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REVIEWS

Impacts of Biology in Therapeutic Management of Malignant Gliomas

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Abstract | Primary malignant brain tumours are one of the most aggressive forms of human cancer. Gliomas constitute the predominant brain tumours and the current review focuses on the biology and current management of the same. Gliomas can occur anywhere in the neuroaxis across all age groups and usually present with symptoms related to mass effects. Magnetic resonance imaging (contrast enhanced) with newer techniques of MRS and MR perfusion giving several additional information, is the current standard diagnostic imaging modality for presumptive diagnosis of brain tumour and histological evaluation is the gold standard for confirmation and further characterisation. Gliomas are heterogenous group of tumours with varied histological types, different grades and varying biology with molecular mechanisms. For the broader purposes, the gliomas are divided into low and high grades. Presently the accepted molecular markers for prognostication and other management purposes are 1p19q deletion, IDH mutation and O6-methylguanine methyltransferase (MGMT) promoter methylation. Currently, surgery remains the standard first line of management in surgical amenable cases and addition of radiation and chemotherapy in cases of high grade tumours. Chemotherapeutic options in cases of brain tumours are essentially limited due to inability to achieve therapeutic concentration caused by blood brain barrier. There has been a tremendous insights in understanding the molecular biology of these tumours and several targeted therapeutic options have been identified. Some of them are already in clinical trials and next decade or so is likely to crystallize the routine use of some of them in the clinics.

Keywords: *Gliomas, molecular markers, management, targetted therapies*

1 Introduction

Gliomas are the most frequently encountered primary brain tumours in adults. Glioblastoma (GBM), the most malignant form is the commonest primary adult malignant brain tumours, which constitute approximately 70%.[1] The causes of glioma are essentially unknown; exposure to radiation is always considered to be one of the known risk environmental factor. Although there seems to be a surge in reports of increased incidence of gliomas secondary to radiofrequency waves from mobile phones in excessive users, it is not yet unequivocally proven.[2] On the other hand, genetic predisposition to gliomas is well known in some rare familial syndromes (e.g. Type 1 and Type 2 neurofibromatosis due to *NF1* and *NF2* mutations, Li Fraumeni syndrome due to *TP53* mutations, melanoma-astrocytoma syndrome due to *CDKN2A* mutations, tuberosis sclerosis due to *TSC1* and *TSC2* mutations, Turcot syndrome due to mismatch repair genes mutations, and Cowden syndrome due to *PTEN* mutations). However, most gliomas (>90%) show sporadic occurrence, suggesting a complex genetic abnormalities

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combined with unknown predisposing environmental factors.

2 Clinical Presentation

Patients with gliomas usually present with seizures, neurological deficits or features related to raised intracranial tension including projectile vomiting, headaches etc. Malignant gliomas are one of the most malignant forms of human cancer. They are very aggressive, widely infiltrative tumours with limited potential for extracranial metastases. Presently, standard magnetic resonance imaging (MRI) with T1, T2 weighted sequences, fluid-attenuated inversion recovery (FLAIR) and contrast (gadolinium) infusion studies is considered to the standard of diagnostic technique for diagnosing and characterizing brain tumours. Standard MRI diagnostic features for brain tumours include—poor margination hypo-iso-signal T1-weighted and hypersignal T2-weighted sequence suggests brain tumour. Additionally, multimodal MRI is also increasingly used now to provide information about the aggressiveness of the tumours like cellularity, metabolism and angiogenesis, like diffusion-weighted imaging can assess tumour cell density and help in distinguishing from brain abscess; Proton magnetic resonance spectroscopy (MRS) can estimate the proliferation of tumour cells (choline to N-acetyl aspartate ratio) and necrosis (lipids or lactates); perfusion MRI and contrast enhanced studies can give information on angiogenesis. Positron Emission Tomography (PET) with radioactive labeled tracers like ^{18}F-fluorodeoxyglucose, ^{18}F-fluoro-dopa, ^{18}F-fluoroethylthyrosine, ^{11}C-methionine are also recently described advanced imaging modalities to detect residual or recurrence of the tumour, but these modalities are not routinely used.[3] Though in most instances neuroimaging is characteristic, in all feasible circumstances histological confirmation of the tumour is mandatory as sometimes neuroimaging may not be able to distinguish primary from metastases and rarely some form of inflammatory or degenerative diseases.

3 Insights in Pathology

Gliomas are pathologically very heterogeneous group of distinct entities. As per the World Health Organization (WHO) classification, gliomas are classified based on the resemblance of the tumour cells with the native constituent normal glial cells—astrocytic, oligodendroglial, and ependymal tumours. Ependymal tumours predominantly occur in pediatric population with three distinct subsets (though histologically inseparable)—supratentorial, posterior fossa and spinal. Histologically, the accepted grading tiers are I, II and III. Subependymoma and myxopapillary ependymomas are Grade I, as they were not shown propensity to progress (but do have the tendency to recur, especially myxopapillary ependymomas) while others, based the mitotic activity, microvascular proliferation and necrosis are graded II (cellular, tanycytic, papillary and clear cell ependymomas) and III (anaplastic ependymomas) for increasing degree of aggressiveness. As regarding astrocytic tumours, they are two distinct subsets—circumscribed and infiltrative. It is the latter that forms the majority and potentially malignant. The circumscribed tumours are pilocytic astrocytomas, which graded I and occur in children with predilection for cerebellum, optic chaisma and brain stem. They are the commonest glial tumour to occur in setting of familial neurofibromatosis 1. The adult gliomas are infiltrating, hemispheric in location and are more debilitating; histologically are astrocytic, oligodendroglial and oligo-astrocytic. Depending on the degree of differentiation, cellularity, cytological anaplasia, mitotic activity, microvascular proliferation and necrosis, the tumours are graded for aggressiveness into II, III and IV. The Grade III tumours are called anaplastic variants (anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma), and are characterized by increased cellularity and frequent mitoses. Presence of necrosis or microvascular proliferation in pure astrocytic tumours is required for histological diagnosis of GBM; while in case of mixed oliogoastroctyic morphology, both necrosis in significant quantum and microvascular proliferation are essential. Together Grade III and IV tumours comprise the clinical entity of 'malignant glioma'. The low grade infiltrating gliomas progress over time to higher grade and eventually leading to GBM, which are termed as 'secondary GBM' and these constitute only 5–10% of all GBMs. The predominant for is 'primary', which arises de novo and constitute 90–95% of all GBMs.[4] These two distinct subtypes have been shown to have distinct molecular pathogenesis—primary GBM are predominantly PTEN (deletion or mutation; loss of function) and EGFR (amplification; gain of function) genes mediated; while secondary are IDH mutation and loss of TP53 gene mediated.[5] Characteristic rampant cellular proliferation in malignant gliomas are due to derangement of cell cycle regulatory pathways with positive influence of different signal transduction pathways occurring due to multiple accumulated genetic and epigenetic alterations. Necrosis and neoangiogenesis are predominantly mediated by hypoxia inducible factor 1 (HIF-1) through many mechanisms, but the predominant mechanism is VEGF and VEGFR mediated pathway. In addition to the angiogenetic effect, VEGF also mediates the infiltrativenesss of the tumours along with plethora of matrix degrading enzymes, which are thought to be secreted by the tumour cells. Of these, the notable and predominant ones are MMP2 and MMP-9.

4 Progress in Molecular Biology

WHO histomorphological classification is based on subjective criteria, lacks reproducibility, and remains imperfect in its ability to predict individual outcomes.[6] Identification of relevant prognostic and predictive biomarkers in gliomas saw the emergence of a molecularly focused approach and represented a profound shift in the approach to diagnosis and treatment of gliomas. (i) The most important molecular breakthrough in brain tumours is the identification of 1p-19q co-deletion, which can be identified by fluorescence in-situ hybridization (FISH) or loss of heterozygousity by PCR.[7] Tumours that contain this translocation have been associated with an oligodendroglial phenotype, a slower course of progression, and a better response to treatments.[8,9] It is now considered mandatory to determine 1p19q status in all oligodendroglial tumours (ii) O6 –methylguanine methyltransferase (MGMT) promoter methylation is one of the most powerful molecular prognosticator in malignant gliomas and also a very good predictive marker for responsiveness to alkylating chemotherapy in malignant gliomas.[10] (iii) Isocitrate dehydrogenase 1 (IDH1; and in rare cases IDH2) mutations have been found in more than two-thirds of low-grade gliomas and anaplastic gliomas, and in secondary glioblastoma; however, these mutations have only very rarely been found in primary glioblastoma (<10%).[11] An IDH1 mutation is a favourable predictor of outcome whatever the histological type and grade.[10,11] (iv) TP53 mutation and overexpression is typically associated with an astrocytic phenotype, but its prognostic implication is unclear.[4] Conversely, some alterations are strongly linked to high-grade anaplastic gliomas and glioblastoma; these alterations are primarily chromosome 10 loss, CDKN2A deletion, and an EGFR amplification that occurs in up to 45% of primary glioblastoma. Of these in about 50% of cases, EGFR amplification is associated with the expression of a constitutively active mutant of EGFR, termed EGFRvIII, characteristic of primary glioblastoma and has been shown to confer a poor prognosis.[12] Transcriptional profiling studies of mRNA expression profiling using unsupervised hierarchical clustering analysis of GBMs revealed four distinct molecular subtypes—Proneural (amplifications of *PDGFRA*, *CDK6*, *CDK4* & *MET*; *IDH1*, *PIK3CA/PIK3R1* & *TP53* mutations), Classical (*EGFR* amplification, loss of *PTEN* & *CDKN2 A*), Mesenchymal (mutations and/or loss of *NF1*, *TP53* and *CDKN2 A)* and Neural (no unique genetic alterations identified). Proneural group has been shown to have prognostic advantage over others and most of the secondary GBMs are of proneural type.[13] Combined genomic and proteomic analyses focused on receptor tyrosine kinases (RTKs) including EGFR, PDGFRA and MET acting as key driver mechanisms, PTEN and NF1 loss as signal pathways activator mechanisms and mutant IDH as metabolic mechanisms for gliomagenesis.

Gliomagenesis is an extremely unstable genetic process with activation of oncogenes, inactivation of tumor suppression genes and genetic mutations. This results in growth factor over-expression, dysregulation of the signaling pathways and altered biochemical reactions, which in turn enhances cellular proliferation supported by angiogenesis, apoptosis resistance and enhanced DNA repair. This process causes transformation of a normal glial cell to a malignant phenotype.

Table 1: WHO 2007 classification of glial tumours.

• Astrocytic neoplasms
– Pilocytic astrocytoma, SEGA (WHO grade I)
– Pilomyxoid astrocytoma, Pleomorphic xanthoastrocytoma, Diffuse astrocytoma (WHO grade II)
– **Anaplastic pleomorphic xanthoastrocytoma (WHO grade III)**
– **Anaplastic astrocytoma (WHO grade III)**
– **Glioblastoma (WHO grade IV)**
• gliosarcoma
• Oligodendroglial neoplasms
– Oligodendroglioma (WHO grade II)
– **Anaplastic Oligodendroglioma (WHO grade III)**
• Oligoastrocytic tumours
– Oligoastrocytoma (WHO grade II)
– **Anaplastic Oligoastrocytoma (WHO grade III)**
• Ependymal tumours
– Subependymoma, Myxopapillary ependymoma (WHO grade I)
– Ependymomas—cellular, papillary, clear cell and tanycytic (WHO grade II)
– **Anaplastic ependymoma (WHO grade III)**

5 Current Standard Management

Safe maximal resection of the tumour is recommended for all forms of tumours to reduce the

Table 2: Standard care of management for glial tumours.

Glial tumours	Newly diagnosed	Recurrence or progression
DFA, Gr II	Resection and Observation or Resection + RT	Re-resection, if possible + RT/CT
OD & OA, Gr II	Resection and Observation or Resection + CT/RT	Re-resection, if possible + CT/RT
AA, Gr III	Resection + RT/CT	Re-resection, if possible + CT/reRT
AO & AOA, Gr III	Resection + CT/RT/CT+RT	Re-resection, if possible + RT/CT
GBM, Gr IV	Resection + CT+RT	Resection + CT/reRT/ newer targeted therapies

symptomatology related to the mass effect, to increase the efficacy of adjuvant therapies and also probably improves the overall survival. Intraoperative visualization of the tumour (intraoperative MRI or by means of 5-aminolaevulinic acid) can help to maximize the resection of high grade tumours.

For GBMs, following surgery, radiation (60 Gy with 1.8–2 Gy fractions) with concomitant administration of temozolomide (75 mg/m^2 per day) followed by temozolomide (TMZ) of 150–200 mg/m^2, 5 days every 28 days for 6–12 cycles (Stupp's regimen) is standard modality of the first line treatment.[14] In some patients, early MRI can show pseudoprogression, and rarely this can be a clinical presentation.[15] A close follow-up for the same is advised. MGMT methylation status is good predictor of outcome in patients treated with TMZ and its knowledge of the same will help in prognosticating the patients. In very old patients (>70 yrs), radiotherapy alone may be preferred, though not shown to greatly alter the quality of life but increase the median survival by 3 months. The beneficiary role of adding TMZ in older patients is not yet clear.[16] In case of relapse setting, second line chemotherapeutic agents like nitrosoureas will be of benefit. Experience from our centre employing the standard Stupp's regimen in GBM reveal a median overall survival (OS) was 17 months (95% CI 13.6–20.3 range 2–92 months) with 2 and 5 year survival probability of 29% and 11%, respectively.[17]

For anaplastic gliomas, surgery followed by standard dose of radiation; TMZ is generally reserved for progression. For tumours composed of oligodendroglial component, TMZ or PCV is added to radiation for 1p19q codeleted tumours; whereas, 1p19q non-deleted cases should be managed like the anaplastic astrocytomas.

In case of low grade gliomas, radiation of 50–54 Gy is the standard of treatment after surgery, but the timing is variable. For 1p19 co-deleted and IDH mutated tumours (especially histology of oligodendroglial) and symptomatically relieved from surgery, deferring radiation therapy for progression is recommended; while for tumours with no deletion for 1p19q and pure astrocytic tumours, radiation therapy should be administered according to the extent of the residual disease (which has to be elicited by a post operative MRI scanning in all cases). For significant large residual tumours, early postoperative RT increases the median progression-free survival by about 2 years, though it does not affect the overall survival.[18]

6 Biological Based Therapies

In view of poor prognosis of gliomas, especially malignant, and limitations of the available current management protocols lead to exploration of alternative treatment approaches. Better understanding of biology with its variability paved ways for novel forms of target based treatment modalities. Agents targeting the tumorigentic pathways like bevacizumab[19] (targeting VEGF, showed great promise in two large phase III randomised concluded trials and final information is awaited and expected to be ready by early next year), EGFR inhibitors (erlotinib, gefitinib and cetuximab), integrin inhibitors (cilengitide in phase 2 and 3 clinical trials)[20] and many others showed progressing results. VEGF inhibitors generally do not demonstrate their 'anti-angiogenic' effects via a reduction of the tumour blood flow; infact they minimize the nexus of abnormal leaky tumour vasculature resulting in shunting of the blood to the normal host vasculature feeding the tumour. The resultant improved efficiency of blood circulation in turn, decreases hypoxia in the tumour bed, therefore enhancing the sensitivity to radiation and delivery of chemotherapeutic agents. Reduction of vascular permeability leads to reduction of vasogenic oedema, which may improve the patient's steroid dependency and quality of life. Finally, anti-VEGF therapy can disrupt the nurturing perivascular niches around self-sustaining glioma stem cells (GSC) leading to their death. Inspite of encouraging initial benefit from bevacizumab therapy in recurrent GBM, most patients progress and succumb to their disease within 6–9 months.

Clinical trials for cancer stem cell inhibitors[21] like hedgehog inhibitors and γ-secretase inhibitors (targeting Notch pathway), and dendritic cell vaccines are also ongoing and data eagerly awaited.[22] Although encouraging, the newer molecular targeted therapies have not yet met clinical expectations in terms of efficacy and mandates more mature data with greater understanding in the mechanisms of resistance and appropriate clinical studies before considering as a standard of care.

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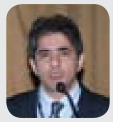

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