Controversies in the management of low grade gliomas

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In more than 75% of cases, the first manifestation of low grade glioma (LGG) is a seizure in a ' young' adult (median age, 35–39 years) who is otherwise in good general health with a normal neurological examination. Much more rarely, progressive deficit, cognitive dysfunction, or intracranial hypertension will reveal the disease. MRI typically shows an unspecific mass which does not enhance after contrast infusion. A preferential location in the ' frontal-temporal-insular' region or ' parasagittal' areas is suggestive of the diagnosis [1]. Occasionally, contrast enhancement is seen or the tumour widely infiltrates the brain at the onset (gliomatosis cerebri). MR spectroscopy and PET scan (fluorodeoxyglucose and methionin) are useful for differential diagnosis and to guide a biopsy but definite diagnosis relies on microscopic examination of a tumour sample. Unfortunately, the WHO classification of LGG remains imperfect because of incomplete reproducibility and lack of specific marker of tumour subtype [2]. As a consequence, the respective frequency of tumour types varies considerably among institutions.

Symptomatic treatment relies mainly on anticonvulsants. A key objective is to obtain a satisfactory control of seizures while minimizing the side effects of treatment. Indeed, frequent seizures or the prescription of multiple antiepileptic drugs have considerable deleterious consequences on quality of life and cognition [3].

Treatment of the tumour includes surgery, radiotherapy and chemotherapy. While the interest of these modalities is clear when LGG undergo malignant progression, an almost ineluctable event, their role at an earlier stage remains debated.

Most authors consider that macroscopically complete resection of the tumour, when technically and functionally possible, is useful but this opinion is based on expert consensus and not on adequate prospective studies which are extremely difficult to perform in this setting. The role of partial resection is unsettled.

Conventional radiotherapy delivers a total dose of 45–54 Gy on the area of T2-weighted hypersignal with a 2–3 cm margin, using 1.8–2 Gy daily fractions. With this schedule, mild to moderate early-delayed increased attention deficit and memory dysfunction is frequent but reversible while the risk of delayed neurotoxicity is very low. The use of higher doses does not affect survival but increases the risk of toxicity. The rate of objective response after radiotherapy is about 50%. A phase III EORTC study has shown that early post operative radiotherapy increased progression free survival (PFS) by approximately two years but did not modify overall survival as compared to ' delayed' radiotherapy administered at the time of obvious clinical-radiological deterioration [4]. Radiosurgical techniques have no indication in LGG except in the setting of carefully evaluated clinical trials.

Chemotherapy is increasingly used in progressive LGG, particularly oligodendrogliomas. Temozolomide is generally preferred to the procarbazine-CCNU-vincristine combination because it is well tolerated and can be administered over extended periods (18–30 months). The objective response rate is approximately 30%–40% when the tumour is treated before it undergoes anaplastic transformation. Response is often delayed (12–18 months), a feature justifying prolonged treatment according to several investigators. Chromosome $1p \pm 19q$ deletion is characteristic of oligodendroglioma. This genetic alteration indicates both a more indolent spontaneous growth of the tumour and a much higher chemosensitivity (>60%) as compared to chromosome 1p intact tumours (<20%) [5]. Other important favourable prognostic factors include a younger age (<40 years), an oligodendroglioma phenotype, a good clinical and cognitive status, and a maximum diameter of the tumour inferior to 5–6 cm [6].

Despite many uncertainties, radiotherapy and/or chemotherapy are generally administered when LGG produce clear-cut symptoms, including pharmacoresistant epilepsy, progressive deficit, substantial cognitive dysfunction (which are often underestimated during routine follow up), or intracranial hypertension.

In the absence of symptoms affecting the quality of life, the interest of starting ' aggressive' treatment

simply because of radiological progression is more questionable when there is no evidence of anaplastic degeneration (rapid development of an area of contrast enhancement).

When treatment is required, the respective place of radiotherapy and/or chemotherapy as well as the impact of molecular changes to guide management is unsettled. There is no alternative to prospective randomised studies to evaluate these issues despite the considerable amount of effort and time that they will require.

References

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