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Tumor Markers and Their Importance in Glioblastoma Diagnosis and Treatment

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ABSTRACT

Glioblastoma is the most common and most aggressive tumor of the central nervous system whose morbidity and mortality remain very high despite all types of treatment (surgical resection, local and systemic chemotherapy). Numerous associated molecular alterations have been reported, but only a few are associated with survival. Despite several investigations and discoveries about this pathology, the survival rate is still very low. However, tumor markers are not currently taken much into account and these are often of importance as they can see the cause and even predict or diagnose early. The purpose of this research is to show the importance of glioblastoma tumor markers as part of the diagnosis of this disease, and also how they influence the choice of treatment, since, according to molecular genetics, according to the results found in this research, there are a variety of markers that increase helping us to identify the pathology and at the same time, if neutralized, can help favorably to the treatment and prognosis of the patient. Such is the case of the YKL40 marker, LRP, RAP, ApoE3, GOLM1, TROY and angiopep-2.

KEYWORDS: Glioblastoma, tumor, nervous system, markers

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INTRODUCTION

Glioblastoma is an aggressive primary central nervous system (CNS) cancer with a median survival of 10-12 months and a 5-year survival rate of 5.1%.(11) Even with maximal treatment, including surgical resection, radiation, and chemotherapy, the current standard of care offers an improvement in median survival to only 13.4-19 months.

Glioblastomas are aggressive tumors of the central nervous system whose prognosis for life is not good when already diagnosed. Glioblastomas represent between 12% and 15% of intracranial neoplasms and more than 60% of astrocytic tumors. They are aggressive tumors classified according to WHO as grade IV, the peak incidence by age varies between 40 and 70 years, most are primary tumors (de novo) and less than 10% emerge from a tumor of low grade malignancy (secondary) that involves more patients younger than 45 years.

The limitation of surgical resection is largely due to the diffusely infiltrating nature of the cancer, preventing a complete removal of cells that infiltrate the normal brain parenchyma however this does not guarantee survival as it is too aggressive and fast growing. The genetic and molecular basis of glioblastoma allows for impressive progress in new treatment approaches, such as gene therapy, molecular therapy and immunotherapy.

Biomarkers are measurable indicators used to predict clinical prognosis and susceptibility to different immunotherapies. They are essential in identifying patients most likely to respond to therapy and in preventing drug effects in those who are unlikely to benefit. Several types of biomarkers, such as cytokines, immune checkpoints and other signaling pathway molecules, can be overexpressed in tumor cells compared to healthy brain tissue.

Currently there is no specific treatment or algorithm for this neoplasm, in addition the indications for surgical resection are very specific and cannot be performed in all patients, it is usually accompanied by radiotherapies and chemotherapies, however in recent years it has been shown that in certain patients treatment results are not usually seen, so more research has been done about molecular receptors and tumor markers because if they are sought they can help to have a more specific treatment that works better for this pathology,

thus improving the prognosis of the patient's life. More research should be done on these markers as they are of great clinical relevance.

This research will be of the documentary type and information will be collected from different medical articles specifically in English dated within the last 3 years, obtained from the digital library, and information will also be collected from 3 updated books.

Nervous tissue is composed of several cellular elements such as neurons and supporting elements, which are divided into central and peripheral supporting cells. The former include astrocytes, oligodendroglia, microglia and ependymal cells. The latter include Schwann cells. The central support cells together with the vascular capillaries form the blood-brain barrier, which are of functional importance for the passage of water-soluble macromolecules and vasogenic cerebral edema. (12) Glioblastoma multiforme is the most frequent tumor of the different types of gliomas that exist and unfortunately the most malignant. It usually originates in the white matter. It can develop from a low-grade astrocytoma that undergoes anaplastic transformation and evolves into a secondary glioblastoma or directly presents as a primary or "de novo" glioblastoma. (13)

Another interesting observation is that glioblastomas (GBMs) present two molecular pathways of transformation: primary GBMs overexpress to a high degree or present mutation of the epidermal growth factor receptor, deletions in the p-16 gene, and mutations in the phosphatase and tensin homolog gene. Secondary GBMs present genetic alterations involving the p-53 gene, as well as overexpression of platelet-derived growth factor A and its receptor α. (12) This distinction into two types of GBM has prognostic implications, more favorable for secondary GBM, and perhaps related to a greater response to multimodal treatment. The p53 / ARF / MDM2 pathway is another central pathway deregulated in the pathogenesis of GBM, being aberrant in 84% of patients. TP53 mutations in GBM are mainly point mutations and oncogenic function variants.(7)

Glioblastoma is mainly diagnosed with various requirements, firstly by imaging such as computed tomography and magnetic resonance imaging, however these do not confirm glioblastoma until biopsy results are obtained. Neuropathologically, glioblastoma is almost always defined by signs of necrosis and anaplasia of the non-neural elements, such as vascular proliferation.

However, lately it has been proposed in various research studies that more emphasis should be placed on tumor markers, since they help to better determine the treatment and prognosis of the disease. Tumor markers are substances produced by both normal cells and tumor cells, although they are produced at much higher levels when cancer is present. In cancer patients, these substances can be found in blood, urine and ascitic or pleural fluid among others. The different tumor markers investigated will be discussed below:

YKL 40 is a secreted biomarker released primarily by macrophages in the context of inflammation and malignancy. It is a glycoprotein, a protein secreted in vitro by the human osteosarcoma cell line, and was named based on its amino acids tyrosine (Y), lysine (K) and leucine (L) and its molecular weight of 40 kDa, these are usually more present in pleural fluid.

This glycoprotein is highly expressed in tissues undergoing rapid proliferation and differentiation. YKL-40 was initially evaluated as a marker of inflammation and is currently used to study exacerbation in bronchial asthma, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis.(1) This glycoprotein was also found to be overexpressed in solid tumors such as breast carcinoma, colorectal cancer, osteosarcoma and glioblastoma multiforme, experiments were carried out to evaluate its role as a tumor marker.(1)

Approximately 38% of patients who have a neoplasm such as breast carcinoma, colorectal cancer, osteosarcoma and glioblastoma multiforme have the YKL-40 marker. It has been found that the YKL-40 protein of positive pleural fluid had a good sensitivity and specificity to diagnose malignant pleural effusion (1), so it does not have such a good sensitivity specifically in glioblastoma, however it has been demonstrated in animals that if this protein is neutralized with antibodies it could serve as a treatment for glioblastoma.

Another receptor that is overexpressed in glioblastoma cells is a low-density lipoprotein receptor (LRP)-related protein. LRP is a multifunctional receptor for natural ligands that bind receptor-associated proteins (RAPs), human melanotransferrin (p97), lactoferrin, and syn- tetic peptides, such as ApoE3 peptide analog and angiopep-2 (ANG). (2)

Angiopep-2 was used to modify paclitaxel-loaded polyethylene glycol (PEG- NP)-based nanoparticles (ANG-PEG-NP-PTX). In vivo antitumor efficacy studies have shown that ANG-PEG-NP-PTX reduces tumor size two-fold compared to Taxol and PEG-NP.

GOLM1 is a Golgi membrane glycoprotein and shows constitutive expression in cells of the epithelial lineage, particularly in the prostate, stomach and within the central nervous system. Because this protein contains a consensus proprotein convertase site and is expressed at high levels in tumors, GOLM1 was evaluated as a potential novel serum tumor biomarker in prostate cancer (PCa) and hepatocellular carcinoma, upregulating GOLM1, which acts as a key component in PDGFA/PDGFRα-mediated glioma progression through AKT activation.(6) However, little is known about the association. and function of GOLM1 in glioma, especially in GBM. The importance of GOLM1 in GBM has not yet been discussed, there have been hypothesized ways to inactivate this protein to treat glioblastoma but there is insufficient information.

Interleukin-13 receptor a2 (IL-13Ra2) is a plasma membrane receptor, which is expressed in 75% of glioblastomas, but absent in normal brain tissue, making it a potential

therapeutic target for glioblastoma treatment. There are many other peptides that bind to various glioblastoma specific targets, such as vascular endothelial growth factor receptor 2 (VEGFR-2), epidermal growth factor receptor (EGFR). (3) Other markers that can be considered when dealing with glioblastoma is PCNA, TOP2 A, however there is not enough information yet on these markers, they are thought to be proliferation related.(8).

An epigenomic study identified a glioma CpG island methylation pattern (G-CIMP) in association with the proneural subtype and with mutations in isocitrate dehydrogenase (IDH) genes. Key markers of subgroup separation included expression of IDH1 R132H mutation and epidermal growth factor receptor (EGFR) vIII (EGFRvIII) mutation, and loss of neurofibromin (NF-1) expression. An inverse relationship was found between IDH1 R132H mutation and expression levels, as well as nuclear localization of beta-catenin and GSC frequency in gliomas.(9)

Elevated levels of angiotensin II type 1 receptor (AGTR1) have been associated with high-grade astrocytomas and poor patient prognosis. In addition, overexpression of AGTR1 has also been linked to multiple human malignancies, including ovarian, kidney, pancreatic, breast, and brain malignancies, whereas in breast cancer (BCa), significant overexpression of AGTR1 represents a human epidermal growth factor (HER2)-negative and estrogen receptor-positive subpopulation, in ovarian cancer, its high expression has been linked to metastasis by promoting multicellular spheroid formation. (4) AGTR1 expression has been observed to inhibit apoptosis while motivating angiogenesis, cell proliferation and inflammation.

Another important marker is TROY (TNFRSF19), a type I transmembrane receptor, a member of the TNF receptor superfamily. TROY is widely expressed during embryonic development, but postnatal expression is more restricted. Elevated expression of aberrant TROY has been reported in several invasive cancers, including colorectal cancer, lung cancer, melanoma, nasopharyngeal carcinoma, prostate cancer and GBM. In glioblastoma, TROY expression has been shown to increase with glial enlargement. Tumor grade correlates negatively with patient survival Increased TROY expression stimulates glioblastoma cell invasion in vitro and in vivo and enhances therapeutic resistance to temozolomide.(10)

Temozolomide is an alkylating drug that causes O6- guanine methylation in DNA, and is a standard first-line drug for glioblastoma. However, it is likely that there are many unknown mechanisms for the antitumor effects of temozolomide, it can suppress tumor growth by activating cPLA2 in glioblastoma cells.(5)

It is unknown whether the antitumor effects of temozolomide may be due in part to phosphorylation of cPLA2 in glioblastoma cells. Since temozolomide is an effective treatment for the development of glioblastoma despite chemoresistance in some cases due to certain tumor markers such as TROY or YKL 40 rendering the drug inadequate or even ineffective.

DISCUSSION

Glioblastoma is one of the most feared neoplasms in the specialty of neurology and oncology, since it has a very poor prognosis and sometimes shows resistance to treatment. Despite the scientific and technological advances that have been made in recent years, the life expectancy of patients suffering from this disease has not yet improved. In recent years, research has been focused on why resistance to certain drugs can occur or if there is a way to detect this disease prematurely, so more research has been focused on tumor markers.

In the present investigation information was compiled about various tumor or molecular markers and firstly the YKL40 marker was found, which is mainly found in the pleural fluid and serves to suspect other pathological processes, but it does not have such a high sensitivity for glioblastoma, but this marker has been investigated more because if there is a way to neutralize it, it can be an effective treatment for this neoplasm. Other markers found more specific for glioblastoma were LRP, RAP, ApoE3 and angiopep-2, but it is only known that these are usually elevated and that angiopep-2 can be used for antitumor treatment, but it has only been demonstrated in animals. GOLM1 is a glycoprotein expressed mainly in gliomas, it is believed that if it is somehow deactivated it can serve as an effective treatment.

Elevated NF-1 is associated with glioblastoma, but there is not much information on this. Elevated levels of angiotensin II receptor type 1 (AGTR1), has been related to high grade astrocytomas and neoplasms of other organs, it inhibits apoptosis while it motivates angiogenesis, cell proliferation and inflammation, if a way to inhibit or deactivate it is found it would also serve as a good treatment but like the others there is not much information about it. TROY is another receptor that is expressed at the moment of suffering from glioblastoma, it is negatively related to the survival of the patient and it has been demonstrated that it interacts with temozolomide and causes resistance, this drug is one of the main ones used for this neoplasm.

According to the information gathered, it is thought that there is not enough information or research about tumor or molecular markers, since there is not an adequate number of articles or information in the most recently updated books. In the diagnosis and treatment of glioblastoma, there is not usually much consideration of markers because some do not consider them to be important.

Currently, more importance should be given to this because there is research that could confirm that these are useful to find a suitable treatment or to diagnose if there could be resistance in some treatments and find another treatment without wasting so much time and that could improve the prognosis of life, but the biggest problem is that there is not enough information or research to back up what was said

above, so we still cannot talk about a drug or official treatment or a new way to diagnose glioblastoma.

CONCLUSION

In this research we tried to focus on the importance of tumor and molecular markers in the pathology of glioblastoma since we observed when we studied this topic that the literature does not usually mention much about tumor markers, and that is why we decided to investigate about them, however, we observed that there is not much variety of information sources such as articles that talk about tumor markers, we observed that there is not much variety of sources of information such as articles that talk about tumor markers and the few that were found that completed the specifications to perform the research mentioned that there is not enough information about them and that they may be important in new ways to diagnose or treat glioblastoma.

Having done this research we realized the importance that these markers can have not only in glioblastoma but also in other pathologies that are very common, however, they are not the results we expected since we thought that there would be more information about them, therefore we hope that in the future more information about this topic will be found and more ways of treatment can be found.

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