National Institute for Heath and Clinical Excellence

Health Technology Appraisal

Title: Carmustine Implants and Temozolomide for the Treatment of Newly Diagnosed High Grade Glioma

Comments on Pentag Assessment Report – Professor G S Cruickshank on behalf of President of SBNS

1. We are grateful to have the opportunity to comment on this technical report which will go before the Appraisal Committee on 23.11.05. Comments related to this report are based on discussions and assessment of the Pentag Report from a range of neurosurgical consultants and healthcare professions who are involved in the delivery of this service to patients with high grade glioma.

2. We have a number of concerns about this report particularly related to its appreciation of the real clinical situation. We are concerned that the report has been compiled without the direct input of the clinicians involved in the delivery of this service and as such has many failings related to its usefulness. We note that a medical panel has been consulted and those noted on the panel are well known to those of us involved in this process. Nonetheless, we are concerned that the Pentag group may have not had a member of that panel or direct clinical input into the technology model report or its assessment. There are, therefore, significant weaknesses in the Technology Report.

3. We are concerned that the report emphasises weaknesses in their submissions and based on "generalisability". There is a common dictum of cost effectiveness

that one would like to be able to treat the largest population of patients with a particular disease as possible. Nonetheless, as recent FDA and MHRA comments make clear, it is important that treatments which show a clear sub population response pattern as has been demonstrated in the recent Temozolomide study (Stupp et al), should balance preference of treatment in terms of the group most likely to respond. In other words, the general principle of selecting a group more likely to respond is a basic principle of cancer therapy and appears to have been discarded by the Pentag group as being a negative description of the cost effectiveness of these particular treatments. This shows a basic misunderstanding of the way in which those given the responsibility of actually prescribing these treatments function.

4. The summary decries the statistical benefits demonstrated for both Gliadel wafers and Temozolomide largely based on dismissing stratification based on data (1.4.2) of its prognostic variables thereby diminishing the differences between groups. In addition, it bases considerable argument on the fact that there may be some measurable differences in opinion about pathology (1.4.1). This is not a failing of the technology related to these trials but as a matter of fact in clinical delivery. In particular, even two pathologists of renown may disagree as to whether a tumour is truly an anaplastic astrocytoma or a glioblastoma multiforme. Thus, even if one was to exclude panel-based decisions on pathology there is still likely to be an operational error which may well be based on biological factors which cannot be easily reconciled at the time at which delivery of, say, Gliadel wafers, i.e. requiring intraoperative insertion after pathology becomes available.

5. There is an emphasis on differences between the intention to treat and per protocol (1.4.2) populations. It is recognised by many well established clinical

trials proposers, e.g. EORTC/RTOG, that intention to treat models are by far the most superior as they reflect clinical judgment and activity in practice. Per protocol require all variables including those which may be significantly important to be nullified between arms and this can lead to exclusion of data which may be very important at determining differences or in reconciling similarities. This becomes particularly obvious when one compares analysis of data for example on BCNU showing median survivals of 2.3 months at confidence intervals and per protocols estimates using unstratified methods which imply lack of statistical significance. Indeed, if one was to take some very standard evidential-based clinical trials which are currently in clinical practice and are relied upon with great certainty, then that effect of using a 'per protocol' assessment by comparison with an ITT is likely to be give an e.g. HR of 0.77 by exclusion of data (1.4.2). This is to be expected and in no way undermines the clinical usefulness of the original data. It just shows that if you apply statistics to only a limited number of data set you can show any result you want. These arguments pertain to the Temozolomide assessments as well.

6. The report gives undue emphasis to the idea that salvage therapy may have made a difference to overall survival (1.1.4). The whole basis of our understanding of chemotherapy in the treatment of high grade glial tumours is that salvage therapy with almost any chemotherapy that has been described in the literature makes very little difference to survival. In particular, the Stewart analysis of all chemotherapy trials done up to 2002 demonstrated clearly that the maximum improvement in survival was likely to be of the order of 5% wherever and whenever treatment was applied. Under these circumstances the use of additional treatments after recurrence has occurred in this particular set of data has no significance at all but emphasis has been placed on the fact that chemosensitivity

is an important factor particularly where there may be an imbalance between anaplastic and glioblastoma between the two arms. In particular, numbers of confounding cases related to anaplastic astrocytoma in these two trials is very small.

It is particularly important to realise the difference between this form of chemotherapy described here and other forms of chemotherapy described in the past is that in the BCNU situation whether the chemotherapy is given immediately at the time of surgery and that the impact of surgery appears to be important where maximal resection has taken place. Similarly with Temozolomide, maximal resection seems to have an important part to play in enhancing the chance of Temozolomide being effective. This makes quite a difference in terms of the way the interpretation of these treatments should be considered where most of the data that is discussed in the Pentag study other than that related to the Westphal and the Stupp report (de novo tumours)is largely data related to recurrent tumours.

7. With respect to the point above, it is also distressing to see that data from the Stupp and Westphal studies is given equal weight to that from limited anecdotal series in the text with a number of unsubstantiated throwaway comments. For example, page 2 section 141 "different central pathologists' assessments suggested there might be a greater imbalance in grade 3 tumours between the arms" refers to observational data in which the completely reverse interpretation could be made if it were written by another author. Such implications have been given greater weight than the evidence suggests.

8. We were pleased to see that the relevance of the 1p19q genetic differences and also the MGMT data generated in relation to the Stupp trial were given relevance to this technical assessment. Whilst we appreciate that this data volume in this area is still currently growing, there is little doubt from the sub analysis of the Stupp study that there are two proportions of patients, with in the treatment arm one of which seem to respond extremely well and the other which did not respond as well, more in line with the control group. The evidence would suggest that this is due to the expression of MGMT in these tumours. This may be a very important point when trying to analyse which subgroups may be more applicable in being selected for treatment in this drug process.

9. The surgical treatment of high grade glial tumours as is discussed in section 3.2.3 has been fraught with difficulty in determining the impact of resection on survival. However, there is little doubt that close interpretation of both the Westphal and Stupp data (BCNU/W and Temozolomide) has a ratio well in favour of patients who have undergone maximal total resection as part of their treatment program. In other words, where we may be unable in a general sense to show direct benefits between minimal resection or biopsy versus total maximal resection, in this particular study where the groups are well described and characterised the benefits of this maximal resection has been demonstrated. This goes back to an earlier statement we have made in which generalising trial results to the whole population of people with high grade glial tumours, would not allow us to select out groups who are more or less likely to be responsive to treatment. The evidence from the Stupp and Westphal studies is that even using the relatively clear selection criteria of patients as described in these two major studies, a significant number of patients could be selected pragmatically from an ongoing referral pattern within the current UK NHS. This would then emphasise the role of

good surgical management in being able to apply use of these two new treatments (BCNU/W and Temozolomide) to gain the maximum effect.

10. We have carefully reviewed the available information on the cost benefits model used. We would take issue with some of the cost analyses that have been used but recognise that for Gliadel the additional costs related to the underlying costs for treatment are relatively small and in proportion to other established treatments for systemic cancers based on the fact that the longer you live the more it costs to treat you. However, a single isolated treatment (eg BCNU/W) will cost an increasingly smaller proportion of the overall cost if that patient does well.

To this one should add the practicality of use of these drugs. In other words, currently both BCNU/W and Temozolomide are used for patients with recurrent brain tumours. If we now choose to use them for *de novo* patients, and we believe that the maximum effect of these drugs is achieved by using them earlier, then reusing the drugs at the time of recurrence may not be so appropriate and that there will be a financial argument for limiting patients at one attempt at either of these drug treatments at the time most opportunity to achieve the maximum benefits. For most patients this is likely to be earlier on in their disease than at the time of recurrence. Under these circumstances the current cost across the NHS for the use of Gliadel and Temozolomide will need to be seen in relation to the new cost of adding more patients to this group who would be applicable but also a null revenue cost to those who already are selected for existing treatments at recurrence. Bearing in mind the heavy use of Temozolomide now in recurrent tumour, this may become an important argument when looking at the overall cost effectiveness of drug treatments for this group of patients.

11. We have looked to try and attempt to understand the model used and the conditions under which it has been tested. It is interesting that the complexity of the model used ends up by demonstrating exactly the same utility figure more or less as that produced by the Gliadel/Link Pharmaceutic team (0.8). This would suggest that there are within the Link model key components which have a significant impact on the utility figure outcome. These key components are not brought out by the Pentag study but do represent a much more clear description of the clinical model in use. In other words, the patient cost in terms of performance and acceptability in receiving Gliadel wafers, for example, has little bearing on the overall costs for management and very little in terms of additional follow-up over that currently required for someone now receiving this treatment. The maintenance of performance level and acceptability is thus undiminished by the process of introduction of the treatment, and the cost benefit issue relates only really to the differences in median survival which are clearly achieved at very low cost in such a model.

12. Taking the concept of the model further forward the same utility figure applied to Temozolomide shows a differential but higher cost benefit figure simply because the follow-up intensity required for Temozolomide is greater than that required for BCNU. There are natural concerns about the amount of outpatient time, blood tests, and so on which must be carried out on a more regular basis in patients receiving concomitant Temozolomide followed by adjuvant Temozolomide.

13. Page 101 paragraph 2 describes an increase in resources needed to place BCNU/W wafers. This is just not true as patients who will be selected for maximal resection would be the ones used for treatment with BCNU/W in the same way as

they are now. There will be a gradual change where surgeons feel that they can perform such maximal resection in patients, but in many ways this largely determines practice at present anyway. The evidence across a number of centres in the UK who have been using these treatments fairly regularly over the last couple of years has been that the costs of inpatient stay, time in theatre, etc, has not been increased.

14. Bearing in mind that the utility model has generated a figure of around 0.8 allows us then to interpret subsequent data with respect to selected groups with more reliability bearing in mind at least two approaches have been used to achieve this figure. If one considers section 5.6.2.3 with respect to BCNU/W, it is clear that the ICER pound per QALY assessment achieves a figure of around about £36,941 for those groups of patients in whom a clearer selection criteria to achieve maximum benefit is placed. Unfortunately, the scenario analysis from Pentag does not make it quite clear who this group is but if one applies the criteria related to the Westphal paper, we are looking at a percentage of the HGG population of around 20-30%. Bearing in mind the current surgical decompression rate for high grade glial tumours runs at nearer 60-70% there certainly would be no requirement for increasing this activity but more of selecting the groups in whom additional wafer placement was appropriate.

15. We note that a similar analysis looking at the cost effectiveness of Temozolomide in the patient group with a good prognosis despite showing an improvement in median survival of 2.5 months and a doubling of two year survival from 10-26%, still costs more in the selected group than for BCNU with an ICER (pound per QALY) of £42,881 increment. Bearing in mind the utility value was already 0.8, in other words indicting very useful benefit, the QALY figure is still

considerably reduced from the initial evaluation over a wider group of applicable patients.

The data from 14 and 15 for selected groups, the QALY estimates described on page 133 and on page 121 for these groups of patients seem much more approachable. Not only that but in practice these figures are likely to be over-estimates where the unique cost of providing treatment has been overstated by the Pentag model (significantly in some areas) thereby reducing costs both to control and treated arm. The increment then estimated would be proportionately less.

16. In summary, this technical assessment represents probably a unique and commendable effort on behalf of Pentag to describe the current status of knowledge related to the use of these two drugs. Like any directed model it fails to cover all the relevant issues, in particular the practicality of use in the clinical situation with respect to appropriate patients. This we think skews the assessment against the use of these two drugs simply because using the generalised ability argument cannot be applied to all patients to achieve the maximum benefit. It is clear when the analysis is used more sensibly then reasonable QALY figures start to appear for what is now a considerable step forward in the management of treatment for these patients. In particular, there are a number of basic floors in the way in which Pentag have used the core data (Stupp and Westphal) disregarding very detailed ITT approaches that these two RCTs have made. Finally, the mixture of high quality RCT data with a small series reports is unhelpful.

We recognise the expensive nature of these drugs but value the effort from Pentag at attempting to quantify elements of this service needed to provide an infrastructure for treating these patients with these new drugs. On balance, the

drug costs based on this background information will need careful consideration by the NICE technology appraisal group in the light of current funding for other solid tumours.