of care'. On the other hand how can we justify using this regimen as a control arm, if the Committee say they cannot recommend its use routinely? In that situation we would be using as control a regime which the committee does not consider 'standard of care'. Scientifically this makes no sense. It would be extremely difficult to interest researchers in an assessment of this regimen in children if we know that a result as positive as that found in adults (by Stupp) would be rejected by NICE. What possible interest can this attract from researchers who will feel that their efforts, even if positive, are likely to be rejected by such a Committee?

I would therefore welcome serious suggestions from the Committee as to how the UK research community could proceed in the light of a refusal from NICE to accept either of these regimens as standard of care. For the committee to 'recommend' research that is either already done, already underway or not feasible is not helpful.

Summary

The diagnosis of glioblastoma is an extreme situation in oncology. Death is inevitable and survivals are short. Such progress as we have has been achieved incrementally by the judicious, successive use of steroids, surgery, radiotherapy and now chemotherapy; which has extended median survival from 2-3 months to around 14 months and has generated a small, but significant number of longer term survivors. The disease affects across the age range including many in middle-life and gives little warning before its onset, bringing with it the imminent prospect of death. Clinicians and patients will know the value of even brief extensions of survival, almost independent of its quality. In these circumstances the uncompromising use of a model based on the assessment by healthy members of the general public of chronic health states is almost certainly inappropriate. The international, almost universal acceptance of the Temozolomide regimen is testimony to these sentiments. I think it would be appropriate for NICE to reconsider its assessment on the basis of the appropriateness of the evaluation and to consider at least limited use of either of these technologies in patients with newly diagnosed glioma.

In summary therefore, I think that the basis on which the NICE decision has been made is questionable, both in terms of the endpoint and in terms of the model used to examine this endpoint. I would consider an approach based on survival and quality of life estimate, as has been done in the publications of Stupp 2005 and Taphoorn 2005 and an economic analysis based on these to be more appropriate.

1. Peninsula, T.A.G., *Carmustine Implants and Temozolomide for the treatment of newly diagnosed high grade glioma.* Confidential report, 2005.
2. Taphoorn, M.J.B., et al., *Health-related quality of life in patients with glioblastoma: A randomised controlled trial.* Lancet Oncology, 2005. **6**(12): p. 937-944.
3. Stupp, R., et al., *Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. [Article].* New England Journal of Medicine March, 2005. **352**(10): p. 987-996.

Reviewer 2. This ACD and the accompanying overview document are excellent and comprehensive summaries of the state of the evidence and fully justify the conclusions presented. The health economic arguments are always difficult and particularly so in a condition with such a poor prognosis as high grade glioma, but the unequal mix of cases in the major trials reviews invalidates their conclusions of benefit from treatments of, at most, marginal effectiveness.