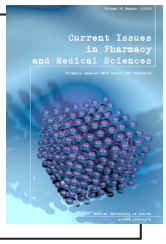
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New therapeutic strategies based on molecularly targeted therapy in glioblastoma – a case report and review of the literature

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ABSTRACT

Glioblastomas are the most common and most lethal forms of malignant primary brain tumor. We present a case report of a patient with III-grade glioma who achieved stable disease (SD) and clinical improvement after trametinib administration. We also report a review of the literature to Current Treatment Guidelines of Glioblastoma and new therapeutic strategies based on molecularly targeted therapy. Traditional treatments, including surgery, radiotherapy, and chemotherapy, have many limitations concerning the prognosis of patients with glioblastomas. Unfortunately, these tumors'recur after primary resection in the majority of cases. There is no standard therapy for recurrence of GBM. Targeted therapy offers a promising new treatment strategy. Regardless of those outstanding results much more can be done in the field of therapeutic options. Most urgent concerns include potent combining molecular targeted therapy with other types of treatments, selecting a group of patients for whom they turn out to be the most beneficial, and addressing adverse events of these molecules.

INTRODUCTION

Anaplastic astrocytomas (AAs) are a group of primary brain and diffusely infiltrating tumors [1,2]. AAs can be divided into subgroups based on 1p/19q co-deletion status and isocitrate dehydrogenese (IDH) mutation status. However, these subgroups have similar molecular profiles and median survival. The tumors with co-deletion of chromosomes 1p and 19q and IDH mutation have better prognosis in comparison to those with IDH mutation and without 1p/19q co-deletion. AA with wild-type IDH have the worst prognosis and share many molecular alterations with glioblastoma [1]. In contrast, presence of the NOA-o4 trial O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is associated with improved progression-free survival (PFS), regardless of treatment allocation [1,3]. Of note: glioblastomas are the most common and most lethal forms of malignant primary brain tumor.

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Case presentation

In August 2020, a 35-year-old man was admitted to the Emergency Department in Lublin with a bilateral, intensifying headache accompanied by weakness and speech disorders for two days. He reported a severe headache which was the most intense before sleep, the pain subsided after taking a painkiller. He noted similar symptoms 6 months ago, which resolved spontaneously. The medical history of his family was unremarkable. In the patient history, viral hepatitis B infection and neurotic disorders were noted. Neurological examination revealed no further deficits, cranial nerves and pupil without deviation. The laboratory tests, including complete blood count, liver function, kidney function, erythrocyte sedimentation rate and metabolic profile, were within normal limits. A computed tomography scan revealed a mass lesion involving the right thalamus and mesencephalon measuring 50×37 mm and ventricular dilatation. Magnetic resonance imaging (MRI) confirmed a tumor of the midline brain. Due to its location, the lesion was considered unresectable. The patient underwent a stereotactic biopsy of the lesion, which demonstrated features consistent with

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World Health Organization (WHO) Grade III. The tumor tissue was preserved for immunohistochemical study. This revealed immunopositive reactions against the glioblastoma multiforme (GBM) biomarkers, with glial-fibrillary-acid-protein (GFAP) positive, MIB-1 (focal positive in 10% of cells), synaptophysin positive, AE1/AE3 negative and LCA positive in small lymphocytes of inflammatory infiltrate. At the same time, the neurosurgeons inserted a ventriculoperitoneal valve. After the operation, the patient was in logical contact and demonstrated good general condition. In December 2021, magnetic resonance imaging (MRI) showed the presence of an irregular cystic lesion with a high signal, both T1-weighted (T1W) and T2-weighted (T2W), which was enhanced after contrast administration. In January 2021, molecular testing confirmed the presence of methylation of the MGMT promoter. Unfortunately, the occurrence of chromosome deletion on 1p and 19q was not confirmed, which significantly worsened the prognosis and decreased the sensitivity to chemotherapy. Moreover, no IDH1 and IDH2 mutations were detected in the genes, which is a negative prognostic factor for patients with AA.

In October 2020, the patient initially received radical radiotherapy (27 fractions of 2 Gy, due to the brainstem location) with concurrent and adjuvant temozolomide (TMZ) chemotherapy. After radiation, MRI verified that the patient had not relapsed. From December 2020 to April 2021, the patient was treated with Temodal: the first cycle was 75 mg/m2/day, and the remainder of the cycles was 200 mg/m2/day for 5 days every 28 days. Unfortunately, the tumor progressed again after completion of six cycles of treatment.

In May 2022, the next line of systemic therapy based on procarbazine, lomustine, and vincristine (PCV) was implemented. After the cycle, 1 day 8 of chemotherapy, grade 2 thrombocytopenia developed.

Foundation One© Next-Generation Sequencing (NGS) was applied to identify new therapeutic strategies. Herein, liquid biopsy testing based on assay of tumor tissue demonstrated neurofibromin 1 (NF1), H3F3A and SOX2 amplification (of note: NF1 amplification remains a predictor of response to treatment with MEK inhibitors such as trametinib).

In light of the above data, trametinib was administered due after pharmaceutical company permission was obtained. Three months after starting therapy, MRI control was conducted, and the results showed a stable disease (SD). SD clinical condition of the patient has improved significantly and treatment has continued since to date.

Throughout the therapeutic period, the patient was treated in in the Department of Clinical Oncology and Chemotherapy in Lublin and in the Radiation Oncology Department in Cancer Hospital of Saint John from Dukla in Lublin. This case report is based on own observations in hospital and on the documents of the patient.

Current Treatment Guidelines of Glioblastoma (GBM)

Glioblastoma (GBM) is a brain cancer that contains a subpopulation of GBM stem-like cells (GSCs) that contribute to therapy-resistance [4]. The standard of care for III-grade glioma consists of maximal surgical resection, followed by chemoradiotherapy and, subsequently, adjuvant temozolomide, which confers a benefit in both progression-free survival (PFS) and overall survival (OS) [5,6]. Trials in diagnosed III glioma have shown survival benefits of the addition of chemotherapy to radiotherapy. Compared with initial treatment with radiotherapy alone, temozolomide and procarbazine, lomustine, and vincristine (PCV) administration have been shown to improve survival [6]. Unfortunately, these tumors recur after primary resection in the majority of cases, and there is no standard therapy for recurrence of GBM. Combining anti-angiogenic therapy to chemotherapy is often considered to be still associated with poor prognosis. According to current knowledge, ~70% of all patients with GBM experience recurrence within 1 year of diagnosis, and the median survival time is merely 14.4 months [7]. The blood-brain barrier significantly limits the access of many systemically administered chemotherapeutics to the tumor, pointing toward a stringent need for new therapeutic patterns.

Surgery

Surgery is regarded as the best choice for astrocytoma treatment [8]. Comprehensive application of surgery and radiotherapy prolong a median survival of 9 to 12 months. However, this management has no effect on the time of the onset of relapse [9].

Chemotherapy

There is evidence suggest that chemotherapy combined with surgery and radiotherapy shows only marginal benefits [10]. However, a meta-analysis of randomized trials confirms the effectiveness of chemotherapy in patients with diagnosed gliomas and should be included in the therapeutic standard [11-13]. The most common applied are nitrosoureas (carmustine [BCNU] and lomustine [CCNU]). Some studies suggest the combination of BCNU and cisplatin or carboplatin should increase response rates. Still, this regimen has moderate toxicity and there were no tangible survival benefits compared with radiation therapy plus BCNU alone [13].

Molecularly targeted therapies

New targeted therapies are continually emerging as promising new clinical strategies.

Inhibitors of vascular endothelial growth factor (VEGF)

Angiogenesis plays an important role in glioblastoma progression. Consequently, the best treatment option should be therapy targeting the complex of glioblastoma microenvironment and tumor vasculature [14]. Hypoxic tumor cells, particularly those surrounding the necrotic core, produce vascular growth factors (VEGF). This process stimulates the formation of new blood vessels from healthy endothelial cells, which plays a main role in glioblastoma development and growth. Adjuvant therapies containing antiangiogenic treatment (AAT) target the VEGF–VEGFR pathway [4]. The anti-angiogenic strategy contains antibodies that bind VEGF and molecule tyrosine kinase inhibitors (TKIs), which block VEGF receptor (VEGFR) activation. Of interest, engineered

peptides or monoclonal antibodies directly block VEGF binding [15].

Bevacizumab

The Food and Drug Administration (FDA) approved the use of bevacizumab (a humanized monoclonal antibody that inhibits VEGF-A) for therapy of recurrent glioblastoma in 2009. Bevacizumab was the first medicament to apply a novel mechanism of actionthat was distinct from cytotoxic chemotherapy. Trials showed that adding bevacizumab to standard chemoradiotherapy improved progression-free survival (PFS), with preservation of quality of life and reduced corticosteroids use. Unfortunately, despite high hopes for the drug and the therapeutic rationale for angiogenic therapies in glioblastoma, no significant improvements in overall survival OS have been achieved [16-18].

Regorafenib

Regorafenib is an oral inhibitor of several kinases involved in the mechanisms that regulate neoangiogenesis processes through inhibition of vascular endothelial growth factor (VEGF) receptors and modifications of the tumor microenvironment. The clinical benefit of regorafenib is well established in metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GIST) and unresectable hepatocellular carcinoma HCC [19,20]. Glioblastomas show a high level of expression of proangiogenic factors, triggering the activation of multiple signaling pathways in the tumor microenvironment, including VEGFR, FGFR, and PDGFR [21,22].

Recently, results of a randomized, multicentre, open-label phase 2 REGOMA trial performed in ten Italian centers have been published. Patients with advanced glioblastoma with documented disease progression after surgery followed by radiotherapy (RT) and (temozolomide) TMZ chemotherapy were randomly assigned to receive regorafenib (REG) or lomustine. At the median follow-up of 15·4 months, regorafenib significantly improved OS (median OS: 7.4 *vs* 5.6 months) and PFS (6-month PFS: 16.9% *vs* 8.3%) when compared with the active comparator, lomustine. However, treatment-related adverse events occurred in 56% and 40%, respectively [23]. Currently, regorafenib therapy is being evaluated in an open-label, randomized, phase 2/3 multi-arm platform GBM AGILE trial in newly diagnosed (ND) and recurrent glioblastoma [24].

Inhibition of mitogen-activated extracellular signal-regulated kinase (MEK)

Molecular-targeted therapies under investigation for NF1-associated gliomas include mTOR-inhibitors and MAPK-inhibitors and, most commonly, MEK-inhibitors. Accordingly, NF1 mutation has been observed in 5-6% of lower grade gliomas and 9-14% of glioblastoma multiforme (GBM) cases, while homozygous deletion of NF1 was observed in 1% of lower grade gliomas and 2-3% of GBMs [25]. The reported outcome was that NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with lower-grade gliomas (II-III), but not in those with GBM70 [26].

Trametinib

Trametinib is an oral highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. In trials of trametinib in NF1-associated low-grade gliomas, there have been 7 cases of Partial Response (PR) lasting more than 6 months, including 2 patients with pilocytic astrocytoma, 2 patients with diffuse astrocytoma and 3 patients with low-grade glioma [27]. Rare Oncology Agnostic Research (ROAR) – a multicentre open-label, single-arm, phase 2 study, documented dabrafenib plus trametinib as having clinically meaningful activity in patients with BRAFV600E mutation-positive recurrent or refractory high-grade and low-grade gliomas, with a safety profile consistent with that in other indications [28].

Selumetinib

The MEK1/2 inhibitor, selumetinib, has demonstrated clinical activity in low-grade glioma. A multicentre, phase 2 trial of the selumetinib in patients with recurrent, refractory or progressive pediatric low-grade glioma after at least one standard therapy, showed long-term benefits and disease control in all (25) patients. The progression-free survival (PFS) at 2 years was 96% [29].

Sapanisertib

Sapanisertib is a dual mTORC1/2 kinase inhibitor. Karisa C. Schreck et al. sought to evaluate the sensitivity of seven genomically characterized, patient-derived glioblastoma neurosphere cell lines to sapanisertib alone or in combination with the MEK1/2 inhibitor, trametinib. The derived data demonstrated that combined MEK/mTOR inhibition is synergistic in glioblastoma cell lines and may be more beneficial in NF1-deficient glioblastoma [30,31].

Another clinical trial found similar trends: combining 2 new oral drugs led to synergized suppressing of the growth of pediatric low-grade glioma (pLGG) by reducing tumor vascularity and endothelial cell growth and migration. According to the report, combination treatment increased median survival by 70%, compared with mono treatment and control cohorts [32]. Additional trials of other MEK inhibitors are still ongoing.

Side effects of therapy with MEK-inhibitors

Overall, MEK-inhibitors are well tolerated with relatively few adverse effects. The most common side effects are cutaneous manifestations such as maculopapular rash, paronychia and acneiform dermatitis [33]. The rash usually occurs in a mild or moderate intensity (I-II degree in 40-64% of patients), rarely in grades 3-4 (in 4-12%) [34]. Generally, skin and nail toxicity are reversible by stopping the medication. No long-term or irreversible side effects were observed. In addition, the treatment with MEK-inhibitors is characterized by an increased risk of undesirable effects, including ocular disorders such as retinal detachment, serous retinopathy and retinal vein occlusion.

BRAF V600 Mutations and *Dabrafenib*

BRAF V600E is a rare mutation in malignant glioma. Burger et al. studied patients with glioma who suffered from markedly disseminated leptomeningeal disease, and used dabrafenib to cross the blood-brain barrier and to enhance concentration in cerebrospinal fluid [35]. The derived evidence suggests employing dabrafenib with a MEK inhibitor such as trametinib to treat malignant melanoma with BRAF mutation [35-37]. Moreover, the new study showed that a combination of dabrafenib with trametinib is clinically meaningful in patients with BRAFV600E mutation-positive recurrent or refractory high-grade glioma [28].

Inhibition of fibroblast growth factor receptor (FGFR) *Infigratinib*

FGFR and TACC- alterations are present in a subgroup of glioblastoma [38]. The most common aberrations occur in receptor FGFR1 and FGFR3 in about 8% of all gliomas [38,39]. Infigratinib is a strong ATP-competitive FGFR1–3–selective tyrosine kinase inhibitor that can be used for the treatment of patients with FGFR-driven conditions [40]. The study by Lassman et al., however, demonstrated that single-agent infigratinib had limited efficacy in patients with recurrent gliomas, except for the subgroups with FGFR1 or FGFR3 point mutations or FGFR3 fusions, with durable disease control lasting > 1 year [40].

Inhibition of tropomyosin receptor kinase (TRK) *Entrektinib* and *Larotrectinib*

Fusions involving neurotrophic tyrosine receptor kinase (NTRK) genes are detected in ≤ 2% of all glioblastomas. Adult NTRK-fused gliomas typically involve NTRK1 and have predominantly high-grade histology [41]. Generally, NTRK fusions are mutually exclusive with other common mitogenic driver alterations that activate MAPK signaling [42].

Entrektinib

Entrectinib is a specific TRK inhibitor that shows antitumor activity against NTRK gene fusion-positive solid tumors. It is approved for use by the FDA (the American Federal Drug Administration) and EMA (European Medical Administration) in patients with tumors harboring a TRK fusion or a ROS1-fusion [43-45]. In trials, entrectinib was found to cross the blood-brain barrier and maintain intracranial therapeutic levels, which is important for the targeted therapies [43,45]. Mayr et al. revealed that combined therapy of entrectinib, trametinib and abemaciclib enhanced the anticancer effects. Moreover, this study also documented that combination of entrectinib with radiotherapy or intrathecal chemotherapy is harmless and also enhances the antitumor activity [43].

Larotrectinib

Larotrectinib is a first-generation, highly selective tropomyosin receptor kinase (TRK) inhibitor that is approved by FDA to treat adult and pediatric patients with TRK fusion-positive cancer. Clinical trials showed the significant advantage of larotrectinib administration in patients with TRK fusion-positive primary central nervous system (CNS) tumors. It demonstrated rapid and durable responses, a high disease control rate and a favorable safety profile [46,47].

Lorlatinib

ALK inhibitors such as lorlatinib are useful for the treatment of primary tumors with ALK-fusion of the central nervous system because the medicament penetrates the central nervous system [48]. Shaw et al. noted that oral lorlatinib treatment attained both systemic and intracranial effects in patients with ALK- and ROS1-positive NSCLC, 72% of whom had metastases to the Central Nervous System [49,50].

CONCLUSION

Considering the great social burden of nervous system neoplasms, the key engagement of today's oncology seems to be finding efficient therapeutic options. Traditional treatments, including surgery, radiotherapy and chemotherapy, have many limitations concerning the prognosis of patients with glioblastomas. Targeted therapy offers a promising new treatment strategy. Last year brought a wide spectrum of novel approaches to neoplasms. Understanding the molecular mechanisms underlying the development of cancer has allowed applying innovative medicines targeting concrete spots in cancerogenesis. Many clinical trials have demonstrated the efficiency of molecular targeted therapies in glioblastoma and other central nervous system neoplasms. After establishing the results of clinical trials, the FDA has decided to approve a few of this pharmaceutics in therapy schemes. Regardless of these outstanding results, much more can be done in the field of therapeutic options. Most urgent concerns include combining molecular targeted therapy with other types of treatments, selecting a group of patients for whom they turn out to be the most beneficial, and addressing the adverse events of these molecules.

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