Treatment of newly diagnosed anaplastic gliomas

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Introduction

Diffuse gliomas are the most frequent primary brain tumours in adults. They are usually classified and graded according to the WHO criteria. Histologically, they are classified into astrocytoma, oligodendroglioma, oligoastrocytoma (which at the genetic level are either oligodendroglioma or astrocytoma) and ependymoma (which are rather rare). Survival of anaplastic or grade 3 tumours depends on the histological subtype: most series report a median survival of 2–4 years for anaplastic astrocytoma and anaplastic oligoastrocytoma, but median survival in anaplastic oligodendroglioma can be up to 6–7 years if 1p/19q loss is present. In addition to histology and 1p/19q status, age and performance status are important prognostic factors.

The diagnosis of grade III tumours

Although in neuro-oncological textbooks grade III tumours are nicely classified into anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic mixed oligoastrocytomas, it has long been recognised that a huge interobserver variation exists in the diagnosis of these tumours, with respect to both classification and grade. Moreover, it remains unclear if anaplastic oligoastrocytomas with necrosis are different from glioblastoma multiforme with oligodendroglial morphology. Necrosis was found to be a poor prognostic factor in AOA, but not in AOD, and it has been suggested to grade AOA into grade 3 and 4 tumours based on the presence or absence of necrosis [1]. The finding that some of these grade III tumours have EGFR amplification and chromosome 10 loss, typical for GBM, demonstrates that histology alone is unable to characterise these tumours fully. This shows on the one hand the limitation of a classification and grading solely by light microscopic examination, but on the hand there is ample evidence that for a good interpretation of molecular findings the histology of the tumour remains crucial. One series suggested that combined 1p/19q loss is, in particular, of prognostic relevance in anaplastic oligodendroglioma, but not in anaplastic oligoastrocytoma [2]. Despite the additional information molecular diagnostics provide on the prognosis of patients this is not yet used to classify these tumours (which will remain so in the 2007 version of the WHO).

Treatment

Surgery followed by radiotherapy has long been the widely accepted mainstay of treatment for high-grade gliomas, which trials included grade 3 tumours. The impact of classical nitrosourea- based adjuvant chemotherapy remained unclear, as demonstrated by the modest improvement of survival that was observed in an MRC meta-analysis on controlled trials on this topic [3]. The study observed a similar survival benefit of adjuvant chemotherapy in AA as compared to GBM, with a two-year survival in AA of 31% after radiotherapy only versus 37% in the chemotherapy group [3]. This lack of a clinically significant increase in survival in AA after adjuvant chemotherapy is by itself disappointing, in view of the sensitivity to temozolomide of recurrent anaplastic astrocytoma with 35% of patients responding compared to recurrent GBM (with only 4–6% of patients responding). The EORTC trial on temozolomide in glioblastoma multiforme has established that radiotherapy with daily temozolomide followed by six cycles of adjuvant temozolomide is the standard of care for GBM. This treatment improves both progression free and overall survival in GBM, which may in particular be true for patients with a methylated promoter of the MGMT gene. Grade 3 tumours were not eligible for this trial however. The question is to what extent the data can be extrapolated to grade III tumours.

In recent years several other trials on adjuvant chemotherapy in grade III tumours have been conducted, with results that emphasise that no simple answer to this question exists. Both the RTOG and

the EORTC investigated the addition of PCV chemotherapy to radiotherapy in newly diagnosed anaplastic oligodendroglioma [4,5]. The RTOG study used neo-adjuvant with a dose intensified PCV schedule whereas the EORTC study used a classical adjuvant design with standard PCV; in both studies the control arm received radiotherapy only (but further treatment at the time of progression was left to the discretion of the treating physician). Most patients received further chemotherapy at the time of progression. Although both studies observed an increase in progression free survival in the PCV arm, this did not translate in an increase in overall survival. In contrast to the EORTC study, the RTOG study did not observe an increase in progression free survival in the non-1p/19q deleted tumours. Patients with 1p/19q loss had a much better outcome (median survival over 6–7 years as compared to 2–3 years in patients without 1p/19q loss), but even in this group early PCV did not improve outcome. In conclusion, both studies show, that in this relatively chemosensitive tumour the timing of chemotherapy is not relevant (at first diagnosis or at recurrence), as long as it is given.

In a still unpublished randomised EORTC study, 193 patients with newly diagnosed anaplastic astrocytoma were randomised to radiotherapy alone or to radiotherapy plus dibromodulciterol and BCNU. At 2 years, 56% of patients in the experimental arm were still alive, versus 49% in the control arm, which is in line with the MRC meta-analysis [3]. Neither this difference nor the trend towards a longer overall survival (OS) (difference in median survival of 3.5 months) and PFS (difference in PFS of 2.4 months) in the patients treated with adjuvant DBD plus BCNU reached statistical significance. A review of old RTOG/ECOG studies also suggests more may not be better: it noted a decreased survival in more aggressively treated anaplastic astrocytoma patients [6]. In large phase II US trials on newly diagnosed AA only 17–30% of patients responded to upfront chemotherapy, which is less than in trials on temozolomide in newly diagnosed GBM. To conclude, one cannot simply extrapolate the findings from a GBM study to other high-grade glioma, but separate trials on grade III tumours need to be organised.

Future directions

Determination of 1p/19q loss is now being introduced into the clinical practice, and may help in some treatment decisions. Similarly, in selected cases the presence of EGFR amplification or chromosome 10 abnormalities may be of help; if present, this suggests at the molecular level a GBM-like tumour. More objective criteria for the diagnosis of grade III tumours are obviously needed.

In view of the available data from controlled trials the treatment of grade III tumours is also still unclear. The superiority of combined chemo-irradiation with temozolomide has not been proven in these tumours. Despite the absence of a formal trial many clinicians today propose upfront temozolomide TMZ as first treatment in 1p/19q loss oligodendroglioma. No data exist to support this change (or to reject that policy), and the approach is in part based on the unproven assumption that RT is likely to induce delayed cognitive deficits. The RTOG study on anaplastic oligodendroglial tumours have shown that up-front chemotherapy is unlikely to yield clinical benefit in patients with tumours without 1p/19q co-deletion [5]. The current questions have led to two new intergroup trials of North American and European cooperative brain tumour groups, for both tumours with and without 1p/19q co-deletions.

Conflict of interest statement

The author has served on Advisory Boards of Schering Plough and their Speakers Bureau.

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