Review Article
Volume 12:10, 2021
DOI: 10.37421/jch.2021.12.601

Journal of
Cytology & Histology

ISSN: 2157-7099 Open Access

Glioblastoma: Novel Therapeutic Approaches

Stanley S. Stylli*

Department of Surgery, University of Melbourne, Royal Melbourne Hospital, Parkville, VIC 3050, Australia

Abstract

Glioblastoma (GBM) is the most widely recognized essential focal sensory system cancer in grown-ups. It is a profoundly obtrusive sickness, making it hard to accomplish a total careful resection, bringing about helpless anticipation with a middle endurance of 12–15 months after conclusion, and under 5% of patients endure over 5 years. Careful, instrument innovation, demonstrative and radio/chemotherapeutic procedures have gradually developed after some time; however this has not converted into huge expansions in persistent endurance. The current norm of care for GBM patients including a medical procedure, radiotherapy, and attendant chemotherapy temozolomide (known as the Stupp convention), has just given an unassuming increment of 2.5 months in middle endurance, since the milestone distribution in 2005. There has been impressive exertion as of late to expand our insight into the sub-atomic scene of GBM through propels in innovation, for example, cutting edge sequencing, which has prompted the delineation of the infection into a few hereditary subtypes. Flow therapies are a long way from acceptable, and concentrate on exploring procured/inborn protection from momentum treatments; confined medication conveyance, inter/intra-tumoral heterogeneity, drug repurposing and a cancer invulnerable shifty climate have been the focal point of extraordinary examination over ongoing years. While the clinical headway of GBM therapeutics has seen restricted movement contrasted with different malignant growths, improvements in clever treatment procedures that are being explored are showing empowering signs for fighting this infection. This point of this audit is to give a short outline of a chose number of these clever helpful methodologies.

Keywords: Glioblastoma • Glioma • Temozolomide • Radiotherapy • Immunotherapy • Novel Therapy • Personalized Treatment • Drug Repurposing

Introduction

It is over a long time since Percival Bailey and Harvey Cushing distributed the principal characterization of mind growths [1] and formulated the term 'glioblastoma multiforme', despite the fact that gliomas had been recently reported. Gliomas are the most widely recognized dangerous growth in grown-ups and they represent around 80% of all mind related malignancies [2]. The twenty-second (22nd) factual report (2012–2016; 408,133 records) distributed by CBTRUS (Central Brain Tumor Registry of the United States) is the biggest populace based essential cerebrum cancer/focal sensory system (CNS) growth vault in the United States [2]. The normal yearly age-changed rate pace of threatening mind/other CNS growths was 7.08 per 100,000 and the most usually happening harmful cerebrum/other CNS cancer was GBM (14.6% of all growths; 48.3% of every single dangerous cancer; 25,510 dangerous growths expected in 2019). GBM likewise represented most of all gliomas (57.3%) with an occurrence pace of 3.22 per 100,000. The five-year relative endurance rate following analysis of a dangerous cerebrum/other CNS cancer was 35.8%, however this was altogether lower for GBM at 6.8%. The occurrence likewise increments with age, with a middle of 65 years. Careful resection alone gave an endurance advantage of around 3–6 months, which expanded to 12.1 months with the incorporation of radiotherapy treatment and a further slight increment to 14.6 months was seen with the expansion of associative and adjuvant temozolomide. The World Health Organization (WHO), groups cerebrum growths utilizing a reviewing framework, with grade I being the most un-forceful and the best guess, to grade IV being the most harmful with the most exceedingly terrible visualization [3]. GBM can present as a once more essential growth (around 90% of GBM patients), without histological/clinical proof of a lower grade sore, or as an optional GBM emerging from lower grade gliomas, for example, a diffuse astrocytoma or anaplastic astrocytoma. Essential and auxiliary GBMs are histopathologically unclear; in any case, optional GBM patients are for the most part more youthful, present with a more good anticipation, and contrast in their atomic mark. In 2010, The Cancer Genome Atlas (TCGA), introduced a multidimensional examination of 216 GBM growth tests fully intent on portraying the GBM genomic scene. A few significant genomic changes were distinguished. Epidermal Growth Factor Receptor (EGFR) enhancement/transformations, Phosphatase and tensin homolog (PTEN) cancellation/changes and CDKN2Ap16INK4a were most often seen in essential GBM, while the genomic adjustments normal to auxiliary GBM included isocitrate dehydrogenase 1/2 (IDH1/2) or Tumor protein 53 (TP53) changes. IDH1 was likewise recognized as the most dependable indicative sub-atomic marker of auxiliary GBM, as the transformation happened all the more often in optional GBM patients which associated with a further developed in general endurance. Enormous scope genomic concentrates, for example, the TCGA prompted the distinguishing proof of four GBM clinical subtypes: mesenchymal, traditional, proneural, and neural, described by irregularities in EGFR, IDH1, neurofibromin 1 (NF1), and platelet-inferred development factor receptor A (PDGFRA). Mesenchymal GBMs show an overexpression of mesenchymal and astrocytic markers, notwithstanding a NF1 cancellation, and are seen in more seasoned patients with a helpless anticipation. The traditional subtype is related with EGFR enhancement, is profoundly proliferative and seen in more established patients, likewise with a helpless anticipation. Forceful, higher-grade cancers are related with these two subtypes. Proneural and neural subtype GBMs are for the most part seen in more youthful patients, present with IDH1, PDGFRA, PIK3C, TP53 modifications (proneural), or qualities associated with sensory system advancement (neural) and are less forceful cancers. Thusly, another grouping was proposed by Verhaak [4], at last prompting a 2016 update of the WHO Classification of CNS growths dependent on the mix of atomic boundaries into symptomatic methods recently dependent on histopathological highlights. This sub-atomic based methodology is basic in deciding the likely reaction to current treatment conventions that might impact patient anticipation and the plan and execution of fittingly designated treatments.

***Address for Correspondence:** Stanley S. Stylli, Department of Surgery, University of Melbourne, Royal Melbourne Hospital, Parkville, VIC 3050, Australia*

Received 16 October 2021; **Accepted** 30 October 2021; **Published** 06 November 2021

Therapeutic Strategies for Glioblastoma

Targeted Therapies

With the headway of cutting edge sequencing and the exhaustive sub-atomic planning of GBM, a few potential targets have been recognized and different procedures are being assessed as medicines for GBM. IDH changes, which

exist in big numbers in optional GBM, include both a misfortune and gain of catalyst work. There is an unusual amassing of 2-hydroxyglutarate (2-HG), which is a driver of tumorigenesis. A few IDH inhibitors are presently being assessed in clinical preliminaries, including AG-120 (mIDH1 inhibitor), AG881 (vague IDH inhibitor), FT-21-2 (mIDH1 inhibitor), and IDH305 (an IDH1 R132H inhibitor). EGFR inhibitors, for example, gefitinib, erlotinib, and afatinib have neglected to show an endurance advantage in GBM, despite the fact that they have been fruitful in different tumors. The initiation of numerous receptor tyrosine kinase (RTK) pathways in GBM has likewise been proposed as a detour for single objective based systems; along these lines, endeavors have been made to assess little atom inhibitors with different targets like Regorafenib. A stage II preliminary showed an expansion in generally endurance for repetitive GBM, while a current worldwide stage I/II preliminary (GBM AGILE) is assessing regorafenib with numerous treatment boundaries for recently and intermittent GBM.

Depatuxizumab Mafodotin, otherwise called ABT-414, is an investigational hostile to EGFR monoclonal neutralizer drug form. ABT-414 focuses on the growth cells by connecting the counter microtubule specialist, monomethyl auristatin F, with a neutralizer coordinated against EGFR or freak EGFRvIII. Members inside a stage I companion who showed EGFR enhancement had an affirmed reaction, and this is right now being explored in a stage II preliminary with ABT-414 and temozolomide in repetitive EGFR-intensified GBM. Monoclonal antibodies address one more class of designated specialists that have been utilized due to their high explicitness and liking to their objectives. Bevacizumab, which ties to VEGF (vascular endothelial development factor), hindering the development of veins, gotten sped up FDA endorsement subsequent to empowering stage I/II preliminaries, yet while stage III investigations showed some drawn out movement free endurance, there was no noticed generally speaking endurance advantage [5–7]. Cetuximab (EGFR monoclonal counter acting agent), likewise neglected to show endurance benefits in stage II preliminaries, recognizing a possible shortcoming in the monoclonal neutralizer treatment procedure with deficient cancer penetrance because of their size and confined capacity in intersection the blood mind obstruction.

Chemotherapy

TMZ has been the primary line treatment following a medical procedure and radiotherapy. This randomized clinical review showed a huge endurance advantage with the expansion of TMZ to radiotherapy (27.2% versus 10.9% endurance at 2 years). Be that as it may, not all GBM patients react to this treatment known as the Stupp convention, while others may ultimately show intrinsic or procured chemoresistance, eventually bringing about growth repeat. A positive prognostic pointer for TMZ-based chemotherapy for recently determined GBM was associated to have MGMT quality methylation.

The director preliminary, examining elective timetables of TMZ treatment, discovered no distinction in result between their treatment conventions, yet they additionally saw that MGMT advertiser methylation was a prognostic marker in the TMZ treatment of repetitive GBM patients. DNA alkylating specialists, known as nitrosoureas including lomustine (CCNU), carmustine (BCNU), and nimustine (ACNU) have been utilized in the treatment of GBM, yet they are for the most part kept away from because of the presence of foundational incidental effects including concealment of bone marrow and extreme kidney/liver poison levels. Be that as it may, improvement in the endurance of intermittent and recently analyzed GBM patients has been as of late saw with the arrangement of carmustine wafers in the resection pit, diminishing foundational incidental effects. In any case, it is expected that the clinical viability of nitrosourea-based treatment conventions will be more noticeable in GBM patients with cancers showing MGMT advertiser methylation [8,9].

Since the advancement of new therapeutics is related with significant expenses and slow advancement to fruitful execution in the center, drug repurposing has arisen as an appealing technique, because of lower costs and an abbreviated time for change to the facility for another sign. For instance, a review testing Metformin, which is used in the administration for diabetes mellitus type 2, shown that the movement free endurance of patients with GBM and metformin-treated diabetes was altogether expanded. Moreover, a joined investigation of 1731 patients in the AVAglio, CENTRIC, and CORE preliminaries didn't show a huge improvement in by and large endurance with metformin, yet there was a huge danger proportion noticed for movement free endurance in these patients at gauge. Nonsteroidal calming medications, for example, celecoxib have been examined because of empowering brings about pre-clinical research center based investigations. The incorporation of celecoxib as an adjuvant to therapeutics, for example, temozolomide, while showing great decency, was uncertain as far as giving a huge endurance advantage. Right now, the DIRECT stage II/III multicenter preliminary is analyzing the adequacy of disulfiram (strong inhibitor of aldehyde dehydrogenase) in a randomized controlled review with GBM patients, due for essential fulfillment toward the finish of 2021.

All things considered, a solitary objective, single-drug technique has been the focal point of medication disclosure, lab based investigations, and clinical treatment. In any case, because of the hereditary heterogeneity of GBM cancers, a multitarget approach with the repurposing of a few medications as a pharmacological therapy convention has been thought of and is in progress. This was at first known as the CUSP9 preliminary; however it has gone through a few adjustments and is currently known as CUSPv3. The genomic profiling of GBM cancers, combined with the bioinformatic coordinate of sub-atomic anomalies with drug libraries and the comparing realized medication focuses in planning a customized drug mixed drink is being assessed [10]. Various chemotherapeutic specialists are being scrutinized, and it is past this publication to examine and list every one of the finished and continuous preliminaries.

Tumor Treating Fields (TT Fields)

In 2011, a therapy innovation known as growth treating fields (TTFs), which uses moderate recurrence (200 KHz), low-force (1 V/cm) constantly conveyed electric fields to specifically target multiplying cancer cells by repressing mitosis was endorsed for the therapy of intermittent GBM by the FDA. The principal TTF gadget endorsed by the FDA, known as NovoTTF-100A, made by Novocure, shows restraint worked, with the field generator being mounted on their shaved scalp. The outcomes from the underlying preliminaries seem, by all accounts, to be empowering; when TTF was joined with TMZ chemotherapy, a huge expansion in general endurance (20.9 months versus 16 months) contrasted with TMZ alone was noticed, shaping the establishment for additional continuous preliminaries inspecting the adequacy of joining TTFields with chemotherapy in the treatment of GBM [11].

Laser Interstitial Therapy

Incidentally, GBM patients may not be possibility for careful debulking of the cancer by means of an open craniotomy, and a moderately new strategy known as 'Laser Interstitial Thermal Therapy' (LITT) is being tested as an expected cytoreductive procedure in annihilating growth cells through a confined raised temperature. It includes the inclusion of a MRI-directed laser-tip test into the cancer to convey low-controlled laser-incited thermotherapy. The underlying examinations have shown that this treatment is protected, and a further developed endurance noticed for patients with growths where troublesome careful access might be reachable.

Radiotherapy

The current norm of care for GBM includes the mix of radiotherapy with chemotherapy. Customarily, entire cerebrum radiation treatment was utilized. Anyway because of the results of openness of the ordinary mind to radiation, like intellectual weakness, current practice uses central radiotherapy therapy. The all out radiotherapy portion of 60 Gy is regularly conveyed more than 30 parts of 2 Gy with adjuvant temozolomide, with the fractionated treatment permitting typical synapses encompassing the cancer therapy region to recuperate between every therapy. Radiation portion acceleration endeavors have brought about expanded tissue harm and incidental effects, with no critical change in endurance, henceforth there has been a work in investigating other potential radiotherapy based procedures. Interstitial brachytherapy which requires the position of radioactive isotopes (or seeds) into the careful cavity isn't a completely new therapy, yet because of proceeding with concerns, for example, radiation spillage into the encompassing mind, endeavors into

improving brachytherapy are in progress, including the delayed conveyance of higher portions of radiation, utilization of elective isotopes, and designated conveyance through the mix of isotopes with monoclonal antibodies. A treatment known as GammaTile, which includes embedding embodied radioactive cesium-131 seeds into the careful hole, was as of late supported by the FDA for the treatment of GBM and needs to date exhibited practicality and wellbeing [12].

Proton Beam Therapy (PBT) has additionally been examined as a remedial choice for GBM, as the related 'Bragg Peak Effect' diminishes radiation openness to the encompassing mind with the utilization of more modest therapy target volumes, accommodating a lower hazard of incidental effects like neurocognitive decrease. Portion heightening examinations have been performed, for certain noticed poison levels, however it has likewise been demonstrated to be a protected treatment choice, bringing about a slight endurance advantage for intermittent GBM. Stage II preliminaries are in progress, assessing the viability of PBT as a bleeding edge treatment contrasted with standard portion radiotherapy with TMZ. The conveyance of high portion radiation to the growth can likewise be accomplished through Gamma Knife Radiosurgery, which has been used for the therapy of repetitive GBM. It has been seen that critical radiation-prompted edema happens in patients who get high radiation dosages; nonetheless, these unfavorable incidental effects were decreased, and patient endurance delayed when joined with bevacizumab [13].

Immunotherapies

Given the achievement that has been exhibited with immunotherapeutic techniques in treating different malignant growths, there has been impressive exertion into additionally making an interpretation of this into a treatment for GBM patients. Generally, the mind is viewed as a safe advantaged organ because of the presence of the blood cerebrum hindrance (BBB) and the shortfall of a lymphatic seepage framework. Notwithstanding, hostile to growth invulnerable reactions have been seen in mind cancers, which are proposed to be worked with by the presence of a lymphatic framework. As a rule, immunotherapy has been more fruitful in treating cancers with a high mutational weight, yet GBM has a low growth mutational weight, while likewise showing an immunosuppressive climate, and the additional complexity that chemotherapeutics can likewise advance an immunosuppressive impact. By and by, as immunotherapy includes outfitting the resistant framework to destroy growth cells, a few unique systems have been investigated with the objective to help have invulnerability against GBM. Safe designated spot barricade has been used to accomplish incitement of the insusceptible framework with a huge exertion zeroing in on hindering the limiting of designated spot receptors on safe cells like Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) (early T-cell restraint) and Programmed Cell Death protein 1 (PD-1) (late T-cell hindrance) to their relating ligands on cancer cells advancing a more powerful T cell reaction against the growth. Various designated spot inhibitors that have been supported for use in a few diseases have been tested in the treatment of intermittent GBM, including nivolumab, pembrolizumab, durvalumab, atezolizumab. The primer outcomes have been not exactly motivating; notwithstanding, there are continuous examinations concerning concentrating on biomarkers that might distinguish which patients might react to designated spot barricade, the mutational heap of the growth as an indicator of reaction, organization of PD-1 antibodies before cancer resection to actuate an early enemy of growth reaction, or break down the impacts of radiotherapy, which might be a synergistic facilitator of reaction to immunotherapy [14].

Immune system microorganism treatment includes the utilization of autologous T-cells, which are hereditarily designed to communicate illusory antigen receptor (CAR) develops and have been FDA-supported for the treatment of hematologic malignancies. A few stage I preliminaries have given empowering indications as far as security, attainability and possible adequacy against applicable GBM surface antigens including IL13Ra2, HER2, EphA2 and EGFRVIII. Despite the fact that the underlying outcomes have been promising, it is expected that, because of the serious level of heterogeneity showed by GBM cancers, T-cell treatment will be regulated as a blend treatment, possibly with invulnerable designated spot bar.

Antibody based procedures are likewise being researched as a possible supportive immunotherapy for GBM by animating an antigen-explicit effector T cell reaction against growth explicit antigens (TSA) or cancer related antigens (TAA). A few methodologies have been used including cell-based conventions (patient-inferred dendritic cell and autologous cancer cell antibodies) and non-cell based conventions (peptide and hotness shock protein immunizations). Designed peptide groupings that give a designated insusceptibility against growth related antigens bound to significant histocompatibility edifices structure the premise of peptide immunizations. An illustration of two peptide antibodies are rindopepimut (EGFRvIII) and SurVaxM (Survivin) [15]. While rindopepimut showed amazing reactions in the beginning stage contemplates, an endurance advantage was not seen in the stage III assessment. In any case, a different stage II review consolidating rindopepimut with temozolomide further developed movement free and generally endurance for GBM patients, just as the exhibit of empowering brings about a stage II review joining rindopepimut with bevacizumab in the treatment of repetitive GBM patients. A stage II review assessing SurVaxM has shown upgrades in movement free and generally speaking endurance [16]. Hotness shock proteins have additionally been used to convey an assortment of cancer antigens and are intended to make an enemy of growth incendiary reaction. HSPPC-96 is one such immunization, which has gone through a stage II, multicenter clinical preliminary for intermittent GBM. Autologous growth cell based antibodies utilize cytotoxic T lymphocytes that are incited with patient-inferred cancer cells, which then, at that point, in this manner get an invulnerable reaction, whenever they are once again introduced once more into the patient. Dendritic cell antibodies depend on understanding inferred dendritic cells that are presented to cleansed cancer explicit antigens or growth cell extricates got from the growth prior to being once again introduced to the patient, accordingly actuating CD8+ and CD4+ T cells. A stage I preliminary with an autologous dendritic cell immunization has shown a relationship between the articulation level of growth related antigens on the glioma cells and delayed generally speaking/movement free quiet endurance. Viral-based treatment that includes conveyance of the quality of premium by means of viral vectors is likewise being examined as a type of immunotherapy for treating GBM. Oncolytic infections can specifically repeat in growth cells, inspiring cytotoxic impacts, at last giving an immunostimulatory impact. DNX-2401 is a replication-equipped adenovirus that utilizes growth explicit integrins to create oncolytic outcomes, though PVSRIPO (lessened polio-rhinovirus fabrication) perceives CD155 (poliovirus receptor), which is generally communicated in cancer cells [17].

Conclusion

The treatment of GBM keeps on being a mind boggling and troublesome test. Past endeavors to discover a fix have just brought about a slight improvement in endurance throughout the most recent 50 years, as the current 5-year endurance rate stays low at <10%. As there are restrictions on the occasions the current remedial methodology of medical procedure, radiotherapy, and chemotherapy can be used, the best original restorative specialist or therapy convention, as a feature of a multimodal system, should capacity to take out any lingering growth. At last, this might be accomplished by the synergistic impacts of joining some of the current restorative techniques momentarily laid out in this publication, including a designated treatment, immunotherapy, chemotherapy, or radiotherapy, as treatment obstruction might conceivably create to a solitary treatment. The improvement of new and novel treatments has been supported by the significant endeavors to interpret the genomic scene of GBM with the development of cutting edge sequencing, prompting alterations in cancer arrangement and the 'sub-atomic' clinical administration of some GBM patients.

Over the long haul, the restorative choices accessible will increment with extra targetable and noteworthy mixes of genomic changes and modifications being uncovered, as just a little division to date have been exhibited to have clinical execution. Significantly, as cancer heterogeneity and patient-to-patient inconstancy adding to the development of GBM and reaction to therapy is driven by the genomics of every growth, a customized therapy approach through the definition of patients into atomic subgroups will be basic in their

assignment to the most fitting novel therapy system that will be accessible later on administration of GBM. The proceeded with cooperation among analysts and clinicians, combined with progressions in innovation, both experimentally and clinically, accommodates a hopeful future that new and powerful medicines will be created for GBM patients.

References

1. Bailey Percival and Harvey Cushing. “A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis.” Lippincott (1926).
2. Ostrom Quinn T, Gino Cioffi, Haley Gittleman, Nirav Patil and Kristin Waite et al. "CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016." *Neuro Oncol* 21(2019): 1-100.
3. Louis David N, Hiroko Ohgaki, Otmar D Wiestler, Webster K Cavenee and Peter C. Burger, et al. "The 2007 WHO classification of tumours of the central nervous system." *Acta Neuropathol* 114(2007):97-109.
4. Verhaak Roel GW, Katherine A Hoadley, Elizabeth Purdom, Victoria Wang and Yuan Qi, et al. "Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1." *Cancer cell* 17(2010):98-110.
5. Gilbert Mark R, Sulman EP and Mehta MP. “Bevacizumab for newly diagnosed glioblastoma." *N Engl J Med* 370(2014):2048-2049.
6. Hamza Mohamed A, Jacob J Mandel, Charles A Conrad, Mark R Gilbert and WK Alfred Yung et al. "Survival outcome of early versus delayed bevacizumab treatment in patients with recurrent glioblastoma." *J. Neurooncol* 119(2014):35-140.
7. Gilbert Mark R, James J Dignam, Terri S Armstrong, Jeffrey S Wefel and Deborah T Blumenthal et al. "A randomized trial of bevacizumab for newly diagnosed glioblastoma." *N Engl J Med* 370(2014):699-708.
8. Taal Walter, Carin CD van der Rijt, Winand NM Dinjens, Peter AE Sillevis Smitt and Agnes AACM Wertenbroek et al. "Treatment of large low-grade oligodendroglial tumors with upfront procarbazine, lomustine, and vincristine chemotherapy with long follow-up: a retrospective cohort study with growth kinetics." *J Neurooncol* 121(2015):365-372.
9. Taal Walter, Hendrika M Oosterkamp, Annemiek ME Walenkamp, Hendrikus J Dubbink and Laurens V. Beerepoot et al. "Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial." *Lancet Oncol* 15(2014):943-953.
10. Byron Sara A, Nhan L Tran, Rebecca F Halperin, Joanna J Phillips and John G. Kuhn et al. "Prospective feasibility trial for genomics-informed treatment in recurrent and progressive glioblastoma." *Clin Cancer Res* 24(2018):295-305.
11. Rahmathulla Gazanfar, Pablo F Recinos, Kambiz Kamian, Alireza M Mohammadi and Manmeet S. Ahluwalia et al. "MRI-guided laser interstitial thermal therapy in neuro-oncology: a review of its current clinical applications." *Oncology* 87(2014):67-82.
12. Gessler Dominic J, Clara Ferreira, Kathryn Dusenbery and Clark C Chen. "GammaTile: surgically targeted radiation therapy for glioblastomas." *Future Oncol* 16(2020):2445-2455.
13. Koga Tomoyuki, Keisuke Maruyama, Minoru Tanaka, Yasushi Ino and Nobuhito Saito et al. "Extended field stereotactic radiosurgery for recurrent glioblastoma." *Cancer* 118(2012):4193-4200.
14. Cloughesy Timothy F, Aaron Y Mochizuki, Joey R Orpilla, Willy Hugo and Alexander H Lee et al. "Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma." *Nat Med* 25(2019):477-486.
15. Fenstermaker Robert A and Michael J Ciesielski. "Challenges in the development of a survivin vaccine (SurVaxM) for malignant glioma." *Expert Rev. Vaccines* 13(2014):377-385.
16. Fenstermaker Robert A, Michael J Ciesielski, Jingxin Qiu, Nuo Yang and Cheryl L Frank et al. "Clinical study of a survivin long peptide vaccine (SurVaxM) in patients with recurrent malignant glioma." *Cancer Immunol Immunother* 65(2016):1339-1352.
17. Desjardins Annick, Matthias Gromeier, James E Herndon, Nike Beaubier and Dani P Bolognesi et al. "Recurrent glioblastoma treated with recombinant poliovirus." *N Engl J Med* 379(2018):150-161.

How to cite this article: Stanley S. Stylli. "Glioblastoma: Novel Therapeutic Approaches." *J Cytol Histol* 12 (2021): 601.