UPDATES IN THE TREATMENT OF HIGH GRADE GLIOMAS

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Abstract
Primary tumors of the central nervous system (CNS) are a major cause of morbidity and mortality, with approximately 18,000 new cases diagnosed annually in the United States and Europe, of which more than half are high-grade glioma malignancy (grade IV). More than half of patients have survival of 5-6 months after diagnosis. This terrible disease with a growing prevalence has no specific tests to a highlight it. Computer tomography, magnetic resonance (with or without contrast substance) is the elective exam. Also there is no cure. Therapy consists of surgical resection of brain tumors, accompanied by adjuvant chemotherapy and radiotherapy.

Key words: multiform glioblastoma, WHO grade III/IV, multimodal treatment.

INTRODUCTION

Malignant tumors of the CNS are classified according to World Health Organization (WHO) criteria based on morphology with physiological cell tumor that resembles most. Pathologists will be identifying tumors with glial cell such as astrocytoma, oligodendroglioma, or ependymoma cells and with neuronal cells as medulloblastoma tumors (*Table 1*) (Cunliffe CH, et al., 2010). Prognosis of a patient diagnosed with a glioma WHO grade III (anaplastic astrocytoma, oligoastrocytoma, or anaplastic oligodendroglioma) is severe with an average survival of 36-48 months. Multiform glioblastoma (WHO grade IV) has an average survival index of 8-15 months since diagnosis. The prognosis of recurrent malignant gliomas resistant to chemo-radiotherapy is extremely serious and survival average is 3-9 months.

Table 1

WHO Classification of high-grade gliomas.

WHO grade III	WHO grade IV
anaplastic astrocytoma	multiform glioblastoma
anaplastic oligodendroglioma	Giant cell glioblastoma
anaplastic oligoastrocytoma	gliosarcoma
anaplastic ependymoma	medulloblastoma
choroid plexus carcinoma	PNET - primitive neuroectodermal tumors
gangliogliom anaplastic	of the CNS.
anaplastic hemangiopericytoma	atypical rhabdoid tumor / teratoid

MATERIAL AND METHODS

The work presents the analysis and synthesis of studies performed up until now, targeting the management of malignant glioma.

DISCUSSION

Microscopically multiform glioblastoma is characterized by the presence of small areas of necrosis surrounded by anaplastic cells. It also highlights the presence of hyperplastic blood vessels important in the differential diagnosis of grade III astrocytomas (Marin S.E. et al., 2010). A patient may present with a variety of signs and symptoms, such as headaches, epileptic seizures, convulsions, focal neurological deficits or behavioral or personality changes (Butowski NA. et al., 2006, Chamberlain M.C., 2011, Isolan G.R. et al., 2010). Classic headache may suggest increased intracranial pressure, the more severe morning and often accompanied by nausea or vomiting. Gliomas' semiology also include sleep disorders, gastrointestinal disorders, impaired memory or concentration, parezeoriparestezii, and bradycardia, dyslexia or even sings of meningitis (Behin A. et al., 2003, cainap C., 2009).

The diagnosis of malignancy is usually based on magnetic resonance imaging (MRI) or computed tomography (CT). Emphasizing a heterogeneous tumor mass surrounded by peritumoral edema solid glioblastomas frequently show a central area of necrosis and edema better represented than in anaplastic glioma. Functional MRI is useful in defining the relationship between sensory and motor areas and helps in neurosurgical planning (Pantelis E. et al., 2010). Diffusion-weighted imaging, diffusion-tensor imaging or contrast-enhanced dynamic MRI estimate the intensity of cerebral blood perfusion and monitor the answer to the adjuvant therapy. (Hoff B.A. et al., 2010). Magnetic resonance spectroscopy detects the intensity of cerebral metabolism and help in the differential diagnosis of a malignant tumor from a benign proliferation or necrosis. Cases of high-grade glioma will record an increase in the peak of the choline, which is equivalent to a membrane turn-over increased, but also a decrease of N-acetylaspartate peak equivalent to the decrease of neuronal cells (Dhermain F.G. et al., 2009). Positron emission tomography using isotopes such as 18F-deoxyglucose, 18F-L-thymidine, 11C-methionine and 3,4-dihydroxy-6-18F-L-phenylalanine are being evaluated for the diagnosis of CNS malignancy and in post-therapeutic follow-up (Lammering G. et al., 2010, Fueger B.J. et al., 2010). MRI studies performed in the first month post-radiotherapy show an increase in contrast enhancement, demonstrating a

transitory increase in the vascular permeability, phenomenon named tumor pseudo progression (Yaman E. et al., 2010).

Differential diagnosis between tumor pseudo progression and real progress is a challenge to modern brain imaging, particularly important in follow-up of patients post-therapy. Evolution of effective therapy of solid tumors was evaluated according to RECIST (Response Evaluation Criteria in Solid tumors) introduced initially in 2000 (Gehan E.A., Tefft M.C., 2000) and recently improved according to RECIST 1.1 criteria (Eisenhauer E. A. et al., 2009). The equivalent of these criteria in neuro-oncology is the MacDonald criteria (*Table 2*), which can evaluate the respond of malignant glioma to therapy (MecDonald D.R. et al., 1990). But MacDonald criteria are not sufficiently accurate in the differential diagnosis between tumor progression and pseudo progression – a crucial difference in establishing the efficiency of therapy and evaluation of randomized clinical trials in neuro-oncology (*Fig. 1 and 2*). A solution was presented in July 2010 at the ASCO conference (Americal Society for Clinical Oncology) by Quant and Wen as Rano criteria (Response Assesment in Neuro-Oncology) (*Table 3*) (Quant E.C., Wen P.Y., 2011).

Table 2.

MacDonald criteria for assessing the development of malignant gliomas

Response	Semiology	Medical Imaging	Therapy
Complet response	Clinically stabile disease	complete disappearance of any tumor mass that captures contrast substance for at least 4 weeks + exclusion of occurrence of new lesions	Exclusion of corticosteroid therapy
Partial response	Stable disease or clinically better	Decrease by> 50% compared to the sum of the perpendicular diameters of all masses visible radiographically for a minimum of 4 weeks + excluding the appearance of new lesions	stable or lower use of corticosteroid medication
Stable response	Clinically stable disease	Does not meet the criteria for a complete response, partial or for progression	Best supportive care
Tumor Progression	Clinical deterioration	Increase by> 25% the amount of perpendicular diameters of lesion imaging	Best supportive care

First-line treatment is complete surgical resection of gliomas. This principle is respected for over 100 years, since the appearance of neuro-oncological surgery, pioneered by Bennets Cushing (Rossitch E. Jr. et al., 1990). Because gliomas grow diffusely, often total resection is not possible, being replaced by partial resection of the primary tumor and leave behind besides reminiscence neoplastic tissue, cavity iso-dense cerebrospinal fluid compared to MRI examination. Planning is important before treatment because the primary tumor can be located in major motor or sensory areas.

In this case, it is desirable a more efficient removal of tumor cells to protect normal brain tissue, essential for physiological processes of the human body. One option is the use of neuronavigation and functional MRI for the differential diagnosis between malignant and normal tissue. But this is a limited option financially. An alternative is craniotomy with the patient awake and intraoperative cortical stimulation (Lubrano V. et al., 2010). This will test basic brain function and rescue normal tissue as possible. It is also accessible the neuropathological investigation based on the use of intraoperative substance PPIX (protoporphyrin IX), a fluorescent heme precursor preferentially taken up by tumor cells (*Fig. 3*) (Valdes P.A. et al., 2010).

Table 3.

RANO criteria

Diagnosis element	Complete response	Partial response	Stable disease	Progression
T1 Lesion gadolinium enhancing	no	> 50 % ↓	< 50% ↓, but > 25% ↑	>25 % ↑
T2/ FLAIR	stable / ↓	stable / ↓	stable / ↓	↑
New lesions	no	no	no	yes
Corticosteroids	no	stable / ↓	stable / ↓	Non applicable
Clinical Status	stable / ↑	stable / ↑	stable/ ↑	↓
Demands	all	all	all	any

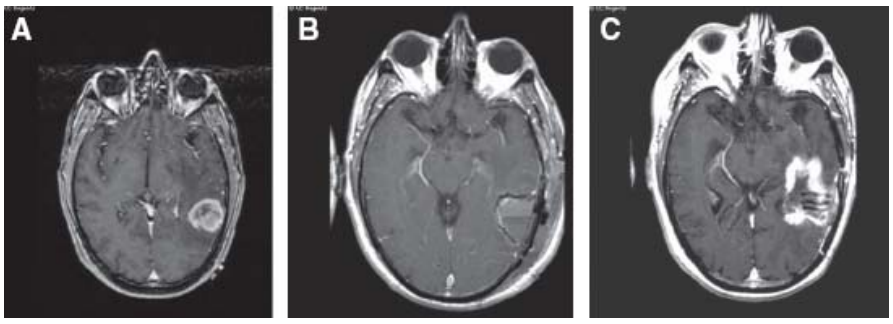

Figure 1. Pseudo progression of a malignant brain tumor post interstitial radiotherapy. A) Axial T1-enhanced MRI shows the tumor mass prior to neurosurgical intervention. B) Immediately post-resection MRI shows changes in brain parenchyma after excision of the tumor mass and 125-I seed placement. C) MRI at 18 months after treatment highlighting pseudo progression, although surgical intervention did not find remnants of neoplasia.

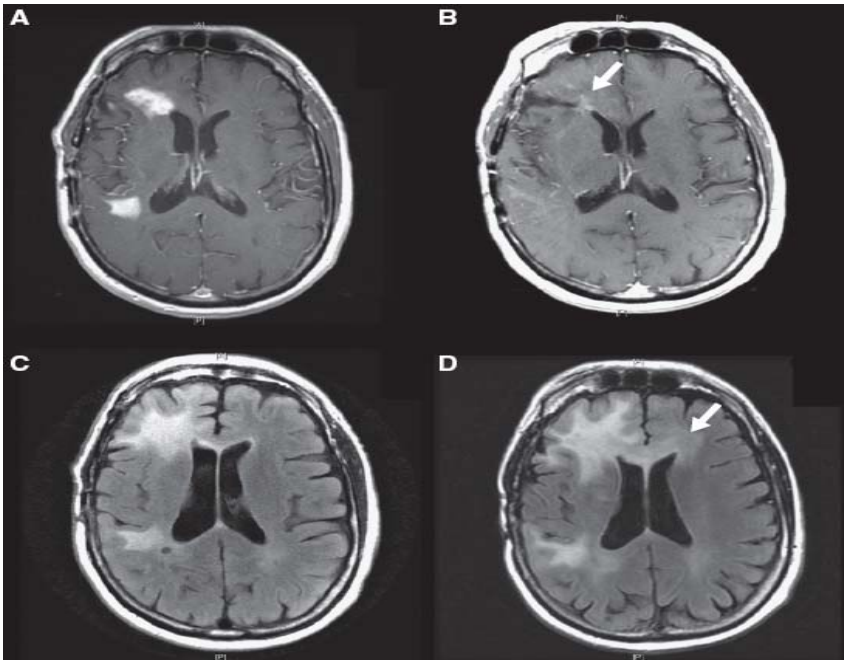

Figure 2. A patient of 54 years with progressive, recurrent glioblastoma, refractory to treatment with TMZ and becacizumab. A) T1-enhanced MRI showing a multifocal glioblastoma right frontal lobe. B) Regression of tumor mass 7 months after therapy, according to MacDonald criteria. C) MRI / FLAIR. D) MRI after another seven months showing corpus callosum invasion and progression of tumor mass in the left frontal lobe.

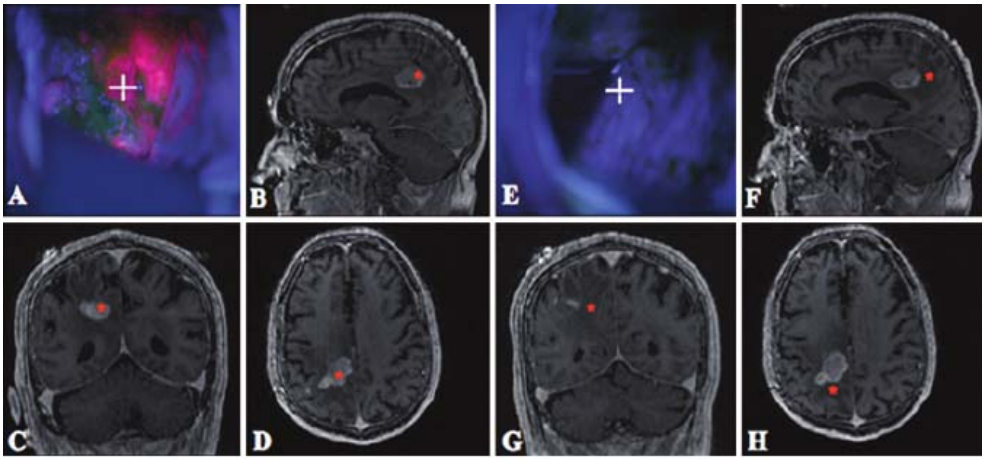

Figure 3. Malignant tumor parietal lobe. A) Intraoperatory view pre-excision - it can be seen taking fluorescent substance by tumor tissue. B-D) MRI showing classic primary tumor mass. E) Intraoperative view of the surgical field after removal of glioma. FH) post-neurosurgery MRI demonstrates macroscopic removal of the tumor mass.

Treatment of malignant glioma is multimodal, including adjuvant chemotherapy and radiotherapy. After resection or excisional biopsy, the standard protocol includes external radiation therapy (RTE) focal fractionated 60Gy in 30-33 fractions distributed with 1.8-2Gy/session irradiation (Stupp R. et al., 2010). In older patients or patients with low performance indicators, there are accepted shorter regimes, hipofractionate 40Gy in 15 sessions of radiation, and if those older than 70 years delivering 50Gy (28 x 1.8 Gy/session) has been shown to be superior compared with best supportive care (Ahmadi R. et al., 2009).

Increasing the dose of irradiation does not affect net benefits, but increases the probability of normal brain tissue necrosis. To minimize these risks there are developed stereotactic irradiation techniques (brachytherapy and radiosurgery) with increasing dose focal irradiation for primary gliomas and offering an alternative rescue therapy (salvage therapy) in patients with recurrent glioma, even in previously irradiated territory.

Originally developed by the Swedish neurosurgeon Lars Leskell, stereotactic radiosurgery propose precise administration of a single dose of radiation to a small focal lesions. RTOG (Radiation Treatment Oncology Group) defines radiosurgery as treatment of tumor foci <4 cm through a framework of Stereotaxis, convergence of multiple radiation fields in a single center, all in a single fraction of irradiation (Oermann E. et al., 2010).

The most common systems are sources of 60Co radiosurgery (Gamma Knife) or Cyber Knife type linear accelerators. Doses are between 15 and 24Gy for target of maximum diameter 20-40mm. Acute side effects such as brain edema, convulsions, aphasia or motor deficits are rare compared to classical radiation. Interstitial brachytherapy consists in placing multiple radioactive sources in tumor bed and enables administration of a complement dose with minimal normal tissue irradiation. The most common isotopes are 125I (low dose rate), 192Ir (high dose rate) or 32P or 90Y (Tselis N. et al., 2007). Radioactive sources may be temporary or permanent, ranging from energy between 30kV (125I) and 300kV (192Ir) being used as additional therapy in the treatment of multimodal gliomas. GliaSite irradiation system consists of administering a liquid 125I isotope as a new approach to intracavitary brachytherapy (Kleinberg L. et al., 2009). This system consists of a silicone balloon attached to a catheter implanted in the cavity resection during surgery and postoperatively filled with the solution of the radionuclide, thereby administering 40-60Gy to the target volume.

Initially, adjuvant chemotherapy consisted nitrosourea based chemotherapy, as carmustine (BCNU) or lomustine (CCNU) and property due to the solubility of these substances to overcome the blood-brain membrane. Subsequently Stupp et al. have demonstrated that ionizing

iradiation concomitant with administration of temozolomide in primary multiform glioblastoma prolongs median survival to 14.6 months. Approximately 15% of cases of glioblastoma can not benefit from standard treatment due to advanced age or low Karnofsky index, treatment consisting of chemotherapy with temozolomide exclusive, criteria ASCO 2010. Standard treatment consists of the injection of 75 mg/m² Temodal day, 7 days a week, about 1 to 2 hours before radiotherapy, during the entire RTE.

Daily administration of temozolomide may induce lymphocytopenia with lower CD4 + lymphocyte count below 200/mm³, possible pneumonia and opportunistic infectious agents, such as Pneumocytis carinii, justifying prophylactic administration of pentamidine or a combination of trimethoprim/ sulfametoxalol throughout chemo-radiotherapy.

Chemotherapy is discontinued if the platelet count falls below 75,000 mm³, or the number of neutrophils are lower than 1500/mm³ (Wen P.Y. et al., 2010).

Multiform glioblastoma shows a thousand times aplification of the VEGF gene compared with grade III gliomas, property that is manifested in terms of pathology and clinical by extremely rich tumor in neovascularization. As a result, it was proposed a multimodal therapy and administration of neovascular glial inhibitors. Bevacizumab is an anti-VEGF monoclonal antibody used successfully in combination with temozolomide (Wick W. et al., 2010), including counting benefits are extended median survival but also to reduce the doses of corticosteroids or relatively low risk of bleeding, even in patients receiving anticoagulant therapy additionally. Systemic chemotherapy in neuro-oncology is a special topic due to the protection of nerve tissue by blood-brain barrier. It is true that in case of malignant tumors, it may be interrupted due to the invasiveness of neoplasia, but not reached optimal concentration of cytotoxic agent. Intrathecal chemotherapy is possible or even under the skin using programmable pumps and Ommaya reservoir (Greenfield J.P., Schwartz T.H., 2008). But there are no large clinical trials, confirming the validity of these techniques as standard therapy.

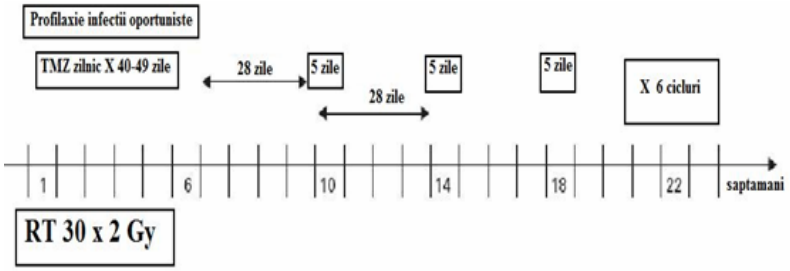

Figure 4. Conduct of malignant glioma therapeutics. (TMZ, temozolomide)

CONCLUSIONS

Despite progress in recent years, standard therapy for malignant gliomas (*Fig.4*) is merely palliative, but if we cure the patient diagnosed with brain cancer and prolong life not just a few months, a different approach is needed. One solution could be molecular targeted therapy and personalized medicine nanotechnology; today we have various preliminary data from in vitro test using laboratory animals or even Phase I or II trials (*Table 4.*) (Grossman S.A. et al., 2010, Hoover J.M. et al., 2010, Drappats J. et al., 2010, Galanis E. et al., 2009).

Table 4.

International Trials Update on molecular targeted therapy of high-grade malignant gliomas.

Drug	Phaze	No. patients	Institution	Details
Cilengitide	I / II	112	NABTT, USA	On going
Temsirolimus	I	46	NCCTG, USA	On going
Cetuximab	I /II	46	University of Medicine from Heidelberg, Germany	Without the use of TMZ
Vatalanib	I /II	180	EORTC, Europe	Study interrupted in phase I
Vorinostat	II	66	Mayo Clinic, USA	Trial of NCCTG
Cilengitide	I / II	52	Centre Hospitalier Vaudois, Laussanne, Switzerland	In association with TMZ
CpG oligonucleotides	II	31	Gustave Roussy Institute, Paris, France	On going
Lenalidomide	I /II	60	Dana Farber Cancer Center / Harvard Medical School, USA	Phase II in combination with TMZ and raditheray
Valproic acid	II	41	National Cancer Institute, USA	Histone deacetylase inhibitor
Carmustine wafer	II	72	Sidney Kimmel Cancer Center Johns Hopkins University, USA	On going

* NABTT – New Approaches to Brain Tumor Therapy CNS Consortium
NCCTG – North Central Cancer Treatment Group
EORTC – European Organisation for Research and Treatment of Cancer
TMZ - Temozolomide

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