Clinical Oncology xxx (2013) 1–3

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

High Grade Glioma — The Arrival of the Molecular Diagnostic Era for Patients over the Age of 65 Years in the UK

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Received 8 February 2013; accepted 18 February 2013

Background

Population-based data confirm that the incidence of high grade glioma (HGG) (glioblastoma multiforme [GBM] and anaplastic astrocytoma) is greatest in patients over the age of 65 years. The mean age of presentation of GBM is 61.3 ± 14.0 years, with nearly 60% of cases occurring in people over 60 years and the incidence is increasing [1,2]. Age is a prognostic factor in the management of GBM and survival decreases for each decade of life above 50 years [3]. An age of 65 years is used as the definition of an older patient, which is in keeping with most developed countries [4]. Despite a number of patients presenting with HGG who are older than 65 years, these patients are underrepresented in clinical trials [5–7]. It is recognised that the prognosis in older patients is poor, even in the context of multimodality therapy. There is a need for a consensus approach to the management of HGG in the older patient, especially as the population is ageing and clinicians are facing the prospect of treating a progressively ageing cohort of patients.

Summary of Published Studies

The European Organization for the Research and Treatment of Cancer (EORTC) assessed the benefit of adding temozolomide (TMZ) to radiation and adjuvant chemotherapy for patients aged 18–70 years with GBM, and showed a significant overall survival benefit for the intervention arm [8]. The median age at entry was 56 years and the median overall survival was 14.6 months. Eighty-three patients were older than 60 years and had a median overall survival of 10.9 months. In a trial assessing the role of carmustine wafers in addition to surgery, the median age was 53 years [9]. The older patient may also receive less intensive treatment: diagnostic biopsy rather than debulking surgery [10] and less radiotherapy and chemotherapy [11–13].

More recent data incorporating modern surgical techniques (including fluorescence-guided cytoreduction) are available for 130 GBM patients with a median age of 68 years. The median overall survival for those who went on to receive radiotherapy and chemotherapy was 16.3 months (range 12–17.2) compared with 11.2 months for those receiving radiotherapy alone [13]. These prospective data are supported by a retrospective analysis [14] and suggest that older patients with GBM will benefit from the best standard of care.

After the emergence of the O6-methylguanine-DNA methyltransferase gene (MGMT) methylation status as a predictor of response to TMZ, the question of whether epigenetic silencing of this gene decreases with age has been raised. However, recent data suggest that there are no significant differences in the proportion of MGMT-methylated tumours in older versus younger patients [15–19]. A case series of 83 patients over the age of 70 years, all of whom received treatment with concurrent chemoradiotherapy for GBM, showed a median overall survival of 15 months and a 2 year overall survival of 28% for MGMT-methylated tumours, whereas unmethylated patients had a median overall survival of 10 months and a 2 year overall survival of only 10% [17]. A series of 22 patients with GBM who were 80 years or older also showed a 17.9 month overall survival in those who were MGMT methylated [18].

The assessment of the methylation status of GBM is not entirely straightforward and is a rapidly developing area. Many studies have used quantitative methylation-specific

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http://dx.doi.org/10.1016/j.clon.2013.03.005

Please cite this article in press as: Jefferies SJ, et al., High Grade Glioma — The Arrival of the Molecular Diagnostic Era for Patients over the Age of 65 Years in the UK, Clinical Oncology (2013), http://dx.doi.org/10.1016/j.clon.2013.03.005

polymerase chain reaction [20]. The potential issues with this approach include false positive/negative results and whether the region and number of CpGs interrogated is relevant. Data are limited on the most important region to analyse, but a number of studies indicate the CpGs at the 3′ end of exon 1 and into intron 1 to be particularly important [21–25]. Although pyrosequencing after bisulphite modification is scientifically most attractive, providing the methylation status at each CpG in a region, this requires a definition of a cut-off level for significant and clinically relevant methylation – something that has not yet been agreed [26]. It is also important to note that the methylation status of glioblastoma tissue is not routinely available at most centres that treat GBM patients in the UK. The introduction of MGMT testing will require sufficient funding. The CNS Improving Outcomes Guidance [27] indicated that the cost of testing 2500 cases in the UK would be in the region of £1 283 090. The centralisation of MGMT testing within the UK would be a solution to providing results quickly at a reduced cost.

Two recent studies have advanced information in the management of the older population with HGG. The Nordic Clinical Brain Tumour Group undertook a large randomised study of TMZ alone versus short-course hypofractionated radiotherapy (34.0 Gy/10 fractions over 2 weeks) or standard 6 week radiotherapy (60 Gy/30 fractions) [28]. The results of this study showed that for all patients treated, overall survival was similar for TMZ and hypofractionated radiotherapy (8.4 months [7.3–9.4] versus 7.4 months [6.4–8.4], $P = 0.12$). Patients over 70 years treated with TMZ or short-course radiotherapy had a longer survival than those treated with standard radiotherapy (hazard ratio 0.35 [0.21–0.56] $P < 0.0001$).

The study assessed promoter methylation of the MGMT using real-time quantitative methylation-specific polymerase chain reaction [20]. Patients treated with TMZ who had MGMT methylation showed significantly improved overall survival compared with those without MGMT methylation (9.7 months [95% confidence interval 8.0–11.4] versus 6.8 months [5.9–7.7], hazard ratio 0.56 [95% confidence interval 0.34–0.93]). No difference was seen in overall survival for those treated with radiotherapy ($P = 0.81$).

The Neuro-oncology Working Group of the German Cancer Society assessed standard radiotherapy (60 Gy in 1.8–2.0 Gy fractions) versus dose-dense TMZ (1 week on/1 week off) in patients with HGG who were over the age of 65 years in the NOA-08 trial [29]. Methylation status was assessed by the same technique as in the Nordic study [21]. The results showed that overall survival was similar in both treatment arms. As in the Nordic study, a similar effect was seen for MGMT methylation and the response to TMZ. The median overall survival for radiotherapy in this study was 9.6 months (95% confidence interval 8.2–10.8), better than the Nordic study. This may be explained by the significantly shorter time to starting radiotherapy in the NOA-08 study (30.5 days [11.0–76] versus 46 [14–119]). Alternatively, the differences may be explained by the exclusion of 39 patients in the NOA-08 analysis who were too unwell to start treatment, whereas all the patients in the Nordic study were evaluated. It should also be noted that the age of entry in the Nordic study was initially 60 years, but this was revised to 65 years halfway through recruitment, after publication of the results from the EORTC study [8].

In both the NOA-08 and the Nordic studies, reported toxicities from TMZ were minimal, mainly nausea, vomiting and myelosuppression. In terms of the optimum dose for radiotherapy, hypofractionated radiotherapy over 2 weeks was better tolerated than the longer fractionation regimen and did not compromise outcome. The longer regimen was associated with significant risks of morbidity and early discontinuation. A randomised Canadian study, which evaluated 40 Gy/15 fractions compared with longer fractionation, also showed similar toxicity, and confirmed the equivalence of the shorter regimen [30]. The results of the EORTC phase III randomised study of 40 Gy/15 fractions with concomitant and adjuvant TMZ will also help us further refine management in this age group.

Summary and Future Recommendations

There is now evidence that MGMT methylation status can be a predictive marker for treatment decisions between primary treatment with TMZ or radiotherapy in older patients with GBM.

Neurosurgery

Studies confirm that the overall prognosis for HGG in this age group is poor. However, for patients of good performance status, cytoreductive surgery should be considered regardless of age. In both the NOA-08 and the Nordic studies, between 60 and 70% of patients had a partial or complete resection. We recommend that optimum surgical resection should be offered to older patients provided they have a World Health Organization performance status of 0 or 1.

MGMT Methylation

We recommend that all older patients considered by the multidisciplinary team suitable for radiotherapy and/or chemotherapy should have their MGMT status assayed by the most robust technique available. British neuropathologists urgently need to establish a recognised standard assay suitable for general application in the clinical arena and funding needs to be found to ensure that all centres undertaking the assay can operate to this standard.

Chemotherapy

These new data confirm that treatment stratification based on methylation status in those over 70 years can now be evidence based, leading to the use of TMZ as first-line treatment for those who are MGMT methylation positive. The NOA-08 and Nordic studies have shown that this is a feasible alternative to radiotherapy for this group. Reported

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toxicities from TMZ from both trials were minimal, mainly nausea, vomiting and myelosuppression.

Radiotherapy

For patients without MGMT methylation, radiotherapy would be the preferred treatment choice. It is important to note that the Nordic and NOA-08 studies used planned conformal radiotherapy volumes, whereas a significant proportion of patients treated in the UK receive parallel-opposed radiotherapy treatment fields, which have the advantage of a short time to start treatment. Radiotherapy treatment regimens should be considered of 34 Gy in 10 fractions for MGMT unmethylated patients with a performance status of 0–1 and 30 Gy in six fractions for those who are performance status 2.

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