Cure Brain Cancer
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Current Knowledge in Brain Cancer Research

Developed for Cure Brain Cancer Foundation
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Introduction

The aim of this descriptive review is to provide a high-level overview of new strategies, developments and milestones in neuro-oncology research with a focus on glioblastoma. The review focuses on describing the current state of research globally, and emerging areas of research that have potential to more immediately improve patient survival and quality of life. This will provide a basis for future, strategic decision making for the Cure Brain Cancer Foundation research program.

The current review (2014) represents an update of the review undertaken in 2011.

Methodology

A broad search was conducted in PubMed using the search terms indicated below (derived from the 2011 review). Inclusion criteria were set to Meta-Analysis, Review, Systematic Review, English, and Cancer. Publication dates were set to Jan 2010 to current (March 2014).

The following search terms were used to identify literature for each of the following subsections.

- (GBM OR glioblastoma glioblastoma multiforme OR brain cancer) AND p53 OR TP53
- (GBM OR glioblastoma glioblastoma multiforme OR oligodendroglioma OR brain cancer) AND 1p OR 19q
- (GBM OR glioblastoma multiforme OR brain cancer) AND (EGFR OR PTEN)
- (GBM OR glioblastoma multiforme OR brain cancer) AND IDH1
- PDL1
- Pilocytic Astrocytomas AND (treatment OR surgery OR radio*)
- (GBM OR glioblastoma multiforme OR oligodendroglioma OR brain cancer) AND (treatment OR surgery OR radio* OR chemo*)
- (Diffuse Intrinsic Pontine Glioma OR DIPG) AND (treatment OR surgery OR radio* OR chemo*)
- CNS Lymphoma AND (treatment OR surgery OR radio* OR chemo*)
- Ependymoma AND (treatment OR surgery OR radio* OR chemo*)
- Medulloblastoma AND (treatment OR surgery OR radio* OR chemo*)
- Meningioma AND (treatment OR surgery OR radio* OR chemo*)
- (Oligoastrocytoma OR Oligodendroglioma) AND treatment OR surgery OR radio* OR chemo*)

Pubmed abstracts were read and relevant reviews sourced. Once relevant literature reviews were sourced and read, additional papers were identified from citations and included if deemed relevant (i.e. snowballing method of literature searching).

A search of the Cochrane Library was made using the following search terms: *brain cancer, brain tumor, brain tumour, GBM, glioma, and glioblastoma*. Five reviews published or updated between 2011 and 2014 were identified.

Aetiology

There is little known about the underlying cause of brain cancer. The only established risk factor is ionising radiation, demonstrated in studies of children receiving cranial irradiation for cancer therapy and *Tinea capitis*, and in individuals exposed to atomic bombs and nuclear weapons testing[1]. A higher incidence has also been observed with increasing age and in men.

A family history of glioma is rarely observed but, when present, is associated with a two-fold increase in the risk of developing glioma. Genome-wide association studies have identified a few susceptibility variants such as 20q13.33 (*RTEL*), 5p15.33 (*TERT*), 9p21.3 (*CDKN2BAS*), 7p11.2 (*EGFR*), 8q24.21 (*CCDC26*), and 11q23.3 (*PHLDB1*), but these genes are only weakly associated with glioma, possibly reflecting multiple molecular subsets. [2]

Having one of the following hereditary disorders may also increase the risk for brain cancer: Neurofibromatosis, Tuberous sclerosis, Von Hippel Lindau disease, Familial Polyposis (Turcot's Syndrome).

There is no established link between an increased risk of glioma and exposure to cell phones and other types of electromagnetic fields, head injury, foods containing *N*-nitroso compounds, aspartame, occupational risk factors, pesticides, or season of birth. [1, 2]

Glioma risk is inversely associated with the presence of atopic diseases such as asthma, eczema, and hay fever.[3] As noted by the authors, 'if the association is causal, it could reflect an effect of heightened immune surveillance on brain tumor development.'

Molecular biology of brain cancer

Introduction

In this section we will outline what has been discovered to date about the molecular causes for each type of brain tumour.

A characteristic of all cancer cells is the presence of multiple changes at the molecular or DNA level. These may include chromosomal aberrations, single DNA base substitutions or mutations, DNA methylation or epigenetic modifications. Molecular changes in tumour cells drive the development and progression of the tumour.[4] Scientists have studied tissue from brain tumours at the molecular level and found that, for example, gene deletions such as the chromosome 1p/19q co-deletion or mutations in proteins such as tumour suppressor p53 are responsible for activating pathways that allow the tumour cells to grow or proliferate out of control. This information is vital as it provides clues for new treatments and could result in targeted therapies directed at the exact tumour type which will be particularly important in the emerging area of personalised medicine.[5, 6] It may also lead to better diagnostic techniques.

Until recently the molecular basis of brain cancer has been very poorly understood, especially compared to other types of cancer. However, in the past few years there has been a global effort to describe and understand the genetic abnormalities present in brain tumours.[7, 8]

Malignant glioma

The most common type of primary malignant brain tumour, accounting for around 70-80% of patients, is malignant glioma. [2]

Within the malignant glioma group, the following subsets & WHO grades have been identified:

- Astrocytoma
  - Grade I Pilocytic Astrocytoma
  - Grade II Diffuse Astrocytoma
  - Grade III Anaplastic Astrocytoma
  - Grade IV Glioblastoma multiforme (GBM)
- Oligodendroglioma

- Grade II
- Grade III Anaplastic Oligodendroglioma

- Ependymomas
  - Grade I Myxompapillary Ependymomas
  - Grade II Ependymoma
  - High-grade Anaplastic Ependymoma
- Mixed Oligoastrocytomas
- Other

The molecular causes of malignant glioma are highly variable or 'heterogeneous' between individual patients[2], even within each subset [9]. At present, with the advent of new technologies such as next generation sequencing and proteomics, the classification of malignant gliomas is changing as more information about the molecular changes occurring at each step of the tumorigenesis process comes to light. [10]

Glioblastoma

Glioblastoma accounts for 82% of cases of malignant glioma. [2] In approximately 90% of cases, glioblastoma (or WHO Grade IV astrocytoma, glioblastoma multiforme, GBM) arises '*de novo*', without evidence of a progressive pathway or precursor lesions; this is termed primary glioblastoma (

Figure 1). Primary glioblastoma tends to occur in patients over 45 years. In patients under 45 years a progressive pathway from astrocytoma (WHO Grade II), to anaplastic astrocytoma (WHO Grade III), and then to secondary glioblastoma (WHO Grade IV) is typical. Secondary glioblastoma accounts for approximately 10% of cases (

Figure 1).

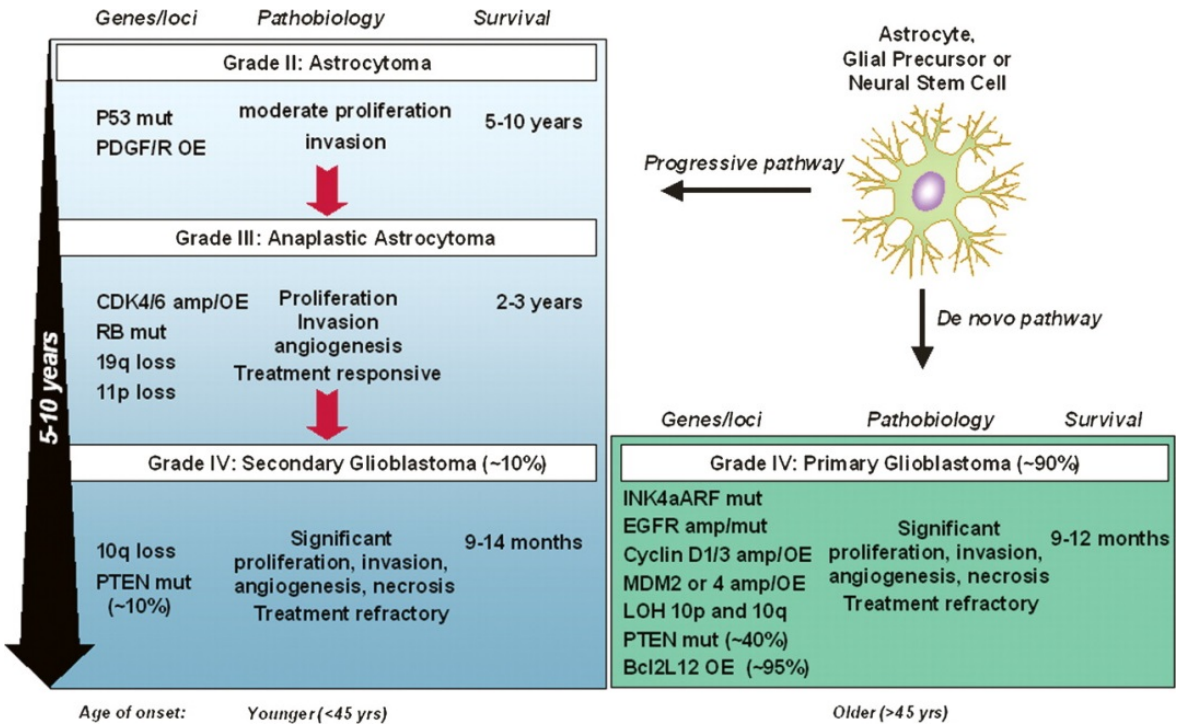


Figure 1. Explanation of the molecular pathways involved in glioblastoma. Adapted from Furnari *et al* 2007, Ref: [11]

It has been observed that in glioblastoma tumours, a higher number of genetic aberrations tend to be linked to shorter survival time. [8] There is typically a high level of chromosomal

instability in glioblastoma tumours and structural abnormalities and changes in the number of chromosomes are common.

Primary glioblastoma

There are many molecular or genetic pathways that may result in primary glioblastoma pathogenesis; however the most frequent can be grouped into: the p53 pathway, the RB1 pathway, the MAPK pathway and the P13K pathway. [12] The Cancer Genome Atlas Research study used integrated analyses of multi-dimensional genomic data to identify deregulation of the RB, p53 and RTK/RAS/PI(3)K pathways as a requisite events in the pathogenesis of most, if not all, glioblastoma tumours.[4]

p53 pathway

Tumour suppressor p53 is a protein encoded by the chromosome 17p gene TP53. The protein is mutated in around 50% of all human cancer tumours and is responsible for the transcription of multiple genes involved in carcinogenesis signalling pathways.[13] [14] For example, the p53 protein is responsible for the transcription of genes involved in apoptosis, angiogenesis, DNA repair, metabolism and oxidative stress. [14]

Wild-type p53 is a 393 amino acid protein with four domains. Around 95% of all known p53 mutations are found in the DNA-binding domain. There are known p53 hotspot mutation spots at codons 175, 245, 248, 249, 273, and 282 accounting for 28 % of p53 mutations. The exact site of the mutation significantly affects protein action on multiple genes and may result in either up regulation or down regulation, for example mutant p53 is responsible for the up regulation of production of epidermal growth factor receptor (EGFR) and down regulation of the phosphatase and tensin homolog protein (PTEN).

Mutations that occur in the part of the p53 protein involved in DNA binding (codons 248 and 273) are known as class I mutations. Those that occur in areas that are critical to the conformational structure of the DNA binding interface are class II mutations (codons 175, 245, 249 and 282). Class II mutations generate a more severe pathological phenotype than class I mutations (Table 1).

In glioblastoma the most commonly observed alterations to the p53 pathway include p53 mutations (30%), ARF deletions (55%), MDM2 amplification (11%), and MDM4 amplification (4%). [4] These disruptions to the p53 pathways are observed in 78% of glioblastoma tumours implying a pivotal role for p53 in disease progression. [4]

P53 also plays a pivotal role in regulating stem cell proliferation, survival and differentiation. The presence of cancer stem cells and stem cell markers, including CD133 and nestin, in glioblastoma tumours has been observed; both are markers for prognosis.[15]

In recent studies, micro-RNAs transcribed from p53 have been shown to alter the expression of genes involved in cell cycle arrest, apoptosis and cellular senescence. Micro-RNAs are small RNA sequences (19-25 nucleotides). In glioma tumours, the micro-RNA-34 family is frequently dysregulated. One study showed that miR-34a was down-regulated in glioma compared to normal brain tissue. In contrast, up-regulation of miR-34a was shown to reduce glioma proliferation, induce apoptosis and limit tumour growth.

In paediatric tumours mutations of the p53 gene are also common with an incidence of between 35–50% which is comparable to the incidence in adult tumours. A specific p53 mutation of amino acid number 72 (Arginine to Proline) is common in both adult and paediatric astrocytomas. [13]

The effects of different p53 mutations on glioblastoma are summarised in Table 1.

Although there is a large body of knowledge regarding tumour suppressor p53, limited progress has been made towards prognostic and therapeutic approaches in glioblastoma. Considerable research efforts are still required into how p53 mutations impact glioblastoma pathogenesis. [14]

Table 1. p53 mutations and effects on GBM. Adapted from England *et al.* 2013, Ref: [14]

Mutation type	Description	Impact on GBM
Effects of p53 mutation		
Loss-of-function	Loss of growth-inhibitory effects that are normally induced by wild-type p53	Unknown, thought to play the most important role of p53 in cancer as whole
Gain-of-function	Upregulation of a distinct subsets of genes from wild-type p53, retention of some nuclear and cytoplasmic functions independent of gene transcription	Mutations to heterogeneous to make conclusions, upregulation in GBM specifically of JAK2, C3ORF26, FRMD5, CYFIP2, NRG1, PPARGC1A, and TMEM108
Dominant-negative	Mutant p53 tetramerize with wild-type p53 and downregulation of anti-tumorigenic wild-type p53 activity	Unknown, thought to play the most important role of p53 in cancer as whole, younger onset of sporadic GBM in dominant-negative (30.4±14.7 years) compared to recessive (55.2± 18.6 years) mutations or wild-type p53
Codon-specific mutation		
Class I mutants	Hotspot mutations (codons R248 and R273) in the p53 DNA-binding domain that interrupt the p53 protein-DNA interface, more amenable to small molecule treatments that normalize p53 structure than class II mutants	Not evaluated in GBM
Class II mutants	Hotspot mutations (codons R175, R245, R249) in the 53 DNA-binding domain that interrupt the p53 protein structure	Not evaluated in GBM, variability in tumor response and formation with codon 175 mutations (R175L vs. R175H vs. R175P) in mouse models of lymphoma and carcinoma
Other important aspects to p53 mutation		
Mutations of p53 signaling pathways	Inactivation of other pathway signaling molecules and cross-feedback loops can influence p53 mutations, single-nucleotide polymorphisms of pathway genes may also play important roles	Mutations of MDM2, MDM4, or p14/ARF are seen in 78 % of GBMs
p53 isoforms, p63, p73	Isoforms of p53 and homologous molecules (p63, p73) that can influence p53 signaling pathways	Increase promoter methylation of p63 and p73 correlate with increased tumor grade, p63 and p73 influence neural stem cell self-renewal and development
Mutations of microRNAs (miR)	19-25 nucleotide non-protein-coding small RNA sequences that downregulate mRNA genes	miR-34a is transactivated by p53, downregulated in glioma compared to normal brain, and downregulated in glioma with mutant p53, upregulation of miR-34a reduced glioma proliferation

RB1 pathway

The retinoblastoma protein (RB1) is a tumour suppressor protein encoded by the gene Rb on chromosome 13. This protein is of central importance in cell cycle regulatory processes.

Another gene, CDKN2A (also called INK4a/ARF), which is deleted in many cancers including glioblastoma, encodes the protein p16. This protein is a key inhibitor of the cell cycle via RB1 pathway signalling.[4, 16]

One study showed 77% of tumour samples harboured RB pathway aberrations with chromosome 9 deletions of CDKN2A (55%), CDKN2B (53%) and CDK4 (14%). [16]

Hypermethylation-mediated silencing of RB1 and CDKN2A is a common observation in primary glioblastoma. [16]

PI3K & MAPK pathways – EGFR

Over-expression of the Epidermal Growth Factor Receptor (EGFR, also called oncogene ErbB, ErbB1, HER1) is a feature of approximately 60% of primary glioblastoma tumours. [17]

EGFR is a transmembrane protein encoded on chromosome 7 that belongs to the tyrosine kinase superfamily. There are two EGFR protein products or 'isoforms' and upon ligand binding, the receptor converts from an inactive form to an active dimer comprised of either two EGFR monomers paired together (homodimeric form) or EGFR paired with another EGFR family member (such as HER2, HER3, or HER4 (heterodimeric form). [18]

EGFR activation, following ligand binding and phosphorylation of the intracellular tyrosine kinase domain, initiates signal transduction [19]; the downstream signalling pathways include the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K/Akt) and the SRC/FAK pathways.[17, 18, 20] Activation of these signal transduction cascades leads to increased cell proliferation, angiogenesis, and reduced apoptosis.

Approximately 10 different glasses of EGFR mutations that commonly occur in glioblastoma tumours have been described. Missense mutations in the EGFR extracellular domain are found in approximately 7% of primary glioblastoma tumours. [18] Mutations or amplifications of the EGFR gene play a key role in many cancers and are commonly seen in primary and rarely in secondary glioblastoma. [17, 21] EGFRvIII is the most frequently observed variant (present in 24-67% of tumours).[19, 22] [20] EGFRvIII has a large portion of the extracellular domain absent, due to a deletion in exons 2-7 of the gene. Despite the deletion, EGFRvIII can still dimerise and phosphorylate, and is therefore still active; studies have shown this variant EGFR form can enhance cell growth, increases PI3K activity and is oncogenic. [7, 20]

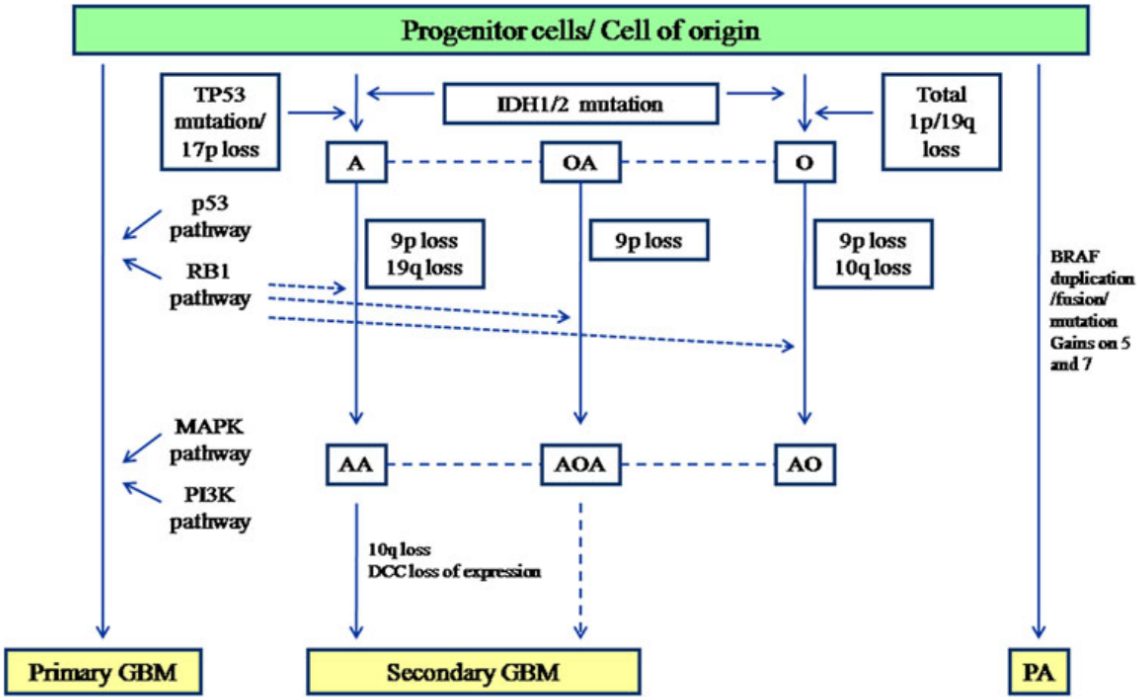
There is evidence that EGFRvIII is a marker for poor prognosis. [18] Although this variant is commonly observed and has been widely studied, the exact mechanism by which the mutation confers oncogenicity is still to be fully understood. [18]

Secondary glioblastoma

For secondary glioblastoma the most frequent pathways and genetic alterations include:[12]

- TP53 mutation and/or loss of chromosome 17p,
- IDH1 and IDH2 mutations
- loss of chromosomes 1p, 9p, 19q, 10q alone or in combination
- RB1 pathway aberrations
- PTEN mutation.

Figure 2. Common pathways to secondary glioblastoma. Adapted from Gupta *et al* 2012, Ref: [12]



TP53/17p loss

The p53 pathway has been described in detail for primary glioblastoma (see previous section). The gene TP53 is located on chromosome 17p.

Chromosome 10q

Chromosome 10q losses are present in over 80% of glioblastoma tumours and are common to both primary and secondary glioblastoma. [23] PTEN is a gene located on chromosome 10q23 encoding a protein phosphatase. [24] MGMT is also located on chromosome 10q26 (see below). Loss of chromosome 10 is less common in anaplastic astrocytoma, which implies that loss of heterozygosity (LOH) is a late step in the pathway to glioblastoma development.[25] LOH on chromosome 10q is associated with reduced survival and may be a useful prognostic indicator. [24, 26]

PTEN

Phosphatase and tensin homologue (PTEN; also known as MMAC phosphatase) is a tumour suppressor and the gene (located on chromosome 10q) is frequently mutated in multiple human cancers, including prostate and breast cancer. PTEN encodes a 403 amino acid protein with phosphatase activity and is a negative regulator of the PI3K/Akt pathway.[27, 28]

PTEN also regulates p53 protein levels. PTEN has three phosphorylation sites located at Ser380, Thr382, and Thr383 and these regulate stability and influence the activity of the enzyme. PTEN plays an important role in regulating cell growth by regulating kinases, such as PI3K, and subsequently AKT.

In mouse models, deletion of the PTEN gene in astrocytoma cell lines increased cell proliferation. In glioblastoma cell lines lacking PTEN, re-introduction suppressed cell proliferation. [20] PTEN is also likely to be involved in cell migration, survival and tumour invasion. [20]

PTEN is either lost due to LOH of chromosome 10q in 50%–70% or aberrant due to mutations in 14%–47% of primary glioblastoma cases. LOH of chromosome 10q is also observed in 54%–63% of secondary glioblastoma. PTEN may be a useful predictive biomarker of glioma response to specific therapies. [20, 24]

Recent studies have shown 7% of anaplastic astrocytomas harboured PTEN mutations but they were absent in low-grade gliomas. There is also evidence to suggest that PTEN loss does not promote tumour growth early in glioblastoma tumour development and is more likely to be linked to heightened invasiveness. [24]

PTEN may also be a useful marker of drug efficacy. A recent study found an association between tumours that expressed the variant EGFRvIII but still had functional PTEN and sensitivity to EGFR inhibitor monotherapy.[20]

Mouse studies have also shown that deletion of both p53 and PTEN in the central nervous system results in an acute-onset high-grade malignant glioma phenotype resembling human primary glioblastoma. [29]

MGMT

The MGMT gene is found on chromosome 10q26 and encodes the DNA repair enzyme O-6-methylguanine-DNA methyltransferase.

In tumour cells the MGMT is often silenced by binding of a methyl group to the promoter CpG rich sites. Silencing of the gene results in a lack of expression of the DNA repair enzyme, and therefore promotes tumour development. Approximately 40-50% of primary glioblastoma tumours [10, 19] and 70% of secondary glioblastoma tumours display epigenetic MGMT silencing. [10] MGMT silencing is also a common feature of 50% to 80% anaplastic gliomas. [16]

Silencing of MGMT enables use of alkylating agents such as temozolomide (TMZ). When MGMT is functioning, such agents are of limited use as the DNA repair enzyme counteracts their functionality. TMZ acts by damaging DNA via addition of a methyl group at the O-6 position; when MGMT is silenced in glioblastoma, this is allows tumour specific action. [10] TMZ induced alkylations lead to DNA damage in the tumour cells, including DNA double strand breaks and mismatches, that in turn cause apoptosis and cytotoxicity in tumour cells. [30]

MGMT silencing through methylation is a prognostic factor for glioblastoma. In anaplastic gliomas, MGMT methylation is a marker of more favourable prognosis, irrespective of the treatment course chosen. There is also evidence that in secondary glioblastoma MGMT methylation may be associated with TP53 mutations, particularly G:C to A:T transition at CpG sites. [16]

Epigenetics

Epigenetic alterations (changes in gene activity that are not caused by changes in the DNA sequence) have been linked with all cancer types and are now recognised to be as important to cancer formation as are gene mutations. Unlike mutations, however, epigenetic states can be altered, and epigenetic therapies hold promise as anti-cancer agents. Most of these aberrations, mainly those involving DNA methylation and deacetylation of histones, change gene expression and genome stability through regulation of local chromatin structure. Recent data suggest that early epigenetic changes occur during tumorigenesis and that they may predispose progenitor cells to further molecular changes that are involved in tumor promotion. [16]

Hypermethylation is not limited to MGMT; many other complex epigenetic mechanisms contribute to the pathways that result in glioblastoma tumours. Hypermethylation of CpG island of gene promoters results in epigenetic-mediated inactivation of many genes associated with tumour suppression (e.g. RB1), cell cycle regulation (e.g. CDKN2A), DNA repair (e.g. MGMT), tumour invasion and apoptosis. [16]

In tissue from a glioblastoma tumour, hundreds, or even thousands of genes are subject to methylation at the CpG island promoter. In a subset of glioblastoma cases, hypomethylation or a reduction in methylation has been observed.[16]

IDH1/2 mutations

Isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) are enzymes that catalyse the oxidative decarboxylation of isocitrate to a-ketoglutarate. The genes for the enzymes are located on chromosomes 2q and 15q respectively. Mutated IDH1 or IDH2 have significantly reduced enzymatic activity.[31]

Around 90% of all IDH1 mutations single nucleotide transition (G to A) at codon 132 resulting in an amino acid change from arginine by histidine. IDH2 mutations in glioblastoma tumours tend to be at the arginine 172 location. [19]

IDH1/2 genes are mutated in 50–80% of astrocytomas, oligodendrogliomas or oligoastrocytomas of grades II and III, and secondary glioblastomas. [32] However, IDH1/2 genes are not usually mutated in primary glioblastoma. Tumours with IDH1/2 mutations always have co-existing TP53

mutations or total 1p/19q loss, suggesting a common origin. Interestingly, IDH1/2 mutations are rare in other human cancers.[32]

Survival is improved for patients with IDH-mutation positive tumours. The exact mechanism by which IDH1/2 mutations contribute to the development of glioblastoma tumours has not been elucidated.

Chromosome 1p/19q co-deletion

Deletions of chromosome 1p and 19q are rare in glioblastoma tumours, occurring in less than 10% of cases. However, LOH or co-deletion of 1p/19q is a frequent observation in oligodendroglioma tumours and is associated with favourable treatment response to first line chemotherapy and improved survival. [24]

Losses of 1p and 19q have been observed in approximately 90% of oligodendroglioma tumours, 50–70% of anaplastic oligodendroglioma, 30–50% of oligoastrocytoma and 20–30% of anaplastic oligoastrocytoma. [10]

The exact mechanism by which the 1p/19q co-deletion confers tumorigenicity is yet to be fully elucidated. Mutations that cause inactivation of the CIC gene, located on chromosome 19q, and the FUBP1 gene, located on chromosome 1p, have been observed in many oligodendroglioma tumours. [10]

MiRNAs

MicroRNAs (miRNAs) are small lengths of RNA that are 18-25 nucleotides long that are involved in the regulation of gene expression. [16, 33]

The importance of miRNAs in the development of human cancers is a relatively new finding and mounting evidence suggests that miRNA levels are critical in development of tumours.

Dysregulation of miRNAs has been observed in glioblastoma [24] with acquired TMZ resistance. In a study of miRNAs from 480 glioblastoma tumour samples The Cancer Genome Atlas dataset high levels of miRNA-326/miRNA-130a and low levels of miRNA-323/miRNA-329/miRNA-155/miRNA-210 were associated with improved survival. Levels of both miRNA-323 and miRNA-329 were higher in patients with no recurrence or a longer time to progression. [24]

Stem cells and stem cell markers

There is evidence that cancer stem cells may play an important role in tumour development. Brain tumour stem cells are predicted to be critical drivers of tumour progression because of their self-renewal capacity and limitless proliferative potential. Studies suggest that stem cells are controlled by a particular microenvironment known as a "niche" and that the abundance of niches increases significantly as tumour grade increases [34].

Recent findings show that cancer stem cells may contribute to the resistance of malignant gliomas to chemo and radiotherapy. [24] The mechanisms of radioresistance are not completely understood, however, cancer cells with an immature stem-like phenotype are hypothesised to play a role in radioresistance as a result of the preferential activation of DNA-damage-response pathways [35].

The sensitivity of glioma stem cells to standard chemotherapy is controversial as current literature presents conflicting experimental data. Chemoresistance results partly from the overexpression of O^6-methylguanine-DNA methyltransferase (MGMT), as well as extrinsic factors that may also contribute to the resistance of glioma stem cells to TMZ, including TMZ concentrations in the brain parenchyma, dosing schemes, hypoxic microenvironments, niche factors, and the re-acquisition of stem cell properties by non-stem cells [36].

The CD133 epitope has been identified as a marker for glioblastoma stem cells may lead to treatments that can target these cells specifically. [24]

There is some evidence that tumours with higher populations of cancer stem cells confer decreased overall and progression-free survival. It has not yet been elucidated as to what cells what the cancer stem cells are derived from. [19]

VEGF

Angiogenesis is the process of new blood vessel formation and is a critical process in the growth of many solid tumours including gliblastomas. Tumour cells release pro-angiogenic factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet derived epidermal growth factor (PDGF), and SF/HGF. [37]

VEGF is considered to be a key driving factor in angiogenesis and has been identified in around 64% glioblastomas. A correlation between VEGF expression and survival time has been reported suggesting that VEGF may be a useful potential prognostic marker. [24]

Pilocytic astrocytoma

Pilocytic astrocytoma is the most commonly occurring paediatric brain tumour accounting for 23.5% of childhood CNS malignancies. [38]

Approximately 20-30% of pilocytic astrocytoma (PA) tumours [39] harbour neurofibromatosis 1 (NF1) mutations. The NF1 gene is found on chromosome 17q11.2 and encodes neurofibromin, a protein with an active region homologous to the catalytic domain GTPase-activating protein. [40]

For Grade I pilocytic astrocytoma BRAF duplication or mutation and gains on chromosomes 5 and 7 are commonly observed. In sporadic pilocytic astrocytoma tumours analysis has shown that between 53%–88% of cases have focal chromosomal gains on chromosome 7q34. The mutations are often caused by a tandem duplication that causes fusion of BRAF with the KIAA1549 gene and activation of the BRAF gene. [38]

Biology of other tumour types

CNS Lymphoma

Primary CNS lymphoma (PCNSL) is an aggressive brain tumour that accounts for 4% of intracranial neoplasms. [41] About 90% of PCNSLs are diffuse large B-cell lymphomas the remainder have Burkitt (5%), lymphoblastic (5%), marginal zone (3%) or T-cell lymphoma histotypes (2–3%). [41, 42]

PCNSL tumours have a high number of somatic mutations and the IGHV4-34 gene is rearranged in 50%–80% of cases. Mutations at known oncogene or tumour suppressor gene loci such as CD95, CMYC13, PAX5, PIM1, PRDM114, and TTF have also been observed. [43]

Diffuse Intrinsic Pontine Glioma (DIPG)

Diffuse intrinsic pontine glioma (DIPG) is a rare, aggressive tumour that primarily affects children. DIPG arises in the glial tissue of the lowest, stem-like part of the brain which controls many of the body's most vital functions. [44]

Until recently the understanding of the molecular biology of DIPG has been poor due to a lack of biopsy tissue because of concerns over morbidity resulting from biopsy methods that have since been discounted. [45]

Recent studies have shown increased EGFR expression in correlation increasing tumour grade. Around 27-40% of DIPG samples exhibited overexpression of EGFR. Chromosome 7 polysomy, has also been reported in 25% of DIPG samples. Amplification of the PDGFRa gene in 36% of samples and the PARP-1 gene in 27% has also been observed in other studies. PTEN loss was also a common observation in DIPG samples. [45]

Ependymoma

Ependymomas may originate from ependymal cells (which line the ventricles of the brain and the center of the spinal cord) or from radial glial cells (cells related to early development of the brain). These are relatively rare tumours.

Both tenascin C, an extracellular matrix molecule, and a copy gain of chromosome 1q, are predictors of poor survival in intracranial ependymoma. [46]

Patients with ependymoma tumours can be divided into two broad subsets, one group, consisting of over 50% of all patients, tends to be younger and have laterally located tumours.

Metastases occur in about 80% of these patients and relapse is more common. Chromosomal anomalies tend to be absent in this group, but activation of EGFR, MAPK etc is apparent. [46]

In the second group of patients, chromosomal anomalies are typical and activation of ciliogenesis and microtubule is observed. [46]

Subependymomas are benign tumours of the central nervous system that usually occur in the ventricular spaces, usually the fourth or lateral ventricles. Their true incidence is unknown as they are often asymptomatic but studies have estimated subependymomas make up 0.2-0.7% of all intracranial tumours. Studies have suggested that chromosomal copy number abnormalities may be involved in the pathogenesis of subependymoma, but further research is needed. [47]

Medulloblastoma

Medulloblastomas are located in the cerebellum and are fast-growing, high-grade tumours which frequently spread to other parts of the central nervous system. Medulloblastomas account for 12-25% of all childhood CNS tumours and are rare in adults.[48-52]

Medulloblastomas are classified as grade IV lesions by the WHO. There are at least 7 different histological subtypes described, with the most commonly occurring classical, accounting for 80%, and desmoplastic, accounting for 15%. [48, 53, 54]

There is a large body of research devoted to understanding the molecular biology of medulloblastoma. [55] Disruption of embryogenesis pathways involved in cellular proliferation and differentiation, chromosomal amplifications and deletions, and association with viral infection, such JC virus and human cytomegalovirus, have all been implicated as playing a role in pathogenesis. [55]

In medulloblastoma frequent gene deletions in pathways involving cell signally are observed such as Sonic Hedgehog, Wnt, Notch and Myc. [48] Up to 40% of medulloblastomas show c-Myc overexpression. [56]

The most common chromosomal aberration is loss of 17p which is observed in around 50% of medulloblastomas. Gains of 17q and 7q copies are also frequently observed. [56]

Meningioma

Anaplastic or malignant meningiomas (grade III) and papillary meningiomas are malignant and tend to invade adjacent brain tissue.

Around 40-80% of meningiomas exhibit loss of chromosome 22q12 a region that encodes the NF2 gene. NF2 produces the Merlin protein which is thought to regulate of cell-to-cell contact and motility. Around 50% of sporadic meningiomas show mutations of the NF2 gene. [57]

Additional copies of the platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR) are also frequently observed in meningiomas. In 5-15% of patients multiple meningiomas occur and people with neurofibromatosis type 2 are at increased risk. There is also evidence that previous radiation to the head or a history of breast cancer may increase a person's risk of meningioma. [57]

Progression of meningiomas is associated with many alterations at the molecular level such as loss of tumour suppressor genes and hypermethylation of CpG islands. Progesterone, androgen and oestrogen receptors are a commonly observed feature of meningiomas. [57]

SMARCB1 mutation may play a role in tumour initiation for multiple meningiomas in familial cases and recently a new susceptibility locus for meningioma has been identified at chromosome 10p12, an area that encodes the MLLT10 gene.[58]

Oligoastrocytoma

An oligoastrocytoma (WHO grade II) contains both abnormal oligodendroglioma and astrocytoma cells and is considered a low-grade tumour. Oligoastrocytoma growth to some extent depends on the relative percentages of astrocytoma and oligodendroglioma cells in the tumour, as astrocytomas tend to grow more rapidly.

Oligoastrocytomas are chemosensitive, with around 70% responding to PCV chemotherapy. [59] Studies have also shown that loss of chromosomes 1p and 19q predicts response to

chemotherapy and prognostic value being associated with increased survival time. [60] Inactivation of the TP53 gene is observed in approximately 50% of astrocytomas. WHO grade II astrocytoma (low grade astrocytomas, LGA) is associated with two common genetic alterations inactivation of the TP53 tumour suppressor gene and loss of chromosome 22q. [61]

Oligodendroglioma

Oligodendrogliomas, WHO grade II and III, are rare accounting for only approximately 2% of primary malignant brain tumours. [62]

The 1p/19q co-deletion is a common feature occurring in approximately 90% of oligodendroglioma tumours. [10] Mutations in IDH-1 and IDH-2 are also common. [62, 63]

Capicua homolog (Drosophila) (CIC) is a large gene located on chromosome 19q13 that encodes a HMG-box transcriptional repressor downstream of the MAPK signalling pathways. Research has shown that it is mutated in around 70% of oligodendrogliomas harbouring the 1p/19q co-deletion but only 7% of oligodendrogliomas without the 1p/19q deletion. [62]

Another large gene, the Far Upstream element Binding Protein 1 (FUBP1) located on chromosome 1p31 has significance in oligodendroglioma molecular biology. The FUBP1 gene encodes a DNA helicase acting as a transcriptional modulator of c-myc oncogene expression. The FUBP1 gene is mutated in 15% of oligodendrogliomas harbouring the 1p/19q co-deletion but is absent in those without the 1p/19q deletion. Research has shown that 75% of FUBP1 mutations occurred in oligodendrogliomas already harbouring the CIC-mutation. [62, 64]

Detection, diagnosis and prognosis

Symptoms

The presenting symptoms of gliomas are determined by several factors including the tumour's size, location and rate of growth.

Common symptoms in patients presenting with a primary brain tumour include: headache nausea/vomiting, cognition changes, personality changes, gait imbalance, urinary incontinence, hemiparesis, aphasia, hemi-neglect, visual field defect, and seizures.[2, 65]

Headaches are relatively frequent, presenting in about 50% of patients at diagnosis, but usually with a nonspecific pain pattern; progressive severity, unilateral localisation, and new-onset headache in a patient older than 50 years are some of the features that may distinguish a tumour-associated headache from a benign headache.

A case-controlled study examined the issue of patients presenting in the primary care setting who were subsequently diagnosed with brain cancer. The study demonstrated that the predictive value of any given symptom, or multiple symptoms, commonly associated with brain tumours is very low. New-onset seizures, had the stingiest predictive value of 1.2%, meaning over 98% of patients with new-onset seizures did not have an underlying brain tumour. And the likelihood of a brain tumour being the underlying cause of headaches is less than one in one thousand.[66, 67]

Cognitive difficulties and personality changes may develop and are often mistaken for psychiatric disorders or dementia, particularly in elderly individuals. Gait imbalance and incontinence may be present, usually in larger tumours with significant mass effect. Focal signs such as hemiparesis, sensory loss, or visual field disturbances are common and reflect tumour location. Occasionally, the development of symptoms is rapid, mimicking a stroke. Language difficulties may be mistaken for confusion or delirium. Seizures are the presenting manifestation in about 20% to 40% of patients, and usually a focal onset is reported.[2]

Current Australian guidelines make the following key points[65]:

- A patient with new onset or recurrent headache uncharacteristic for that patient should also be imaged, particularly if there are focal neurological symptoms and signs

- Patients presenting with a first seizure should have adequate neuro-imaging with MRI
- All patients who present with focal neurological symptoms (such as hemiparesis, dysphasia, dysarthria, neglect, hemianopia, dressing apraxia) require neuro-imaging to establish the cause of these symptoms

Radiology/Imaging

The aims of imaging of brain tumours are primarily to diagnose or refine a suspected diagnosis, and then to optimally localise and characterise them. It is important to assess for potentially life-threatening changes that may necessitate the use of more emergent treatment. An imaging diagnosis of a brain tumour may be the result of the assessment of a clinical syndrome.

Over the past three decades, there has been a change from invasive techniques which often demonstrated tumours by indirect means, to advanced cross-sectional imaging modalities which now directly illustrate these lesions. Computed tomography (CT) and magnetic resonance imaging (MRI) currently form the mainstay of brain tumour imaging. MRI has largely replaced CT scanning in the management of patients with brain tumours, with CT only used in initial imaging and in monitoring acutely changing neurological symptoms.

MRI has the benefit of being more specific and sensitive than CT, particularly in the context of evaluating non-enhancing lesions. MRI can also generate images in three planes (axial, coronal and saggital), whereas CT generates images only in the axial plane. MRI imaging modalities including MR spectroscopy, perfusion imaging and diffusion scanning; all of which are beneficial in differential diagnosis of other high grade gliomas, such as, anaplastic astrocytoma and anaplastic ependymoma, primary CNS lymphoma, metastatic tumours, brain abscess and other neurologic processes. [68, 69]

Nevertheless, while both imaging techniques like reveal morphological information, they are limited in their potential to assess specific and reproducible information about biology and activity of the tumour.

More recently, the use of molecular imaging with Positron Emission Tomography (PET) has been investigated in neuro-oncology. The advantage provided by PET is the ability to provide additional metabolic information of the tumour, for patient management as well as for evaluation of newly developed therapeutics [70]

The use of PET with radiolabelled glucose and amino acid analogues aids in the diagnosis of tumours, differentiates between recurrent tumours and radiation necrosis, and guides biopsy or treatment. 11C-methionine (MET) is the most popular amino acid tracer used in PET imaging of brain tumours. Because of its characteristics, MET PET provides a high detection rate of brain tumours and good lesion delineation.[71] The emergence of new fluorinated amino acid tracers such as [18F]Fluoroethyl-l-tyrosine (FET) will likely increase the availability and utility of PET for patients with primary brain tumours. PET can characterise brain tumours by investigating other metabolic processes such as DNA synthesis or thymidine kinase activity, phospholipid membrane biosynthesis, hypoxia, receptor binding and oxygen metabolism and blood flow, which will be important in the future assessment of targeted therapy. [72]

Note, there is an inherent problem with constructing evidence-based guidelines in radiology, in part because of the rapidly evolving technology in CT, MRI, PET, and also nuclear medicine techniques [65]

Most recently, novel aptamer substrates are being used detect tumour cells circulating in peripheral blood to improve early detection and/or monitoring residual disease after treatment. Aptamers are small single-stranded nucleic acids that fold into a well-defined three-dimensional structure. They show a high affinity and specificity for their target molecules. Research has shown that anti-EGFR RNA aptamer substrates can specifically recognise, capture, and isolate both human and murine GBM cells expressing wild-type EGFR and mutant EGFRvIII with high sensitivity and specificity. [73]

Pseudoprogression

Pseudoprogression is the term used for the changes observed after radiotherapy that mimic tumour progression. When concomitant radiotherapy plus TMZ became the treatment of choice for malignant glioma, the incidence of pseudoprogression increased. [74-76]

Pseudoprogression is a sub-acute reaction that results in oedema, inflammation and increased vessel permeability giving rise to increased contrast on MRI. This effect is found to decrease, or at least stabilise, over time and occurs more often in those with methylated MGMT promoter tumours.[2] Distinguishing tumour recurrence from pseudoprogression and radiation necrosis, is a frequently encountered difficulty in glioblastoma treatment. [77]

Prognosis

When considering the prognosis of a patient with glioblastoma a number of factors need to be taken into account including: [78]

- Positive predictors
  - Age (<60 years)
  - Pre-operative Karnofsky Performance Status (KPS) score (>70)
  - Gross total resection
  - Combined radiotherapy and chemotherapy
  - Reoperation
- Negative predictors
  - Older age (>60 years)
  - Ki-67 overexpression
  - Incomplete resection
  - Large tumour size (>4cm)
  - Location (paraventricular & crossing midline)
  - No combined radiotherapy and chemotherapy
  - Post-operative complications

A recent review by Chaudhry et al. (2013) found that the strongest consistent predictors of survival are the age of the patient and the preoperative Karnofsky Performance Status (KPS) score.[78]

In addition, potential biomarkers may also provide information about prognosis particularly in relation to responsiveness to chemotherapeutic agents (Table 2 & Table 3). [24, 79]

Table 2. Molecular and metabolic alterations in GBM and their potential biomarker status. Adapted from McNamara et al 2013, Ref: [24]

Molecular/metabolic alteration	Possible biomarker status
O(6)-methlyguanine-DNA-methyltransferase (MGMT) promoter methylation	Prognostic, predictive
Loss of heterozygosity chromosome 1p 19q	No prognostic significance
Loss of heterozygosity 10q	Prognostic
Isocitrate dehydrogenase (IDH) mutational status	Prognostic
Epidermal growth factor receptor (EGFR)	Prognostic
Epidermal growth factor, latrophilin, & 7 transmembrane domain-containing protein 1 on chromosome 1 (ELTD1)	Diagnostic, potentially prognostic
Vascular endothelial growth factor (VEGF)	Potentially prognostic
Tumor suppressor protein p53	Diagnostic
Phosphatase and tensin homolog (PTEN)	Prognostic, possibly predictive
p16INK4a gene	Inconsistent findings
Cytochrome c oxidase (CcO)	Potentially prognostic

Phospholipid metabolites	Potentially predictive
Telomerase messenger expression (hTERT messenger ribonucleic acid [mRNA])	Potentially diagnostic, prognostic
microRNAs (miRNAs)	Diagnostic, prognostic
Cancer stem cell markers	Potentially prognostic

Table 3. Prognostic/predictive molecular markers in high-grade gliomas. From Masui et al 2012, Ref: [10]

	MGMT *methylation*	IDH1/2 *mutation*	*1p/19q codeletion*	*EGFR and PI3K pathway**	*p53 pathway mutation*	*Rb pathway mutation*	*Stem-cell markers**	*miRNA**
Anaplastic glioma (Grade III)	Prognostic (AA, AO, AOA)	Prognostic (AA, AO)	Prognostic/predictive (AO)	Negatively prognostic (AA)	Marginal	Marginal	Negatively prognostic?	Negatively prognostic?
Glioblastoma (Grade IV)	Prognostic/predictive	Prognostic	Prognostic?	Negatively prognostic/predictive?†	Marginal	Marginal	Negatively prognostic?	Negatively prognostic?

Generally, a prognostic marker is considered to allow for estimating the outcome in a treatment-independent manner, whereas a predictive marker is of value in the context of a specific therapy.
*These factors could benefit us in the prediction of aggressive nature of gliomas.
†It might be predictive for molecular targeted therapies.
AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma.

Treatment

Introduction

The approaches to tumour treatment for glioma are based on the histological finding, grade of the tumour and age and medical condition of the patient. Options for treatment include resection, radiation and chemotherapy either alone or in combination. [41] Advances in knowledge about the molecular biology of tumours and how this relates to treatment response has opened up new opportunities for personalised treatment regimes. [41]

The current standard of care for patients with newly diagnosed glioblastoma includes maximum safe tumour resection followed by a 6 week course of radiotherapy with concomitant systemic therapy using the alkylating agent TMZ and followed by 6 months of adjuvant TMZ. [41, 66]

Surgical management

There is evidence that centralised care and high volume units with skilled teams of health professionals improve patient outcomes. [80, 81] In an analysis of resections or biopsies for primary brain cancer there was evidence that large-volume centres had lower postoperative mortality rates than those with smaller volumes, for craniotomies (odds ratio [OR] 0.75 for a ten-fold larger caseload) and for biopsies (OR 0.54). [80]

Surgical resection

The current *Australian Clinical Practice Guidelines for the management of adult gliomas: astrocytomas and oligodendrogliomas [65]* recommend the following surgical management for different grades of glioma:

For low-grade astrocytoma:

- There is definitely a role for attempted resection of a LGA. It should probably be done at the time of diagnosis for the following potential benefits: more accurate diagnosis, palliation of symptoms, extension of survival, reduced chance of malignant transformation and possible cure.
- Recommendation of resection should be tempered if the tumour is diffuse, located in an eloquent area or less than 10cm^3 in volume.

- Standard microsurgical techniques should be employed with the addition of stereotactic guidance if available.
- Awake surgery or cortical mapping are optional but may reduce the incidence of postoperative neurological deficit if the aim of surgery is to palliate and secure a diagnosis rather than prolong life or achieve a cure.

For high-grade astrocytoma:

- A tissue diagnosis should be obtained in all patients with suspected high-grade astrocytoma before commencing definitive treatment.
- Anti-neoplastic treatment should not be offered without a tissue diagnosis unless biopsy is considered too dangerous.
- Patients with high-grade astrocytoma should have surgery for tumour resection if safe as this extends survival when compared to biopsy alone.
- Patients with high-grade astrocytoma should have surgery for maximal tumour resection, aiming for gross macroscopic resection if safe, as this extends survival when compared to biopsy, subtotal or partial resection.
- Patients with high-grade astrocytoma who are over the age of 65 or have poor performance status should have surgery for tumour resection if they are fit for surgery, as this extends survival when compared to biopsy alone.
- Patients with high-grade astrocytoma benefit from implantation of carmustine wafers at the time of surgical resection of tumour as they provide a modest survival benefit of 8 to 11 weeks.
- Patients with recurrent high-grade astrocytoma, particularly younger, asymptomatic patients, may benefit from resection of tumour.
- Surgery for patients with high-grade astrocytomas should be conducted in accredited facilities complying with all relevant State, Federal, professional and educational policies, standards and guidelines.
- Surgery for patients with high-grade astrocytomas should be conducted in a multidisciplinary environment with input from neuroradiology, intensive care, medical and radiation oncology, neuropathology, neurology, specialist surgery and nursing and allied health services.
- Surgery for patients with high-grade astrocytomas should be conducted in a facility where an operating microscope, ultrasonic surgical aspirator and cortical mapping equipment are available.
- Intra-operative frameless neuronavigation improves extent of resection and survival of patients with high-grade astrocytoma compared to unguided microsurgery, and its use is recommended.

For Oligodendrogliomas:

- All patients with suspected oligodendroglioma (OG) or oligoastrocytoma (OA) should undergo a biopsy for histological confirmation of tumour type and grade and to permit molecular analysis.
- Maximal gross surgical resection is recommended where technically feasible, as this has been shown to increase survival.
- All suspected OGs or OAs must undergo histological confirmation as radiological features alone are inadequate for diagnosis and staging.
- Observation only may be an acceptable strategy in grade II tumours with good prognostic features.

For childhood glioma tumours a consensus statement on surgical approaches has been developed using the Delphi consensus approach. [82]

A recent Cochrane review examining biopsy versus resection for *low*-grade glioma was unable to draw conclusions due to a lack of suitable studies. [83] The authors identified no RCTs of biopsy or resection. They concluded that: 'Currently there are no randomized clinical trials or

controlled clinical trials available on which to base clinical decisions. Therefore, physicians must approach each case individually and weigh the risks and benefits of each intervention until further evidence is available. Future research could focus on randomized clinical trials to determine outcomes benefits for biopsy versus resection.'

Another Cochrane review, updated in 2011, examining biopsy versus resection for *high*-grade glioma (HGG) concluded that: 'There is no high quality evidence on biopsy versus resection for HGG that can be used to guide management. The single included RCT is of inadequate methodology to reach reliable conclusions. Further large multi-centred RCTs are required to conclusively answer the question of whether biopsy or resection is the best initial surgical management for HGG.' [84]

Image guidance

A 2014 Cochrane review [85] examined the benefits of image-guided surgery for the resection of brain tumours. Four relevant randomised clinical trials were identified using four different techniques iMRI, 5-aminolevulinic acid (5-ALA) fluorescence guided surgery, neuronavigation and DTI-neuronavigation.

The authors concluded that: 'There is low to very low quality evidence (according to GRADE criteria) that image guided surgery using iMRI, 5-ALA or DTI-neuronavigation increases the proportion of patients with high grade glioma that have a complete tumour resection on post-operative MRI. There is a theoretical concern that maximising the extent of resection may lead to more frequent adverse events but this was poorly reported in the included studies. Effects of image guided surgery on survival and quality of life are unclear. Further research, including studies of ultrasound guided surgery, is needed.'

Intra-operative MRI (iMRI) is an emerging technique that is expensive and not widely available at present. iMRI is that reduces inaccuracies resulting from intraoperative brain shift that may occur during traditional surgical methods. It allows the extent of resection to be maximised and intra-operative complications minimised. [65, 86]

Surgery guided by 5-ALA fluorescence is a technique where fluorescently labelled markers are used to highlight the tumour and the resection is carried out under fluorescence. Tumours and healthy brain tissue can be displayed intra-operatively in contrasting colours, allowing for more complete tumour resection. A recent study of the use of 5-ALA for glioblastoma resection found that strong fluorescence identified solid tumour with 100% positive predictive value. Invaded tissue beyond the solid tumour mass was identified by vague fluorescence with 97% positive predictive value and 66% negative predictive value. The mean tumour volume resected was 99.8% as determined by pre and post-operative MRI. [87] Similar methods have been developed using chlorotoxin, a key toxin in scorpion venom which has been shown to bind specifically to glioma cell surface as a specific chloride channel and matrix metalloproteinase-2 blocker [88]

Awake craniotomy

There is evidence that more extensive surgical resection is associated with improved life expectancy for both low-grade and high-grade glioma patients. Intraoperative stimulation mapping is a method that allows surgeons to maximise the extent of tumour resection whilst still minimising morbidity. It is particularly relevant to the resection of gliomas present within or adjacent to language pathways. Unlike motor function, speech and language are distributed widely across the brain. Using language-mapping techniques, in conjunction with standardised neuroanesthesia and neuromonitoring, postoperative language retention may be improved. [21]

Medical management

The current standard of care for the medical management of newly diagnosed glioblastoma, following resection, includes the addition of TMZ to radiation therapy (RT) which was found in a 2005 clinical trial to significantly prolong survival. [89]However, the benefit of TMZ is fairly modest with a median overall survival 12.1 months for RT alone compared to 14.6 months for RT combined with TMZ. [37, 89] New therapies, including immunotherapy, vaccines and the use of nanoparticles are emerging methods of medical management.

Improved knowledge the molecular pathogenesis of glioblastoma biology has allowed for the identification of new potential therapeutic targets. A number of these new agents are now undergoing clinical trials (see table). [37]

At present, the majority of medical management pre-clinical and clinical studies are focused on:

i. the identification of mechanisms to overcome TMZ resistance
ii. the development of molecular targeted and anti-angiogenic agents
iii. immunotherapy
iv. drug combination [90]

Table 4. Selected targeted agents in clinical trails for glioblastoma. Adapted from Quant et al 2010 [37]

Target	Mechanism of Action	Molecular Agent	Other Targets
Growth factors and growth factor receptors			
EGFR	Reversible small-molecule inhibitor	Erlotinib (OSI-774, Tarceva)	
		Gefitinib (ZD1839, Iressa)	
		Lapatinib (GW-572016, Tykerb)	HER2
		Vandetanib (ZD-6474, Zactima)	VEGFR
	Irreversible small-molecule inhibitor	BIBW-2992	HER2
		PF-00299804	HER2, HER4
	Monoclonal antibody	Cetuximab (Erbitux)	
		Nimotuzumab (h-R3, TheraCIM, TheraLOC)	
		EMD 55 900	
		Iodine-125 labeled monoclonal antibody-425	
EGFRvIII	Peptide based vaccine	CDX-110	
	Monoclonal antibody	mAb 806	
SF/HGF	Monoclonal antibody	AMG-102	
PDGFR	Small-molecule inhibitor	Cediranib (AZD-2171, Recentin)	VEGFR, c-Kit
		Dasatinib (BMS-354825, Sprycel)	Src, Abl, VEGFR, Flt-3
		Imatinib mesylate (STI-571, Gleevec)	Bcr-Abl, c-Fms, c-Kit
		Pazopanib (GW-786034)	VEGFR, c-Kit
		Sorafenib (BAY-439006, Nexavar)	VEGFR, Raf, c-Kit
		Sunitinib (SU-11248, Sutent)	VEGFR, c-Kit, Flt-3
		Tandutinib (MLN-518)	Flt-3, c-Kit
		Vatalanib (PTK-787/AK-222584)	VEGFR, c-Kit, c-Fms
PDGFR-α	Monoclonal antibody	IMC-3G3	
Intracellular signaling			
Ras	Farnesyl transferase inhibitor	Lonafarnib (SCH-66336, Sarasar)	
		Tipifarnib (R115777, Zanestra)	
Raf	Small-molecule inhibitor	Sorafenib (BAY-439006, Nexavar)	VEGFR, PDGFR, Flt-3, c-Kit, FGFR
mTOR	Small-molecule inhibitor	Ridaforolimus (AP-23573)	
		Everolimus (RAD-001, Afinitor)	
		Sirolimus (Rapamycin, Rapamune)	
		Temsirolimus (CCI-779, Torisel)	
		XL-765	PI3K
PI3K	Small-molecule inhibitor	XL-765	mTOR
		XL147	
		BKM 120	
Akt	Alkylphospholipid	Perifosine (KRX-0401)	
	Small-molecule inhibitor	MK2206	
PKC	Small-molecule inhibitor	Enzastaurin (LY-317615)	
Tumor vasculature			
VEGF	Soluble decoy receptor	Afibercept (VEGF-Trap)	
	Monoclonal antibody	Bevacizumab (Avastin)	
VEGFR	Small-molecule inhibitor	Cediranib (AZD-2171, Recentin)	PDGFR, c-Kit
		Dasatinib (BMS-354825, Sprycel)	Src, Abl, PDGFR, Flt-3
		Pazopanib (GW-786034)	PDGFR, c-Kit
		Sorafenib (BAY-439006, Nexavar)	PDGFR, Raf, c-Kit
		Sunitinib (SU-11248, Sutent)	PDGFR, c-Kit, Flt-3
		Vandetanib (ZD-6474, Zactima)	EGFR
		Vatalanib (PTK-787/AK-222584)	PDGFR, c-Kit, c-Fms
		XL184	Met
		Foretinib	Met, PDGFR
	Adnectin	CT-332 (Angiocept)	
	Monoclonal antibody	IMC-1121B	

(*continued on next page*)

Target	Mechanism of Action	Molecular Agent	Other Targets
Met	Small-molecule inhibitor	XL184	VEGFR
Integrins	Small-molecule inhibitor	Cilengitide (EMD-121974) ATN-161	
Cytokines			
TGF-β	Antisense oligonucleotide	AP 12009	
Protein turnover			
	Proteasome inhibitor	Bortezomib (MLN-341, Velcade)	
Chromatin remodeling			
	HDAC inhibitor	Vorinostat (SAHA, Zolinza) Panobinostat (LBH589)	
Heat shock proteins			
	HSP90 inhibitor	Tanespimycin (17-AAG, KOS-953)	
DNA repair			
	PARP inhibitor	ABT-888 BSI-201	

Abbreviations: EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; SF/HGF, scatter factor/hepatic growth factor; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Temozolomide & other chemotherapy agents

TMZ is an oral alkylating agent that penetrates the blood-brain barrier. In the body TMZ is rapidly converted MTIC, an agent that prevents cell division by interrupting normal DNA replication. [90] Treatment of glioblastoma with TMZ began in the USA in 1999 and since this time modest improvements in patient glioblastoma survival times have been observed. [91]

A 2013 Cochrane review [92] of TMZ use found three high quality clinical trials and observed that TMZ increased survival (HR 0.84, CI 0.50 to 0.68, P < 0.001) and time to progression (HR 0.52, CI 0.42 to 0.64, P < 0.0001). There were no significant impacts on quality of life and only a low incidence of early adverse events. Grade 3/4 haematological toxicity was observed in 5-14% of patients and longer term adverse effects of TMZ are still unknown. [92]

For recurrent glioblastoma only one trial was included; TMZ did not increase overall survival but it did increase time to progression (HR 0.68, CI 0.51 to 0.90, P = 0.008). [92]

Most tumours eventually develop resistance to TMZ and there is no standard chemotherapy for recurrent or progressive glioblastoma because of unfavourable outcomes with currently available cytotoxic therapies. [37]

Another method of delivery of chemotherapy is the use of wafers that are impregnated with chemotherapy agents and inserted directly into the cavity at the time of resection. A 2011 Cochrane review [93] assessed two randomised controlled trials of the effect of carmustine (Gliadel®) impregnated wafers in high-grade glioma. Survival was increased with the wafers compared to placebo (HR 0.65, 95% CI 0.48 to 0.86, P = 0.003). For recurrent disease no significant survival increase was observed (HR 0.83, 95% CI 0.62 to 1.10, P = 0.2). Adverse events were not more common with the wafers compared to placebo. [93]

The authors concluded that: 'Carmustine impregnated wafers (Gliadel®) result in improved survival without an increased incidence of adverse events over placebo wafers when used for primary disease therapy. There is no evidence of benefit for any other outcome measures. In recurrent disease Gliadel®does not appear to confer any additional benefit.'

Another Cochrane review of adjuvant treatment of anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) included two randomised controlled trials investigating surgery plus RT plus early PCV chemotherapy (procarbazine, lomustine, and vincristine) compared to surgery plus RT alone. No survival benefit was observed with the addition of early PCV chemotherapy, however an increase in progression free survival was observed following PCV chemotherapy before surgery or after surgery and RT. [60]

Drug repurposing

To improve prognosis in recurrent glioblastoma the *International Initiative for Accelerated Improvement of Glioblastoma Care* developed a treatment protocol based on a combination of drugs not traditionally thought of as cytotoxic chemotherapy agents but that have a robust history of being well-tolerated and are already marketed and used for other non-cancer indications. [94]

Focus was on adding drugs which met the following criteria: a) were pharmacologically well characterised, b) had a low likelihood of adding to patient side effect burden, c) had evidence for interfering with a recognised, well-characterised growth promoting element of glioblastoma, and d) were coordinated, as an ensemble had reasonable likelihood of concerted activity against key biological features of glioblastoma growth.

Nine drugs meet these criteria and the authors propose a treatment protocol that adds them to continuous low dose TMZ in patients with recurrent disease after primary treatment with the Stupp Protocol. The nine adjuvant drug regimen, Coordinated Undermining of Survival Paths, (CUSP9) are: aprepitant, artesunate, auranofin, captopril, copper gluconate, disulfiram, ketoconazole, nelfinavir, and sertraline.

CUSP9 is weighted towards interference with glioblastoma stem cell function, which offers a higher reward yet similar risks as targeting the tumour cell population as a whole. The authors conclude that 'over 99% of patients will experience progression post-primary treatment and the short median survival of patients with gliolbastoma warrant taking the measured and manageable risks of CUSP9'. [94]

Radiation therapy

Up until recently, whole brain radiation therapy (WBRT) was the treatment of choice for brain cancer. Now, use of stereotactic radiosurgery (SRS) is becoming more common in selected patients.

Image-guided radiotherapy enables a precise radiation dose delivery and can reduce treatment time in glioblastoma and toxicity. Preservation of neurocognitive function may also be improved. A recent review recommended that future prospective trials for primary brain tumours or brain metastasis should include image-guided radiotherapy to assess its efficacy to impact on patient quality of life. [95]

Stereotactic radiosurgery

Stereotactic radiosurgery is a relatively new treatment option for glioblastoma. High energy beams are accurately focussed on a selected intracranial target. There are several methods to deliver these high energy beams. A linear accelerator or LINAC rotating on a gantry (X-Knife, Novalis) or manipulated with a robotic arm (CyberKnife) may be used. Alternatively cobalt sources placed into a helmet (Gamma-Knife) may be used.

Radiosurgery has the advantage of being non-invasive and can be performed as an outpatient procedure. Radiosurgery is often used in patients with recurrent glioblastoma to avoid further surgical procedures or in addition to conventional radiotherapy. [96]

A recent review highlighted the need for further research of this technique stating that further evidence in the form of phase III randomised trials is needed to assess the durability of stereotactic radiosurgery for treating patients in specific clinical situations. [97]

In a small retrospective review of 18 patients with biopsy-confirmed recurring or unresectable pilocytic astrocytoma undergoing stereotactic radiosurgery, it was found that 11 patients with tumour-related symptoms improved after SRS. Symptomatic edema after SRS occurred in 8 patients, which resolved with short-term corticosteroid therapy in the majority of those without early disease progression. The authors concluded that: 'Radiosurgery has low permanent radiation-related morbidity and durable local tumour control, making it a meaningful treatment option for patients with recurrent or unresectable pilocytic astrocytoma in whom surgery and/or external beam radiotherapy has failed. [98]

Hypo-fractionated stereotactic radiosurgery may also provide treatment benefits. [99]

Immune therapies

Immune cells in the tumour microenvironment have an important role in regulating tumour progression. Therefore, stimulating immune reactions to tumours can be an attractive therapeutic and prevention strategy. Each tumour has its own unique set of genomic and epigenomic changes, which can influence the host immune response to tumour.

Antibodies

Nimotuzumab is an antibody directed at EGFR and in clinical trials for treatment of glioblastoma and DIPG. [100] Nimotuzumab is a monoclonal G1 humanised antibody against human EGFR (HER) 1. It was derived from a mouse (murine) antibody raised to EGFR from placenta. The antibody was humanised by grafting the complementarity determining regions to a human IgG1 gene.

For DIPG there have been promising results with Nimotuzumab treatment in Phase II and III trials with significantly increased survival time. [100] In a recent Phase III trial of Nimotuzumab in adult glioblastoma patients, that included radiotherapy and TMZ plus Nimotuzumab versus control, found no overall improvement in survival but the sub-group analyses showed some differences approaching significance. [100]

The authors concluded that: 'future studies of the efficacy of nimotuzumab should focus on patients with non-methylated MGMT and EGFR-positive glioblastomas that present with residual tumour after surgery. Therefore, future studies of the efficacy of nimotuzumab should focus on patients with non-methylated MGMT and EGFR-positive glioblastomas that present with residual tumour after surgery.' [100]

Bevacizumab is another humanised monoclonal antibody with anti-angiogenic action. Bevacizumab targets VEGF and has been shown to significantly improve response to radiotherapy but only confers a modest survival time increase. [101]

Active immunotherapy

Active immunotherapy relies on stimulation of the patient's immune system to increase the immune response to target tumour cells. This is achieved by either boosting the entire immune system or by training the immune system to attack the tumour specifically via tumour antigens. [102]

To date the immunotherapy strategies that have been used for glioma can be divided into three broad categories:

i. **Immune priming** (active immunotherapy) – sensitisation of immune cells to tumour antigens using various vaccination protocols
ii. **Immunomodulation** (passive immunotherapy) – involves targeting cytokines in the tumour microenvironment or using immune molecules to specifically target tumour cells
iii. **Adoptive immunotherapy** - involves harvesting the patient's immune cells, followed by activation and expansion in the laboratory prior to re-infusion. [103, 104]

The blood brain barrier and lack of lymphatic drainage in the brain have both been obstacles to research into this area. The blood brain barrier separates the peripheral circulation and the central nervous system, preventing immune cells and antibodies from crossing into the brain. Instead, the microglia perform immune function in the brain.[102] Evidence of the role of T cells within glioma has led to the development of novel immunotherapeutic strategies. [103]

These obstacles have been overcome by using dendritic cells as the antigen presenting cells. In a review that included 21 studies, including both patients with recurrent and newly diagnosed glioblastoma, the use of dendritic cell vaccines has been analysed. Overall, the studies suggest that vaccination with autologous dendritic cells that are loaded with autologous tumour cells increase progression free and overall survival when administered as adjuvant. However, large randomised clinical trials were recommended by the authors to confirm this trend. [102]

Vaccines

Vaccines currently under development have been reviewed by Aguilar *et al.* (2012). A number of vaccine approaches have been evaluated for glioblastoma [105].

Dendritic-cell–based vaccines have been a common approach. In this method dendrocytes (the antigen-presenting cells) are loaded with tumour associated antigens and returned the patient so that a T cells immune mediated response to those antigens can be raised. Aguilar *et al*. cited 13 different clinical trials that have been undertaken to test vaccines produced by this method.

Peptide vaccines are another approach, such as the EGFRvIII vaccine, where a synthetic peptide derived from the tumour-specific mutated segment of EGFRvIII (PEP-3) conjugated to keyhole limpet hemocyanin (PEPvIII-KLH). This vaccine is administered with GM-CSF (granulocyte macrophage colony stimulating factor) GM-CSF, a cytokine that promotes dendritic cell maturation and function and is utilised to enhance vaccine immunogenicity.[17]

Another approach to stimulate a vaccine effect is the use of autologous tumour cells or peptides mixed with an adjuvant to stimulate an immune response.

Gene transfer can also be used to create a vaccine *in situ* by direct transfer of a specific antigenic molecule, transfer of immune-modulating molecules, such as cytokines, or by the creation of conditions to generate a local immune response.

In another 2013 review of the current approaches to vaccine therapy for glioblastoma by Reardon *et al*., the authors concluded: 'A variety of vaccination approaches are in various stages of clinical development for malignant glioma patients based on encouraging, albeit preliminary, evidence of therapeutic benefit. In the next 1–2 years, data from ongoing randomised trials will better clarify the potential for these reagents in this disease indication. Nonetheless, much work remains to optimise vaccination approaches.' [101]

Salvage therapies

Only modest benefit has been observed in currently available salvage therapies for patients with recurrent glioblastoma. Re-irradiation as salvage therapy has been explored, however this exposes healthy brain to supertherapeutic doses resulting in significant rates of radionecrosis and resulting morbidity. [106] Stereotactic radiosurgery offers a noninvasive therapeutic option allowing the administration of high-dose, precise radiotherapy and can be administered in a single or a few treatments. Single-fraction stereotactic radiosurgery has been observed to have modest utility as a palliative interventions, however it has been associated with high rates of re-operation because of associated toxicity [65]

Fractionated stereotactic radiotherapy may offer some improvement in overall survival with minimal toxicity for patients with previously treated malignant gliomas. Fractionated stereotactic radiotherapy allows precise treatment delivery while decreasing the dose to surrounding critical structures, reducing toxicity associated with stereotactic radiotherapy. [107]

Hypofractionated stereotactic radiotherapy is able to deliver treatment over two weeks with standard fractionation schemes. In a recent, large cohort study (n= 147) of patients with recurrent high grade glioma, hypofractionated stereotactic radiotherapy was observed to have with survival benefit independent of re-operation or concomitant chemotherapy and in addition was well tolerated with minimal adverse effects [99].

Emerging therapies

Gene therapy

Gene therapy as related to brain cancer can be defined as the targeted transfer of genetic material into tumour cells for therapeutic purposes and has the ability to target invasive tumour cells that are resistant to conventional therapy and give rise to recurrent disease. Although gene therapy has shown promise in preclinical applications, it has not met clinical expectations due to various impediments related to the nature of the type of tumour and its location. The obstructions ofgene therapy include: the anatomical barriers and physiological aspects of the brain that decrease transduction efficiency, tumour heterogeneity and invasiveness that challenge vector targeting and delivery as well as a lack of a satisfactory preclinical model to study glioma. [108]

The main gene therapy strategies that have been employed as possible strategies for glioblastoma are suicide gene therapy, genetic immunotherapy and oncolytic virotherapy. [108]

Suicide gene therapy has been the most commonly used gene therapy using the enzyme-prodrug suicide gene therapy system. In this approach, viral vectors or cell carriers are genetically modified to express genes for an enzyme that can convert an inactive pro-drug into toxic metabolites at the tumour site.

To date, around 17 different clinical trials have evaluated the use of adenoviral, retroviral or non-viral vector based delivery methods with modest or no improvement in median survival time. Two of the most researched suicide genes that have been trialled for glioblastoma are the HSV-tk system - herpes simplex type 1 thymidine kinase (HSV-tk) and CD/5-FC system - the cytosine deaminase/5-fluorocytosine (CD/5-FC) gene therapy system.

HSV-tk converts the inactive pro-drug ganciclovir into a toxic metabolite called GCV-triphosphate. The HSV-tk system is delivered into the tumour cavity by replication-defective retrovirus, adenovirus, cell carrier and reovirus packing cells. [108]

Nanoparticles

Another emerging area is the use of nanoparticles, which have been studied as a method to overcome the problems with getting treatments across the blood–brain barrier. Nanoparticles represent an innovative tool in research and therapies in brain cancer due to their capacity of self-assembly, small size, increased stability, biocompatibility, tumour-specific targeting using antibodies or ligands, encapsulation and delivery of antineoplastic drugs, and increasing the contact surface between cells and nanomaterials. Nanoparticles can exploit some biological pathways to achieve specific delivery to cellular and intracellular targets, including transport across the blood-brain barrier, which many anticancer drugs cannot bypass. Magnetic nanoparticles have also been used for imaging and diagnosis. [109]

There are a number of different types of nanoparticles currently in the early phases of research and development. Nanoparticles may be biodegradable polymers that can be loaded with chemotherapeutic drugs to induce toxicity. For example, nanoparticles made from liposomes have been used to improve the delivery of the chemotherapeutic agent paclitaxel, which is hydrophobic and problematic to get across the blood brain barrier the BBB is also poor. Paclitaxel has been conjugated to liposomes to improve solubility and laboratory studies are underway to test this method of drug delivery. [109]

Magnetic drug targeting of magnetised nanoparticles bound to anti-cancer agents is another method under development [110]. Ferrofluids containing the magnetic particles conjugated to anti-tumour agents are injected intravenously and then concentrated to the tumour using an external magnetic field. Such particles may provide a new method for glioma-targeted drug delivery. [111, 112] [113]

Stem cell therapy

Targeting cancer stem cells has emerged as a treatment option. Stem cells have a multipotent function, have self-renewal potential and resistance to chemotherapy and radiotherapy. Five methods are currently. [114]

Cho et al (2013) [114] review five methods being used to target GBM stem cells: One is to develop a new chemotherapeutic agent specific to CSCs. A second is to use a radiosensitiSer to enhance the radiotherapy effect on CSCs. A third is to use immune cells to attack the CSCs. In a fourth method, an agent is used to promote CSCs to differentiate into normal cells. Finally, ongoing gene therapy may be helpful. The authors conclude: 'the combination of conventional surgery, chemo- therapy, and radiotherapy with stem cell-orientated ther- apy may provide a new promising treatment for reducing GBM recurrence and improve the survival rate.'

Recent research has discovered that sorafenib, disulforam and metformin may have potential with a direct effect on cancer stem cells viability in a number of tumours including glioblastoma. [90]

Sorafenib (SO) is an oral multikinase inhibitor, which targets several tyrosine kinases receptors (RTK), involved in tumour growth progression and neoangiogenesis including VEGFR, PDGFR and fibroblast growth factor receptor 1 (FGFR1).

Disulfiram (tetraethylthiuram disulfide, DSF) is an inhibitor of the aldehyde dehydrogenase (ALDH) enzyme family, and in TMZ resistant glioblastoma stem cells has been found to reduce *in vitro* cell growth.

Metformin is an anti-diabetic drug used to treat type II diabetes and polycystic ovary syndrome. Patients treated with metformin exhibit reduced cancer-related mortality leading to investigations of the potential anti-tumour effects of the drug. The exact molecular mechanism is yet to be elucidated but studies so far point to either indirect action via the reduction of systemic levels of insulin or glucose, or direct impact directly on tumour growth.[90]

Personalised medicine

Genome sequencing has lead to the advent of personalised medicine (also called precision medicine). Personalised medicine uses the data gather from genome sequencing to predict disease development or to tailor treatment to an individual. Glioblastoma is a highly heterogeneous malignancy and recent research has highlighted the fact that specific targeted therapies are useful only in certain molecular subsets. Molecular classification of each individual tumour to identify markers that define these subsets and to predict response to chemotherapeutic agents is an emerging development area in glioblastoma treatment.[19]

In 2012, the Radiation Therapy Oncology Group 9402 and European Organisation for Research and Treatment of Cancer 26951 trials reported long-term follow up results that demonstrated an overall survival benefit from radiotherapy plus PCV was confined to patients with anaplastic oligodendroglial tumours with the 1p/19q codeletion. [5, 6] MGMT promoter methylation has also been associated with improved outcome in patients with anaplastic astrocytoma (AA) and anaplastic oligoastrocytoma (AOA) treated with TMZ at recurrence. [10]

There are now calls for routine tumour testing for 1p/19q and MGMT for glioblastoma patients and EGFR, IDH1, IDH2 testing should also be considered. [5, 17]

Blood-brain-barrier research

Another focus for new research has been on disruption of blood brain barrier in order to facilitate administration of anti-cancer agents to the tumour site. Studies in animal models have found that focused ultrasound can enhance the penetration drugs through the blood brain barrier without causing significant adverse effects. [115]

Tumour-specific treatment and outcomes

Outcomes following surgical resection (median survival) have been observed as:

- 10 years for low- grade oligodendroglioma
- 5-8 years for low-grade astrocytoma
- 1-7 years for anaplastic oligodendroglioma.
- 3 years for anaplastic astrocytoma
- 1 year for glioblastoma

Younger age, good preoperative performance status and gross macroscopic resection are all commonly associated with longer survival. [65]

Glioblastoma

The current standard of care for patients with newly diagnosed glioblastoma includes maximum safe tumour resection followed by a 6 week course of radiotherapy with concomitant systemic therapy using TMZ and followed by 6 months of adjuvant TMZ. [41, 89]

Because of the diffuse nature of glioblastoma, focal radiotherapy techniques such as stereotactic radiosurgery are not particularly beneficial. The use of intensity-modulated radiotherapy is popular because of its improved targeting. [2]

Treatment of other tumour types

SCNS Lymphoma

Chemo-radiotherapy is the treatment of choice for CNS lymphoma. Chemo-radiotherapy has been studied in several clinical trials and following varying regimens complete remission was obtained in 30%–87% of cases and 5-year overall survival rates of between 30% and 50%. [43]

Diffuse Intrinsic Pontine Glioma (DIPG)

Median overall survival ranges from 4–17 months and one, two and three year survival range from 14–70%, 0–25% and 0–10%, respectively. A variety of therapeutic strategies have been utilised in DIPG, but there is no standard treatment. Outcomes of various clinical trials are reviewed by Jansen *et al.* (2012). [45]

Nimotuzumab has also shown promise in DIPG, with a nearly threefold longer survival time of responders versus non-responders in a Phase II trial. [100]

Ependymoma

Surgery is the treatment of choice for ependymomas with the primary goals being to achieve complete tumour resection and to remove obstacles to CSF flow. Surgical resection has been significantly associated with better overall and progression-free survival. Radiotherapy is also utilised management of intracranial ependymomas. There is limited clinical evidence for benefit and ependymomas are thought to be relatively radioresistant. There is also a lack of evidence regarding the use of chemotherapy but in the case of recurrence platinum-based agents have better response rates (31-67%) compared to non-platinum-based agents (11-13%). [116]

Medulloblastoma

Surgery is the first-line treatment for medulloblastoma with the aim of restoring normal CSF flow in the case of an obstructive hydrocephalus and to achieve full resection of the tumour. Complete resection results in a significantly better prognosis. Surgery along is insufficient to achieve long-term remission. Radiotherapy is the second-line treatment of choice and consensus is that therapy should start no later than 4-6 weeks postoperatively and last no longer than 50 days.

Chemotherapy is currently given as adjuvant to the majority of patients and may be used to avoid radiotherapy in infants. The best evidence is for chemotherapy, using lomustine, vincristine and cisplatin for up to 8 cycles after conventional dose radiotherapy and concomitant vincristine. [48]

Meningioma

Surgical resection and post-operative radiation therapy are recommended for WHO grade II and III meningiomas to reduce recurrence rates. Clinical studies to assess the optimal timing and modality of post-operative radiation are still being conducted and are reviewed by Walcott *et al.* (2013). [117]

Oligoastrocytoma

Losses of 1p and 19q have been observed in approximately 30–50% of oligoastrocytoma and 20–30% of anaplastic oligoastrocytoma. [10] Median survival is 2- 3 years for grade III astrocytoma. [2, 24] Treatment is radiotherapy followed by adjuvant chemotherapy. [60]

Oligodendroglioma

Anaplastic (WHO Grade III) Oligodendrogliomas with 1q/19p co-deletion are more responsive to therapy with a median survival of 3-6 years. Addition of chemotherapy to radio therapy prolongs progression-free and overallsurvival. [2, 24]

LOH or co-deletion of 1p/19q is a frequent observation in approximately 90% of oligodendroglioma tumours and is a prognostic and predictive factor of response to PCV chemotherapy. Routine medical management of oligodendroglioma now requires assessment of 1p/19q status to deliver the best treatment. [62, 64]

Summary

The 2013 paper by Antonio Omuro and Lisa DeAngelis *(Glioblastoma and Other Malignant Gliomas. A Clinical Review)* [2] provides an appropriate summary to this review:

'Although malignant glioma remains an incurable disease, treatment options have been expanding and improving because of better understanding of the complex molecular biology of these tumors, their microenvironment, and immunologic interactions with the host. Several novel promising therapies are under evaluation, including trials of targeted agents directed at receptor tyrosine kinases and signal transduction pathways, alternative anti-angiogenic agents, gene therapy, immunotherapy, reirradiation, radiolabeled drugs, and many others. Such treatments address the marked tumor heterogeneity, and many are being designed for very specific and small subgroups of patients whose tumors share distinct molecular and genetic characteristics. Participation in clinical trials and molecular screening of large numbers of patients are important to improving the care of future patients.'

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