MANAGEMENT OF PATIENTS WITH HIGH-GRADE GLIOMA

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ABSTRACT

The scientific basis for the surgical management of patients with glioma is rapidly evolving. The infiltrative nature of these cancers precludes a surgical cure, but despite this, cytoreductive surgery remains central to high-quality patient's care. In addition to tissue sampling for accurate histopathological diagnosis and molecular genetic characterisation, clinical benefit from decompression of space-occupying lesions and microsurgical cytoreduction has been reported in patients with different grades of glioma. By integrating advanced surgical techniques with molecular genetic characterisation of the disease and targeted radiotherapy and chemotherapy, it is possible to construct a programme of personalised surgical therapy throughout the patient's journey. The goal of therapeutic packages tailored to each patient is to optimise patient safety and clinical outcome, and must be delivered in a multidisciplinary setting. Here we review the current concepts that underlie surgical management of patients with high-grade glioma.

Keywords: High-grade glioma, surgery, adjuvant therapy, prognosis.

INTRODUCTION

Gliomas are the most common primary central nervous system tumours. Malignant gliomas account for 60-75% of all gliomas and comprise glioblastoma multiforme (GBM) (incidence 5/100,000, World Health Organization [WHO] Grade 4), anaplastic astrocytoma (AA) (WHO Grade 3), mixed anaplastic oligoastrocytoma (AnO) (WHO Grade 3), and anaplastic oligodendroglioma (AO) (WHO Grade 3).[1] These tumours can develop at any time, the peak incidence being in the fifth and sixth decades of life.[2] Despite continuous improvements in therapeutic modalities, outcome remains poor with a median survival (MS) of <15 months.[3] The most common and aggressive malignant glioma is GBM with an average survival of 1 year.[4] Patients with anaplastic glioma have a moderately better prognosis with a MS of approximately 3-7 years for AA and AO, respectively.[5,6] The initial management of malignant gliomas involves maximal safe resection utilising modern technology. Because of high propensity of malignant gliomas for local invasion, adjuvant therapies are recommended. Recent studies have suggested that the grouping of patients, based on their molecular genetic signatures, will enable more efficacious targeted therapies.

HETEROGENEITY AND MOLECULAR MARKERS IN GBM

GBM is widely known for its immense inter and intratumoural heterogeneity in terms of cellular, genetic, epigenetic, and molecular composition.[7-9] There are four different subtypes: classic, proneural, neural, and mesenchymal. The first is associated with extensive epidermal growth factor receptor (EGFR) amplification and expression of EGFRvIII, accompanied by loss of phosphatase and tensin homologue (PTEN). The proneural type

exhibits platelet-derived growth factor receptor amplification and enriches for mutations in p53, isocitrate dehydrogenase (IDH) 1 and 2, and cyclin-dependent kinase (CDK) 6 and 4. Neural GBMs are connected to markers such as NEF1 and elevated ERBB2 levels. Lastly, mesenchymal GBM are associated with loss of PTEN and CDK inhibitor 2a. A hierarchical cancer stem cell model has not yet been identified for GBM. Although the identification of brain cancer stem cells has been linked to the expression of several cell surface markers, none of them appear to be universal or specific.[7,10,11]

Identification of molecular changes in high-grade glioma (HGG) provides an advanced understanding for survival and treatment response. There are specific biomarkers that have been studied in recent years such as O6-methylguanine methyltransferase (MGMT) promoter methylation (Figure 1), 1p/19q chromosomal co-deletion, mutations of IDH 1 and 2, and EGFR alterations. MGMT encodes a DNA repair protein that removes alkyl groups from the O6 position of guanine counteracting alkylating agent chemotherapy.[12] The epigenetic methylation of the MGMT promoter is proven to be a predictive biomarker of response to temozolomide (TMZ) chemotherapy with longer overall survival (OS) and response to alkylating chemotherapy in patients with GBM.[13,14] In patients with anaplastic gliomas, MGMT promoter methylation is prognostic for those receiving chemoradiotherapy.

Combined loss of heterozygosity on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is the molecular signature of oligodendroglial tumours.[15] This aberration is seen in 60-80% of AO, and 20-30% of AnO.[16] Loss of chromosome 1p and 19q is prognostically significant for Grade 3 glioma patients who receive chemoradiotherapy, and predictive to benefit from procarbazine, lomustine, and vincristine (PCV) in patients with AO.[17,18] Its value in GBM is not known. Most IDH mutations involve the *IDH1* gene. IDH1 mutations are found in a vast majority of diffuse low-grade and anaplastic glioma and secondary GBM, and rarely in primary GBM.[19] It was shown that IDH1 mutation represents a very early oncogenic event, and is a strong prognostic marker in patients with HGG.[20]

The most common EGFR alteration in malignant gliomas is amplification. Approximately 40% of GBMs with EGFR amplification have EGFR mutations, most commonly deletion of exons 2-7 that produce EGFRvIII, leading to constitutive receptor activation.[21,22] EGFR inhibitors have been studied in Phase II trials with either recurrent or newly diagnosed malignant gliomas, but neither showed improved survival.[23-25] Haas et al.[26] reported that EGFR amplification was predictive of erlotinib response. However, other studies have not confirmed this result, or have suggested different markers.[27-29] Rindopepimut, a peptide vaccine against EGFRvIII is currently being evaluated in a Phase III trial.[30]

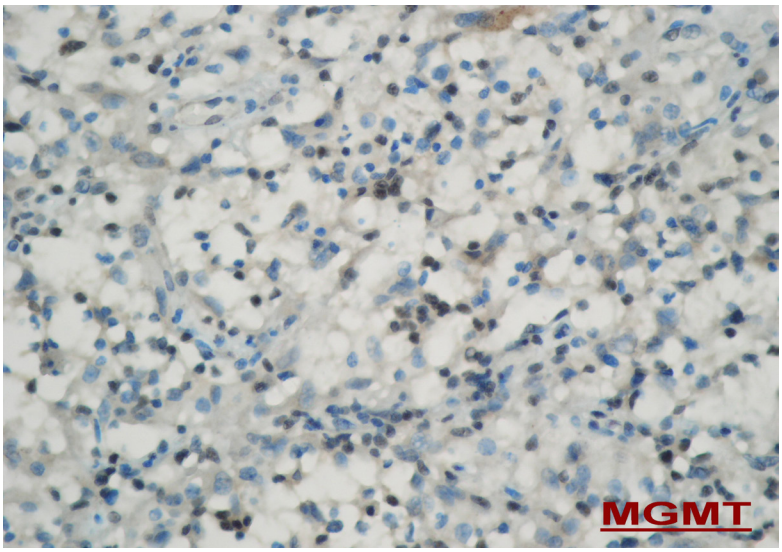

Figure 1: O6-methylguanine methyltransferase (MGMT) promoter methylation is a strong prognostic factor in patients with glioblastoma (MGMT; streptavidin-biotinylated complement; x200).

SURGICAL RESECTION

Rationale for Surgery

Surgical resection is the initial step. Studies have shown that the extent of resection is an important prognostic factor for OS.[31] Cytoreductive surgery of HGG also provides a more representative histological sample[32] and enables a rapid log kill of tumour cells.[33] Reduction of tumour load leads to relief of increased intracranial pressure and peritumoural oedema (PO).[34] It also decreases preoperative epileptic seizures that are observed in 25-40% of patients with HGG.[35] Recently, post-hoc analysis of three large prospective randomised controlled trials (RCTs) has provided valid evidence for the effect of resection on patient survival.[36-39] This also illustrated the facilitation of adjuvant treatments with extensive resection.

In a study by Westphal et al.,[40] 240 patients with newly diagnosed malignant glioma were randomised to receive resection with biodegradable 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) wafer or placebo wafer implantation, followed by radiotherapy. Complete resection was defined as removal of >90% of tumour tissue on postoperative radiographs. In both the BCNU wafer group and the placebo wafer group, complete resections led to longer survival. The BCNU wafer arm resulted in longer survival compared to the placebo wafer arm in both subgroups (13.9 versus 11.6 months). In addition, MS for the BCNU wafer group was longer in the complete resection subgroup (14.8 versus 12.1 months). This result indicated that the efficacy of BCNU wafer therapy increased with extensive resection.

The European Organization for Research Trials in Cancer (EORTC)-National Cancer Institute of Canada (NCIC) trial study randomised 573 patients with newly diagnosed malignant glioma to receive concomitant radiochemotherapy, followed by adjuvant TMZ or radiotherapy alone.[38,41] Patients with complete resections survived longer. However, the extent of resection was assessed subjectively. Analysis of 5-year OS favoured combined chemoradiotherapy over radiotherapy alone (14.6 versus 12.1 months). Furthermore, median gain in survival time was greatest in the complete resection subgroup (plus 4.1 months) compared to the partial resection subgroup (plus 1.8 months) and the biopsy subgroup (plus 1.5 months). Thus, this study has shown that more extensive surgery enhances the effect of radiochemotherapy.

In another study by Stummer et al.,[36] patients with newly diagnosed malignant glioma were randomised to receive 5-aminolevulinic acid (5-ALA) fluorescence-guided resection or conventional microsurgery, followed by radiotherapy. Patients with complete resections survived longer (16.7 versus 11.8 months). In a more recent prospective study of 166 patients with GBM, the completeness of resection was determined by magnetic resonance imaging (MRI) obtained within 72 hours of operation.[37] The absence of visible contrast-enhancing disease was associated with prolonged progression-free survival (PFS) and OS. The median OS of patients without residual enhancing disease exceeded the follow-up period of 24 months (mean 23.6 months; range 21.4–25.8). The extent of resection is an important predictor of OS. Gross resection at recurrence might be able to overcome the negative prognostic effect of an incomplete initial resection.[30]

Intraoperative Techniques for Patient Safety

Maximal resection with minimisation of postoperative neurological deficit is an important goal in the initial management.[42] In order to more reliably identify tumour and functionally important brain areas, advanced intraoperative techniques have been developed. Awake craniotomy with intraoperative cortical/subcortical mapping and monitoring is the gold standard.[43,44] Intraoperative neuronavigation has also become a commonly used surgical adjunct. However, its accuracy is compromised by brain shift.[45] Integration of real-time updated imaging data sets from intraoperative MRI into neuronavigation can minimise this error.[46]

A simpler and more cost-efficient intraoperative tool for maximal safe resection is the use of 5-ALA fluorescence.[47-50] Fluorescence has a high predictive value to detect contrast-enhancing HGG and anaplastic foci of low-grade glioma. The principle behind this is the accumulation of fluorescent porphyrins in malignant glioma led by the metabolic precursor, 5-ALA.[51] Clinical application has been validated in the RCT by Stummer et al.,[47] where its use almost doubled the number of patients with complete resections.[47] Despite these improvements, complete surgical resection is impossible due to the invasive nature of malignant gliomas. In order to prevent recurrence, surgery must be followed by adjuvant therapies such as radiotherapy, chemotherapy, or both (Figure 2).[52,53]

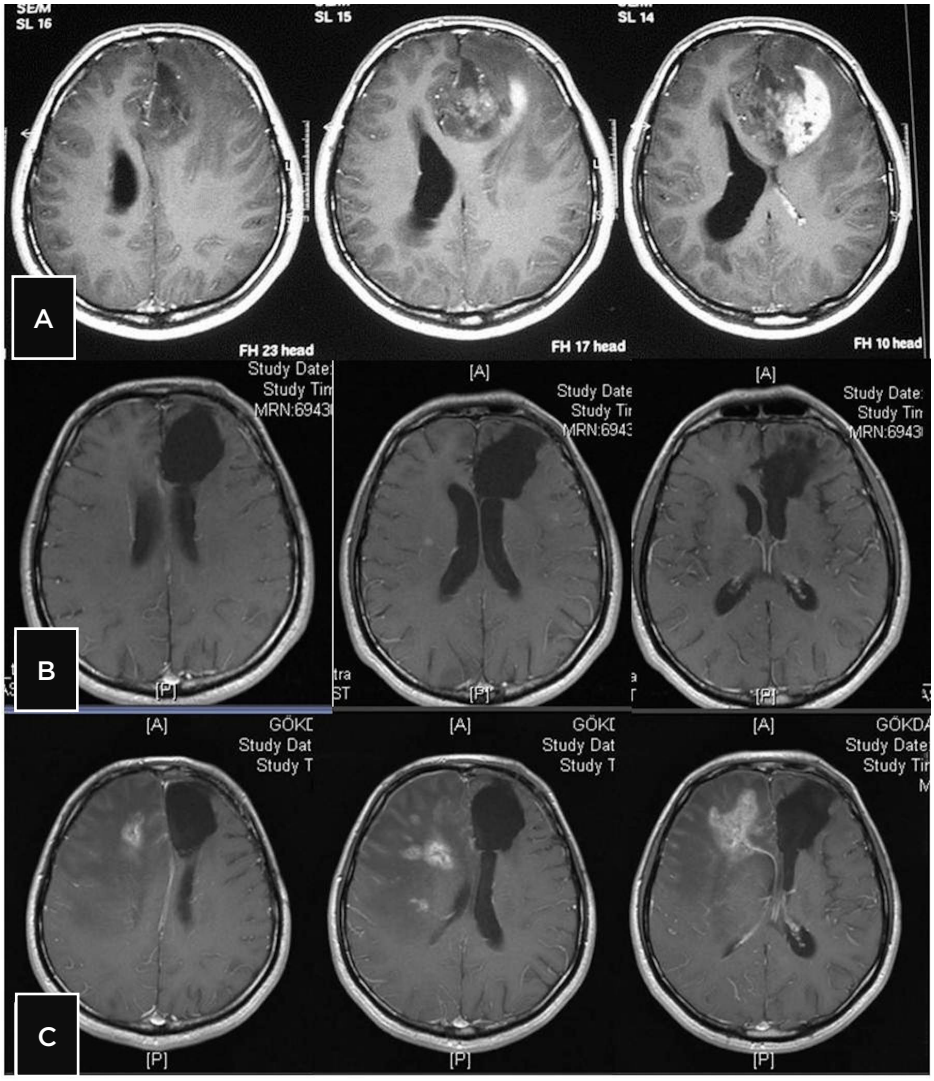

Figure 2: A) A 30-year-old male with a newly diagnosed glioblastoma multiforme (GBM) underwent an initial resection. Preoperative gadolinium-enhanced magnetic resonance imaging (MRI) showed a heterogeneously enhancing lesion in the left frontal lobe. B) Post-operative gadolinium-enhanced MRI at 3 months showed total resection of the tumour. C) Gadolinium-enhanced MRI at 18 months revealed multiple ring-enhancing lesions in the right frontal lobe after chemoradiation. The patient underwent a second resection due to clinical deterioration. Histological analysis performed for multiple regions of the lesion revealed radiation necrosis.

RADIOTHERAPY

The rationale for radiotherapy after surgical resection is a significant enhancement in survival. Due to its powerful survival benefit, radiotherapy has been implemented as a central treatment modality. Based on adjuvant radiotherapy studies, standard radiotherapy for HGG has been defined as fractionated focal radiotherapy with a dose of 60 Gy in 1.8-2.0 Gy daily fractions in 6 weeks.[54] In 1978, the Brain Tumor Study Group randomised patients with malignant glioma to one of four study arms after surgical resection.[55] The arms were: best supportive care after surgery, BCNU chemotherapy alone, whole brain radiotherapy (WBRT) alone to a dose of 50-60 Gy, and BCNU chemotherapy combined with radiotherapy. MS was 4.3 months for the best supportive care arm, 6.3 months for the chemotherapy alone arm, 9.4 months for the radiotherapy alone arm, and 10.1 months for the chemoradiotherapy arm. These results showed a significant survival benefit for patients receiving adjuvant radiotherapy.

In order to maximise the survival benefit, the brain volume of radiation delivery has been investigated. It was observed that recurrent HGG after WBRT

occurred within 2 cm of the original tumour site in 80–90%,[56] while <10% developed multifocal recurrence.[57] Therefore, radiation delivery has evolved to focal radiotherapy called involved field radiotherapy. Involved field radiotherapy is delivered not only to radiographically defined tumour volume but also to 1-2 cm margin of the tumour in order to prevent local recurrence.[58]

CHEMOTHERAPY

GBM

Concomitant chemoradiation with TMZ followed by six cycles of adjuvant TMZ constitutes the current standard management for the adjuvant therapy of GBM.[59] This is based on the pivotal EORTC-NCIC trial that yielded results favouring combined chemoradiotherapy with TMZ over radiotherapy alone.[41] According to a 5-year analysis of the trial, for patients with MGMT methylation the 2-year survival rates were 49% and 24% with chemoradiotherapy and with radiotherapy alone, respectively, whereas, for those without MGMT methylation, the 2-year survival rates were 15% and 2%, respectively.[60] This confirms that MGMT promoter methylation is correlated with response of GBM to TMZ chemotherapy.[61] TMZ itself is also a powerful MGMT-depleting agent, so higher doses could possibly overcome resistance of non-MGMT methylated tumours, although hematotoxicity remains a dose-limiting problem.[62] The Phase III Radiation Therapy Oncology Group 0525 trial stratified 833 patients with GBM according to clinical factors and MGMT methylation status.[60] Patients were randomly assigned to standard (150-200 mg/m^2 daily for 5 days, every 28 days) or dose-dense TMZ (75 to 100 mg/m^2 days 1-21, every 4 weeks). Although results confirmed the prognostic role of MGMT status, no statistically significant difference was observed. Nevertheless, this demonstrated the feasibility of large-scale, prospective tumour collection and molecular stratification that is promising for further research.[61]

BCNU wafers have been approved as a treatment option for malignant glioma.[63] Implantation of BCNU wafer into the resection cavity, prior to radiotherapy, has been shown to prolong survival compared to radiotherapy alone.[64] Although retrospective studies showed positive results for the safety and efficacy of the combination of BCNU wafer with standard TMZ chemotherapy,[64] Phase III prospective randomised trials are needed to evaluate the place of BCNU wafers in modern neuro-oncology practice.

Anaplastic Glioma

Radiotherapy with concurrent and adjuvant TMZ is recommended for most patients with AA, especially for the ones with negative prognostic factors including wild-type IDH1/IDH2 and older age. Adjuvant chemotherapy alone with delayed radiotherapy was compared to adjuvant radiotherapy alone with delayed chemotherapy in the Neuro-Oncology Working Group of the German Cancer Society (NOA)-04 trial.[65] 318 patients with anaplastic gliomas were randomised to adjuvant chemotherapy, with radiotherapy delayed until progression or to adjuvant radiotherapy, with chemotherapy delayed until progression. Patients were randomly assigned to either TMZ or PCV for chemotherapy, either as the initial or the delayed treatment. Analysis of 54 months follow-up showed that the time to treatment failure of those receiving chemotherapy initially and those receiving radiotherapy first was similar (44 versus 43 months). There was no significant difference in time to treatment failure between those managed by TMZ and those managed by PCV. In a retrospective analysis of patients with AA, adjuvant TMZ was as effective and better tolerated than PCV.[66] Therefore, it is frequently used in lieu of PCV in combination with postoperative radiotherapy.[67,68]

MANAGEMENT OF PATIENTS WITH RECURRENT HGG

Despite the highest standard of care, the recurrence rate remains high. A decision to re-operate should be made in a multi-disciplinary team setting, as the role of surgery in recurrent HGG remains controversial. There are insufficient data to support specific practice guidelines,[69] a situation that has not changed in over 10 years.[70] Validated criteria for patient selection have not been established, but focal recurrence, good performance status, and a multi-disciplinary rationale constitute good clinical practice. Unfortunately, the number of appropriate patients remains limited.[71]

In a prospective, single-arm, uncontrolled Phase II study that recruited 40 patients with recurrent HGG (WHO Grade 4 and 3),[72] 5-ALA fluorescence had a predictive value of 97.2% (95% CI: 85.5-99.9%) in tissue that had a pathologic appearance under white light. Sample analysis revealed 342/

354 biopsies taken from fluorescing areas showed tumour histopathologically (positive predictive value [PPV] of 96.6%). Stratified by fluorescence quality, histopathological analysis showed primarily solid tumour for strong fluorescence and infiltrative tumour for weak fluorescence. For normal appearing tissue with strong as well as weak fluorescence, 146/157 biopsies (93% PPV [95% CI: 87.8-96.5%]) showed infiltrating tumour. Scar tissue and areas of necrosis did not fluoresce. These data support the use of 5-ALA as an adjunct to surgery in recurrent HGG.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), a key promoter of tumour neovascularisation. In a randomised non-comparative Phase II trial for recurrent GBM, 167 patients received either bevacizumab alone or in combination with irinotecan.[73] The objective response rates with bevacizumab alone or in combination with irinotecan were 28% and 38%, respectively. The 6-month PFS rates and OS were 43% and 50%, and 9.2 and 8.7 months, respectively. The high response rate and 6-month PFS led to its approval by the FDA in the United States in 2009 as a single-agent chemotherapy for recurrent GBM. However, it was rejected by the European Union due to the lack of data for improved OS. Recently, two Phase III trials on newly diagnosed GBM have investigated the use of bevacizumab with standard chemoradiotherapy with TMZ.[74] They have demonstrated improved PFS in patients treated with both bevacizumab and standard chemoradiotherapy, but they have failed to demonstrate a prolonged overall survival. Other anti-angiogenic agents such as cediranib, a VEGF receptor 2-inhibitor, and cilengitide, an integrin inhibitor, exhibited promising results in Phase II trials on recurrent GBM.[75-77] But both agents failed to deliver in subsequent Phase III trials, where they were combined with other drugs,[78,79] as neither PFS, nor OS, were improved.

Re-irradiation is another treatment option for recurrent HGG but its efficacy is limited. Although no RCTs have been performed, retrospective studies indicated stereotactic radiotherapy and stereotactic radiosurgery as the most effective approaches for re-irradiation.[80,81]

Patients suffering from HGG often exhibit seizures caused by the high extracellular glutamate concentration, which can reach up to 20 mM, causing excitotoxicity in peritumoural areas.[82,83] Patients can be treated with seizure medication to relieve the symptoms, although side-effects have to be taken into account and weighted against their benefit.[84] In a new clinical Phase II trial, levetiracetam and pregabalin have been found to exhibit a good antiepileptic effect without causing any intolerable side-effects.[85] Another treatment option, often part of palliative care, is the use of steroid based medication, such as dexamethasone.[86] Steroids are normally used to relieve symptoms of PO, but cause a variety of unwanted side-effects.[87] Therefore, other treatment modalities are taken into consideration, such as angiotensin II inhibitors, which interfere with the VEGF pathway, a key driver of oedema and angiogenesis.[88]

MANAGEMENT OF HGG IN THE ELDERLY

The incidence of HGG increases with age, with nearly 60% of cases occurring in patients over the age of 70.[89] The role of surgery in the elderly patient remains controversial. Due to concerns over elderly patients' ability to cope with therapy and its toxicity, they may receive less intensive treatment: diagnostic biopsy rather than debulking surgery,[90] and less radiotherapy and chemotherapy.[91-95] Thus, elderly patients are under represented in clinical trials. For instance, in a trial assessing the role of carmustine wafers in addition to surgery the median age was 53 years.[96] The EORTC undertook a study assessing the benefit of adding TMZ to radiation and adjuvant chemotherapy for patients aged 18-70 with GBM, which demonstrated a significant survival benefit.[97] The median age at entry was 56 years and the MS was 14.6 months. 83 patients were older than 60 and had a MS of 10.9 months.

More recent data incorporating modern surgical techniques, including the use of fluorescence guided cytoreduction, are available for 130 GBM patients with a median age of 68. The MS for those who went on to receive radiotherapy and chemotherapy was 16.3 months (range 12-17.2) compared to 11.2 months for those receiving radiotherapy alone.[98] Two recent studies have further advanced our understanding of the management of the elderly population with HGG.[95,96] Both NOA-08 and the Nordic studies support the use of TMZ alone in MGMT ethylated elderly GBM and radiotherapy alone for unmethylated patients, although this has yet to become established in UK practice.[97]

These prospective data are supported by a retrospective analysis,[99] and suggest that elderly patients will benefit from more aggressive management that incorporates biomarker-based treatment stratification.

CONCLUSION

Malignant gliomas should be removed via technological adjuncts that maximise tumour resection and minimise neurologic injury. Surgical resection should be pursued by adjuvant therapies for prevention of recurrence. However, despite recent improvements in management of HGGs, the MS still remains poor. In order for more effective interventions to take place, further studies should focus on targeted therapies and personalised care. Previously tested targeted drugs have failed to improve survival.[77] However, advancements in genomic profiling of gliomas and detection of molecular signatures might lead to the discovery of new targets for personalised therapy.

REFERENCES

1. Louis DN et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114(4):97-109.

2. Stupp R et al. High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v190-3.

3. Stupp R, Weber DC. The role of radio- and chemotherapy in glioblastoma. Onkologie. 2005;28(6-7):315-7.

4. Smith AA et al. A novel approach to the discovery of survival biomarkers in glioblastoma using a joint analysis of DNA methylation and gene expression. Epigenetics. 2014;doi:10.4161/epi.28571. [Epub ahead of print].

5. Prados MD et al. Phase III randomized study of radiotherapy plus procarbazine, lomustine, and vincristine with or without BUdR for treatment of anaplastic astrocytoma: final report of RTOG 9404. Int J Radiat Oncol Biol Phys. 2004;58(4):1147-52.

6. van den Bent MJ. Advances in the biology and treatment of oligodendrogliomas. Curr Opin Neurol. 2004;17(6):675-80.

7. Walker C et al. Biology, genetics and imaging of glial cell tumours. Br J Radiol. 2011;84 Spec No 2:S90–106.

8. Furnari FB et al. Malignant astrocytic glioma: genetics, biology, and paths to treatment. Genes Dev. 2007;21(21): 2683–710.

9. Li W, Graeber MB. The molecular profile of microglia under the influence of glioma. Neuro Oncol. 2012;14(8):958-78.

10. Donovan LK, Pilkington GJ. CD133: holy of grail of neuro-oncology or promiscuous red-herring? Cell Prolif. 2012;45(6):527–37.

11. Campos B et al. Expression and regulation of AC133 and CD133 in glioblastoma. Glia. 2011;59(12):1974-86.

12. Weller M et al. Molecular neuro-oncology in clinical practice: a new horizon. Lancet Oncol. 2013;14(9):e370-9.

13. Hegi ME et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997-1003.

14. Weller M et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol. 2009;27(34):5743-50.

15. Aldape K et al. Clinicopathologic aspects of 1p/19q loss and the diagnosis of oligodendroglioma. Arch Pathol Lab Med. 2007;131(4):242-51.

16. Jeuken JW et al. Molecular pathogenesis of oligodendroglial tumors. J Neurooncol. 2004;70(4):161-81.

17. Cairncross JG et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst. 1998;90(19):1473-9.

18. van den Bent MJ et al. 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. 2013;31(3): 344-50.

19. Watanabe T et al. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. Am J Pathol. 2009;174(4):1149-53.

20. Sanson M et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol. 2009;27(25): 4150-4.

21. Ohgaki H et al. Genetic pathways to glioblastoma: a population-based study. Cancer Res. 2004;64(19):6892-9.

22. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol. 2007;170(5):1445-53.

23. Raizer JJ et al. A phase II trial of erlotinib in patients with recurrent malignant gliomas and nonprogressive glioblastoma multiforme postradiation therapy. Neuro Oncol. 2010;12(1):95-103.

24. Rich JN et al. Phase II trial of gefitinib in recurrent glioblastoma. J Clin Oncol. 2004;22(1):133-42.

25. Yung WK et al. Safety and efficacy of erlotinib in first-relapse glioblastoma: a phase II open-label study. Neuro Oncol. 2010;12(10):1061-70.

26. Haas-Kogan DA et al. Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib. J Natl Cancer Inst. 2005;97(12):880-7.

27. Mellinghoff IK et al. Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. N Engl J Med. 2005;353(19):2012-24.

28. Lassman AB et al. Molecular study of malignant gliomas treated with epidermal growth factor receptor inhibitors: tissue analysis from North American Brain Tumor Consortium Trials 01-03 and 00-01. Clin Cancer Res. 2005;11(21):7841-50.

29. Blayney DW. Enhancing quality through innovation: American Society of Clinical Oncology presidential address 2010. J Clin Oncol. 2010;28(28):4283-8.

30. Friedman HS et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733-40.

31. Bloch O et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117(6):1032-8.

32. Pang BC et al. The role of surgery in high-grade glioma--is surgical resection justified? A review of the current knowledge. Ann Acad Med Singapore. 2007;36(5):358-63.

33. McCarter MD, Fong Y. Role for surgical cytoreduction in multimodality treatments for cancer. Ann Surg Oncol. 2001;8(1):38-43.

34. Stummer W et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery:

a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article. J Neurosurg. 2011;114(3):613-23.

35. van Breemen MS et al. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol. 2009;256(9): 1519-26.

36. Stummer W et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7(5):392-401.

37. Stummer W et al. Prospective cohort study of radiotherapy with concomitant and adjuvant temozolomide chemotherapy for glioblastoma patients with no or minimal residual enhancing tumor load after surgery. J Neurooncol. 2012;108(1):89-97.

38. Stupp R et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.

39. Westphal M et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol. 2003;5(4):79-88.

40. Westphal M et al. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. Acta Neurochir (Wien). 2006;148(3): 269-75.

41. Stupp R et al. 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. 2009;10(5):459-66.

42. Soffietti R et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. Eur J Neurol. 2010;17(9):1124-33.

43. Zhang Z et al. Surgical strategies for glioma involving language areas. Chin Med J (Engl). 2008;121(18):1800-5.

44. Sanai N, Berger MS. Operative techniques for gliomas and the value of extent of resection. Neurotherapeutics. 2009;6(3):478-86.

45. Rasmussen IA Jr et al. Functional neuronavigation combined with intra-operative 3D ultrasound: initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta Neurochir (Wien). 2007;149(4):365-78.

46. Kubben PL, van Santbrink H. Intraoperative magnetic resonance imaging for high grade glioma resection: evidence-based or wishful thinking? Surg Neurol Int. 2013;4:1.

47. Stummer W et al. 5-Aminolevulinic acid-derived tumor fluorescence: the diagnostic accuracy of visible fluorescence qualities as corroborated by spectrometry and histology and postoperative imaging. Neurosurgery. 2014;74(3):310-9.

48. Feigl GC et al. Resection of malignant brain tumors in eloquent cortical areas: a new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring. J Neurosurg. 2010;113(4): 352-7.

49. Panciani PP et al. Fluorescence and image guided resection in high grade glioma. Clin Neurol Neurosurg. 2012;114(1):37-41.

50. Schucht P et al. Gross total resection rates in contemporary glioblastoma surgery: results of an institutional protocol combining 5-aminolevulinic acid intraoperative fluorescence imaging and brain mapping. Neurosurgery. 2012;71(5):927-35.

51. Stummer W et al. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg. 2000;93(6):1003-13.

52. Giese A. Glioma invasion--pattern of dissemination by mechanisms of invasion and surgical intervention, pattern of gene expression and its regulatory control by tumorsuppressor p53 and proto-oncogene ETS-1. Acta Neurochir Suppl. 2003;88:153-62.

53. Walker MD. The contemporary role of chemotherapy in the treatment of malignant brain tumor. Clin Neurosurg. 1978;25:388-96.

54. Buatti J et al. Radiation therapy of pathologically confirmed newly diagnosed glioblastoma in adults. J Neurooncol. 2008;89(3):313-37.

55. Choucair AK et al. Quality of life and neuropsychological evaluation for patients with malignant astrocytomas: RTOG 91-14. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1997;38(1):9-20.

56. Laperriere N et al. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol. 2002;64(3):259-73.

57. Barnett GH et al. Stereotactic radiosurgery--an organized neurosurgery-sanctioned definition. J Neurosurg. 2007;106(1):1-5.

58. Yang LJ et al. Temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme: a systematic review. Cancer Invest. 2014;32(4):31-6.

59. Olson RA et al. Prognostic and predictive value of epigenetic silencing of MGMT in patients with high grade gliomas: a systematic review and meta-analysis. J Neurooncol. 2011;105(4): 325-35.

60. Gilbert MR et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013;31(32):4085-91.

61. Hegi ME et al. Epigenetic deregulation of DNA repair and its potential for therapy. Clin Cancer Res. 2009;15(16):5026-31.

62. Lawson HC et al. Interstitial chemotherapy for malignant gliomas: the Johns Hopkins experience. J Neurooncol. 2007;83(1):61-70.

63. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. Expert Rev Anticancer Ther. 2008;8(3):343-59.

64. Gutenberg A et al. The combination of carmustine wafers and temozolomide for the treatment of malignant gliomas. A comprehensive review of the rationale and clinical experience. J Neurooncol. 2013;113(4):163-74.

65. Wick W et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol. 2009;27(35):5874-80.

66. Brandes AA et al. Survival following adjuvant PCV or temozolomide for anaplastic astrocytoma. Neuro Oncol. 2006;8(3):253-60.

67. Abrey LE. Anaplastic oligodendroglioma. Curr Neurol Neurosci Rep. 2007;7(3):189-90.

68. Kouwenhoven MC et al. Molecular analysis of anaplastic oligodendroglial tumors in a prospective randomized study: a report from EORTC study 26951. Neuro Oncol. 2009;11(6):737-46.

69. Soults CB et al. Evidence-based review of the role of reoperation in the management of malignant glioma. Neurosurg Focus. 1998;4(6):e11.

70. Barbagallo GM et al. 'Recurrent' glioblastoma multiforme, when should we reoperate? Br J Neurosurg. 2008;22(3):452-5.

71. Mandl ES et al. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. Surg Neurol. 2008;69(5):506-9.

72. Nabavi A et al. Five-aminolevulinic acid for fluorescence-guided resection of recurrent malignant gliomas: a phase ii study. Neurosurgery. 2009;65(6):1070-6.

73. Chinot OL et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709-22.

74. Gilbert MR et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699-708.

75. Batchelor TT et al. Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. J Clin Oncol. 2010;28(17):2817-23.

76. Nabors LB et al. Phase I and correlative biology study of cilengitide in patients with recurrent malignant glioma. J Clin Oncol. 2007;25(13):1651-7.

77. Reardon DA et al. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. J Clin Oncol. 2008;26(34):5610-7.

78. Batchelor TT et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol. 2013;31(26):3212-8.

79. Soffietti R et al. What have we learned from trials on antiangiogenic agents in glioblastoma? Expert Rev Neurother. 2014;14(1):1-3.

80. Niyazi M et al. Therapeutic options for recurrent malignant glioma. Radiother Oncol. 2011;98(1):1-14.

81. Romanelli P et al. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma multiforme. Neurosurg Focus. 2009;27(6):E8.

82. Ye ZC et al. Compromised glutamate transport in human glioma cells: reduction-mislocalization of sodium-dependent glutamate transporters and enhanced activity of cystine-glutamate exchange. J Neurosci. 1999;19(24): 10767–77.

83. Buckingham SC et al. Glutamate release by primary brain tumors induces epileptic activity. Nat Med. 2011;17(10):1269–74.

84. Englot DJ et al. Characteristics and treatment of seizures in patients with high-gradeglioma: a review. Neurosurg Clin N Am. 2012;23(2):227-35.

85. Rossetti AO et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro Oncol. 2014;16(4):584-8.

86. Roth P et al. Steroids in neurooncology: actions, indications, side-effects. Curr Opin Neurol. 2010;23(6):597-602.

87. Check JH et al. Evidence that Mifepristone, a progesterone receptor antagonist, can cross the blood brain barrier and provide palliative benefits for glioblastoma multiforme grade IV. Anticancer Res. 2014;34(5):2385-8.

88. Carpentier AF et al. Steroid-sparing effects of angiotensin-II inhibitors in glioblastoma patients. Eur J Neurol. 2012;19(10):1337-42.

89. Laws ER et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg. 2003;99(3):467-73.

90. Iwamoto FM et al. Patterns of care in elderly glioblastoma patients. Ann Neurol. 2008;64(6):628-34.

91. Kita D et al. Age as a predictive factor in glioblastomas: population-based study. Neuroepidemiology. 2009;33(1):17-22.

92. Stummer W et al. Favorable outcome in the elderly cohort treated by concomitant temozolomide radiochemotherapy in a multicentric phase II safety study of 5-ALA. J Neurooncol. 2011;103(4):361-70.

93. Laperriere N et al. Optimal management of elderly patients with glioblastoma. Cancer Treat Rev. 2013;39(4):350-7.

94. Tanaka S et al. Presentation, management, and outcome of newly diagnosed glioblastoma in elderly patients. J Neurosurg. 2013;118(4):786-98.

95. Wick W et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol. 2012;13(7):707-15.

96. Malmström A et al. 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. 2012;13(9): 916-26.

97. 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. Clin Oncol (R Coll Radiol). 2013;25(7):391-3.

98. Scott JG et al. Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases. Neuro Oncol. 2011;13(4):428-36.

99. Masui K et al. Review: molecular pathology in adult high-grade gliomas: from molecular diagnostics to target therapies. Neuropathol Appl Neurobiol. 2012;38(3):271-91.