TO: NICE: Comments from NHS QIS nominated expert on PenTAG Evaluation of carmustine implants and temozolomide in the treatment of glioblastoma multeforme

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For simplicity I will discuss the submission for temozolomide (TMZ) and BCNU separately

Temozolomide

Since the release of the early results at ASCO in 2004, the regimen used in the EORTC-NCIC study has been adopted as the standard of care throughout the world and has been incorporated into national funding streams in Sweden, Austria, Spain, Canada, Australia and many other countries. Though the median survival increased only two months with the addition of TMZ, it is **the increase in the proportion of patients living two years from 1 in 10 to 1 in 4** that has convinced neuro-oncologists that this treatment should be available for fit patients with this devastating condition.

General Comments on PenTAG report

I have some serious concerns about the document as it has been produced primarily due to a number of assumptions which have been made within the PenTAG cost effectiveness model. Though a number of experts were consulted in the preparation of this document, there is an obvious miss-interpretation of the data due to a lack of specialist knowledge.
Principally my concerns are

- the over emphasis on the inclusion of a small number of grade III patients in the EORTC-NCIC trial, this is simply a fact of life when treating this illness. Pathologists have differing opinions on the exact diagnosis. The important issue is that the local pathologist, on whose opinion the management decisions are made, thought the lesion was a GBM.
- the utility calculation grossly over-estimate the impact of this treatment on the patients quality of life. Patients in the trial with grade 3 or 4 toxicity may have only experienced such severe side effects for a short period so it is inappropriate to assume such a low utility value for patients in the RT+TMZ arms of the study. Though the QOL has not yet been published in full (in press) there was not significant difference between the study arms.
- Costs of treatment at relapse are removed from the calculation, which is inappropriate as patients are less likely to receive TMZ again if they have received it in the adjuvant phase. Whereas those who have not received it during this time period are highly likely to do so.
- Though the 'industry' cost effectiveness model undoubtedly has some problems particularly due to the censuring of the data after two years, it should be remembered that these data are based on actual patients who have received the study medication therefore their data should be given greater weight than a theoretical model. It would

be useful for the reviewers to see this original report and for these data to be applied to the PenTAG model.

- The total costs have apparently been based on all patients receiving this treatment, whereas in reality less than 50% of patients presenting with a GBM will be suitable for this treatment. The biology of the disease, particularly in the elderly, means that it will not be used out with a clinical trial setting in older and less fit patients

Specific comments

Section 3
Guidelines do exist, they were published by the Royal College of Physicians in around 1998.

Radiotherapy – this treatment is generally well tolerated and as evidenced by the control arm of the EORTC-NCIC trial which demonstrated a 4.9% grade 3 or 4 fatigue but all other grade 3 or 4 toxicities occurred in less than 1% of the population.

TMZ costs – these apparently assume that all patients will receive the TMZ rather than a more realistic around 50% of patients.

Section 4 Systematic review

Randomisation – the large TMZ study was run by the EORTC an internationally renowned clinical trials organisation with a standard method of telephone randomisation to which all investigators are blinded to the sequence of treatment allocation (computerised).

The inclusion of 7-8% non-GBM patients is irrelevant and a sub-group analysis not required. There are multiple publications demonstrating that there is significant variability in the reporting of brain tumours by even highly specialist neuro-pathologists due to the subtlety of the features required for each diagnosis. Therefore, in any standard population to which this treatment will be applied, there will be a number of patients who may not have a GBM if the pathology were reviewed at another centre. For this reasons most large neuro-oncology centres have a consensus opinion for the final diagnosis.

Bias

Performance bias - the use of post-progression chemotherapy, the fact that more patients in the RT only arm (72% v 58%) received chemotherapy at progression would have actually reduced the impact of the trial medication.

Attrition bias – it is inevitable that more patients will withdraw from a treatment which lasts six months when compared to one that lasts six weeks. As the primary endpoint is survival such drop-outs are irrelevant.

Blinding – it is impossible to blind a study with a myelo-suppressive agent against a placebo as any blood tests taken prior to the next cycle, or if the patient becomes unwell, will immediately unblind the investigators.

Post-operative randomisation– it would not be ethical to randomise such patients pre-operatively. Though this was essential in the BCNU trial, it was not in the TMZ studies and it imperative that any patient offered entry into a clinical trial is in a sufficiently good clinical condition to undergo the study treatment. Only around 50-60% of patients with a pathological diagnosis of GBM (unpublished Scottish audit data) are sufficiently fit to receive such a treatment.

External validity
GBM in older patients is a different disease, with predominantly primary GBM with a more aggressive phenotype and hence a shorter survival. To subject such patients to a protracted course of radiotherapy, which would occupy the majority of their life expectancy, would be unethical. It is unlikely that this treatment would be used in the over 70's therefore their exclusion in this trial is appropriate.

These data cannot be applied to patients with Grade III tumours and indeed a number of follow-up studies by the EORTC, NCRN and other groups are proposed.

Outcome measures
The calculation of overall survival and time to progression free survival from randomisation is standard practice in oncology trials.

Effectiveness
As stated above, the inclusion of a number of patients felt at central review not to be GBM is irrelevant to everyday clinical practice as this will be inevitable.

The subgroup analysis according to MGMT status – only a proportion of the patients in the whole EORTC-NCIC study had this test performed, particularly it should be noted, none of the French patients (the test failed to work because of the method of tissue preservation). So the opinion of the EORTC Brain Tumour Group and other International experts is that this test cannot be currently be relied upon to select patients for TMZ – a second international study examining two different dose levels of TMZ and prospectively testing the impact of MGMT status is proposed and will open in 2006.

Toxicity
The results are reported as per the studies and are within expected and acceptable frequency. The visual disturbance reported in both arms is likely to be due to steroids.

Comparison of BCNU and TMZ
I agree that such a comparison would be hazardous and not particularly helpful.

<u>Cost effectiveness</u>

The 'industry' cost-effectiveness study on the TMZ study was conducted by a well recognised university department in conjunction with the EORTC BTG. Inevitably the cost-effectiveness data were collected in mainland Europe, as few UK centres recruited to this trial. I agree that by only including the data for the first 24 months after randomisation the

costs in the more expensive 'progressive phase' of the study group would have been excluded.

I am uncertain as to the reasoning behind PenTAG group's concern about including the costs of chemotherapy at progression, as this will inevitably be clinical practice. Currently those patients who have not had chemotherapy at presentation, receive either PCV or TMZ (centre dependant) or enter the BR12 study (comparing the two regimens) at progression, therefore it is important that these costs are included. Their second calculation after the removal of treatment at progression is therefore incorrect as this will not be the clinical picture. If patients are not given TMZ during the early phase of their illness, it is highly likely that it will be given at a later date, thereby reducing difference in costs between the two study arms. In addition, a patient who relapses within a year of adjuvant TMZ is unlikely to be treated again with the same drug as it would be effective. Therefore it is highly relevant to include these costs in the calculation of the costs for management of patients out with a trial setting.

Other limitations – only data on 224 patients – this was not a commercially sponsored study but was conducted by the EORTC and NCIC. Therefore there were insufficient resources to collect health economic data across the whole population. Also collecting any data, including QOL data, is notoriously difficult in this group of patients, particularly towards the end of their life. A paper on the QOL data in this trial has been written up and will be published soon in Lancet Oncology.

PenTAG analysis

The utility model assumes 18% of patients in the concomitant phase of their illness had nausea, vomiting and infections that might require hospital admission. This is an incorrect assumption. In the trial 0.7% of patients had grade 3 or 4 nausea and 3.1% grade 3 or 4 infection. Only such severe toxicity could necessitate admission to hospital. In addition, a patient maybe graded as having such a level of toxicity when it is present only of a single day. The utility of 0.74 therefore grossly over estimates the impact of this treatment on the patients quality of life. Similar over-estimates have been made of the adjuvant phase.

Health care costs

The other 'expert opinion' on potential healthcare costs appear reasonable. However, I am uncertain as to how many cycles of chemotherapy during the adjuvant phase of the treatment were included in the model. It is important to realise that in the trial only 50% of the patients received all six cycles of chemotherapy and careful assessment during this phase is mandatory to ensure progressing patients do not continue to receive this potentially toxic agent and hence significantly reducing health care costs. If the model calculates the proportion of non-progressed patients at each time point and therefore only allows such patients to continue this therapy this been taken into account, but it would be useful to know the median number cycles delivered to the theoretical population.

Conclusion

I am concerned that the health care costs collected from the actual trial have not been used in the models. I am uncertain as to the reasons behind this. Was the EORTC BTG approached for these data directly so they could be incorporated in the PenTAG model? If

not, such an approach should be made before any final conclusions about the cost utility of this regimen are made.

BCNU wafers

I have less concern about the analysis for the cost effectiveness of BCNU wafers as the data, particularly regarding the impact on survival, are much weaker.

General comments

- The imbalance in pathological type in the studies was unavoidable as the pre-operative diagnosis would have been a 'best guess' from the radiological appearances. Frozen section, on-table pathology, cannot provide a detailed diagnosis and can only identify whether or not the lesion is a high grade glioma. In addition, it was suggested that a separate analysis should be conducted examining the 1p19q of the anaplastic oligodendroglioma (AO). It should be noted that the chemosensitivity of patients with AO does not correlate as well for gene loss as it does for grade II oligodendroglioma.

- As with the TMZ study the exclusion of patients over 65 is reasonable as patients over this age are infrequently fit enough to undergo a tumour resection and hence have wafers inserted.

- For reasons stated above the survival analysis should be performed on the whole group, not just the GBM cases. However, any survival advantage identified by these studies is small and non significant by 12 months. Though it should be noted that even though the potential concerns with the non-protocol analysis, the FDA did feel there was sufficient evidence to grant a licence for the use of BCNU wafers in newly diagnosed patients

- As the intervention appears to have minimal impact on overall and progression free survival it is unlikely to be a cost-effective intervention.

- Obviously it is important in any cost effectiveness analysis not only to look at the costs of the intervention but the overall health care costs. This should have therefore been included in the 'industry' submission

- The PenTAG model assumes a utility of 0.73 for patients in the study arm due to presence of seizures and blurred vision, however seizures were actually more frequent in the control arm (13.3 v 9.2%) and blurred vision a consequence of steroids. This is therefore an over-estimate of the impact of BCNU wafers on the patients quality of life.

Conclusions

With a very marginal impact on outcome, the conclusion that BCNU wafers are not cost effective seems reasonable.