Editorial

Annals of Oncology 14: 1695–1696, 2003
DOI: 10.1093/annonc/mdg501

Promises and controversies in the management of low-grade glioma

Low-grade gliomas (LGGs) are a heterogeneous group of relatively slow-growing primary tumors of astrocytic and/or oligodendroglial origin. Peak incidence occurs in the second and third decade of life. Many patients will present with easily controlled seizures and will remain stable for many years, whereas others may progress rapidly, with increasing neurological symptoms, to a higher-grade tumor. Although morphologically indistinguishable at diagnosis, the time interval to progression varies considerably from a few months to several years. To date treatment options were limited to surgery when feasible, and radiotherapy and palliative chemotherapy at recurrence. Oligodendroglioma with specific molecular changes (allelic loss on chromosomes 1p and 19q) have been recognized over the last decade to be a distinct subgroup with a better prognosis and a particular sensitivity to chemotherapy [1]. New chemotherapy agents against malignant glioma are currently in development, and temozolomide, a novel alkylating agent, has been approved for the treatment of recurrent malignant (high-grade) glioma [2].

In this issue, two prospective phase II trials report radiological and clinical response to single agent temozolomide chemotherapy in patients with LGG, albeit based on quite different patient populations. A British study included patients with stable or progressive disease and who have not received any prior chemo- or radiotherapy [3]. In the study from Italy patients were required to have progressive disease, over two-thirds of their patients had received prior radiotherapy and one-third had also received previous chemotherapy [4]. No repeat histological confirmation was performed, but on repeat surgery anaplastic features were present in eight of 16 operated patients. Contrast enhancement on MRI, another sign of possible malignant transformation, was present in 60% of patients. Interestingly, although the objective response rates are quite different between the two trials (10% in the British trial compared with 47% in the Italian trial), when minor responses are also considered, the tumor regression rates are 57% and 56%, respectively. There is inherent difficulty with response assessment in the brain, where tumor cannot always be distinguished from associated edema and normal tissue. In some patients the radiological response was only demonstrated after several months of therapy. Sophisticated imaging techniques like positron emission tomography (PET) using amino acid traces or functional imaging (e.g. MR spectroscopy) may be of help in the future.

Progression-free survival in the British study was 94% and 76% at 1 and 2 years, respectively, while, despite the higher response rate, in the Italian trial more than half of the patients had progressed within 1 year, reflecting the different patient populations. In LGG initial and long-term symptom control and quality of life are end points as important as tumor shrinking on imaging. Both studies document a clinical benefit with improvement in seizure control in about half of the patients.

The British study had to be closed prematurely short of only a few additional patients. The authors indicate 'availability of the investigational agent' as the reason. Conducting clinical research is becoming increasingly difficult. The desire of patients to be treated with a new agent paired with a strong pressure by the pharmaceutical industry to prescribe new and expensive drugs hamper accrual into trials. New techniques or therapeutic options will thus never be fully explored nor properly evaluated. Additional obstacles come from the health authorities and regulatory bodies warranting specific additional insurance coverage and industrial funding for most protocols, while similar treatments outside clinical trials can be freely prescribed.

Where do these reports lead us? Should patients with LGG now be considered for primary chemotherapy? At initial diagnosis many patients do not require any specific therapy, but rather careful psychological guidance. Surgery should be attempted for precise diagnosis and in cases where a complete resection can be achieved [5, 6]. Based on two randomized trials, the European Organization for Research and Treatment of Cancer (EORTC) provides us with a useful prognostic score for identifying patients with the worst prognosis who are most likely to benefit from therapy [7]. Age ≥40 years, astrocytic tumor type, tumor size >6 cm, tumor crossing the midline and neurological deficit at diagnosis were identified as independent prognostic factors, and the presence of three or more of these factors was associated with an unfavorable prognosis.

For patients with unfavorable prognostic factors radiotherapy currently remains the established treatment option. Two randomized trials have examined the dose of radiotherapy and there appears to be no survival benefit for total doses >45–50 Gy [8, 9]. Of concern with frequently ill-defined and diffusely infiltrating tumors are the required large radiation volumes, which may lead to debilitating late sequelae in patients who will survive for many years [10, 11]. Highly conformal radiation techniques (e.g. intensity-modulated radiotherapy) combined with co-registered MR and PET imaging may limit the amount of normal brain tissue irradiated [12–14].

The timing of radiation therapy was the object of a randomized trial comparing immediate radiotherapy with delayed radiotherapy at progression [15]. Although time to progression was longer in the immediate therapy group, progressing patients whose radiotherapy had been delayed could be successfully salvaged, and survival was identical in both arms. Two-thirds of the progressing patients subsequently received radiation accounting for only 38%

of the patients in the observation group. Thus, radiotherapy could be withheld in almost two-thirds of patients for >5 years.

Whether primary chemotherapy with the currently available drugs allows the delay of radiation and its sequelae remains to be demonstrated. Secondary malignancies are to be expected with long-term alkylating agent chemotherapy. A randomized trial comparing standard radiotherapy to chemotherapy will be conducted by the EORTC and the National Cancer Institute of Canada. In contrast to the present reports, temozolomide will be administered as a low-dose continuous schedule. Chronic drug exposure may be critical for response in a slow-growing indolent tumor. In this trial patients will only be treated at documented progression or in the presence of unfavorable prognostic factors. Patients will be prospectively stratified for histological and for molecular markers (1p loss). This allows the identification of subgroups of patients who are more likely to benefit from one or from the other treatment modality.

Management of LGG remains a challenging task. More precise definition of tumor entities, including also specific molecular markers, is necessary to identify patients in need of a more aggressive treatment strategy. Evaluation of the known prognostic factors by an experienced multidisciplinary team is the basis for any treatment recommendation or for watchful waiting. The role of chemotherapy and new biological agents currently in development needs to be established in well-designed clinical trials. Long-term toxicity is of concern in a disease where patients may live for many years.

R. Stupp[1], B. G. Baumert[2]
[1]Multidisciplinary Oncology Center, University Hospital, Lausanne, Switzerland; [2]Department of Radiation-Oncology, University Hospital, Maastricht, The Netherlands
(E-mail: Roger.Stupp@chuv.hospvd.ch or b.baumert@rtil.nl)

References

1. Cairncross JG, Ueki K, Zlatescu MC et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998; 90: 1473–1479.
2. Stupp R, Gander M, Leyvraz S, Newlands E. Current and future developments in the use of temozolomide in the treatment of brain tumors. Lancet Oncol 2001; 2: 552–560.
3. Brada M, Viviers L, Abson C et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. Ann Oncol 2003; 14: 1715–1721.
4. Pace A, Vidiri A, Galiè E et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann Oncol 2003; 14: 1722–1726.
5. Berger MS, Deliganis AV, Dobbins J, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer 1994; 74: 1784–1791.
6. Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. J Neurosurg 2001; 95: 735–745.
7. Pignatti F, van den Bent M, Curran D et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002; 20: 2076–2084.
8. Karim AB, Maat B, Hatlevoll R et al. A randomized trial on dose–response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 1996; 36: 549–556.
9. Shaw E, Arusell R, Scheithauer B et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002; 20: 2267–2276.
10. Klein M, Heimans JJ, Aaronson NK et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet 2002; 360: 1361–1368.
11. Surma-aho O, Niemela M, Vilkki J et al. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. Neurology 2001; 56: 1285–1290.
12. Nuutinen J, Sonninen P, Lehikoinen P et al. Radiotherapy treatment planning and long-term follow-up with [^{11}C]methionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys 2000; 48: 43–52.
13. McKnight TR, von dem Bussche MH, Vigneron DB et al. Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. J Neurosurg 2002; 97: 794–802.
14. Pirzkall A, Nelson SJ, McKnight TR et al. Metabolic imaging of low-grade gliomas with three-dimensional magnetic resonance spectroscopy. Int J Radiat Oncol Biol Phys 2002; 53: 1254–1264.
15. Karim AB, Afra D, Cornu P et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. Int J Radiat Oncol Biol Phys 2002; 52: 316–324.