Pharmacology & Therapeutics 152 (2015) 63–82

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M. Panagiotidis

Glioblastoma multiforme: Pathogenesis and treatment

Constantinos Alifieris, Dimitrios T. Trafalis *

Laboratory of Pharmacology, Medical School, University of Athens, Athens, Greece

ARTICLE INFO

Available online 2 May 2015

Keywords:
Glioblastoma
Treatment
Review
Pharmacology
Targeted therapy
Stem cell

ABSTRACT

Each year, about 5–6 cases out of 100,000 people are diagnosed with primary malignant brain tumors, of which about 80% are malignant gliomas (MGs). Glioblastoma multiforme (GBM) accounts for more than half of MG cases. They are associated with high morbidity and mortality. Despite current multimodality treatment efforts including maximal surgical resection if feasible, followed by a combination of radiotherapy and/or chemotherapy, the median survival is short: only about 15 months. A deeper understanding of the pathogenesis of these tumors has presented opportunities for newer therapies to evolve and an expectation of better control of this disease. Lately, efforts have been made to investigate tumor resistance, which results from complex alternate signaling pathways, the existence of glioma stem-cells, the influence of the blood-brain barrier as well as the expression of 0^6-methylguanine-DNA methyltransferase. In this paper, we review up-to-date information on MGs treatment including current approaches, novel drug-delivering strategies, molecular targeted agents and immunomodulative treatments, and discuss future treatment perspectives.

Contents

1. Introduction

Each year, about 5–6 cases out of 100,000 people are diagnosed with primary malignant brain tumors, of which about 80% are malignant gliomas (MGs) (Schwartzbaum et al, 2006; Stupp et al., 2010b). Gliomas, the most common group of primary brain tumours, include astrocytomas, oligodendrogliomas and ependymomas. According to World Health Organization (WHO) malignant gliomas are subcategorized into grade III/IV tumors such as anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma and anaplastic ependymomas, as well as grade IV/IV tumors, as glioblastoma multiforme (GBM). The WHO grade is assigned based on certain pathological features, such as nuclear atypia, mitotic activity, vascular proliferation, necrosis, proliferative potential and features clinical course and treatment outcome (Louis et al., 2007). Its incidence in the United States is estimated around 3:100,000 while more than 10,000 cases are diagnosed annually. It constitutes 45.2% of all malignant central nervous system (CNS) tumors, 80% of all primary malignant CNS tumors

Abbreviations: AKT, protein kinase B; BBB, blood-brain barrier; BCNU, carmustin; CCNU, lomustin; c-MET, hepatocyte growth factor receptor; EGF(R), epidermal growth factor (receptor); EGFRvIII, epidermal growth factor receptor variant III; ERK, extracellular signal-regulated kinases; FTI, farnesyltransferase inhibitor; GBM, glioblastoma multiforme; Gli1, glioma-associated oncogene-1; HDAC, histone deacetylase 1; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; Hsp, heat-shock protein; IDH1, NADP + -dependent isocitrate dehydrogenase; MAb, monoclonal antibody; MAPK, mitogen-activated protein kinases; MG, malignant glioma; MGMT, O6-methylguanine-DNA methyltransferase; miRNA, micro ribonucleic acid; MRI, magnetic resonance imaging; MTKI, multitargeted tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; OS, overall survival; PARP-1, poly(ADP-ribose)polymerase-1; PCV, procarbazine, lomustine and vincristine; PDGF(R), platelet-derived growth factor (receptor); PFS, progression-free survival; PFS-6, six-month progression-free survival; PI3K, phosphotidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RT, radiotherapy; SHH, sonic hedgehog; STAT3, signal transducer and activator of transcription 3; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; TTP, time-to-progression; VEGF(R), vascular endothelial growth factor (receptor).

* Corresponding author at: Lab. Of Pharmacology, Medical School, University of Athens, 75 Mikras Asias Str., 11527-Goudi, Athens, Greece (Building 16, 1st floor). Tel.: +30 210 746 2587; fax: +30 210 746 2504.
E-mail address: dtrafal@med.uoa.gr (D.T. Trafalis).

http://dx.doi.org/10.1016/j.pharmthera.2015.05.005
0163-7258/

and approximately 54.4% of all malignant gliomas. Mean age at diagnosis is 64 years and it is 1.5 times more common in men than women and 2 times more common in whites compared to blacks (Ostrom et al., 2013). The incidence has increased slightly over the past 20 years mostly due to improved radiologic diagnosis and especially in elderly (Fisher et al., 2007). In terms of treatment, grade III tumors and GBM are grouped together and treated similarly.

Clinically, patients with GBM may present with headaches, focal neurologic deficits, confusion, memory loss, personality changes or with seizures. Diagnosis and treatment response is suggested by magnetic resonance imaging (MRI) and the use of adjunct technology such as functional MRI, diffusion-weighted imaging, diffusion tensor imaging, dynamic contrast-enhanced MRI, perfusion imaging, proton magnetic resonance spectroscopy and positron-emission tomography (Wen & Kesari, 2008).

Etiologically, there are known linked risk factors that lead to development of GBM Environmental risk factors include primarily exposure to therapeutic ionizing radiation and factors such as vinyl chloride or pesticides, smoking, petroleum refining or production work and employment in synthetic rubber manufacturing (Wrensch et al., 2002). Additional factors such as exposure to residential electromagnetic fields, formaldehyde, diagnostic irradiation and cell phones have not been proven to lead to GBM. However, regarding cell phone irradiation, a metanalysis released in 2007 did show increased incidence among people who used cell phones for at least 10 years and especially those who had mostly unilateral exposure (Hardell et al., 2007).

Currently, maximal surgical resection plus radiotherapy plus concomitant and adjuvant temozolomide or carmustin wafers (Gliadel) is the standard of care in patients younger than 70 years old with newly diagnosed GBM. However, recurrence seems to be the rule despite standard care. Lately, attention has been given to understand the initial molecular pathogenesis of these tumors including alterations in cellular signal transduction pathways, the occurrence of resistance to therapy and to find methods to penetrate easier the natural blood-brain barrier (BBB). Despite these efforts to treat however, it remains an incurable disease and the prognosis falls in a poor survival range of 12–15 months (median 14.6 months) and a mean survival rate of only 3.3% at 2 years and 1.2% at 3 years (Scott et al., 1998; Stupp et al., 2005).

Glioma stem cells contribute to resistance to standard radiotherapy via preferential activation of DNA-damage-response pathways; and to standard chemotherapy via O^6-methylguanine-DNA methyltransferase (MGMT), the inhibition of apoptosis and the up-regulation of multidrug resistance genes (Dean et al., 2005). Thus, current efforts are directed towards personalized treatment through blocking prime signaling pathways in gliomagenesis, surpassing acquired resistance and by penetration of BBB. In this article we review the current concepts as well as emerging advances in the treatment of GBM with an emphasis on chemotherapy and targeted agents.

2. Pathogenesis

The ongoing research on the pathogenesis of malignant gliomas has given opportunities for newer therapies to evolve as well as promises for better control of the disease. Efforts are given to understand the development of tumor resistance (Dean et al., 2005; Furnari et al., 2007).

A small subgroup (about 5%) of patients with gliomas, is associated with certain hereditary syndromes (Farrell & Plotkin, 2007) (Table 1). All other patients with gliomas represent sporadic cases. An important aspect of the pathogenesis of gliomas is that malignant transformation results from the sequential accumulation of genetic alterations and abnormal regulation of growth factor signaling pathways. Aberrant proliferations is thus mediated via molecules such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF) and loss of phosphotensin analogue (PTEN). Downstream cascades in the growth signaling pathways (including PI3K/AKT) may be triggered (Wen & Kesari, 2008). Also, when those tumors recur, they often show progression to a higher histologic grade and thus, acquire a different name; this actually is a representation of progression along a classification scheme, the natural course of the disease, rather than a new disease (Louis, 2006). Among the alterations that are most frequently seen in low-grade astrocytomas are mutations affecting p53 and overexpression of platelet-derived growth factor α (PDGF-α) and its receptor. The transition to a higher grade is associated to disruption of RB, p16/CDKNαA and 19q tumor suppressor genes (Louis, 2006).

2.1. GBM clinical subtypes

GBM, is usually described in two different clinical forms, primary and secondary GBM (Kleihues & Ohgaki, 1999). Primary GBM, is the most common form (about 95%) and arises typically de novo, within 3–6 months, in older patients. Secondary GBM arises from prior low-grade astrocytomas (over 10–15 years) in younger patients. While primary and secondary forms show some molecular differences, the end result is pretty much the same since the same pathways are affected and respond similarly to current standard treatment. Primary GBM often has amplified, mutated epidermal-growth factor receptor (EGFR) which encodes altered EGFR (known as EGFRvIII) whereas secondary GBM has increased signaling through PDGF-A receptor. Both types of mutations lead to increased tyrosine kinase receptor (TKR) activity and consequently to activation of RAS and PI3K pathways. Again, primary GBM have commonly amplification of MDM2 gene (encodes for an inhibitor of p53), PTEN mutations and homozygous deletions of CDKN2A whereas secondary GBM usually has more prevalent p53 mutations, IDH1 mutations, MET amplification and overexpression of PDGFRA. Finally, progression of low-grade glioma to high-grade is associated with inactivation of the retinoblastoma gene (RB1) and increased activity of human double minute 2 (HDM2) (Kleihues & Ohgaki, 1999;

Table 1
Hereditary risk factors for GBM.

Syndrome	Gene	Associations
Neurofibromatosis type 1 (NF1)	NF1	Neurofibromas
Neurofibromatosis type 2 (NF2)	NF2	Schwannomas, ependymomas, meningiomas
Li-Fraumeni syndrome	TP53	Sarcomas, breast cancer, leukemia, adrenal cortex carcinoma, medulloblastomas
Hereditary non-polyposis colorectal cancer (HNPCC/Lynch syndrome), Turcot syndrome/Brain tumor-polyposis syndrome (BTPS)	DNA mismatch repair (MSH2, MLH1, MSH6, PMS1, PMS2)	Colorectal adenomas, adenocarcinoma
Multiple endocrine neoplasia type 1 (MEN1)	MEN1	Primary hyperparathyroidism, pancreatic endocrine tumors, pituitary adenomas
Nevoid basal cell carcinoma syndrome (NBCCS), Gorlin-Gotz syndrome	PTC CH	Basal cell carcinomas, medulloblastomas, ovarian fibromas
Tuberous sclerosis complex (TSC)	TSC1, TSC2	Renal angiomyolipomas, retinal glial hamartomas, cardiac rhabdomyomas