Chapter 3

Novel Endocrine Targets for GBM Therapy

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Abstract

Astrocytomas are brain tumors from glial cells, and they are classified by the World Health Organization (WHO) as astrocytoma, grade I or benign; astrocytoma, grade II or malignant; anaplastic astrocytoma, grade III; and glioblastoma multiforme or grade IV. The high-grade gliomas have an incidence of 6.03/100,000. The frequency of GBM is higher in men than in woman by a 50%. The survival of patients with GBM varied between 14 and 18 months, and less than 10% patients survive for 5 years. The main treatments for GBM consist of surgical tumor resection, radiotherapy, and chemotherapy. These tumors present different endocrine characteristics, such as expression of aromatase enzyme, estrogen, progesterone, as well as testosterone receptors. In addition, patients with GBM produce estradiol in high concentrations when compared to those with low-grade astrocytomas. The highest mRNA expression of ERα and aromatase in GBM patients had been postulated as prognostic biomarkers. The aromatase inhibitors had been used in the treatment of breast cancer in postmenopausal women with satisfactory results. At present time, several research groups are interested in testing these inhibitors for treating GBM.

Keywords: glioblastoma, endocrine characteristics, estradiol receptor, aromatase, aromatase inhibitors

1. Introduction

Glioblastoma multiforme (GBM) tumor occurs either as a primary tumor when it is formed de novo or a secondary tumor when the tumor progresses from grade II or III to grade IV. GBM is a diffuse and infiltrative tumor with a high mitotic activity, nuclear atypia, pleomorphism, and necrosis. GBM is the most frequently occurring brain tumor (12–15%) and represents 50–60% of all astrocytomas. There are two variants of glioblastoma: Glioblastoma of giant cells and gliosarcoma. GBM affects the cerebral hemispheres, mostly the white substance of the cerebral hemispheres. GBM primary has a bad prognostic due to its molecular heterogeneity. On the basis of its transcriptional subtype, GBM primary is also classified as neural, classical, and mesenchymal as well as proneural for GBM secondary. In GBM primary occurs the amplification of epidermal growth factor (EGF), and the *PTEN* gene is mutated in 45% of GBM primary cases, whereas in GBM secondary, the EGF amplification does not occur. The chromosome alteration in GBM involves a loss of the chromosome 10. The treatment for this kind of tumor after a safe surgical process also involves radiotherapy (RT) and the pharmacological treatment using the alkylating agent Temozolamide (TMZ), and different combinations of this agent with antitumor drugs such as the Bevacizumab. In spite of these treatments, there is a short survival period for GBM patients (14–18 months), which promotes the development of different clinical trials (II or III) to provide the patient a treatment with a better outcome. These new approaches are based on the molecular aspects of GBM to make the treatments more individualized.. This chapter describes the main GBM endocrine and molecular characteristics now known and makes a proposal on future treatments for GBM patients on the basis of these molecular characteristics.

2. Epidemiology

The incidence can change by age; in adults, for example, gliomas are the most frequent primary central nervous system tumors recurring in 70% of the patients. The average age of patients with GBM primary is 62 years, while for secondary GBM patients, it is approximately 45 years. The ethnicity and geographical localization are also of great importance in their epidemiology [1]. These tumors represent about 31% of newly diagnosed tumors in the United States and 81% of malignant tumors of the brain. The incidence of brain cancer in Europe is of 5.5/100,000 individuals, and the minor incidence is in sub-Saharan Africa with 0.8/100,000 individuals [2]. High-grade gliomas, anaplastic astrocytoma (AA) and GBM, have an incidence of 6.03/100,000 [3,4]. It has been shown that the incidence of GBM with respect to gender and ethnicity was different. The white people had the highest incidence of 2.5/100,000, Latin white people 1.8/100,000, and black people 1.5/100,000 [5].

3. Molecular characteristics of GBM

The current molecular characterization of GBM has allowed different classifications of the tumor subtypes and revealed intracellular pathways that might contribute to the development

of new and effective therapeutic targets. The new molecular classification can distinguish individual somatic mutations within the same tumor grade, since tumors are highly variable from patient to patient [6,7]. Thus, using molecular markers facilitate study of heterogeneity of glioma, and subsequently its diagnosis and treatment.

Intensive molecular analyses have revealed a variety of deregulated genetic pathways involved in the DNA damage and repair, apoptosis, cell migration, angiogenesis, and in the cell cycle. Molecular analyses show that they arise from different genomic alterations, which may influence the response to therapy. The Cancer Genome Atlas (TCGA) Research Network (2008) has established a comprehensive catalog of genomic abnormalities driving tumor genesis, thus subclassifying glioblastoma into at least four molecular subtypes, featuring distinct genetic, epigenetic, and transcriptional alterations [6,8]. Tumor variants are classified based on somatic mutations as: isocitrate dehydrogenase (IDH) and Tumor Protein (TP53). Glioblastoma is also classified based on it´s transcriptional signature as: classical, mesenchymal, neural or proneural. Classification is also given by variations in the number of gene copies, by mutations in Epidermal Growth Factor Receptor (EGFR) or by DNA hypermethylation of promotor-associated CpG islands [9].

The majority of glioblastoma cases are primary brain tumors that grow rapidly without major clinical or histological evidence of a less malignant precursor lesion. These tumors mainly affect the elderly and are genetically characterized by loss of heterozygosity (LOH) on 10q, EGFR amplification, p16INK4a deletion, and fosfatidilinositol-3,4,5-trisfosfato 3-fosfatasa (*PTEN*) mutations [10,11]. Secondary glioblastoma tumors develop through progression from low-grade diffuse astrocytoma or AA and are pronounced in younger patients [12]. The disruption of tumor-suppressor gene *TP53* is implicated in the progression of many types of human malignancies; adult glioblastoma patients with *TP53* mutation may have a more severe consequence than those without *TP53* mutations [10]. It has also been shown that *TP53* mutations, but not *p53* expression, correlate with a more aggressive form of the disease. Studies have also reported that glioblastoma with *TP53* mutations are more frequent in women than in men, and may occur in younger patients [13]. In addition, some studies suggest that *TP53* mutations may occur in patients of any age group. In contrast, EGFR amplification preferentially occurs in older patients. Thus, multiple genes are involved in the initiation of the disease, and variability occurs in different age and sex groups in the progression of GBM. It is of interest that after careful analysis of age and disease progression, no significant difference in survival was observed in patients with primary and secondary glioblastoma. During the progression of glioblastoma, additional mutations and genetic alterations accumulate, which may alter disease severity and patient survival.

GBM primary and secondary can also differ significantly, depending on their pattern of promoter methylation and in the expression of profiles at the RNA and protein levels. LOH on 10q is shown to be most frequent in both primary and secondary glioblastomas [14]. *TP53* mutations are detected early in the pathway, and frequent genetic alterations can lead to secondary glioblastoma. In 77 Japanese patients with GBM primary, 22% had *TP53* mutations, 21% *PTEN* mutations, 32% *EGFR* amplification, 42% *p16 INK4a* homozygous deletion, and 69% LOH on chromosome 10q in those patients [15]. The frequencies of these

genetic alterations at the population level were similar to those reported in Europe. This study noted a positive association between *EGFR* amplification and *p16 INK4a* deletion.

4. Glioblastoma multiforme risk factors

GBM is the most aggressive form of malignant glioma. Several syndromes are associated with the increased incidence of GBM, such as Lynch syndrome, Li–Fraumeni syndrome, melanoma–neural system tumor syndrome, Ollier disease, and Maffucci syndrome [16]. A small proportion (5–10%) of patients has a family history of glioma. Genes too exist that are involved in gliomagenesis and participate in glioma growth, such as telomerase reverse transcriptase (TERT) [17], *EGFR* [18,19], coiled-coil domain containing protein 26 (*CCDC26*) [20],Cyclin-dependent Kinase inhibitor 2B [17], *TP53* [21,22,23], and the regulator of telomere elongation helicase 1 (*RTEL1*) [24,25].

5. Endocrine characteristics of GBM

5.1. Estrogen receptors

GBM exhibits different endocrine characteristics. GBM expresses high levels of estrogen receptor alpha (mRNA ERα) and low levels of estrogen receptor beta (ERß); expression of mRNA ERα is positively correlated to the survival of GBM patients and could be used as a prognostic factor [26]. In contrast, the low expression of ERß in GBM has been related to a worse prognosis for survival and could be used as a biomarker for prognosis too [27,28]. Furthermore, activation of the signaling pathways induced by ERβ suppresses glioma growth in a model in vivo [29].

The coactivator family of estrogen receptors (SRC) is composed of three members, SRC-1, SRC-2, and SRC-3 [30,31]. SRC-1 increases the transcriptional activity of ER [32,33]; it also participates in the tumor progression and survival of several lines of human cancer [34,35]. SRC-2 is localized in different regions of the brain and mediates a variety of steroids-dependent functions [36,37]. SRC-3 is overexpressed in different types of cancer (breast, ovary, prostate, stomach, endometrium, esophagus, and pancreas) [38,39,40,41]. In astrocytoma cell lines, SRC1 and SRC-3 have been detected [42]. 17-/*i*> estradiol induces the growth of several cell lines of human astrocytoma through the ERα, and its interaction with SRC-1 and SRC3 suggests that ERα has an important role in the growth of astrocytoma [43].

5.2. Progesterone receptors in GBM

Progesterone receptors (PRs) are expressed in 100% of high-grade astrocytomas. The predominant isoform expression of PR in GBM is PRB. In astrocytomas, the molecular mechanisms involved in the differential expression of PR isoforms are unknown. It is important to know what PR isoform is expressed in the brain tumor, because progesterone can exert different cell functions depending on the expression pattern of PR isoforms [44,45].

In several cell contexts, human PRB functions as a transcriptional activator of progesterone-responsive genes, whereas PRA acts a repressor of transcriptional steroid hormone receptors inclusive PRB [46]; PR expression assessed by immunohistochemistry directly correlates with the histological grades of astrocytomas; these results suggest that PR-positive tumors possess a high proliferative potential [47]. However, no conclusive data exists about the PR as a marker of prognosis.

Progesterone significantly decreases GBM tumor growth and promotes the survival time in approximately 60% of mice. Synergistic effects of progesterone and Temozolomide (TMZ) have been observed in the glioblastoma cell lines U87MG and U118MG. A significant decrease in PCNA (a marker of cell proliferation) expression in both U87MG and U118 cell lines was observed by the effect of progesterone alone (80 μM) or by the combination of 80 μM progesterone and 100 μM TMZ, when compared to control, and this has a significantly statistic outcome than that with TMZ alone. Cell survival was reduced in 58%, with the combined treatment of progesterone and TMZ (P 80 μM + TMZ 100 μM after) when compared to that with MTZ alone. Further, progesterone inhibited O-6-methylguanine-DNA-methyltransferase (MGMT) expression as well as the EGFR/PI3K/AkT/mTOR signaling pathway, which is highly active in GBM. Progesterone + TMZ also inhibited the cell migration, suggesting that the combination therapy could contain the spread of tumor in vivo [48].

5.3. Androgen receptor in GBM

The androgen receptor (AR) is present in astrocytomas of low and high grades, with a higher expression in AA compared to astrocytomas grade I, II, and GBM. AR expression no affect the survival time of GBM patients [49,50] described a higher expression of AR in GBM tumors in women and men compared to periphery normal brain tissue.

5.4. Aromatase

Aromatase is an enzyme encoded by *CYP19* gene localized in chromosome 15q 21.2. It converts androgens in estrogens; this enzyme is expressed mainly in ovary, testis, placenta, brain, lung, stomach, and adipose tissue [51]. Aromatase is composed of 503 amino acids and is the major source for estrogen production in postmenopausal women. The aromatase works in three steps; first, the C19 methyl group of androgenic substrate is oxidized to formic acid in concomitant aromatization of ring A to the characteristic phenolic ring A of estrogen [52].

Aromatase expression in GBM tumor is negatively correlated to the survival of GBM patients and has been proposed as a possible prognosis biomarker for astrocytomas [29].

17–ß estradiol levels in GBM tumor are highest, compared to low-grade astrocytomas (I, II) or astrocytoma anaplastic (grade III). The concentration of 17–ß estradiol in GBM seems to be directly involved in the tumor growth.

6. GBM treatment

GBM tumors show a large number of aberrations with a pronounced mitotic activity, neoangiogenesis, and necrosis. Its proliferative rate is three to five times more than the proliferative rate in AA [53].

On the basis of a recent GBM classification as proneural, neural, classical, and mesenchymal, diverse types of treatments must be created to make a molecular personalized therapy [6] (**Table 1**). Performing molecular assays is complex, as their cost may be an obstacle for a routine use.

Treatment	Overall survival (OS)	Progression-free survival (PFS)	Side effects	Author
TMZ/RT	14.6 months	6.9 months	Myelosuppression	Stupp (2005)
RT	12.1 months	5.0 months	Skin reactions, cardiac complications	Stupp (2005)
Bev/TMZ /RT	20.5 months	10.7 months	Myelosuppression, arterial thromboembolism, gastrointestinal perforation	Gilbert (2014) Chinot (2014)
Bev	15.7	10.6	Arterial thromboembolism, arterial gastrointestinal perforation	
Cilengitide/RT	26.3 months	13.5 months		Stupp (2014)
Nimotuzumab/RT	22.3 months	7.7 months	Headache, nausea, vomiting, anemia, myalgia	Westphal (2015)
Nimustine	28.4 months	18.9 months	Chest pain and cianosis peribucal	Kim (2011)
Enzastaurin	17.1 months	9 months	Lymphopenia	Wick (2013)
Tipifarnib	80.3 weeks	18.1 weeks	Headache, nausea, vomiting	Ducassou (2013)
Everolimus	13.9 months	11.3 months	Anemia, higher levels of cholesterol in the blood, low phosphorus	Hainsworth (2012)

Table 1. Effects on survival of different treatments for GBM patients and their side effects.

The standard treatment for GBM patients includes brain radiation, a maximal surgery and .chemotherapy with the alkylating agent TMZ.

A larger number of new drugs and virus-based therapy are being evaluated in phase II and III trials as well.

In a phase III trial including recently diagnosed GBM patients, the median overall survival (OS) for GBM patients was 14.6 months with chemotherapy and RT, and 12.1 months with RT alone with a median follow-up of 28 months [63].

In phase III of another study, 978 patients received standard radiation and TMZ with or without Bevacizumab, an angiogenesis inhibitor used at 10 mg/kg, every 2 weeks with a median follow-up of 20.5 months. The OS between bevacizumab group and placebo group was no different, and side effects such as hypertension, thromboembolic events, intestinal perforation, and neutropenia were more common in the bevacizumab group. The progression-free survival (PFS) was significantly improved in the experimental arm (10.7 vs 7.3 months, $P = 0.007$) [64]. In another phase (III) trial with 458 patients, newly diagnosed GBM received radiation and TMZ with or without bevacizumab (10 mg/kg each for 2 weeks and TMZ for six cycles). With bevacizumab monotherapy (15 mg/kg), the median of PFS was of 10.6 months in the bevacizumab group as compared to 6.2 months in the placebo group.

6.1. Aromatase inhibitors (AIs)

The conversion of androstenedione and testosterone to estrogens can be blocked by the aromatase inhibitors; these pharmacological agents have a high specific activity to reduce, importantly, estrogen production. The AIs are classified in two types: I.—steroid inhibitors and II.—nonsteroid inhibitors; they are reactive species that bind covalently and irreversibly or noncovalently and reversibly to aromatase, respectively. The latter class interacts with the heme cofactor by employing its azole moiety. Third generation inhibitors are composed of triazole derivatives: anastrozole, letrozole, and the steroidal examestane. These inhibitors provided greater clinical benefits with a robust aromatase inhibition of 98% or more. The aromatase inhibitors have been successfully used for the treatment of estrogen receptor-positive breast cancer in postmenopausal women [65]. Letrozole has a more potent inhibitory effect on estrogen synthesis than anastrozole [66]. Letrozole has been tested in a GBM model using Sprague–Dawley rats orthotopically implanted with C6 cells. Imaging analysis employing μPET/CT showed an important reduction in the volume of tumor (>75%) after 8 days of letrozole treatment (4 mg/kg/day) [67].

The AIs, namely 3b-hydroxyandrost-4-en-17-one (1), androst-4-en-17-one (12), 4a,5a-epoxy androstan-17-one (13a), and 5a-androst-2-en-17-one (16), induced an antiproliferative effect on MCF7 breast cancer cells, and this effect was due to a cell cycle arrest and cell death by apoptosis [68]. Table 1 shows different treatments for GBM and their effect on OS. It also exhibits the progression-free survival, with the side effects observed in these studies.

6.2. Hormone release growth hormone (GHRH) inhibitors

GHRH inhibitors had been used for the treatment of various cancers or disorders that express growth hormone (GH) or GHRH production. GHRH antagonists suppress GH or insulin-like growth factor (IGF-1) in transgenic mice overexpressing the *GHRH* gene; GHRH antagonists can inhibit the rat pituitary tumor cells overexpressing the GHRH receptors (p-GHRH-R). These antagonists also inhibit GH secretion [70]. There is evidence that GHRH antagonists are well tolerated in humans; however, more phase I–III clinical trials are necessary to probe the efficiency of these antagonists [71]. GHRH antagonists inhibit cancers that depend on IGF-1 as a growth factor [72–74]. GHRH antagonists can also inhibit various autocrine factors such as GHRH, GH, or VEGF by binding to the tumoral GHRH receptors, resulting in a tumor

growth suppression [75,76]. In addition, GHRH antagonists could provoke tumor cell death by active cell pathways producing apoptosis [77,78].

The presence of the GHRH-R variant SV1 differs from the pGHRH by a short segment of the extracellular ligand-binding domain of the receptor protein in normal tissue and in various neoplastic tumors, lymphomas, small-cell lung carcinomas, pancreatic cancer, glioblastomas, and prostate cancer [79–81]. In several experimentally formed tumors, GHRH antagonist inhibits the growth and metastasis of cells expressing these receptor types. This inhibition occurs by binding to the full length of the GHRH-R or SV1 [79,80,82]. Kovácks et al., 2010 observed a strong GH release inhibition by the JV-1-63, reducing tumor growth (46%) of DBTRG-05 glioblastomas. Their experiments were conducted on nude mice. JV-1-63 antagonists caused an upregulation of mRNA expression of pGHRHR and downregulation of SV1 expression in vitro [82].

The use of aromatase and GHRH inhibitors could have a clinical use in patients with GBM once adequate phase II or III clinical trials are made.

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