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REVIEW ARTICLE OPEN ACCESS

Genomic Mutation Profiling of the Malignant Glioblastoma and Relationship Between the Genetic Pathways and Prevalence: A Comprehensive Review

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Abstract

Glioblastoma is the world's most prevalent, infiltrative, and aggressive form of malignant tumors affecting the human brain. Studies show that glioblastoma has a higher frequency of genomic mutations than any other type of human brain cancers and tumors. The glioblastoma human brain cancer due to genomic instability has developed more top therapy-resistant characteristics, which makes it hard to treat. Clinical genomic studies focused on cells related to the proliferation of glioblastoma, which is the Glioblastoma Stem Cells (GSCs) have helped identify the genetic pathways associated with the development of malignant brain tumors. Studies on the alterations in genetic structure in genetic pathways promote the understanding of the glioblastoma and the diagnostics of the malignancy of brain tumors among populations. This also helps in the detection of genomic alterations due to the development of glioblastoma and its genomic instability and the development of clinical therapies to counter the disease. Though number mutations are occurring in driver genes associated with the growth of glioblastoma, only genomic alterations in PTEN, TP53, EGFR, PIK3R1, PIK3CA, NF1, RB1, IDH1 and LoH have been focused on this review. The genomic mutations in the linked genetic pathways are responsible for the distinction of the development of glioblastoma as either primary or secondary glioblastoma. This review paper focuses on the genomic profiling of glioblastoma to outline the gene mutations that drive the prevalence and aggressiveness of malignant brain cancer. It explores the role of genetics in the pathophysiology of glioblastoma, liked genetic pathways, and the genomic alterations to these genetic pathways. The genomic mutation profiling of the malignant glioblastoma will help create an understanding of the relationship between the genetic pathways and the prevalence of the brain tumors. The genetic mutation analysis will of the glioblastoma further focus on the available therapies used in the management and treatment of glioblastoma and other potential therapies that are being developed or in clinical trial phases. The review will further focus on the future of glioblastoma diagnostics, prognosis, and the management of patients with the cancer.

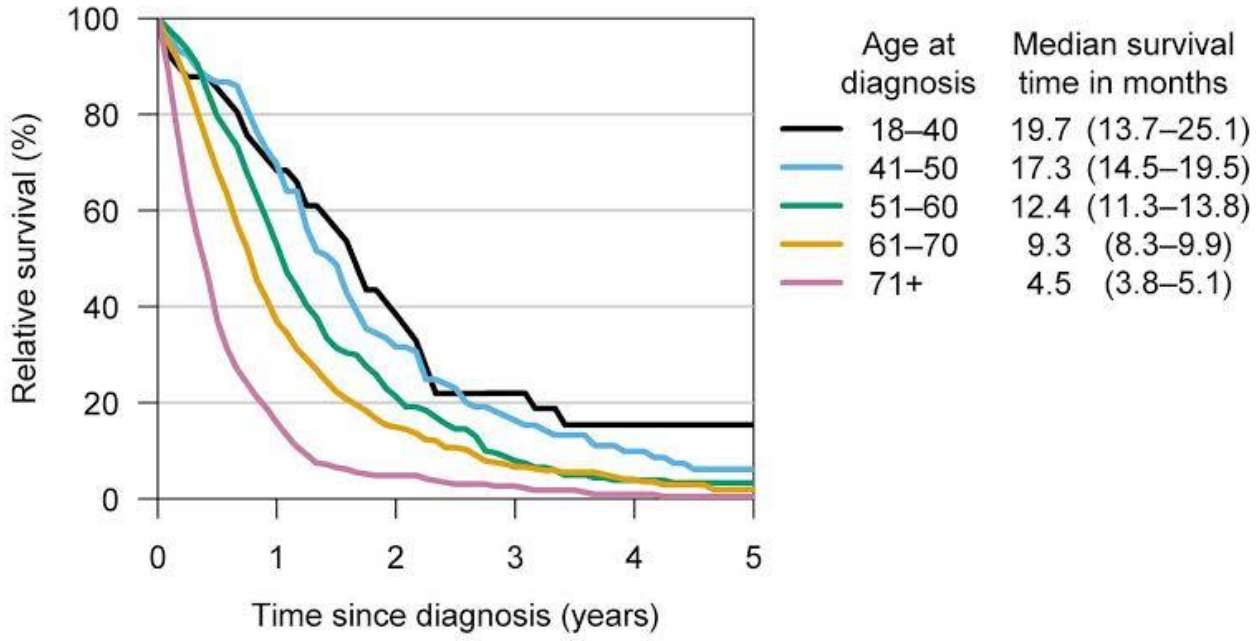
Keywords: Genomic mutation, glioblastoma, altered genes, therapies, management.

INTRODUCTION

Glioblastoma multiforme (GBM) also known as glioblastoma is a fast-growing glioma and the most prevalent and aggressive form of human brain cancers [1]. The glioblastoma multiforme has been noted to be extremely aggressive of all glia tumors with their origin within the central nervous system (CNS) [2]. The glioma has been noted to develop from glial cells specifically astrocytes and oligodendrocytes that are responsible for the health of the nerve cells within the nervous system. This type of cancer has proved to be rapid in its development, to have a high invasion potential and rate to adjacent brain cells [3]. Glioblastoma exists as primary and secondary glioblastomas which are two distinct subtypes of the disease that affect patients of all ages and develop distinctly of different genetic pathways [4]. Primary gliobalstoma develops form diffuse astrocytoma or anaplastic astrocytoma mostly de nova meaning that the disease can develop a clinical background or without histological evidence of previous less malignant lesion [5], note that primary glioblastomas develop rapidly and may progress from low grade astrocytomas to form high grade gliomas. The primary glioblastomas mostly manifest in elderly patients. The invasive nature of cancer cells associated with glioblastoma have been described by Holland [2], as the tumor cells exhibition of a migratory nature away from the primary tumor mass through the normal parenchyma and collecting below the pial margin, surrounding the neurons and vessels within the brain and spreading through the tracks of the white matter in a migratory behavior that mimics the primitive migratory

behavior of neoplastic cells reacquisition during the development of the central nervous system (CNS). The results of such a migratory behavior of the gliomas from the main tumor results in the infiltration of cell brains across the CNS and affecting the parts of the brain those that are essential for the survival of brain cancer patients. This migratory nature of the gliomas facilitates the development of grade IV astrocytoma and explains the evolution of the secondary glioblastoma. This means that secondary glioblastoma develops from the progression of the primary glioblastoma [6]. The occurrence of secondary glioblastoma has been identified mostly in younger patients [5]. It is hard to distinguish between primary and secondary glioblastomas histologically, but both differ based on their genetic and epigenetic profiles [7].

Figure1: Brain cancer survival rates (https://www.medicalxpress.com)



Though glioblastoma is aggressive in the brain, its occurrence is limited to the Central Nervous Systems (CNS) and has not been found to spread outside of the brain. The infiltration of the parts of the brain that support the survival of the cancer patients increases the rates of occurrence of deaths associated with glioblastoma [2]. Statistics show that that glioblastoma has a high mortality rate as most of the patients who suffer from the disease are more likely to succumb to the disease in a year, with none of the patients having long term survival. Observations made on the survival of glioblastoma patients showed a median of approximately 12 months for most of the patients, however, with the development of some therapeutic procedures aimed at managing the disease, long term survival of three of a few more years has been achieved in 3% to 5% of the patients diagnosed with glioblastoma [8]. However, the recent developments in glioblastoma therapies show some potential in extending the life expectancy of the patients. The glioblastoma human brain cancer due to genomic instability has developed higher therapy-resistant characteristics, which makes it hard to treat.

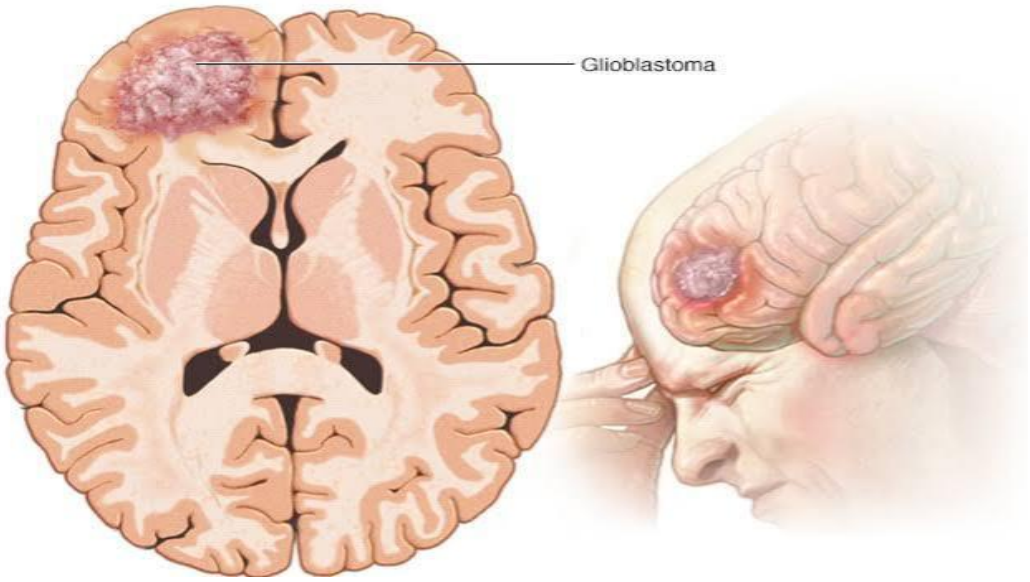
The development of human cancers is associated with mutations in human DNA. These mutations alter the genomic constitution of human cells. Genetic mutations induce changes in the way human cells grow and function. The uniqueness of human DNA has made the development of cancer to be unique to every individual, making it harder to develop the necessary therapies for the development of suitable treatments. This uniqueness of the growth of the glioblastoma tumors based on the individual patient's genetic composition poses a challenge to the therapeutic procedures and methods that may be developed generally for the treatment of these malignant tumors. Different genomic alterations in the genetic pathways lead to abnormal cell growth and development, both primary and secondary glioblastoma. The existence of the heterogeneous driver cells amplifies the progressiveness and recurrences of glioblastoma form the affected cells activation of the malignant tumors in adjacent brain cells leading to the development of secondary glioblastoma [9]. Years of research and advances in molecular cell studies have enabled the identification and characterization of oncogenic mutations associated with the development of glioblastoma brain tumors and other types of cancers. Alterations occurring in specific genetic pathways are associated with the development of either primary or secondary glioblastoma [9]. Primary glioblastoma has been associated with alterations in genetic pathways and associated with less malignant precursor lesion that are genetically characterized with loss of heterozygosity 10q, amplification of the EGFR genetic pathway, the deletion of the $p16^{INK4a}$ gene, and muatation occurring in the PTEN genetic pathway [6]. The genetic alterations associated with secondary glioblastoma are mostly manifested through TP53 mutations [7]. Other than the genetic alterations occurring in the TP53 genes, secondary glioblastoma develop from the progression of less malignant tumors slowly to more malignant tumors occurring due to the gene amplifications associated with primary glioblastoma [6]. Cheng, Wu, Guryanova, Huang, Huang, Rich, and Bao, S [3] have noted that glioblastoma has an increased cellular heterogeneity with self-renewing glioblastoma stem cells which increases its

frequency of genomic mutations than any other type of human brain cancers and tumors. Snuderl, Fazlollahi, Le, Nitta, Zhelyazkova, et al [9] add that the heterogeneity of tumors explains the progression of the tumors from less malignant ones to malignant brain tumors. The genetic mutations are due the damage in DNA during cell replication and development. Mutations are beneficial to the development of diversity in genetic lineage and natural selection to take place and further for the benefit of evolution of organisms, however higher than normal mutations a risk factor for dangerous health conditions with cancer being the major risk [10]. Tubss [10] defines the higher-than-normal rate of mutations occurring within the cells during DNA replication is termed to as genomic instability. The genomic instability of glioblastoma tumors has become a problem that has affected the efficacy of drugs and therapies targeted at treating glioblastoma [11]. The resistance of the glioblastoma to drugs and existing therapies and its aggressiveness in growth and development has further been associated with the heterogeneity of brain tumors [9]. Due to glioblastoma's high malignancy, rapid growth, aggressiveness, ability to invade other brain cells and the recurrence of the glioblastomas rapidly in other parts of the brain, the World Health Organization (WHO) has graded glioblastoma as Grade IV brain tumor.

Evidence from oncological studies has shown that the ability of tumors to develop and progress is a result of a subset of cells that form within the tumor, which have been identified as cancer stem cells [12]. Lathia, Gallagher, heddleston et al [13] described the cancer stem cells (CSCs) as a population of tumor cells that have shown properties that are essential for the maintenance of tumors, tumor metastasis, and the resistance of tumors to administered therapies. Cancer stem cells cells associated with glioblastoma; glioblastoma stem cells (GSCs) are responsible for the maintenance of glioblastomas [14]. The suppression of certain biological processes due to alteration in the normal cell replication processes promote the development and growth of the glioblastoma stem cells, GSCs self-renewal, tumorigenesis. The cancer stem cells can therefore be said to have a parallel role to the one played by normal stem cells. The identification of the cancer stem cells helps in cancer prognosis. This identification and the definition of the cancer stem cells has further aided in the development of different targeted therapies that have shown some level of effectiveness by targeting the malignant cells [15]. Advances in cancer diagnostics have noted that glioblastoma tumors develop in star-shaped glial cells known as astrocytes and oligodendrocytes that are responsible for the health of the nerve cells within the human brain. Glioblastoma stem cells have shown to have the capability to form neurospheres and the capacity to self-renew, differentiate, and to form new groups of stem cells in clusters which bear different phenotypes from the original glioblastoma tumor [16]. The differentiation of the glioblastoma and the formation of new phenotypically different spheres of new malignant tumors lead to the creation of secondary glioblastoma.

Figure 2: Glioblastoma development, Source (www.mayoclinic.org)

Studies focused glioblastoma have added knowledge to the understanding of the characteristics of glioblastoma biology such as the behavior of the glioblastoma malignant brain tumors, the molecular



characteristics of the astrocytomas, and the development of knowledge on the existence of glioblastoma in different genetic pathways and the susceptible pathways [1]. Despite the advancements made in understanding glioblastoma, a few therapies have been developed to counter the development and aggressiveness of the central nervous system cancer. Developments made in the understanding the molecular and genomic alterations associated with the growth of glioblastoma have led to the development of several glioblastoma diagnostics with the recent approach to glioblastoma diagnostics utilizing genomic methods paving the way to the development of modern clinical trial drugs and therapies for the treatment and management of malignant brain tumors.

GENOMIC MUTATIONS OF GLIOBLASTOMA

The development of either the primary or secondary glioblastoma is based on the type of genomic pathways that

are affected. The glioblastoma tumors development can be genetically categorized in the genetic pathways they appear and the genetic mutations that are amplified in these genetic pathways [6]. The glioblastoma etiology is still not well defined to date. Despite the lack of enough information on the actual factors behind the development and the growth of the malignant tumors in the central nervous system, it has been identified that errors occurring in polymerase randomly during the division and differentiation of stem cells lead to genomic alterations in oncogenes and tumor suppressor genes [17]. Substantial evidence drawn from studies targeted at understanding cell replication and the development of tumors in humans has shown that even at the lowest and random occurrences of errors in DNA polymerase during the division of stem cells, each time such an error occurs, each stem cell replicates its DNA with the polymerase error resulting in phenotypically diverse stem cells [18]. The resultant replicated cells will have increased exposure to damage as the miscoded DNA information is progressed across the dividing and differentiating stem cells. The polymerase errors result in alterations of the DNA alteration in oncogenic pathways associated with the development of glioblastoma. The revisions occur in specific oncogenes and tumor suppressor genes in which the mutations in these genes result in the development and progression of glioblastoma. The particular driver oncogenes and tumor suppressor genes associated with the growth of glioblastoma include PTEN, TP53, EGFR, PIK3R1, PIK3CA, NF1, RB1, and IDH1. Additional alterations that occur in genes lead to the loss of heterozygosity of cells resulting in the development of glioblastoma. Glioblastomas mostly have mutations occurring in the PTEN, TP53, IDH, and in the EGFR oncogenic and tumor suppressor genes. These glioblastoma associated genes are used in prognostic markers in the development of therapies. Most of the variations in glioblastoma tend to happen in the gene body CpG sites altering the transitions of sequences of the CGA codons [19]. Though most of these alterations may not be directly correlated with DNA polymerase errors during cell replication, the mutations occurring in the genes linked with the development of glioblastoma are thought to be directly dependent on the number of stem cells replication and cases where DNA is single-stranded and exposed to reactive molecules which accelerate the damaging of the DNA and the total loss of the entire gene [17].

PTEN Tumor Suppressor and Mutations of PTEN

Phosphatase and Tensin Homolog Deleted on Chromosome 10 (PTEN) is a dual phosphatase which exhibits both protein and lipid phosphatase activities. PTEN has been linked to the suppression of tumor development and the regulation of the growth and survival of cells in the body [20]. Studies carried out recently on the functions of PTEN have discovered that the PTEN pathway acts as a metabolic regulator [20]. PTEN acts both on polypeptides and phosphoinositide substrates limiting their abilities and maintaining cell homeostasis [21]. The tumor suppression activity of the PTEN protein product is an enzymatic one that involves the removal of the phosphate groups from intracellular polypeptides and phosphoinositide signaling molecules during cell activities [22]. Mutations in the PTEN tumor suppressor pathway are the most frequent genomic alterations occurring in almost all oncogenic mutations leading to the development of glioblastoma [18]. Oncogenic mutation studies have shown that PTEN is the most mutated gene in nearly 30% of all tumors classified as Grade IV and specifically in glioblastoma. Studies focused on the mutations of base codons in PTEN showed that 141 codons out of the 403 codons found in PTEN could mutate form a single transition error in the base codon substitution [17]. PTEN mutations in glioblastoma occur both in the CGA codons and CGB codons. The alterations in CGA codons form nonsense mutations. Glioblastoma cohorts in PTEN nonsense mutation have been observed to occur as C•G→T•A in the CGA codons [17]. The other type of variation in the PTEN occurs in the CGB codons forming the missense mutations. The mutations alter the functions of the PTEN as a tumor suppressor leading to an increased replication and survival of stem cells with an altered sequence and the development of tumors.

TP53 Pathways and Mutations in TP53

The TP53 gene is a tumor suppressor gene that has that plays a role in several cellular processes. It has functions in the regulations of cell cycles, regulating the death of cells, and senescence by acting as a gene transcription regulator in downstream genes such as CDKN1A linked to the provision of the cell cycle, PUMA which regulates apoptosis, multi genes 14-3-3σ and XPC which are active in responding to DNA damage and repair [23]. TP53 has also been linked to the regulation of cell metabolism as extras in the functions of the gene. The TP53 genetic pathway has also been noted to play a crucial role in the management of cell differentiation and neovascularization [6].

TP53 mutations are the most detected genomic rearrangements in two-thirds of precursor low-grade diffuse astrocytomas, with the same frequency of TP53 detections tumor tissues occurring in anaplastic astrocytomas and the resulting secondary glioblastoma [23]. TP53 mutations in secondary glioblastoma occur in the pathway's GCA codons with the highest variations occurring in 248 and 273 codons while in primary glioblastoma, mutations in CPG sites occur in the G•C→A•T transitions [6]. The increase in the genomic stability in glioblastomas during the development of the tumors leads to less specified genomic mutation patterns in TP53 that may occur both in primary and secondary glioblastomas [23].

The damage of TP53 due to mutations activates the TP53, which induces the transcription of genes with DNA polymerase ERRORS [6]. The alteration of the TP53 pathways impairs its functions leading to unregulated cell apoptosis, genomic instability, uncontrolled angiogenesis, and unregulated cell metabolism and tumor progression. The mutations in TP53 lead increased glioblastoma cell invasion, facilitated migration, and the proliferation of glioblastoma tumor cells, the cells evading death, and the progression of stemness of cancer cells [23]. The mutated TP53 is strongly linked to the poor prognosis for the survival of patients with glioblastoma and further the increase in MGMT expression leading to increased resistance of glioblastoma to specific targeted drug therapies such as temozolomide [24].

EGFR Oncogene and Mutations in EGFR

Epidermal growth factor receptor (EGFR) of the most amplified genes in gliomas [25]. Most malignant tumors in the head have shown to have overexpressed EGFR. The epidermal growth factor receptor belongs to a family of receptor tyrosine kinases (ErbBs), which are involved in the regulatory functions of cell proliferation, cell survival, cell division and differentiation, and the migration of the cells [26]. The ErbB family of receptors has been identified in several studies to carry out redundant and restricted functions in the development of mammals and most humans and play an active role in the maintenance of tissues through facilitating cell proliferation and division in the adult mammal [27]. EGFR glioblastoma linked mutations occur in the kinase domain [25]. Mutations in glioblastoma related to EGFR have been observed to be shared in the extracellular domain of EGFR, with A89→V/D and G598V predominating presumably due to their effect on increasing receptor auto-phosphorylation in the absence of ligand [6]. The genomic alterations on the epidermal growth factor receptors lead to the loss of the regulation of the functions of the growth factor receptors leading to the development of malignant tumors, mostly cancer [26]. The features of epidermal growth factor receptors in cell differentiation, structure, cell processes regulation, and roles in the development and progression of diseases and cancerous tumors make the gene a target for studies aimed at developing glioblastoma cancer therapy.

Loss of Heterozygosity (LOH)

Loss of heterozygosity (LOH) most frequent gene alteration for both primary and secondary glioblastomas; it occurs in 60-90% of cases [6]. Observations of mutation patterns show that this type of mutation appears to occur only in glioblastoma multiforme. The LoH alterations have not been observed in other tumor grades. Loss of heterozygosity is linked to errors during cell division, chromothripsis, conversion of genes and errors occurring during gene repair [28]. LoH results in a complete loss of gene and the surrounding chromosomal region. "*LOH at 10q plus 1 or 2 of the additional gene mutations appear to be frequent alterations and are most likely major players in the development of glioblastomas*" [26]. The LoH mutation defines the outcomes of the glioblastoma and has been associated with poor patient survival [29].

PIK3R1 and PIK3CA and Mutations in PIK3R1 and PIK3CA

Functional studies on lymphoblastoid cells with the PIK3R1 have shown that PIK3R1 plays a crucial function in the phosphatidylinositol three kinases (PI3K) signaling cascade which adds to the regulation of cell growth, proliferation, and survival [30]. The phosphoinositide 3-kinase (PI3K) pathway has been identified frequently in alteration in glioblastoma [31]. The PI3K path has been identified as critical in regulating the responses of cells to growth factors and other environmental factors after the development, division, and differentiation of the cells. A study focused on showing that somatic mutations of PIK3R1 promote gliomagenesis noted that, "*Somatic mutations of PIK3R1 are observed in multiple tumor types, but the tumorigenic activity of these mutations has not been demonstrated in glioblastoma but the somatic mutations in the iSH2 domain of PIK3R1 act as an oncogenic driver even"* [21]. Studies of glioblastoma samples focused on the mutations of PIK3RI in glioblastoma identified the presence of the variations in PIK3R1 encoding p85α protein, which is an active protein in the regulation of the catalytic activities of p110α kinase encoded by PIK3CA [6]. The study identified the mutation of the CGN codons in PIK3R1 during the transition as *G376R (GGA→AGA), K379N (AAA→AAT), and D560G/H (GAC→GGC/CAC).* These genomic mutations occur in the iSH2 domain of PIK3R1 and encode P85α, causing PI3K to impair its regulation, the signaling cascade, cell growth, and cell survival-promoting the glioblastoma tumorigenesis [30].

RB1 Tumor Suppressor Gene and Mutations in RB1

The retinoblastoma susceptibility gene (RB1) is the earliest ever defined tumor suppressor gene, [32]. The RB1 gene is associated with providing instructions to the cells to make a protein called pRB. The pRB protein regulates the growth of cells and controlling the frequency of cell division, thus acting as a tumor suppressor [34]. The pRB protein regulates and controls the growth of new cells and the the rate of cell division by inhibiting other proteins from authorizing the replication of DNA [34]. The pRB regulation of the process of DNA replication by controls cell division and helps prevent the damage of DNA and the growth of tumors [33]. The protein has also been noted to interact with other proteins to regulate cell survival, apoptosis, and cell differentiation [34]. The retinoblastoma susceptibility gene study with 928 codons, in which showed that only 8% of the codons had been identified to mutate in glioblastoma in C•G→T•A transitions [35]. The mutation of RB1 in glioblastoma impairs the functions of the Rb1 pathway leading to uncontrolled cell cycle progression. Further, it makes the tumor suppressor gene ineffective, allowing for the replication of DNA and initiation of cell division by unauthorized proteins [36].

IDH and Variants IDH1 and IDH2 Mutations

With efforts been invested heavily in the developments and advancements into genetic sequencing and bioinformatics, the results have seen the achievement of higher glioblastoma prognosis through the understanding of the genes and mutations occurring in these genes. The advanced studies have led to the identification of variations in the gene for the enzyme NADP+ -specific isocitrate dehydrogenase, which is commonly referred to here as IDH. IDH is closely linked with the increased chances of survival for patients who have the mutation of the mutations in IDH [6]. Genetic analyses of tissue samples drawn from glioblastoma tumors indicate that the occurrence of IDH mutations in glioblastoma tumors is infrequent with a prevalence rate of roughly 10 percent across most of the affected populations [6]. The past studies have shown that the prevalence rate of IDH genetic alterations is shared in astrocytes and primary glioblastoma precursor stem cells [37]. However, recent studies have noted that IDH mutations occur mostly most of the studied secondary glioblastomas with a prevalence rate of 70-80% with the presence of the mutations rarely identified in primary glioblastoma [25]. IDH mutations occur in lower-grade gliomas have chances of development and progressing to higher grade brain tumors and developing in secondary glioblastomas [6]. Different mutations of IDH in glioblastoma have been identified across populations. IDH mutations have shown to exist as either the wild type, the IDH wild-type or IDH1 blue, and the IDH mutant gene, which is referred to as

IDH mutated or IDH2. The IDH mutation variants determine the survival rates of the patients. The glioblastoma patients who happen to be harboring the IDH1 variant have been noted to survive for a period of up to 15 months while the IDH2 option shows to the extent the survival periods of the glioblastoma patients to a median of 30 months [37]. In recent times, glioblastomas are differentiated by the variant of IDH-wildtype or IDH-mutated, which is determined by the presence of recurrent hotspot mutations in isocitrate dehydrogenases IDH1 and IDH2 [1]. Studies aimed at understanding the variations in mutations occurring in IDH help with priceless information on cancer prognosis and specifically mutations and variants of IDH in glioblastoma and the molecular structure responsible for the development and the pathogenesis of secondary glioblastoma.

MOLECULAR DIAGNOSTICS

A lot of research has been focused on glioblastoma but despite the intensity of the research, the complexity of the glioblastoma biology largely remains uncovered [38]. The World Health Organization (WHO) has been the primary source of information on central nervous system tumor classification, tumor grading, and the criteria for tumor diagnosis. The current oncological researches are focused on the epigenetics and molecular composition of tumors to develop an understanding of the etiology of brain tumors and cancers in general. A lot of progress has been made when it comes to molecular diagnostic and subtyping of brain tumors for accurate diagnostics and the development of novel therapies. The developments made on the understanding of brain tumor molecular pathogenesis have updated the clinical practice of molecular diagnostics and the guidelines given by the WHO [39]. Molecular biology studies on glioblastoma have focused on the tumors' behavior, molecular features of glioblastomas, and the heterogeneity of the tumors to advanced targeted therapies applicable in clinical treatment and management of glioblastoma. Molecular diagnostics investigates if the hereditary adjustments in astrocytomas have been conducted to recognize conduits resulting in glioblastoma. This kind of diagnosis is an imperative foundation for the emerging modified treatment of glioblastomas. Molecular diagnostics makes use of classical molecular markers of with clinical implications on the histological classification of brain tumors with a lot of efforts aimed at identifying new molecular markers that may help in developing the novel treatments for human gliobalstoma [40]. Tanaka, Louis, Curry, Btachelor and Dietruch [41] add that advances made understanding the molecular pathogenesis of glioblastoma enables the development of novel treatment and management drugs and approaches for glioblastoma such as the use of molecular targeted agents in developed therapies, with the identification and the validation of diagnostic, prognostic and predictive biomarkers contributing to the design of clinical therapy trials. Eder and Kalman [42] note that further understanding of glioblastoma pathogenesis using multidimensional data on molecular markers helps in the classification of the brain cancer into subgroups based on the distinct biological features of the tumors and their clinical correlations. The classical molecular diagnostics and glioblastoma grading have been based on the status of the p53 and the epidermal growth factor receptor (EGFR) [43]. This glioblastoma diagnosis approach has been based on studying the mutation of the p53 growth suppressor DNA and the EGFR and their clinical implications. Current researches on the molecular pathogenesis of gliobalstoma have identified alterations on the biomarkers such as 1p/19q codeletion, O^{6}-methylguanine methyltransferase (MGMT) promoter methylation and isocitratee dehydrogenase-1 (IDH1) to bear clinical implications in glioblastoma diagnosis, grading and therapy development and the prediction of response to therapies [43]. Magnetic resonance spectroscopy (MRS) intermediated recognition of oncometabolite 2-hydroxyglutarate (2HG) formed in cells sheltering mutations in the isocitrate dehydrogenase1 (IDH1). Potential scanning research presented constructive connection concerning 2HG concentrations growth cellularity, which varies meaningfully amongst low, vs.-high-grade gliomas. These statistics offer the basis for including 2HG MRS within scientific exercise IDH-mutated gliomas [44]. Genetic alterations of type 1p/19q codeletion and IDH1 are viewed as favorable prognostic markers during the classification of gliomas due to their link to oligodendroglial morphology and lower grade: grade 2 and 3 glioma more than glioblastoma with the MGMT promoter methylation emerging as the most predictive marker for glioblastoma prognosis [43]. These oncological biomarkers however vary on impact and implications as per individual patients and may require extra validation when it comes to the selection of patients for singe target therapies, the identification of resistance of glioblastoma to the available therapies, and the molecular genetic profiling of glioblastoma. A lot of controversy exists in molecular diagnostics as some researchers have noted that fragments drawn from the same tumor mass could be tested and the results be classified into at least two different glioblastoma molecular subtypes [42]. Such intra-tumor transcriptome variations lead to biased development of targeted therapies and failure of the developed treatments or selective development of resistance to therapies.

There is a substantial curiosity in next-generation sequencing-based knowledge since it enables wide-ranging planning of genetic alterations, for example (single nucleotide polymorphism) SNP, merging, and duplicate digit discrepancies and the epigenetic setting of RNA methylation in head tumors. There is a necessity for a particular technique to outline glioblastomas from neighboring standard brain muscles throughout the operation. Numerous intraoperative scanning methods have been established for delineating the surgery edge in brain growths; these comprise MRI, neuronavigation, Raman spectroscopy, ultrasound, and visual fluorescence scanning. Joined with the innovation of disparity representatives, both optical fluorescence scanning and MRI have better-quality resect ability of head growths. The fluorescence-directed operation utilizes preoperative 5-ALA for intraoperative therapy of glioblastoma muscle. It allows the neurosurgeon to distinguish the healthy brain from the tumor for attaining a more general surgery of the growth cell parallel to that possible usage of predictable theatre area light.

Novelty

Glioblastoma is the world's most widespread, infiltrative, and aggressive kind of malignant brain tumor. Studies reveal glioblastoma has a higher frequency than any other human brain cancer and tumors. Human brain tumor glioblastoma has evolved more top-resistant features due to genetic instability,

making treatment harder. Clinical genomic researches focused on glioblastoma-related cells, Glioblastoma Stem Cells (GSCs), helped reveal genetic pathways linked to malignant brain cancers. Studies of genomic structure variations in genomic pathways boost understanding of glioblastoma and brain tumor malignancy diagnosis. Although other mutations exist in glioblastoma-related driver genes, this review focused primarily on PTEN, TP53, EGFR, PIK3R1, PIK3CA, NF1, RB1, IDH1, and LoH genomic anomalies. Genomic changes are responsible for identifying glioblastoma development as either primary or secondary glioblastoma. This research focuses on glioblastoma genomic profiling to outline gene changes causing the prevalence and aggressiveness of malignant malignancy. It explores the role of genetics in glioblastoma pathophysiology, including genetic pathways and genomic modifications to genetic processes. Analysis of malignant glioblastoma genomic mutation will assist in understanding the link between genetic pathways and the occurrence of brain tumors. Glioblastoma will also focus on available drugs used to develop glioblastoma and other possible treatments or clinical trials.

Glioblastoma multiforme (GBM) is a fast-growing glioma and the most prevalent and aggressive form of human brain cancer. Glioblastoma multiforme was the most aggressive of all glia malignancies originating within the central nervous system (CNS) [2]. Glioma was observed to grow primarily astrocytes and oligodendrocytes from glial cells responsible for nervous system nerve cell health. This type of cancer has proven to be quick in its development, having significant potential for invasion and a rate of nearby brain cells [3]. Glioblastoma arises as primary and secondary glioblastomas, two distinct kinds of disease that affect people of all ages and have separate genetic pathways [4]. Primary glioblastoma develops from diffuse astrocytoma or anaplastic astrocytoma, mostly de novo meaning that the disease may create a clinical backdrop or without historical evidence of prior less malignant lesion [5], note that primary glioblastomas develop swiftly and may advance from low-grade astrocytoma's to produce high-grade gliomas. Primary glioblastomas mainly occur in older persons. The effects of such glioma's migratory behavior from the primary tumor result in cell brain infiltration across the CNS and disrupt brain areas critical for brain cancer patients' survival. This glioma migratory character favors the development of grade IV astrocytoma and explains secondary glioblastoma evolution. This suggests secondary glioblastoma develops from original glioblastoma progression [4]. Secondary glioblastoma was observed predominantly in younger patients.

Glioblastoma-focused studies have added knowledge to comprehend the characteristics of glioblastoma biology, such as the behavior of glioblastoma-malignant brain tumors, the molecular features of astrocytoma's, and the development of knowledge on the occurrence of glioblastoma in various genetic pathways and vulnerable pathways [1]. Despite advances in understanding glioblastoma, several medicines were created to oppose the development and aggressiveness of central nervous system cancer. Developments in understanding molecular and genomic changes associated with glioblastoma growth have led to several glioblastoma diagnostics with a recent approach to glioblastoma diagnostics using genomic methods that pave the way for the development of modern clinical trial drugs for the treatment and management of malignant brain tumors.

Either primary or secondary glioblastoma formation is based on the type of genomic pathways involved. The development of glioblastoma tumors can be genetically characterized in the genetic pathways they occur, and congenital abnormalities amplified in these genetic pathways [6]. Despite the lack of sufficient information on the fundamental factors behind the development and growth of malignant tumors in the central nervous system, errors occurring in polymerase randomly during stem cell division and differentiation have resulted in genomic alterations in oncogenes and tumor suppressor genes [17]. Substantial evidence from studies aimed at understanding cell replication and human tumor development has shown that even at the lowest and random occurrence of DNA polymerase errors during stem cell division, each stem cell replicates its DNA with a polymerase error resulting in phenotypically diverse stem cells [18]. As miscoded DNA information progresses between dividing and differentiating stem cells, the resulting duplicated cells will have higher exposure to harm. Polymerase mistakes result in DNA changes in oncogenic pathways associated with glioblastoma formation. Revisions occur in particular oncogenes and tumor suppressor genes, where mutations in these genes result in glioblastoma formation and progression.

Driver oncogenes and tumor suppressor genes related to glioblastoma proliferation include PTEN, TP53, EGFR, PIK3R1, PIK3CA, NF1, RB1, and IDH1. Additional gene changes result in cell heterozygosity loss culminating in glioblastoma formation. Most glioblastomas have mutations in the genes PTEN, TP53, IDH, oncogenic, and tumor suppressor EGFR. These glioblastoma-associated genes are employed in therapy development in prognostic indicators. Most glioma alterations seem to occur in the gene body CpG sites changing the transitions of CGA codon sequences [19]. Although most of these changes may not be directly correlated with DNA polymerase errors during cell replication, mutations occurring in genes linked to the development of glioblastoma are believed to be directly dependent on the number of stem cell replication and cases where DNA is single-stranded and exposed to reactive molecules that accelerate DNA and total damage.

Much study has focused on glioblastoma. However, despite study intensity, the complexity of glioblastoma biology remains mostly uncovered [38]. The World Health Organization (WHO) was the primary source of tumor categorization information on the central nervous system, tumor grading, and tumor diagnosis standards. Current oncological research focuses on tumor epigenetics and molecular composition to establish a general understanding of brain tumor causation and malignancies. Much progress has been achieved in the molecular diagnosis and subtyping of brain cancers for accurate diagnosis and development of new therapeutics. Understanding brain tumor molecular pathogenesis has improved WHO's clinical practice of molecular diagnosis and guidelines. Molecular biology studies on glioblastoma focused on tumor behavior, glioblastoma molecular characteristics, and tumor heterogeneity to

advanced targeted, helpful therapeutics in clinical treatment and glioblastoma management. Molecular diagnostics explores whether genetic changes in astrocytoma have been performed to recognize glioblastoma-induced conduits. Molecular diagnostics uses classical molecular markers with clinical consequences for the histological classification of brain tumors, with a great deal of work to uncover new molecular markers that may help create novel treatments for human glioblastoma [43]. Classical molecular diagnosis and glioblastoma grading were based on p53 status and receptor epidermal growth factor (EGFR). This approach to glioblastoma diagnosis was based on researching the mutation and clinical implications of p53 growth suppressor DNA and EGFR. Current research on glioblastoma molecular pathogenesis has identified biomarker alterations such as 1p/19q codeletion, O 6-methylguanine methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase-1 (IDH1) to bear clinical implications in glioblastoma diagnosis, grading and therapy development, and prediction of therapy response. Intermediate detection of oncometabolite 2-hydroxyglutarate (2HG) in cells that harbor mutations in isocitrate dehydrogenase1 (IDH1). Genetic alterations of type 1p/19q codeletion and IDH1 are considered good prognostic markers during the classification of gliomas due to their link to oligodendroglia morphology and lower grade: grade 2 and 3 glioma more than glioblastoma with MGMT promoter methylation emerging as the most predictive marker for glioblastoma prognosis [43].

There is considerable curiosity in sequencing-based knowledge of the next generation. It allows wide-ranging planning of genetic modifications SNP, merging and duplicating digit discrepancies, and epigenetic RNA methylation in head cancers. A unique strategy requires outlining glioblastomas from nearby ordinary brain muscles during the operation. Numerous intraoperative scanning modalities have been developed to delineate the surgical border of brain growth, including MRI, neuronavigation, Raman spectroscopy, ultrasound, and visual fluorescence scanning. With the innovation of disparity representations, both optical fluorescence scanning and MRI have improved head growth resect ability. The fluorescence-driven operation uses 5-ALA pre-operative glioblastoma muscle treatment. It helps the neurosurgeon separate the healthy brain from the tumor for more general growth cell surgery similar to the possible use of predicted theater area light.

Although advanced studies have focused on the development of glioblastoma tumors and the identification of the genetic pathways linked to the disease and the genomic changes leading to its development, and few therapies have been developed to counter it is aggressive, glioblastoma multiforme has remained evasive to these therapies [1]. Only a few clinical treatments have been created. The few potential medicines are available to oppose distinct mutations of glioblastoma encounter particular challenges that typically make medications useless or inapplicable. Current and typical treatments for glioblastoma are multimodal, mainly using surgery and chemotherapy.

Glioblastoma is the most prevalent intracranial malignancy with a poor prognosis. Although surgery, chemotherapy, and radiation have been extensively used in brain tumor management, glioblastoma has shown histological heterogeneity that has made it difficult to eradicate using conventional methods as such therapies leave residual glioblastoma cancer cells that may be missed during radiography leading to glioblastoma resurgence [49]. Residual tumor volume after surgery for glioblastoma has been identified as a high-risk comeback and reduces patient survival chances after surgery or therapy utilizing standard methods [50].

Recurrent glioblastoma is more likely to be resistant to medications and therapies available, and targeted therapies may not function at the individual patient level. Glioblastoma's incurable nature needs a multi-therapy approach to cure brain cancer with minimal damage to good tissue. Future glioblastoma therapies rely on using tailored personal immunity therapy and stereotactic radiosurgery. Future glioblastoma management and treatment will combine these innovative treatments with the current intracranial cancer treatment regimen and develop techniques to administer such innovative medicines safely. DNA changes cause brain tumors. Changing DNA during cell mitosis alters the normal processes that normal cells undergo and disrupt the functioning of glial cells that are crucial for the nervous system's health. This allows cells connected to brain cancer to keep diving and expand, leading to tumor development within the brain. Glioblastoma remains human brain cancer's most prevalent and fatal strain. Understanding the genes and genetic mutations in different genes leading to common phenotypic glioblastoma will assist produce information on glioblastoma pathophysiology and prognoses that can be connected to distinct mutations.

COMMON THERAPIES FOR GLIOBLASTOMA MUTATIONS

Even though advanced studies focused on the development of glioblastoma tumors and identification of the genetic pathways linked with the disease and the genomic alterations that lead to its development and few therapies have been developed to counter it is aggressive however, glioblastoma multiforme has remained evasive to these therapies [2]. Only a few therapies have been developed for clinical applications. The few available potential therapies developed to counter various glioblastoma mutations face specific barriers that mostly render the therapies ineffective or inapplicable in most cases. The current and common therapies for glioblastoma are multimodal and include the use of majorly surgery and chemotherapy.

Surgery

Surgery is the most utilized form of therapy in the management of most cancer cases. Surgical procedures have been considered as a sure of managing glioblastomas in patients without causing harm to the brain and risk injuries to the brain tissues and loss of neurological functions [45]. Though several risks have been associated with the management of glioblastomas using surgery, new and surgical assistive intraoperative technologies are improving the glioblastoma and other cancer surgical therapies and reducing the procedures'' morbidity profile [46]. The novel surgical navigation systems, however expensive, are allowing for the

operation of previously inoperable tumors to be operated with reduced risks of brain tissue injuries. Due to the heterogeneity of glioblastoma tumors and the location of the tumors in the human brain and the risks that surgery to remove such tumors pose and also to improve the efficiency of the surgery, a lot of modifications have been made to brain tumor surgery.

Modifications in Surgery

Extensive improvements have been increasing in medical procedures. In the pre-brain picture, MRI and CT age, preoperative analysis with pneumoencephalography which generally exhibited the position and weight movement and brainy angiography elevated doubt of cancer, which needed to be established by histological inspection [2]. Like contemporary modification, neurosurgery of glioblastomas 60 years back was unpolished as likened to a thorough examination of nonthreatening brain tumors since it was measured a relaxing process to release the intracranial burden and lengthen life for some months with acceptance to the point that the longsuffering individual was due to perish.

Besides offering a satisfactory example for histological investigation and exclusion of a mass to decrease elevated intracranial pressure, removal of a tumor offers a crack for the use of native therapies for the annihilation of remaining tumor quantity and preclusion of reappearance. The biggest exclusion that is constant with neurological protection is generally conducted and has been revealed to lengthen existence but does not decrease death. Major extirpation of the growth is regularly targeted at nevertheless is not imaginable because of intrusion of the tumor into the immediate brain.

Modifications in brain scanning methods have donated significantly to refining the preparation of surgical practice. Intraoperative scanning, mainly the usage of 5-aminolevulinic acid and MRI aids in outlining the restrictions of glioblastoma and for making most of the degree of surgery successful. In line with a methodical appraisal of randomized scientific experiments, the influence of scan-guided surgical procedures on quality and survival of life is undefined. Methods, for example, cortical planning, fluorescence-directed operation, and intraoperative form spectrometry, are regularly utilized in the theatre for brain growth removal. Visual consistency tomography, still in the investigational phase, might fill the necessity for a non-invasive method for real-time difference concerning normal brain and tumor. Postoperative scanning offers a valuable standard for the dimension of residual tumor and additional assessment of reaction to adjunctive treatments.

One of the key improvements in neurosurgical practices was the establishment of a surgical optical microscope, which had an extraordinary impact on refining cerebrovascular operation. It offers enhanced therapy of peculiarity between the normal brain and tumor to evade injury to normal arrangements. Other modifications in apparatuses for eliminating tumor material comprise ultrasonic aspiration to minimalize shock and “laser vaporization” to decrease hemorrhage and abolish cells in tumor base by thermal influence. The surgical procedure is enhanced with improvements in radiotherapy and chemotherapy that will be labeled distinctly. Besides general postoperative and cranial chemotherapy radiotherapy, the surgical procedure offers a chance to use a number of treatments throughout the process. Models are the establishment of chemotherapeutic representatives and photodynamic psychoanalysis.

Chemotherapy

Chemotherapy has been one of the most preferred brain tumor management therapies. While it has been proven that chemotherapy improves overall survival in patients with the most malignant primary brain tumors, it does so in only about 20 percent of all patients, and physicians cannot readily predict which patients will benefit before treatment. As chemotherapy has been growing ineffective over time, research have focused on developing new concurrent therapies to work with chemotherapy. Trials are carried out to concurrently use Proton beam therapy with chemotherapy for glioblastoma management to combat the growing resistance of glioblastoma to existing therapies [47].

The treatment of both primary and secondary glioblastoma faces some challenges that arise from the characteristics of glioblastoma that not only increase the malignancy and drug resistance of the tumors but also make it hard to administer available therapies. Glioblastoma has high genomic stability and heterogeneity, which makes it impossible for the development of specific target drugs for the tumors [8]. Further, as the development of gliomas is associated with alterations occurring in genes during stem divisions and the uniqueness of individual DNA, it makes it further harder to develop a single specified cure for glioblastoma. Glioblastomas have also shown to higher capabilities of migrating to and augmenting in cells adjacent to the malignant tumors and with to be the most prevalent metastatic form of cancer affecting humans. Glioblastomas are also localized in the brain, which is very sensitive. The mind cannot further repair itself in instances of tissue or cell damage, further adding to the progression and development of tumors. The use of chemotherapy and other treatments targeting glioblastoma and other brain tumors have led to increased neurotoxicity pushing for the development of other trial therapies.

Improvements in the Provision of Chemotherapy

To avoid general poisonousness of chemotherapy, numerous approaches have been utilized to restrict application to the tumor, for example, grafts in growth fissure following medical excision, directed provision to glioblastoma as result of systemic management, and careful provision of advanced concentrations to the growth, for example through intraarterial chemotherapy. The provision of (monoclonal antibodies) MAbs in glioblastoma will be deliberated in the subsequent unit on resistant therapy [48]. The provision of anticancer medications is restricted by their incapability to grasp therapeutic points in head tumors with greatly accepted dose routines. Medication directed by conjugating with protein, for example, transferrin, has been broadly considered, as a directing particle transferrin aids in the transference of medication to glioblastoma, which comprises plentiful transferrin receptors outwards. Transferrin-holding healing drugs may be directed to their place of accomplishment on brain growth. Thermosensitive liposomes may be condensed medications to issue them at the objective location in the tumor in reaction to hyperthermia devoid of revealing the adjacent regular brain to poisonousness.

Convection-Enhanced Delivery

Convection-enhanced delivery (CED) includes the straight provision of healing agents to the head by vaccination or a pipe pushing the agent via interstitial places under a force gradient instead of unreceptive circulation. It has been utilized for both chemotherapy medications and for the supply of macromolecules of a few organic treatments for glioblastoma. A number of chemotherapeutic medications utilized for glioblastoma, for example, temozolomide and nitrosoureas, may pass the undamaged BBB, however bigger particles, for example, MAbs might never do so. BBB absorptivity might be improved in glioblastoma; nevertheless, this is not a consistent element in evaluating the provision of healing for brain growths. Numerous approaches for medication provision through the BBB have been pronounced; a number of these include avoiding the BBB. Disturbance of BBB permits unrestrained channel of the medication into the brain adjoining the growth instead of the growth itself, which might give neurotoxic influences. Organized channels via the BBB with directed provision to the growth, as labeled in part on nanobiotechnology-centered provision is nontoxic and more operative. The blood-brain barrier inhibits the majority of particles that are bigger than ~500 Da. Several medications are deprived of access to the very areas where they would be operative, therefore restraining the medical usage of the majority of anticancer medications for handling brain growths. Every anticancer proxy exhibited several penetrability for BBB, even though the connection of its porousness to therapeutic effectiveness is not apparent. Even though numerous native therapies have endeavoured to avoid this blood-tumor barrier, native therapies must be more established to offer healing agents in more reserved places because of the vastly infiltrative process of prime gliomas.

Intra-Arterial Chemotherapy

Provision of chemotherapy to the brain through Intraarterial offers several provision top medication concentrations in the growth rather than a similar medication dosage offered systemically because of harm to the blood-brain barricade and neo vasculature within the growth. Nevertheless, randomized experiments on people with glioblastoma have not revealed a persistence benefit with intraarterial BCNU as linked to venous management. The limits of this method are substantial neurologic and vascular poisonousness that may result in graphic loss, knock, and leukoencephalopathy [6]. Even though the poisonousness of "intra-arterial chemotherapy" may be condensed by utilizing methotrexate-and carboplatin-based treatments, additional scientific educations are required to control its usefulness in the handling of glioblastoma. Physical investigational research has established the possibility of straight supply to glioma and brain muscle of cationic liposomes. This might signify an operative technique of supplying anti-glioma medications to glioblastoma in people with a problem, for example, cationic liposomes accrue at greater concentrations within the peritumoral brain as compared in the growth basic and are engaged for an extensive time.

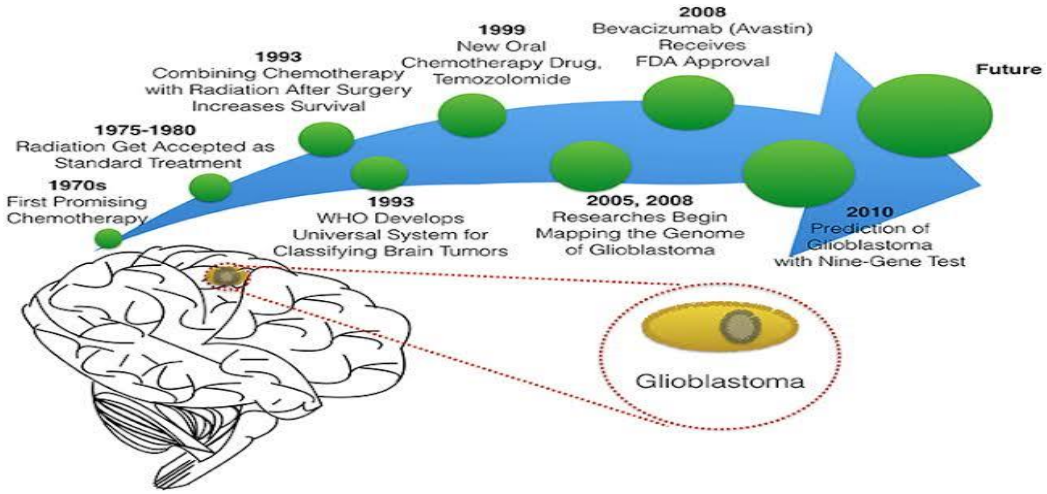
THE FUTURE OF GLIOBLASTOMA TREATMENT AND MANAGEMENT

Glioblastoma is the most common intracranial cancer up to date remains to have poor prognosis. Though surgery, chemotherapy and radiation have been extensively used in the management of brain tumors, glioblastoma has shown histological heterogeneity that has made it hard to completely eradicate using the conventional methods as such therapies leave residual glioblastoma cancer cells that may be missed during radiography and lead to glioblastoma resurgence [49]. The volume of residual tumor after surgery for glioblastoma has been identified to be high risking resurgence and lowering the chances of patient survival after the surgery or treatment using the conventional methods [50]. The complete resection of glioblastoma cancer cells is somewhat hard as residual cancer cells that have invaded the parenchyma may not be identified under radiographic imaging [49]. Recurrent glioblastoma is more likely to be resistant to available drugs and therapies and the use of targeted therapies may not work at the individual patient level. The incurable nature of glioblastoma requires a multi-therapy approach in order to completely cure the brain cancer with minimum damage to healthy tissue. Research is ongoing to develop novel therapies and improve on the existing treatment and glioblastoma management approaches that enable complete eradication of the brain cancer and increase survival chances and periods post therapy. The modern and future therapeutics of glioblastoma are expected to be successful in complete eradication of glioblastoma and related brain cancers by harnessing the synergy of the existing therapies and procedures and the novel glioblastoma therapeutics. The future therapeutics of glioblastoma are focused on the use of personal immunity targeted therapy (Immune therapy) and stereotactic radiosurgery. The management and treatment of glioblastoma in the future will be focused on integrating these novel therapies with the current intracranial cancer treatment regimen and the development of strategies to safely administer such novel glioblastoma therapeutics.

Immune Therapy

Novel immune based glioblastoma therapies are being developed and tried in the management and treatment of glioblastoma and other intracranial and human cancers. Immune therapy is an innovative treatment to glioblastoma and other types of cancers that makes use of the patient's body immune systems to target and attack developing malignant cells in the body [51]. Immune therapy is developed under the use of genes to develop personalized treatment. It harnesses the immunity of the body to fight the development of abnormal cells and tumors. This novel therapy is an approach that promises to overcome several drug resistance and drug delivery barriers that are specific to glioblastoma and other types of cancers of the central nervous system. Other than the other the application of immune therapy in the treatment of cancer, other applications of treatments exploiting the immune organization and the cell growth microenvironment in the body are being discovered. A drop of immune cells and a strong compromise of the remaining immune cells are evident in most of the patients with glioblastoma. It is not identified whether the development of glioblastoma is responsible for the drop and compromise of the immune cancer cells or it is the presence of the reduced number of immune cells and the

existence of pre compromised immune cells that lead to the development of glioblastoma.



Different types of novel immunotherapies such as the dendritic cell (DC) vaccine, heat shock protein vaccines, and epidermal growth factor receptor (EGFTRvIII) vaccines have been clinically tried and positive results in the treatment of glioblastoma [52]. The efficiency of the immune based therapies in managing glioblastoma has been observed to be amplified by combining the novel vaccine therapies with the conventional therapeutics. Glioblastoma due to the heterogeneity of its cancer cells has continued to be resistant to must availably drugs. Other therapies used for the treatments such as chemotherapy and radiation are growing dangerous due the side effects that have been observed on patients post treatment. Peptide and Dendritic cell inoculations have moved in medical experiments, with hopeful signs of action described in preclinical research and prompt stage experiments. These inspiring outcomes require additional approval in the continuing, more significant randomized trials [51]. Further immune cells focused approaches comprise CAR T/NK cells re-directed to specific growth antigens, e.g., EGFRvIII, which have established hopeful antitumor effectiveness in animal representations and are presently evaluated in numerous stage I/II experiments [53]. The administration of these vaccines boosts the immune cells to fight the developing cancer cells by replenishing the knowledge of the immune cells of the existence of the cancer cells and fight their development. Nevertheless, these different approaches will necessitate additional adjustment and optimization determinations, and prices and mechanical matters related to cell-based treatment will possibly lower its general use. Based on the studies carried out, immunotherapy promises to complement and improve the current treatment regimens such as chemoradiation [52].

Stereotactic Radiosurgery

Stereotactic radiosurgery makes use of multiple converging beams of highly charged x-rays, gamma rays or protons that are delivered to a discrete radiographically defined treatment area [54]. The delivery of the high radiation dose is precise and is applied in the treatment of various intracranial and skull base lessions [55]. As observed in earlier uses of radiation therapies, the unintentional damage to DNA and health tissue has been recorded as one of the side effects of radiation as an option. The use of stereotactic radiosurgery in cancer treatment as it includes the use of radiation; the high energy beams are tightly and precisely focused and targeted accurately on the abnormal cell tissues to avoid the damage of normal and healthy tissue [54]. The recurrence of glioblastoma after surgery or conventional radiotherapy has proved through history to be difficult to manage due to health of the health of the central system and toxicity of the settings of conventional therapies. The recurrent glioblastoma has also grown resistant to conventional drugs and radiotherapy requiring an advanced approach that can precisely target the resurgence brain cancer. Stereotactic radiosurgery has been successfully used synergistically with brain tumor resection to reduce the effects of the surgery such as local recurrence of the tumors and the effects of post-operative conventional radiotherapy to the cognitive abilities of the patient [56]. The stereotactic radiosurgery combined with immunotherapy provide hopes for a novel targeted therapy with the potential to eradicate glioblastoma and other cancers [57]

CONCLUSIONS

Brain cancers are caused by alterations in the DNA. The alteration of DNA during cell mitosis affects the normal processes that normal cells undergo and impair the functions glial cells that are responsible for the health of the nerve cells within the nervous system. This enables brain cancer related cells to keep diving and progressing in growth leading to the development of tumors within the brain. Glioblastoma remains to be the most prevalent and lethal strain of human brain cancers. Understanding the genes and genetic mutations that occur in the different genes leading to the common phenotypic glioblastoma will help to develop the information on the pathophysiology of glioblastoma and the prognoses that can be linked to the different mutations. The prevalence, progression, and lethality of glioblastoma are associated with the different genetic variants that are associated with the disease. The connection between the developments of glioblastoma and individual human genetics and the genetic

heterogeneity of glioblastoma has led to the development of biased and imbalanced therapies. At the DNA level, it is found that glioblastomas have increased genomic instability explaining the prevalence, rapid progression, and metastatic capability of the tumors. The rearrangements of genomes during cell division and differentiation are thought to be continuous during the development of tumors. The different mutations in oncogenic genes and tumor suppressor genes are associated with the metastasis of glioblastoma and the integrated development of drug resistance by the tumors. The localization of the tumors in the brains also makes it hard to make use of several available choice therapies. The future of brain tumor therapies will be developed from continuous laboratory research and advances in the studies focused on the molecular base of brain tumors. Understanding the molecular aspects of brain tumors will enable researchers profile the tumors and develop targeted therapies based on the profile of the tumors. Continuously carrying out clinical trials of novel potential therapies and improve the therapies for the advancement of the brain tumor treatment.

Gene symbol	Gene name	The function of the encoded protein	Point of mutation (%)
EGFR	Epidermal growth factor receptor	Regulator of cell signaling involved in cell proliferation and survival	14–15
ERBB2	V-erb-b2-erythroblastic leukemia viral oncogene homolog 2	Regulator of cell signaling involved in cell proliferation and survival	0–7
IDH1	Isocitrate dehydrogenase 1	NADPH production	12–20
NF1	Neurofibromin 1	Regulator of cell signaling involved in cell proliferation and survival	15–17
PIK3CA	Phosphoinositide-3-kinase catalytic alpha	Regulator of cell signaling involved in cell proliferation and survival	7–10
PIK3R1	Phosphoinositide-3-kinase regulatory 1	Regulator of cell signaling involved in cell proliferation and survival	7–8
PTEN	Phosphatase and tensin homolog	Regulator of cell signaling involved in cell proliferation and survival	24–37
PTPRD	Protein tyrosine phosphatase receptor type D	Regulator of cell signaling involved in cell proliferation and survival	0–6
RB1	Retinoblastoma 1	Regulator of cell cycle	8–13
TP53	Tumor protein p53	Apoptosis	31–38

Table 1: Genes commonly mutated in glioblastoma [27]

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