CASE REPORT

Small Cell Glioblastoma: a Glioblastoma Subtype with an Unexpected Response

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Abstract

Small cell glioblastoma is a subtype of glioblastoma, an uncommon, with poor prognosis. Due to its rarity, reports of molecular genetics and immunohistochemistry are required to understand the tumor behavior. We report here the clinical history and results of the molecular analysis of a patient diagnosed with small cell glioblastoma.

Keywords: small cell glioblastoma, molecular markers, carboplatin, bevacizumab.

Abstract

Glioblastomul cu celulă mică este un tip de glioblastom rar, cu prognostic prost. Din cauza rarității sale, rezultatele de genetică moleculară și imunohistochimie sunt necesare pentru înțelegerea comportamentului tumorii. Prezentăm aici evoluția clinică și rezultatele analizei moleculare, ale unui pacient diagnosticat cu glioblastom cu celulă mică.

Cuvinte cheie: glioblastom cu celulă mică, marker moleculari, carboplatin, bevacizumab.

INTRODUCTION

Glioblastoma (GBM) is the most aggressive, malignant (WHO grade IV) and most common brain tumor in adults that is defined by a great cellular and molecular heterogeneity.

Accumulating evidence suggests that this heterogeneity is one of the main features of tumorigenesis responsible for therapy resistance in GBM.

Even after receiving optimal therapy consisting of surgical resection, concurrent chemoradiotherapy with

Temozolomide (TMZ) and adjuvant six cycles TMZ, the median survival for glioblastoma patients is 14.6 months, with a two-year survival rate of 26.5% and five years survival rate of 9.8%¹.

Until recently, the histopathological classification by microscopic observation of specimen has been the only approach for pathologist and clinicians. The new *World Health Organization* (WHO 2016) Classification of Tumors of the CNS is based on the integration both histological and molecular criteria and enables more-precise tumor categorization².

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For the following years, a lot of information obtained from clinical and laboratory studies is expected to highlight the relevance and impact of this classification on diagnosis, prognosis and therapy³.

Small cell glioblastoma has been described and added as a pattern of glioblastoma in the 2016 WHO classification scheme, and is 10% of all glioblastoma cases^{4,5}.

As in GBM, the prognosis for small cell glioblastoma is poor, with a median survival time of 11 months⁵.

METHODS AND RESULTS

A 62-year-old male (Karnofsky = 80) with medical history of hypertension and type II diabetes mellitus developed headaches, difficulties in controlling right arm and right leg, rare moments of confusion, fatigue.

A 35/52/50 mm tumor mass, irregular, with necrosis areas and significant vasogenic edema, in the temporo-insular left regions with extension into the insular lobe and Sylvian sulcus which exert a mass effect on midline structures was visible on brain MRI.

On July 13th 2017, a subtotal resection was performed, with marked clinical improvement, postoperative evaluation of the patient indicating a 100 points Karnofsky performance status.

Pathology was consistent with a small cell glioblastoma. The bulletins of molecular genetics and immunohistochemistry show: IDH1 mutation, MGMT status unmethylated, homozygous deletions of cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), absence of 1p/19q codeletion and epidermal growth factor receptor (EGFR) amplification.

Radiation and TMZ were started one month later, according to the Stupp protocol. Therefore, the patient underwent adjuvant radiotherapy and TMZ. Radiotherapy has been administered using Intensity Modulated (IMRT) technique up to a total dose of 59,4 Gray, using a conventional 1.8 Gy fractionation scheme. During radiotherapy TMZ was administered using a 75 mg/m²/day regimen.

At follow-up MRI of the brain, approximately 5 weeks after completion of the therapy, partial response was reported.

Temozolomide was subsequently continued at 150 mg/m² daily five days out of a 28-day cycle for the first cycle and increased to 200 mg/m² for two next cycles.

A subsequent brain MRI was performed on February 04th 2018 and revealed tumor progression.

Based on the multidisciplinary board decision, Irinotecan 125 mg/m² every two weeks was added to the TMZ therapy for another 3 months.

Unfortunately, the follow up brain MRI performed, on April 26th of 2018, revealed progression tumor and an increase of the surrounding edema.

Furthermore, there is a new glioblastoma focus in the hypothalamus and new edema anteriorly to the thalamus and the internal capsule.

Lomustine treatment was initiated, but only one cycle, patient performance stats decreased to a 60 points Karnofsky score, evaluation MRI confirming tumor progression to the hypothalamus and thalamus and to the left occipital site (axial dimensions of 71/46 mm and caudal cranium of 57 mm).

A multidisciplinary board decided treatment with Bevacizumab (10 mg / kg, to 2 weeks) and Carboplatin /AUC5 to 4 weeks. Also, re-irradiation was taken into consideration.

Following the first treatment cycle, at neurological examination, an improved performance status of 80 points Karnofsky score was found.

The patient underwent re-irradiation up to a total dose of 8 Gy using volumetric-modulated arc therapy (VMAT) technique using a hypofractionated regimen of 4 Gy/fraction. Bevacizumab was not discontinued during radiotherapy.

At follow-up clinical examination the patient was found stationary, the brain MRI indicating a regression of the tumor (axial dimensions of 63/31 mm and caudal cranium of 40 mm) (Figure 1).

Figure 1. MRI reveals tumor reduction after therapy.

DISCUSSIONS

Small cell glioblastoma is a rare histological pattern of GBM, frequently resemble as anaplastic oligodendroglioma, being often misdiagnosed^{2,4,6}.

Small cell glioblastoma is defined by a monomorphic population of densely packed small, round neoplastic cells, with a high nuclear /cytoplasm ratio, a minimal atypia but with increased mitotic activity. In this situation, the determination of 1p/19q co-deletion (present in 80% of oligodendroglioma cases, and absent in GBM) and EGFR amplification (described in 83% of small cell GB cases and absent in oligodendroglioma) are very useful diagnostic tools⁵.

Significant progress has been made in the molecular markers analysis of brain tumors in the last few years. The clinical interest has focused on three molecular markers that have demonstrated significant clinical relevance: MGMT methylation status, IDH1 mutation and 1p/19q co-deletion.

The methylation status of the O-6-methylguanine-DNA methyltransferase (MGMT) promoter have prognostic and predictive value.

GBM with MGMT methylation status benefit from chemotherapy with alkylating-agents and therefore, have a better evolution, compared to GBM with unmethylated MGMT status⁷.

The simultaneous deletion of genetic material on chromosomal short arm 1 and on chromosomal long arm 19, known as 1p/19q codeletion or loss of heterozygosity=LOH, became a genetic signature of oligodendroglial tumors².

The IDH-1 and IDH-2 genes encode two critical metabolic enzymes, involved in the Krebs cycle, DNA repair and epigenetic regulation. Isocitrate dehydrogenase-1 is present in the peroxisomes and cytosol, while isocitrate dehydrogenase-2 it is present in the mitochondria.

These enzymes catalyze the oxidative carboxylation of isocitrate to alpha-ketoglutarate, CO₂ and NADP⁺ to NADPH, thus playing an important role in cellular defense against oxidative stress, while mutant isoforms IDH-1 (R132H) and IDH-2 (R172K) catalyze the conversion of α -ketoglutarate into the 2-hydroxyglutarate oncometabolite.

Thus, mutations may decrease NADPH formation, resulting in increased oxidative and hypoxic stress, ADN lesion^{8,9}.

The IDH1 gene mutations are the most common in codon 132 (IDH 1 R132H) while the IDH2 gene mutations are less frequent (about 3%) and are identi-

fied in codon 172 and associated with oligodendroglial tumors¹⁰.

IDH status has a diagnostic role in clinical practice: it makes possible to distinguish diffuse gliomas from reactive glioma or other tumor entities such as central neurocytoma, pilocytic astrocytoma; makes the difference between primary and secondary GBM¹¹.

Several studies have found the IDH1/2 mutation is strongly associated with a better prognosis¹².

In our case, as additional finding we observed is a CDNK2A/B homozygous deletion. Such a finding in an IDH mutated glioblastoma argues unfortunately for an unfavorable prognosis¹³.

According with our observation, a study has shown that platinum-based cytotoxic agents, specifically cisplatin induces *in vitro* sensitivity in IDH1 mutation cancer cells¹⁴.

However, the IDH status has no defined role in clinical decision making yet, within a tumor entity.

The treatment options for patients with recurrent/progressive glioblastoma are: surgery, re-irradiation, chemotherapy or immunotherapy.

Multiple chemotherapy options are available for second-line treatment, but no standard of care has been established. TMZ rechallenge, lomustine, irinotecan, carboplatin or bevacizumab if is available, represent widely accepted therapeutic options¹⁵.

Results reported so far have been generally discouraging in terms of overall survival; furthermore, the impact of the treatments on quality of life in patients is difficult to evaluate.

CONCLUSION

Glioblastoma is an incurable disease and new therapeutic approaches to improve survival are urgently needed. So far, despite the efforts, little progress has been made in the treatment of patients with glioblastoma.

Further research is needed on the role of IDH mutation as a predictor of the GBM response to the regimen of Bevacizumab and Carboplatin, re-irradiation.

Source of funding

This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/159/1.5/S/135760, co-financed by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Abbreviations:

GBM	glioblastoma multiforme
WHO	World Health Organization
TMZ	temozolomide
MRI	magnetic resonance imaging
CNS	central nervous system
IDH	isocitrate dehydrogenase
MGMT	O-6-methylguanine-DNA methyltransferase
EGFR	epidermal growth factor receptor
IMRT	image modulated radiotherapy
VMAT	volumetric modulated arc therapy
CDNK2A/B	cyclin-dependent kinase inhibitor 2A/B

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