Pergamon

European Journal of Cancer Vol. 32A, No. 13, pp. 2193–2194, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00400-S

Editorial

Chemotherapy of High-grade Gliomas: Beginning of a New Era or the End of the Old?

M. Brada and G. Sharpe

Neuro-oncology Unit & Academic Unit of Radiotherapy & Oncology, The Institute of Cancer Research & The Royal Marsden NHS Trust, Downs Road, Sutton, Surrey SM2 5PT, U.K.

TO ANYONE familiar with the treatment of recurrent high-grade glioma, the results reported by Sanson and associates in this issue of the Journal (pages 2229–2235) may signal a new era for conventional chemotherapy. Are we seeing a new, potentially effective chemotherapy regimen in this largely chemoresistant disease?

The use of salvage chemotherapy in adults with recurrent high-grade glioma, particularly those who have already received adjuvant chemotherapy, is not a fruitful activity. The chance of obtaining a sustained response with conventional chemotherapy is small and the median survival is measured in weeks. Nevertheless, with the knowledge that they are dealing with a largely untreatable disease, clinicians are under pressure to offer new, usually experimental treatment, with the hope of some benefit to the patient. It is reasonable to give in to such requests provided that the new treatment has a chance of improving quality of life/functional status and if, as part of a research protocol, it generates objective data enabling the development of more effective treatment strategies.

Unfortunately, despite a large number of phase II studies and continued use of chemotherapy in patients with recurrent high-grade glioma, information on the palliative efficacy of chemotherapy is not easy to find. This may be due to the difficulty of measuring quality of life (QoL) and functional status in brain tumour patients. With new QoL scales [1] and functional indices [2, 3], this should no longer be an obstacle.

How good are current phase II studies in providing information on the efficacy of drugs in patients with high-grade glioma? Despite 20 years of 'promising' chemotherapy in recurrent gliomas, there are still precious few chemotherapy regimens offering true survival benefit. Apart from nitrosoureas [4, 5], none of the new and not so new agents and combinations have so far lived up to expectations when transferred from phase II studies to primary therapy, although admittedly not all have been subjected to randomised studies.

The primary endpoint of chemotherapy efficacy used in phase II studies in patients with gliomas is response. It is largely assessed as a change in the size of an enhancing lesion on CT (computer tomography) or MRI (magnetic resonance imaging), although, by convention, overall response also takes into account a change in clinical status [6]. It is recognised that this form of assessment of response in glial tumours is difficult and unreliable. Studies need to avoid the confounding problem of surgery, which makes it impossible to distinguish response from evolution of postsurgical changes. It is also important to take into account patient selection and its effect on response as well as survival [7].

It has been suggested that the objectivity of response assessment could be improved by strict central review of radiology. This is unlikely to be attainable and will not resolve the overall difficulty of evaluating changes which we interpret as response. Could better imaging modalities improve the situation? MRI undoubtedly gives clearer images than CT but usually does not add much to the ambiguity of response assessment, which relies on changing dimensions of regions of enhancement assumed to correspond to tumour size. New information on the metabolic state of tumours using PET (positron emission tomography) or MR spectroscopy holds promise and may serve as an early indicator of chemotherapy efficacy. However, it is early days and at least initially, such approaches may only be useful in weeding out ineffective treatments. Before being accepted as surrogate endpoints of efficacy in phase II studies, such new imaging modalities will need to be evaluated against appropriate hard clinical endpoints.

Perhaps we should ask a more fundamental question: are conventional oncological criteria of response when translated into the CNS a useful and a true measure of chemotherapy efficacy in gliomas? The poor correlation between responses measured in phase II studies and survival in adjuvant studies suggests that there is something amiss with the methodology. We know with some confidence that disappearance of a systemic mass on imaging equates with tumour cell kill. However, it is not clear if, within the brain, a reduction in the size of an enhancing abnormality represents either a loss of tumour cells or other processes, such as an alteration in the properties of blood–tumour or blood–brain barrier. Even if indicative of tumour cell kill,

Correspondence to M. Brada.
Received 20 Sep. 1996; accepted 24 Sep. 1996.

the assessment of radiological response is difficult. Attempts at standardisation using a combination of clinical and imaging criteria [6] go only part way to solving the problem. An agreed definition of response provides a common language, but it is not clear if it translates any better into the principal endpoint of chemotherapy efficacy which in high-grade glioma is survival. A possible conclusion is that the criteria in current use may not measure true tumour response as seen outside the CNS. Alternatively, high-grade gliomas are not particularly chemosensitive tumours and in our eagerness we accept too low a threshold of response as evidence of efficacy.

All that said, what can we conclude about the combination of ifosfamide, carboplatin and etoposide (ICE). The apparently favourable response rate using relatively strict response criteria is interesting, particularly with the reported 14% rate of complete response not frequently encountered in recurrent gliomas treated with chemotherapy alone. Nevertheless, the overall response rate is not outside the confidence intervals of response rate reported for other platinum-based salvage therapies or for newer agents such as temozolomide, and the seemingly favourable result may, at least in part, be due to patient selection. Although ICE is an interesting combination, it is difficult to recommend it to patients as a truly 'effective' second-line treatment as the palliative benefit is not reported and the regimen carries considerable toxicity. The currently overstretched healthcare system is unlikely to look kindly at the suggestion of adding the high cost of growth factors to an already costly short-term palliative treatment in this group of patients. As for the future of ICE as a potential adjuvant or neoadjuvant chemotherapy, it will have to join the long list of promising regimes.

Where do we go next? Undoubtedly, we must continue to look for new and better ways of treating patients with high-grade glioma, but this has to be in a manner which is likely to yield truly effective new treatments. Currently, desperate patients with gliomas are bombarded by an over abundance of novel treatments, which often enter the clinical arena on the basis of limited evidence of efficacy, and this is particularly true for fashionable biological treatment approaches. A wide choice of promising but largely ineffective treatments does not represent progress. Instead, it creates a general smoke screen of information, confusing for clinicians and patients alike, and results in costly dilution of research efforts. It seems that the methods of assessment of efficacy of new drugs in gliomas have not lived up to expectation. Those interested in real progress, rather than short-term gain, should concentrate on the development of methods which will help to find effective regimens and weed out useless treatments.

1. Osoba, D, Aaronson N, Sneeuw K, Hsu M-A, Yung W, Brada M, Newlands E. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer specific questionnaires. *Qual Life Res* 1196, **5,** 139–150.
2. Grant, R, Slattery J, Gregor A, Whittle IR. Recording neurological impairment in clinical trials of glioma. *J Neuro-oncol* 1994, **19,** 37–49
3. Brazil LC, Thomas R, Laing R, Hines F, Gurrero G, Ashley S, Brada M. Verbally administered Barthel Index as functional assessment in brain tumour patients. *J Neuro-Oncol* 1996, **21,** 71.
4. Fine HA, Dear KB, Loeffler JS, Black P, P CG. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993, **71,** 2585–2597.
5. Stenning S, Freedman L, Bleehen N. An overview of published results from randomized studies of nitrosoureas in primary high grade malignant glioma. *Br J Cancer* 1987, **56,** 89.
6. MacDonald DR, Cascino TL, Schold SCJ, Cairncross G. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990, **8,** 1277–1280.
7. Rajan B, Ross GM, Lim CC, *et al.* Survival in patients with recurrent glioma as a measure of treatment efficacy: prognostic factors following nitrosourea chemotherapy. *Eur J Cancer* 1994, **30A,** 1809–1815.