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NCRI Brain Tumour Clinical Studies Group

Response to NICE appraisal consultation document on the use of carmustine implants and temozolomide in patients with newly diagnosed high grade glioma

Introduction

The NCRI Brain Tumour Clinical Studies Group (BTCSG) is disappointed by the appraisal consultation document from NICE on the use of carmustine implants and temozolomide in patients with newly diagnosed high grade glioma (HGG). The recommendations do not support important clinical developments for patients with one of the most lethal cancers, and will undermine research efforts in the future. It is particularly disappointing that the appraisal consultation document was written without direct input from any neuro-oncologist, nor any brain tumour patient representative. Although an appraisal of cost effectiveness is an essential component of any appraisal, the BTCSG has concerns over the methodology used, and the lack of inclusion of a parameter representing the social value of the life of a patient with HGG. The recommendations within the consultation document are not supported by any opinion leaders, at home or abroad, nor even by any of the Committee's own experts. The Group believes that NICE has a duty to look beyond simple assessment of cost or cost effectiveness, in order to support the rational introduction of clinical developments of value to patients and to promote current research efforts.

The clinical context for patients with high grade glioma

A typical patient with a grade IV glioma (glioblastoma), treated with radical intent using current protocols, has a dismal prognosis, with a median survival of only 9 – 10 months. Although CNS tumours account for only 2% of crude mortality for cancer, the individual patient burden is much higher, with an average of 20 years of life lost (AYLL) per patient affected. This low figure results from the combination of a low cure rate in patients who may be affected at a young age. This loss of life per patient is greater than for any other adult cancer, and this has not been taken into account in the NICE appraisal. The advances in disease-free and overall survival which have been achieved with carmustine implants and temozolomide represent the biggest step forward in the radical treatment of HGG for half a century or more. Patients with these tumours do not have a significant media presence, in large part because of the poor outlook, and this reduces the influence they have on debates over public health matters.

CNS tumours also attract an extremely small proportion of research spending, only 1.5% of the NCRI spending in 2002. Patients with CNS tumours have not only a poor outlook clinically, but can also expect only a minimum of financial support for research for their condition. The annual NCRI research spending divided by the average years of life lost is lower for CNS tumours than any other adult cancer except cancer of the corpus uteri, and is almost 20 times lower than the figure for breast cancer.

Research implications
The BTCSG has grave reservations regarding the impact on future research if these recommendations are implemented.

Firstly, it is difficult to see how the pharmaceutical industry would in future wish to support or develop any research in the area of CNS tumours, or indeed for any uncommon cancer with a low public profile. It would normally be accepted that the availability of 2 randomised controlled trials (RCTs) with the same result constitutes a very high level of evidence of effect, and would lead to incorporation into clinical practice. This is the case for temozolomide (TMZ). If introduction of a new treatment with this level of evidence is not permitted, particularly given the size of the advantage and the clinical context, there can be no expectation of further support in the UK for drug-related research. This would apply across the complete spectrum of drug development, from the development of new agents at one end to the conduct of Phase III RCTs at the other.

Secondly, this result might affect even the more common cancer sites if this appraisal is considered to set a precedent. If this did occur, then very significant levels of support might be lost from the UK.

Thirdly, there is no motivation internationally to address the same question again, so it is unlikely that repeat studies could ever be run. Within the UK, such a further study would be very difficult. It is unlikely that scientific funding could be obtained for a further study within the UK, given that excellent, consistent evidence already exists. Moreover, assuming that the trial were restricted to those most likely to benefit, numbers would be relatively limited, and accrual would take several years. For these reasons it is hard to see how the UK will ever be able to introduce new treatments from the foundation of solid research.

Fourthly, the use of TMZ in particular is now viewed as a standard of care across the western world. All future clinical studies, including Phase III trials, are expected to include TMZ as part of a standard treatment arm. If this is not permitted within conventional care in the UK, it is unlikely that we would be able to join other multi-national studies, such as those run by the European Organisation for Research and Treatment of Cancer (EORTC). This will also impact on trials for paediatric patients. There is no expectation that the additional costs for this treatment in the UK would be met by a pharmaceutical company.

Fifthly, any future UK study of developments in other treatment modalities (such as surgery, radiotherapy (RT) or gene therapy) or of tumour imaging if linked to patient outcome, is unlikely to be recognised or accepted internationally. This is liable to present important problems for academic clinical science in this area in the UK, making publication and funding harder to obtain, and to lead to further disillusionment. It will also make it impossible to influence international practice.

Sixthly, efforts to develop markers which describe tumour behaviour or response to treatment will be rendered useless. This applies to fundamental molecular science of HGG but also to novel imaging technologies, such as MR spectroscopy and diffusion tensor imaging. These techniques need to be fully appraised now, but cannot be developed to be tested in Phase III trials unless optimal current treatment, as accepted world-wide, is available.

Seventhly, failure to include new, proven agents into experimental treatment programmes may reduce their efficacy to the extent of rendering them non-curative. This may lead to inappropriate abandonment of clinical studies which could be of value to patients in the UK, and more widely. For example, studies of neurosurgery, radiotherapy, and gene therapy, as well as new pharmaceutical products, are in development. Part of the assessment of a new strategy is to assess its efficacy. Unless this can be within the context of the best available treatment programme, it may be less likely to show an effect, and its value will be questioned even if the trial is positive.

Finally, it is unhelpful for the Committee to recommend research in areas which have already been conducted, are already underway, such as the NCRI BR12 study, or are not feasible, such as a study of TMZ in children alone.

Temozolomide

TMZ combined with radiotherapy has been assessed in two separate randomised clinical trials, the larger of which has been run by the European Organisation for Research and Treatment of Cancer (EORTC). This study was carried out robustly and shows a substantial, clinically important difference, with improved disease-free and overall survival in the combined modality arm. Following the publication of the results from these two trials, particularly the EORTC trial, combined temozolomide plus radiotherapy has become a standard of care, at least for patients with glioblastoma (Grade IV glioma) within Western Europe and North America. Against this background, it will be exceptionally difficult for the UK alone to carry out a further research study addressing the same question. Moreover, it is relatively unlikely that Cancer Research UK would consider it appropriate to fund such a study, given that two well conducted randomised controlled trials are already available, showing a statistically and clinically significant difference in outcome with the new treatment. Whilst research questions do remain, such as the importance of MGMT within tumours, the underlying clinical question is unlikely to be addressed again. This leads to an invidious problem in the UK if the existing evidence cannot be accepted, where we would be unable to deliver the highest quality of clinical care available abroad, whilst also being unable to conduct a further study to substantiate the benefits.

The EORTC study enrolled patients with Performance Status (PS) in the range 0-2. UK practice more typically treats radically only those patients with PS of 0, or 1 in exceptional cases. That study contained in the 2 arms 49% and 47% of patients with PS of 1, and 12% and 13% of patients with PS 2. The study also treated patients up to the age of 70. Both PS and age are very strong determinants of survival. We recommend that the Committee review the potential value and cost effectiveness if combined TMZ + RT is restricted to the better prognosis group of patients, which more realistically reflects actual UK practice.

This would restrict use to perhaps half of the patients treated in the EORTC trial, representing approximately 20-30% of patients with HGG, but would achieve the greatest advantage in disease-free and overall survival, and a substantially reduced cost per QALY. The EORTC has also published recently evidence to show that administration of TMZ concurrently with RT does not adversely affect quality of life in patients with glioblastoma.

The NCRI Brain Tumour Group is keen to develop further studies with existing technologies and new drugs. Within the international context, for patients with glioblastoma, a control arm including temozolomide plus radiotherapy will be essential. Any such study would be difficult to resource unless this treatment was part of routine

clinical practice. In effect, if NICE disallows the use of concurrent temozolomide with radiotherapy, further randomised trials of new treatments for patients with glioblastoma may become impossible in the UK. Even studies to evaluate different (possibly cheaper) TMZ schedules are likely to be impossible.

The EORTC study had better results in both arms of the trial than standard treatment in the UK. This might in part be due to the high proportions of patients in both arms who underwent resection. This has led to pressure to increase the proportion of patients undergoing resection, at least in some centres in the UK, which demonstrates that the clinical community is able and willing to respond to developments to improve patient outcome. This impetus may be lost if the underlying evidence base is deemed to be irrelevant, and would further disadvantage patients with glioblastoma in the UK.

TMZ with RT has become a standard of care in Western Europe and North America. In an informal study of 11 member countries of the EORTC Brain Tumour Group other than the UK, only in Latvia is this not considered standard treatment now. In Australia and Canada the regime has also become the standard. This demonstrates the isolated position into which NICE will force the UK neuro-oncology community, with great disservice to patient care and research effort.

Currently, typical patients have very high expectations of treatment with temozolomide, which has been extensively publicised over the last few years. There will be major psychological distress caused for patients coming to terms with the lack of availability of this treatment. It is likely, given the clinical improvement demonstrated in the RCTs, that patients will be able to obtain concurrent RT+TMZ treatment in the private sector, undermining equity of access to health care. It is also possible that patients will seek treatment abroad and challenge the legal position of the NHS in Europe.

Carmustine (Gliadel) implants

Since carmustine implants have been accepted for use within the NHS in Scotland for the treatment of newly diagnosed HGG, difficulties from post-code prescribing are likely to emerge.

Although the difference in median survival after carmustine implants was modest, at only 2.2 months, this represents a 19% absolute improvement. Particularly important are the differences at longer survival times. To raise the 3 year survival from 1.7% (which is a typical figure) to 9.2% is extremely important in this disease. Although patient numbers are small, this difference suggests a powerful effect, at least in a subset of patients. It also suggests an opportunity for future work to identify this group and to build further on this foundation.

Given the improvement in 2 year and 3 year survival, it is inconceivable that there is no effect on disease free survival times in those patients who survive to these periods. This demonstrates a flaw in the appraisal, which needs to be carefully reviewed by NICE.

At present it is not possible to identify accurately a subgroup of patients who will benefit most from treatment including carmustine implants, but this represents an important area for development. Such studies might actually reduce the amount of Gliadel actually used,

delivering better clinical and financial value. If no first line use is allowed by NICE, then such studies are unlikely to be possible, in the UK.

Failure to allow consideration of the use of carmustine implants will reduce the potential to develop additional chemotherapy, or viral agents, for incorporation into implantable polymers. This will reduce potential clinical developments and inhibit UK developments which might be commercially exploitable.

Although there are concerns that the rate of intra-cranial hypertension was higher in the carmustine implant group in the largest RCT, this provides a basis for development of surgical techniques to improve this complication rate.

Specific comments on the consultation document

Paragraph 2.6 is factually incorrect in implying that if resection is not possible then palliative treatment is usual. Deep-seated tumours may not be suitable for resection, but in young patients with good performance status radical treatment is appropriate.

Paragraph 3.5. TMZ may also act synergistically with RT, producing better tumour cell kill than either modality alone, in effect sensitising tumour to the effects of RT. It is not clear that other agents, such as PCV necessarily act in the same way.

Paragraph 4.1.5. It is unlikely that there is no effect on disease free survival, at least in the subgroup of patients who survive to 3 years or beyond. A 5 times increase in 3 year survival of cannot occur without some difference in disease free survival.

Section 4.2. The main conclusions from the appraisal appear to be based predominantly on the cost-effectiveness estimates. The health economic analysis method is novel and has not been validated. In addition, there has been no effort to examine the cost effectiveness in subgroups of patients with higher survival. These groups have been well defined by the RCT of Temozolomide and RT and it is these patients who are likely to gain most from adjuvant treatment. There has been no focus on the clinical context of a rare tumour with very high loss of life per affected patient, ie AYLL. This is likely to relate to the loss of future earnings, which should at least be considered in an assessment.

There are concerns over the use of the QALY model, which is based on members of the general public who are well assessing chronic, hypothetical health states. It is also generally accepted that the use of QALY's in extreme health states is questionable. Particularly in the case of glioblastoma, patients are more likely to value an extension of survival, at almost any cost to themselves, and value their 'symptomatic' health state only secondarily. This model also takes no account of the value of extension of life to relatives. Finally, there is no attempt to estimate the value of the life to society, such as with the use of the "Value of a Statistical Life" (VOSL).

It was admitted by the Peninsula Group that they did not find a validated source of utility values for patients with high grade glioma from which to calculate their QALYs. They therefore developed their own, using quality of life data from a small subset of patients. The method of selection and the composition of this group are not given, and the resulting QALY analysis cannot be considered to have been validated. The conclusions are therefore not necessarily as robust as is suggested.

The model they used is particularly sensitive to the median survival. It is possible that use of survival at 2 years, rather than the median survival, may alter the results of the modelling. The costs of treatment appear not to include the costs of TMZ as second line chemotherapy at relapse, in patients who have been treated with RT alone. In fact, in the context of primary treatment with RT alone, many relapsed patients will receive TMZ after PCV. This will increase the costs of the radiotherapy only treatment, and decrease the cost differential.

Paragraph 4.2.3. It is curious that the AG were concerned at the use of median (rather than mean) time to symptoms since median time is considered more robust by oncology statisticians. The use of median times avoids skewing resulting from occasional patients with unusually long times.

Paragraph 4.2.4. The committee should justify their reasons for assuming that the incremental cost-effectiveness ratio (ICER) was under estimated and should discuss the treatment costs the AG felt were omitted. Since the decision to operate is made independently of the availability of the carmustine wafers, additional treatment costs to those for the wafers are fixed.

Paragraph 4.3.3. A comparison of TMZ with PCV is currently under trial, including quality of life measures, in the BR12 RCT, run by the NCRI BTCSG. Although this is addressing efficacy and toxicity at relapse, it will suggest which is would be more effective as a treatment at first presentation. It is also important that absolute numbers of long term survivors cannot be a useful measure when extremely few patients reach even 3 – 4 years with standard treatment. A simple count of numbers of patients surviving does not represent a statistical test of a difference between treatment arms.

The suggestion that other chemotherapies may be as effective when given concurrently with RT is supposition. TMZ is given daily, continuously throughout RT. The mechanisms of interaction of TMZ with RT are likely to be different from PCV, and the bone marrow toxicity from PCV would prevent its concurrent use.

Paragraph 4.3.4. The longer survival in the control arm of the EORTC study compared to conventional UK outcome is likely to be due to the increased proportion of patients undergoing more radical surgery and earlier radiotherapy. This is a separate issue from that of the addition of TMZ or carmustine implants. It can be used as an argument to improve surgical management and timing of RT, but not as an argument against concurrent or adjuvant chemotherapy. The use of the concomitant regime to start within a specified time after surgery could be an effective driver to improve RT waiting times in this patient group.

Paragraph 4.3.5. This is factually incorrect, in suggesting that there was a ‘placebo arm’ in the EORTC trial of TMZ + RT. The statement suggests that the Committee may have misunderstood the study, and therefore its analysis.

Paragraph 4.3.7. Quality of life is improved for patients who are without neurological deficit. Prolongation of survival without deficit is a very important endpoint. It is important to note that patients may function independently until relapse, without the need for expensive community care. It is possible that delay to progression may lead to a reduced time to death, and a consequent reduction in burden and cost to community

services. Though this is not proven, and remains an important research question, it is suggested by the EORTC trial of timing of RT in low grade glioma. We recommend that the Committee review this aspect of treatment, balancing increased costs of care in the community against treatment costs, and appraise the effect on quality of life.

Paragraph 4.3.9. Since the Committee dismisses the economic analyses for both carmustine and TMZ on grounds relating to "assumptions" and "omissions" which are not specified, it would be helpful for the Committee to open its own methods to scrutiny. Their model is based on estimates of survival of only 2 of the four RCTs, and considers estimates of the effect of the disease on health-related quality of life which is recognised as difficult to quantify.

Paragraph 4.3.13. The assumption that MGMT status will be a strong predictive indicator of response is based on a single study in which only 50% of tumours could be assessed. Moreover, a formal test for interaction with treatment effect was non-significant, therefore giving no good evidence on which to select which patients should get temozolomide. This cannot be used as an argument against treating the whole GBM population until these data are validated in additional studies.

Paragraph 5.2. As noted above, failure to permit an appropriate standard of care will prevent the very research recommended here. It is unhelpful for the Committee to recommend repeating research which has already been accepted by the international community, to suggest work which is already underway, or which is impractical.

Paragraph 7.2. The suggestion that the 2 agents should be evaluated in further clinical trials is well intentioned, but unlikely to be supported or supportable by the scientific community, given the Class 1 evidence now available. Thus the recommendations of the committee are likely to result in a Catch 22 situation that will impede clinical research and prevent implementation of treatment which can significantly improve the outcome of brain tumour patients in the UK.

Conclusions

The recommendations from the Committee have important negative implications for clinical care, and research. The NCRI Brain Tumour Clinical Studies Group believes that NICE has a duty to reconsider cost issues for a good prognosis group of patients, and to support important clinical developments which will also underpin future research.

Dr Roma Armstrong
Professor Michael Brada
Dr Neil Burnet
Dr Helen Campbell
Mrs Sheila Casserly
Professor Peter Collins
Professor Garth Cruickshank
Ms Wendy Fulcher
Dr Georgina Gerrard
Dr Brian Haylock
Mr David Jellinek

Professor Richard Kaplan
Ms Kate Law
Dr Siow Ming Lee
Professor Roy Rampling
Dr Jeremy Rees
Dr Susan Short
Ms Sally Stenning
Ms Rebecca Stratford
Professor Roger Taylor

For the NCRI Brain Tumour Clinical Studies Group