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LETTER TO THE EDITOR

Developments in Glioblastoma-Specific Molecular Treatment

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Dear Editor,

In terms of incidence, recurrence rate, and biological activity, glioblastoma, abbreviated as GB, is the most prevalent kind of high-grade intracranial malignant tumor [1]. Approximately 0.59-3.69 per 100,000 people are diagnosed with GBM with a median onset age of 63.0 years, making up 15.4% of all primary brain tumors and 45.6% of all malignant brain tumors every year. Males have age-adjusted morbidity of 3.97, while females have a morbidity of 2.53 per 100,000. GBMs impact roughly 1500 people in Italy each year, whereas in the United States, 12,120 instances of GBM were identified [2, 3].

Based on differences in their genomes, GB may be subdivided into the following four primary subtypes: (1) classical, (2) neural, (3) mesenchymal, and (4) pro-neural. These four categories each have a unique gene alteration pattern, suggesting that patients may benefit from individualized treatment approaches. In addition, several studies have concluded that various gene subtypes and distributions of gene alterations reflect a variety of immunological states in the tumor microenvironment [4].

This kind of cancer arises from the astrocytic lineage. It is not known from where these cells originated; they might be glial precursor cells or neural stem cells, but they are not mature astrocytes. GBM cells quickly penetrate the surrounding brain tissue, producing a histopathological inflammatory pattern that is characterized by endothelial necrosis as a consequence. GBMs are high-grade (IV) gliomas that have angiogenesis, robust proliferation, and a distinctive necrotic lesion known as “pseudopalissading necrosis.” They also have microvascular proliferations that are often related to thrombosis. The invasiveness of GBM is rooted in the many signaling pathways and interactions between the tumor and its surroundings as well as its host cells [4 - 6].

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Surgical resection, followed by adjuvant radiation with concurrent oral temozolomide, followed by adjuvant chemotherapy with TMZ alone, is the standard treatment for newly diagnosed GBM in persons up to the age of 70. Even with this treatment regimen, more than 90% of GB patients will have recurrence and progression [7]. Standard radiotherapy treatment plans for cancer patients use 30-33 fractions of irradiation at 180-200cGy each fraction, for a total dose of 5940 cGy to 6000 cGy. Survival rates at two years (27.2% *vs*. 10.9%) and five years (27.2% *vs*. 10.9%) have also shown that this regimen improves overall survival (11.1 percent *vs*. 14.6%). The typical overall survival period for individuals with primary GB is 12–15 months, with a 5-year survival rate of just 9.8 percent [8].

Tumor hypoxic zones may have higher amounts of altered, self-maintaining mesenchymal cancer stem cells, leading to palisading necrosis and the initiation of tumor development. Patients with GBM have a poor outlook despite a variety of treatment choices. Tumors that are resistant to treatment, tumor invasion, migration, and immunodeficiency are all factors that make them difficult to treat [9]. High-throughput screening and genetic data have made understanding the pathophysiology of glial tumors easier. Significant cellular heterogeneity and a hierarchical structure with GSCs exhibiting a therapy-resistant phenotype may explain tumor recurrence and local invasiveness and, as a result, may be a target for future therapeutics [10].

Therapies for this neoplasia have a significant failure rate, linked to the persistence of self-renewing glioma stem cells (GSCs), which repopulate treated tumors. Performance status, age, grade, specific markers, and possibly the extent of resection are prognostic factors involved in survival. If the IDH1/2 gene is mutated, the prognosis may improve [11].

The median survival duration for patients with glioblastoma has risen in recent years thanks to the development of tumor treatment fields (TTfields), although this improvement has lasted for less than 20 months [12]. And since there aren't any good treatments for recurrent Glioblastoma (rGB), the average patient only has 6–11 months

of overall survival. High levels of vascular endothelial growth factor (VEGF) expression and robust angiogenesis are hallmarks of this malignancy. For rGB, the FDA has approved bevacizumab, a humanized monoclonal antibody against VEGF, as the standard gold treatment for reducing tumor blood flow and volume [13, 14]. However, BEV has been shown to alter tumor blood vessels and produce vascular malformations, which may render tumors more hypoxic and resistant to treatment. Glioblastoma research at every level, from preclinical to clinical, with the challenges to the treatment of rGB is the main focus of this report [15 - 19].

Recently, there has been a surge in interest in the use of immunotherapy, which employs a patient's T cells transduced with a tumor antigen (TA)-specific chimeric antigen receptor as an effector mechanism (CAR). This technique has shown excellent clinical responses in individuals with hematological malignancies, but it has had little success in patients with solid tumors, including GBM, so far [20].

Recent research indicates that various glioma characteristics, such as malignancy, resistance to treatment, and relapses, are linked to epigenetic changes in tumor-specific genes. Runt-related transcription factor 3 (RUNX3) is a possible tumor suppressor gene since its inactivation has been linked to cancer development. Steponaits *et al.,* found that RUNX3 is unregulated at both the epigenetic (methylation) and functional (protein expression) levels from the beginning of gliomagenesis and that these alterations are closely related to patient age and survival as well as pathological tumor grade [21]. Because the gene is methylated and repressed in GBM cell lines, the functional analysis demonstrated putative-oncosupressive activity of RUNX3 in astrocytomas, and restoration of RUNX3 expression dramatically decreased tumor cell viability. The research found that the frequency of RUNX3 gene methylation increases during gliomagenesis, whereas RUNX3 protein expression decreases dramatically in astrocytic origin tumors of various grades, and that these variations are closely linked to patient clinicopathological characteristics. RUNX3's considerable influence on patient survival as well as other clinicopathological aspects, suggests that the gene might be used as a prognostic marker in astrocytomas [22, 23].

Aurora kinases, a kind of serine/threonine kinase, are one of the most searched therapeutic targets for glioblastoma. They are a protein family made up of three members: Aurora-A, Aurora-B, and Aurora-C, all of which play diverse functions in cell division by regulating chromosomal segregation. These genes are dysregulated in glioblastoma. In GBM, inhibiting Aurora kinases has a synergistic or sensitizing impact with radio, chemo, or other targeted agents. Several Aurora kinase inhibitors are now being tested in humans. A significant body of research indicates that inhibiting these proteins may be a potential technique for treating this cancer. Magalhaes *et al.*, work offers persuasive evidence that these proteins play an important role in GBM development and might be exploited as therapeutic targets for tumor therapy [24]. According to the review, inhibiting Aurora kinases may reduce the development of GBM cells *in vivo* and *in vitro*, with promising preclinical outcomes. Several Aurora kinase inhibitors have been shown to have lethal effects in GBM, either alone or in conjunction with chemotherapeutic drugs, and a limited number of them have entered clinical trials. Based on the data presented here, the use of Aurora kinase inhibitors in single or combination exposure may provide new options for individuals suffering from this deadly malignancy.

GBM cell behavior and plasticity were studied using live cell imaging [25]. These researchers used TSA and SAHA to pharmacologically decrease HDAC activity in GBM cell lines (U87-MG) as well as primary tumors (GBM011). After 72 hours of *in vitro* therapy with an HDAC inhibitor, GBM cells formed tunneling tubes that seemed to be independent of TGF-induced EMT [11]. When HDAC activity was suppressed, voltage-sensitive Ca^{++} signaling in live cells was shown to be impaired. Cell competence and plasticity are diminished when HDAC activity is suppressed *in vitro*, as shown by the decrease in Vimentin and Connexin gene expression. Xenografts were used to study the impact of GBM oncospheres on the embryonic neural tube of a chick. GBM cells implanted into the embryonic neural tube following treatment with HDAC inhibitors developed HNK-1 ectopically for the first time, a tumor suppressor marker associated with improved survival. The first time we've shown that HDAC inhibition affects tumor cell shape and capacity to react effectively to environmental signals *in vivo*. GBM treatment may be improved by addressing epigenetics, which is critical to tumor cell plasticity [26].

The blood-brain barrier (BBB) is made up of special endothelial cells that help generate blood arteries in the brain. Brain tissue can only be protected from potentially dangerous substances if the BBB allows the flow of physiologically essential molecules. High-molecular-weight compounds are prevented from entering the brain parenchyma due to occluding cell junctions that block off the endothelium. This results in significantly more selective filtration than other capillaries' endothelial cells. An extra “barrier” is provided by the “glial limiting membrane” that surrounds the BBB's endothelial cells. Though BBB structural integrity is typically disrupted in individuals with GBM, drug delivery to GBM remains a serious issue. When the BBB is bypassed in different ways, tumors are better able to absorb therapeutic medications [27]. In a study, researchers use convection-enhanced delivery (CED), a treatment combining radiation and chemotherapy with various anticancer medicines. CED-based strategies were tested in phase II and phase III clinical trials to see whether they were as successful as other approaches. For this reason, drug absorption by the tumor is enhanced and CED's bypass of the BBB avoids systemic toxicities.

Patients with newly diagnosed and long-term glioblastoma (GBM) who are currently getting TTFields treatment were recruited from around the globe to participate in research designed to gather real-world patient-reported quality-of-life (QoL) data. Patients who had previously been diagnosed with GBM and got TTFields reported a significant improvement in their health during the duration of their therapy. Patients who have been treated with TTFields for an extended period have indicated that the treatment had no impact on their quality of life. Quality of life increases noticeably with time after a

diagnosis. This is true for those whose illness is stable as well as for those whose illness is progressing [28].

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Wang TJC, Wu CC, Jani A, *et al.* Hypofractioned radiotherapy *versus* standard fractioned radiotherapy with concurrent temozolomide in elderly patients with newly diagnosed Glioblastoma. Pract Radiat Oncol 2016; 6(5): 306-14.

[2] Darlix A, Zouaoui S, Rigau V, *et al.* Epidemiology for primary brain tumors: A nationwide population-based study. J Neurooncol 2017; 131(3): 525-46. [http://dx.doi.org/10.1007/s11060-016-2318-3] [PMID: 27853959]

[3] Mattei V, Santilli F, Martellucci S, *et al.* The importance of tumor stem cells in glioblastoma resistance therapy. Int J Mol Sci 2021; 22(8): 3863. [http://dx.doi.org/10.3390/ijms22083863] [PMID: 33917954]

[4] Wang X, Lu J, Guo G, Yu J. Immunotherapy for recurrent glioblastoma: Practical insights and challenging prospects. Cell Death Dis 2021; 12(4): 299. [http://dx.doi.org/10.1038/s41419-021-03568-0] [PMID: 33741903]

[5] Thakkar JP, Dolecek TA, Horbinski C, *et al.* Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 2014; 23(10): 1985-96. [http://dx.doi.org/10.1158/1055-9965.EPI-14-0275] [PMID: 25053711]

[6] Italian Cancer Registry Association. Cancer Data. Available from: http://www.registri-tumori.it/PDF/AIOM2019/I_numeri_del_cancro_2019.pdf

[7] Wu W, Klockow JL, Zhang M, *et al.* Glioblastoma Multiforme (GBM): An overview of current therapies and mechanisms of resistance. Pharmacol Res 2021; 171: 105780. [http://dx.doi.org/10.1016/j.phrs.2021.105780]

[8] Jenkinson MD, Barone DG, Bryant A, *et al.* Intraoperative imaging technology to maximise extent of resection for glioma. Cochr Database Syst Rev 2018; 1: CD012788.

[9] Ashby LS, Smith KA, Stea B. Gliadel wafer implantation combined with standard radiotherapy and concurrent followed by adjuvant temozolomide for treatment of newly diagnosed high-grade glioma: A systematic literature review. World J Surg Oncol 2016; 14(1): 225. [http://dx.doi.org/10.1186/s12957-016-0975-5] [PMID: 27557526]

[10] Akimoto J. Photodynamic therapy for malignant brain tumors. Neurol Med Chir 2016; 56(4): 151-7. [http://dx.doi.org/10.2176/nmc.ra.2015-0296] [PMID: 26888042]

[11] Delgado LPD, Corrales GEM. Survival in glioblastoma: A review on the impact of treatment modalities. Clin Transl Oncol 2016; 18(11): 1062-71. [http://dx.doi.org/10.1007/s12094-016-1497-x] [PMID: 26960561]

[12] Hottinger AF, Pacheco P, Stupp R. Tumor treating fields: A novel treatment modality and its use in brain tumors. Neuro oncol 2016; 18(10): 1338-49. [http://dx.doi.org/10.1093/neuonc/now182] [PMID: 27664860]

[13] Lamborn KR, Yung WKA, Chang SM, *et al.* Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro oncol 2008; 10(2): 162-70. [http://dx.doi.org/10.1215/15228517-2007-062] [PMID: 18356283]

[14] Wu W, Lamborn KR, Buckner JC, *et al.* Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma. Neuro oncol 2010; 12(2): 164-72. [http://dx.doi.org/10.1093/neuonc/nop019] [PMID: 20150383]

[15] Clarke JL, Ennis MM, Yung WKA, *et al.* Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma? Neuro-oncol 2011; 13(10): 1118-24. [http://dx.doi.org/10.1093/neuonc/nor110] [PMID: 21813511]

[16] Batchelor TT, Duda DG, Di Tomaso E, *et al.* Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. J Clin Oncol 2010; 28(17): 2817-23. [http://dx.doi.org/10.1200/JCO.2009.26.3988] [PMID: 20458050]

[17] Scott BJ, Quant EC, McNamara MB, Ryg PA, Batchelor TT, Wen PY. Bevacizumab salvage therapy following progression in high-grade glioma patients treated with VEGF receptor tyrosine kinase inhibitors. Neuro oncol 2010; 12(6): 603-7. [http://dx.doi.org/10.1093/neuonc/nop073] [PMID: 20156808]

[18] Friedman HS. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009; 27: 4733-40. [http://dx.doi.org/10.1200/JCO.2008.19.8721]

[19] Pàez RM, Allen E, Hudock J, *et al.* Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 2009; 15(3): 220-31. [http://dx.doi.org/10.1016/j.ccr.2009.01.027] [PMID: 19249680]

[20] Maggs L, Cattaneo G, Dal AE, Moghaddam AS, Ferrone S. CAR T cell-based immunotherapy for the treatment of glioblastoma. Front Neurosci 2021; 15: 662064. [http://dx.doi.org/10.3389/fnins.2021.662064] [PMID: 34113233]

[21] Steponaitis G, Kazlauskas A, Vaitkienė P, Deltuva VP, Mikuciunas M, Skiriutė D. Oncosuppressive role of RUNX3 in human astrocytomas. J Oncol 2019; 2019: 1232434. [http://dx.doi.org/10.1155/2019/1232434] [PMID: 31467531]

[22] Ito Y, Miyazono K. RUNX transcription factors as key targets of TGF-β superfamily signaling. Curr Opin Genet Dev 2003; 13(1): 43-7. [http://dx.doi.org/10.1016/S0959-437X(03)00007-8] [PMID: 12573434]

[23] Whittle MC, Hingorani SR. Runx3 and cell fate decisions in pancreas cancer. Adv Exp Med Biol 2017; 962: 333-52. [http://dx.doi.org/10.1007/978-981-10-3233-2_21] [PMID: 28299667]

[24] De Almeida MT, De Sousa GR, Alencastro VCG, Tone LG, Valera ET, Borges KS. The therapeutic potential of aurora kinases targeting in glioblastoma: From preclinical research to translational oncology. J Mol Med 2020; 98(4): 495-512. [http://dx.doi.org/10.1007/s00109-020-01895-x] [PMID: 32219470]

[25] Chen J, He Z, Zhu D, Hui B, Li RYM, Yue XG. Mu-Net: Multi-path upsampling convolution network for medical image segmentation. Comp Model Eng Sci 2022; 1-25.

[26] Lee DH, Ryu HW, Won HR, Kwon SH. Advances in epigenetic glioblastoma therapy. Oncotarget 2017; 8(11): 18577-89. [http://dx.doi.org/10.18632/oncotarget.14612]

[27] D'Amico RS, Aghi MK, Vogelbaum MA, Bruce JN. Convection-enhanced drug delivery for glioblastoma: A review. J Neurooncol 2021; 151(3): 415-27. [http://dx.doi.org/10.1007/s11060-020-03408-9] [PMID: 33611708]

[28] Palmer JD, Chuang PY, Chavez G, Wang BCM, Proescholdt C. Health-related quality of life for glioblastoma short and long-term survivors receiving treatment with TTfields. J Clin Oncol 2021; 39(S15): 2055. [http://dx.doi.org/10.1200/JCO.2021.39.15_suppl.2055]