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REVIEW

Updates in the management of high-grade glioma

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Abstract The management of high-grade glioma (HGG) has evolved significantly over the last decade. Patients are managed in a multidisciplinary team setting in order to ensure their care is guided by the most current evidenced based treatments. The outcome in patients with HGG, while still poor, has improved in terms of both survival and quality of life during illness. This review discusses a number of developments seen in the management of HGG over the last 5 years.

Keywords Glioblastoma · Oligodendroglioma · Bevacizumab · Temozolomide · PCV

Introduction

Gliomas account for the majority of primary CNS tumours and are most commonly high-grade, characterised by aggressive growth and poor prognosis. Treatment is determined by a number of different prognostic factors including age of the patient, performance status, tumour location and histological grade. There have been a number of advances in the diagnosis and management of HGG which are reviewed here.

Longer-term data on chemo-radiotherapy for GBM

The gold standard management of patients with newly diagnosed GBM under the age of 70 years is now maximal safe resection with concomitant chemoradiation using temozolomide, an oral alkylating agent, followed by six cycles of adjuvant temozolomide. This is based on the pivotal EORTC trial reported in 2004, demonstrating a hazard ratio for death of 0.63 (95 % CI 0.52–0.75) using this regimen compared with radiotherapy alone, with median survival increasing from 12.1 to 14.6 months and 2-year survival rates from 10.4 to 26.5 % [1]. The 5-year follow-up of this cohort was published recently by Stupp et al. [2] and showed that the survival advantage was maintained in the chemoradiation group (5 year overall survival 9.8 %compared to 1.9 %). The fact that 10 % of patients with GBM are now surviving 5 years has not previously been reported in any prospective study and raises the expectation of important improvements in survival with other new agents.

There is increasing awareness of the role of epigenetic modifications in determining response to treatment. In GBM, one of the most important prognostic factors for improved survival is reduced availability of the DNA repair protein methyl guanyl methyl transferase (MGMT), whose gene expression is prevented by methylation of a promoter region upstream from the coding region. MGMT promoter methylation has been shown to be associated with improved survival in patients treated with chemoradiation. Important data were reported by Stupp et al. [2] in their 2009 paper on 206 cases where MGMT promoter methylation status was known. Their analysis provided long-term information on the effect of MGMT status, confirming that it is a strong prognostic factor in GBM, with an overall hazard ratio of 0.49 (0.32–0.76) for 5-year survival. Additionally, within the limits of small numbers, the analysis also confirmed that MGMT status was predictive of TMZ response, at least in terms of progression-free survival. Finally, this report confirmed long-term efficacy

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of combination treatment in the 60–70 years age group (HR 0.7, 95 % CI 0.5–0.97).

First line therapy in older patients with high grade glioma

The seminal study that prompted the widespread use of chemo-radiotherapy in GBM in 2004 also reported age greater than 70 years to be a poor prognostic factor and suggested that TMZ/RT may be less efficacious and poorly tolerated in the older age group [1]. In general, patients greater than 70 with GBM are treated with best supportive care or biopsy/limited debulking followed by a short course of radiotherapy. Two recent studies suggest that single agent temozolomide may be an alternative to radiotherapy in older patients, who traditionally experience more treatment toxicity from brain irradiation.

The Nordic phase-3 trial randomized nearly 300 glioblastoma patients to one of three treatments: TMZ 200 mg/m^2 in a standard 5 days per month schedule, standard RT (60 Gy), or hypofractionated RT (34 Gy in 10 fractions) [3]. Overall, there was longer survival with TMZ compared to standard RT (9.3 vs. 6.0 months) and a trend towards longer survival with hypofractionated RT compared to standard RT (7.7 vs. 6.0 months). Interestingly, this effect was demonstrated to arise from the subgroup of patients >70 years only, in which both TMZ ($p < 0.001$) and hypofractionated RT ($p = 0.02$) were superior to standard RT. Furthermore, there was a trend in the >70 years group for superiority of TMZ over hypofractionated RT ($p = 0.09$). MGMT promoter methylation had no effect on response to RT, but predicted better response to TMZ (HR 0.56, $p = 0.02$).

The NOA-08 trial randomly assigned nearly 400 patients over the age of 65 years with anaplastic astrocytoma or glioblastoma to either TMZ (100 mg/m^2 in a dense 7 days on/7 days off schedule) or RT (60 Gy) [4]. The results showed that TMZ monotherapy was non-inferior to radiotherapy in terms of overall survival (OS) or progression-free survival (PFS). Additionally, it was shown that MGMT promoter methylation significantly predicted the effect of TMZ on progression free survival (not overall survival). Compared to the RT group as a reference, patients with MGMT promoter methylation responded better to TMZ than radiotherapy (HR 0.53) while those without promoter methylation tumours did worse on TMZ (HR 1.95).

In both trials, quality of life was equivalent or superior in the TMZ groups but there was, as expected, an excess of haematological adverse events. The treatment was well tolerated. These trials indicate that TMZ monotherapy is equivalent and possibly superior to standard RT in patients over 65 years. Importantly, MGMT promoter status seems to strongly predict better outcomes and greater benefit from TMZ, and should be considered when deciding on treatment. This oral alkylating agent is administered orally and can be commenced rapidly once the treatment decision is made. This has to be balanced against the longer duration of treatment and the risk of haematological adverse events. The brief (2-week) hypofractionated RT reported in the Nordic trial is also a valid option, based on their data.

Bevacizumab in recurrent glioblastoma multiforme

Bevacizumab (Avastin) is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is a crucial factor for angiogenesis [5] and bevacizumab is currently used in a number of cancers. Improved overall survival has been shown in non-small cell lung cancer [6] and advanced colorectal cancer [7]. Progression-free survival is improved in other cancers, including metastatic renal tumours [8] and advanced breast carcinoma [9]. GBM is a highly angiogenic tumour, and one of its histo-pathological hallmarks is microvascular proliferation [10]. Based on the results of a Phase II study of irinotecan and bevacizumab in recurrent GBM, which showed an improvement in 6-month progression-free survival, the FDA approved its use in 2009 [11]. This decision has prejudiced further studies to evaluate its role in recurrent GBM.

There are a number of published case series and prospective studies that provide data on the use of bevacizumab in patients with recurrent glioblastoma, both as monontherapy and in combination with other chemotherapy. While a small number of retrospective reports suggest improved survival [12–14], most reports and all prospective data seem to agree that the drug improves progression-free survival and quality of life in approximately two-thirds of recurrent glioblastoma patients, but has no significant effect on overall survival [11, 15–35]. This is further confirmed in two large (c. 500 cases) meta-analyses [36, 37]. Also consistently reported is that the drug is well tolerated with the main concerns being bleeding or, less commonly, thrombosis. There is evidence for other effects on tumour behaviour, with many patients experiencing out-of-radiotherapy-field progression [38].

In the absence of large randomized control trials, these data are our best estimate of the effect of bevacizumab in recurrent glioblastoma. Bevacizumab is expensive (in the region of £10,000 GBP per month) and given the lack of an effect on overall survival it is highly unlikely that it will become available for UK patients with recurrent GBM, based on current NICE criteria. If patients more likely to respond could be identified, the potentially important effects on quality of life and delayed progression in a

proportion of patients may justify its use. In terms of newly-diagnosed GBM, interim analyses of trials examining chemoradiation plus or minus bevacizumab have also failed to demonstrate any improvement in overall survival in patients treated with bevacizumab at diagnosis, and possibly worse QoL, although there is again an effect on progression-free survival [39, 40].

Adjuvant therapy in grade III (anaplastic) oligodendroglioma

Oligodendrogliomas are chemosensitive tumours, characterised by the presence of co-deletion of chromosomes 1p/19q, which has been known to be associated with a prolonged and durable response to PCV chemotherapy since the 1990s [41]. Two randomised controlled trials of PCV in anaplastic oligodendroglioma were published in 2006; the EORTC trial of adjuvant PCV [42] and the North American trial of neo-adjuvant PCV [43]. While both showed improved PFS, neither could not demonstrate improved overall survival from the addition of PCV chemotherapy. Both trials confirmed the strong prognostic value of 1p/19q codeletion but neither found a predictive role.

The 12-year follow-up data has recently been analysed for both cohorts. The European group shows a significant overall survival benefit in patients treated with PCV (median 42.3 vs. 30.6 months), particularly in those with 1p/19q co-deletion (median not reached vs. 112 months, HR 0.56). There was no substantial evidence for a benefit from PCV in patients without 1p/19q co-deletion [44]. The 12-year data from the North American study again validates 1p/19q co-deletion as a positive prognostic factor. In addition, while there is no benefit of treatment with PCV in the non-deleted group of patients, those with co-deletion are demonstrated to have statistically significantly better overall survival (median 14.7 compared to 7.3 years, HR 0.59) and PFS [45].

These data now inform us that standard of care for patients with anaplastic oligodendroglioma who carry the 1p/19q co-deletion is post-surgical radiotherapy followed by PCV chemotherapy. It is unclear, whether temozolomide may provide a similar benefit in this group.

Conclusions

The management of CNS gliomas continues to evolve. This brief review describes recent developments that impact on patient management, and highlights the dynamic nature of this progressive field. The speed at which optimal patient management can change supports the importance of the multidisciplinary team model in the assessment and treatment of glioma patients.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996
2. Stupp R, Hegi ME, Mason WP, van den Bent MJ et al (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 10(5):459–466
3. Malmstrom A, Gronberg BH, Marosi C, Stupp R et al (2012) Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 13(9):916–926
4. Wick W, Platten M, Meisner C, Felsberg J et al (2012) Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 13(7):707–715
5. Bergers G, Benjamin LE (2003) Tumorigenesis and the angiogenic switch. Nat Rev Cancer 3(6):401–410
6. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS et al (2004) Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22(11):2184–2191
7. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350(23):2335–2342
8. Yang JC, Haworth L, Sherry RM, Hwu P et al (2003) A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 349(5):427–434
9. Miller K, Wang M, Gralow J, Dickler M et al (2007) Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357(26):2666–2676
10. Tuettenberg J, Friedel C, Vajkoczy P (2006) Angiogenesis in malignant glioma—a target for antitumor therapy? Crit Rev Oncol Hematol 59(3):181–193
11. Kreisl TN, Kim L, Moore K, Duic P et al (2009) Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 27(5):740–745
12. Cai LB, Li J, Lai MY, Shan CG et al (2013) Bevacizumab rescue therapy extends the survival in patients with recurrent malignant glioma. Chin J Cancer Res 25(2):206–211
13. Gil MJ, de Las Penas R, Reynes G, Balana C et al (2012) Bevacizumab plus irinotecan in recurrent malignant glioma shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO). Anticancer Drugs 23(6):659–665
14. Vauleon E, Mesbah H, Gedouin D, Lecouillard I et al (2012) Retrospective analysis of 24 recurrent glioblastoma after chemoradiation and treated with nitrosoureas or irinotecan and bevacizumab. Bull Cancer 99(2):121–126
15. Cecchi M, Vaiani M, Ceroti M, Banfi R (2013) A retrospective observational analysis to evaluate the off-label use of

bevacizumab alone or with irinotecan in recurrent glioblastoma. Int J Clin Pharm 25(3):483–487
16. Chamberlain MC, Johnston S (2009) Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. J Neurooncol 91(3):359–367
17. Desjardins A, Reardon DA, Coan A, Marcello J et al (2012) Bevacizumab and daily temozolomide for recurrent glioblastoma. Cancer 118(5):1302–1312
18. Desjardins A, Reardon DA, Herndon JE 2nd, Marcello J et al (2008) Bevacizumab plus irinotecan in recurrent WHO grade 3 malignant gliomas. Clin Cancer Res 14(21):7068–7073
19. Friedman HS, Prados MD, Wen PY, Mikkelsen T et al (2009) Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27(28):4733–4740
20. Lassen U, Sorensen M, Gaziel TB, Hasselbalch B et al (2013) Phase II study of Bevacizumab and Temsirolimus combination therapy for recurrent glioblastoma multiforme. Anticancer Res 33(4):1657–1660
21. Nagane M, Nishikawa R, Narita Y, Kobayashi H et al (2012) Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. Jpn J Clin Oncol 42(10):887–895
22. Nagpal S, Harsh G, Recht L (2011) Bevacizumab improves quality of life in patients with recurrent glioblastoma. Chemother Res Pract 2011:602812
23. Narayana A, Kelly P, Golfinos J, Parker E et al (2009) Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: impact on local control and patient survival. J Neurosurg 110(1):173–180
24. Nghiemphu PL, Liu W, Lee Y, Than T et al (2009) Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. Neurology 72(14):1217–1222
25. Norden AD, Young GS, Setayesh K, Muzikansky A et al (2008) Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 70(10):779–787
26. Quant EC, Norden AD, Drappatz J, Muzikansky A et al (2009) Role of a second chemotherapy in recurrent malignant glioma patients who progress on bevacizumab. Neuro Oncol 11(5):550–555
27. Raizer JJ, Grimm S, Chamberlain MC, Nicholas MK et al (2010) A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. Cancer 116(22):5297–5305
28. Reardon DA, Desjardins A, Peters KB, Gururangan S et al (2012) Phase II study of carboplatin, irinotecan, and bevacizumab for bevacizumab naive, recurrent glioblastoma. J Neurooncol 107(1): 155–164
29. Ruiz-Sanchez D, Calero MA, Sastre-Heres AJ, Garcia MT et al (2012) Effectiveness of the bevacizumab-irinotecan regimen in the treatment of recurrent glioblastoma multiforme: comparison with other second-line treatments without this regimen. Oncol Lett 4(5):1114–1118
30. Sahebjam S, Garoufalis E, Guiot MC, Muanza T et al (2013) Bevacizumab use for recurrent high-grade glioma at McGill University Hospital. Can J Neurol Sci 40(2):241–246
31. Seystahl K, Wiestler B, Hundsberger T, Happold C et al (2013) Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. Eur Neurol 69(2):95–101
32. Taillibert S, Vincent LA, Granger B, Marie Y et al (2009) Bevacizumab and irinotecan for recurrent oligodendroglial tumors. Neurology 72(18):1601–1606
33. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Dowell JM et al (2007) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13(4):1253–1259
34. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J et al (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25(30):4722–4729
35. Zuniga RM, Torcuator R, Jain R, Anderson J et al (2009) Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neurooncol 91(3):329–336
36. Wong ET, Gautam S, Malchow C, Lun M et al (2011) Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. J Natl Compr Cancer Netw 9(4):403–407
37. Zhang G, Huang S, Wang Z (2012) A meta-analysis of bevacizumab alone and in combination with irinotecan in the treatment of patients with recurrent glioblastoma multiforme. J Clin Neurosci 19(12):1636–1640
38. Shields LB, Kadner R, Vitaz TW, Spalding AC (2013) Concurrent bevacizumab and temozolomide alter the patterns of failure in radiation treatment of glioblastoma multiforme. Radiat Oncol 8(1):101
39. Chinot O, Wick W, Mason W, Henriksson R et al (2012) Phase III trial of bevacizumab added to standard radiotherapy and temozolamide for newly-diagnosed glioblastoma: mature progression-free survival and preliminary overall survival results in AVAGLIO. Neuro Oncol 14(suppl 6):OT–03
40. Gilbert MR, Dignam J, Won M, Blumenthal DT et al (2013) Phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM). J Clin Oncol 31(suppl):abstr 1
41. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK et al (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 90(19):1473–1479
42. van den Bent MJ, Carpentier AF, Brandes AA, Sanson M et al (2006) Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 24(18):2715–2722
43. Cairncross G, Berkey B, Shaw E, Jenkins R et al (2006) Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 24(18):2707–2714
44. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM et al (2013) Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 31(3):344–350
45. Cairncross G, Wang M, Shaw E, Jenkins R et al (2013) Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 31(3):337–343