National Institute for Health and Clinical Excellence

Health Technology Appraisal

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

Personal Statement

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Introduction

I work as a paediatric oncologist at the University Hospital Nottingham, a post I have held since 1990. During the last fifteen years, I have taken a specific interest in the development of clinical services, translational research and basic science research related to CNS tumours of childhood and adolescence. In this capacity, I have fulfilled the role of Chairman of the UK Children's Cancer Study Group (UKCCSG) Brain Tumour Committee from 1990-1997 and remain a member of that Committee. I am currently Chairman of the International Society of Paediatric Oncology (SIOP) Brain Tumour Trials Committee which co-ordinates the efforts of fourteen European countries to conduct clinical trials in neuro-oncology in children and young people and this Committee is currently extending its collaboration to the United States. I was one of the two co-Chairmen of the Royal College of Paediatrics & Child Health document "Guidance for Services for Children with Brain & Spinal Tumours" published in 1997 and distributed by the Department of Health and lead editor of the recently-published book "Brain & Spinal Tumors of Childhood" by Arnold 2004, which is the first book in this subject in Europe.

Astrocytoma

I am currently Chairman of the UKCCSG Astrocytoma Sub-Group which has one phase I trial open investigating Tarceva in brain stem glioma in collaboration with the New Agents Group of the UKCCSG; a second trial open for low grade glioma which is a randomised phase III trial investigating the role of chemotherapy in low grade gliomas of childhood; a phase II trial of temozolomide/cisplatin in collaboration with the French Paediatric Oncology Group (SFOP). We are currently developing a new study in the investigation of temozolomide in brain stem glioma.

In my clinical practice as paediatric oncologist I have worked as part of a multi-disciplinary team in the UK since 1990, Chairing the paediatric neuro-oncology multi-disciplinary team at the University Hospital Nottingham until 2001 when the adult neuro-oncologists joined this group. Consequently I have participated in five years of adult neuro-oncology multi-disciplinary discussion, contributing to the development of novel approaches to investigation and therapy in adult practice as well as paediatrics. In my daily clinical practice I care for patients from diagnosis, supporting them through surgery, radiotherapy, rehabilitation and palliative care including home palliative care.

Epidemiology/Lost Effectiveness

As a paediatric oncologist, I note that the scope of the document excludes children because there are no randomised trials of temozolomide suitable for the review process. It may seem, therefore, that this review is irrelevant to children and young people. However, as this is a NICE and Health Technology Assessment and will be used by health providers to justify or

reject funding for these treatments, and as glioblastoma multiforme is a disease that occurs throughout life with a peak in childhood and a second peak in the seventies, it is my view that more precise statements about the interpretation of this advice with respect to children and young people should be made than are currently provided in this document. The NICE and HTA groups may or may not be aware that nationally it is common practice for over 60% of children being diagnosed with cancer and leukaemia to be included in clinical trials as part of their primary therapy. Many of these trials use conventional drugs funded by the health services. A very small proportion of these are commercially funded because of the unattractive financial prospects for drug development in childhood for the commercial sector. If the NICE guidance does not recommend funding for either of the treatments proposed, this may be used as a justification for non-funding of TMZ/BCNU Gliadel in non-commercial trials which are the norm in paediatric practice.

I note that the epidemiology of glioblastoma and high grade astrocytomas, as depicted on page 11, shows a markedly skewed distribution of tumours to the older age group (mode 65-70 yrs). This fact, coupled with the poor survival rates, frequently results in rapid death of those who develop this tumour who are most commonly in the elderly age group. However, a substantial proportion of patients (30-50%) present with this disease during their childhood, adolescence or working lives, ie under 64 years of age, their survival is longer. The conclusions with respect to health economic analysis is not age stratified and does not take into account the economic losses of an early death in these younger age groups. It is this younger age group for whom I have particular comments to make with respect to interpreting the information presented in this report.

In childhood and adolescence, the young people have, on average, an expectation of 50-65 life years. The diagnosis of a life-threatening cancer, such as glioblastoma multiforme, is a devastating experience for the children and particularly the family and represents the potential loss of these life years to society. The impotence of current therapies, the inevitable risk of severe acquired disability in a young person and the impact on their ability to participate in full-time education, vocational training or the workplace, makes presenting the information at diagnosis a devastating experience for all concerned. This, coupled with the prolonged history of no clinical progress in treating this tumour type and the nihilistic attitude prevalent in adult neuro-oncology, means there is a sense of hopelessness and despair that is palpable and has generated national political movements to promote enhanced awareness for politicians and health planners for this group of patients. These patients are, by virtue of their severe disease, their short lifespan, their acquired disability and the devastation of their diagnosis, severely disadvantaged, consequently. These factors are not acknowledged in any palpable way within this document and the forensic analysis of the cost effectiveness of both of these new, easily tolerated treatments. Furthermore, there is no positive proposal made to address the obvious benefits of production of nationally funded biological and molecular testing

programmes, to permit definition with greater precision, of the groups of patients who would benefit from these new treatments.

Recommendations for consideration

Age stratification: This report should be revised with an age-stratified analysis which includes the economic costs of loss of early life for children, young people, and those in early-mid adulthood.

Future trials: Specific recommendations should be made about optimising the design of future trials in this tumour group with respect to age stratification for this reason.

National funding for biological studies: Consideration be given to the development of national funding for biological markers of chemo-sensitivity such as chromosomal losses on 1p, 10q and 19q and MGMT gene status to be made available for all patients with grades 3, 4 astrocytoma as well as oligoastrocytoma and oligodendroglioma as part of their routine clinical assessment to complement the inevitable imprecision associated with histological grading of astrocytic tumours which has reduced the power of studies linked to Gliadel and temozolomide in this review.

Special consideration for public consultation of NICE recommendations: A recent publication by Chang and Barker in Cancer 2005 104; 1975-1984 uses population data concerning 10,987 patients with supratentorial glioblastoma registered on the SEER public-use data from 1988-2001 in the USA. They are able to show from this large population-based group that the one year survival was 26%, two year survival was 7.3% and the five year survival was 2.4%. However, they were also able to demonstrate a statistically significant ($p<0.001$) survival advantage for those who are married compared to those who are unmarried. This influence of marital status on survival could be interpreted to indicate the impact of family support being a critical factor dictating patient survival and to emphasise the importance of taking into account relatives' views with respect to any clinical advice that this group chooses to provide. It would seem that they are important therapeutic partners in clinical care through their care and advocacy. Their contribution to the patients' survival rates might be argued to be a zero cost benefit to set against the currently judged high QUALY cost for these treatments. In such circumstances to be told that the government is disinclined to spend £5832 on their loved one thereby denying them an average of four months life (an additional 12-25% of their life expectancy) would seem to be incompatible with humanitarian care in a first world society. I would suggest the NICE Committee interprets this data and its detailed analysis in a way that offers, rather than denies, hope for those patients and families who are called to face up to this serious, life-threatening and disabling cancer.

Conclusion

For two new single agents to achieve statistically significant improvements in survival for this, the most malignant and rapidly fatal tumour in humans, is an extraordinary scientific achievement. To disregard these advances because an incomplete, yet forensic cost analysis fails to meet an arbitrary economic threshold, where the economic losses linked to early death and the unmeasured costs of effective family care are disregarded , would seem, politically, to be a decision taken in isolation from the “real world” of clinical practice and family life.

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