Glial Tumors: The Current State of Scientific Knowledge

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INTRODUCTION

Glial tumors are the most common primary brain tumors. They are derived from astrocytes, oligodendroglial cells, and ependyma. The majority of glial tumors are malignant, and the median survival of patients with glioblastoma is between 12 and 24 months. Improvement in the outcome of patients will depend on a better understanding of the scientific basis of gliomagenesis and the translation of such knowledge to the clinical setting.

EPIDEMIOLOGY

Primary brain tumors continue to be among the top 10 causes of cancer-related death in the United States, despite a comparatively low incidence to other cancers. Approximately 14 per 100,000 people in the United States are diagnosed with primary brain tumors each year, and roughly 7 per 100,000 people are diagnosed with primary malignant brain tumors. It is estimated that more than 81,000 people in the United States are living with a primary malignant brain tumor.[8]

Recently, there has been conjecture that brain tumor incidence is increasing. Analysis of this speculation is complicated by diagnostic discrepancies and ascertainment bias in registry data. However, after extensive review, this apparent increase is most likely caused by factors such as better diagnostic procedures, improved access to medical care, and enhanced care for the elderly—all leading to greater detection rather than an actual increase in incidence.[50] Nevertheless, diagnosis and registration methods that are more standardized and unbiased must become established and widely used before such speculation is truly resolved.

Age, Gender, Ethnicity, and Geography

Although there is no population that is not at risk for developing glioma, there is some correlation between incidence and characteristics, such as age, gender, ethnicity, and geography. A glioma can occur at any age and the average age of onset for glioblastoma is 62 years. In general, gliomas affect male patients 40% more frequently than female patients. This difference is most evident when women are of child-bearing capacity, suggesting a possible protective effect provided by female hormones.

Brain tumor incidence tends to be higher in countries with more-developed medical care; however, this is not always the case. For example, the incidence rate for malignant brain tumors in Japan is less than half that in Northern Europe.[50] In the United States, gliomas are more common in whites than in African Americans, Hispanics, Chinese, Japanese, and Filipinos. These dissimilarities are difficult to attribute exclusively to differences in diagnostic practices. Conceivably, genetic differences among races influence incidence in a manner that has yet to be uncovered. Chan et al. showed that, among adults with astrocytic glioma of any grade, tumors from whites had different genetic abnormalities than those from other races. Such discoveries necessitate further research into the possibility that differences in genetics among races play a significant role in tumorigenesis.[46]

Risk Factors

Research into the causes of brain tumors is mired by many factors, including the relative rarity of the disease and rapid death of patients with aggressive subtypes. To date, studies have revealed little regarding specific causal factors, but several variables have been shown to confer increased risk for developing the disease. For instance, high-dose therapeutic ionizing radiation to the head, administered for benign conditions or for cancer treatment, has been shown to increase the risk of glioma, meningioma, and nerve sheath tumors.[13]

Other established risk factors include the hereditary genetic syndromes. However, these syndromes explain less than 5% of glioma cases. Outside of these known genetic syndromes, information on familial aggregation is limited. There may be a slightly increased incidence of glioma among first-degree relatives. There is gender predominance with malignant gliomas being more common in male patients than female patients. Nonetheless, a well-defined mode of inheritance is not readily evident. Several families in whom gliomas are found in multiple generations have been followed over time, but the pattern of inheritance is unclear because tumors seem to skip generations, have variable times of onset, and, in parent-child pairs, the child is often diagnosed before the parent.[35] Segregation analyses of familial glioma support

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an autosomal recessive mode of inheritance, but a multifactorial model has not been excluded. Other segregation analyses favor a polygenic model. Investigators have initiated studies of genetic polymorphisms that, when coupled with certain environmental exposures, may lead to brain tumors. Better explanation and the relevance of this information continue to be delayed by low incidence of disease, and further studies are needed.

Numerous noninherited risk factors have been examined in relation to brain tumors. Several studies have suggested a possible role for the immune system in tumorigenesis. For instance, people who received polio vaccines contaminated with the SV40 virus have been shown to be at increased risk for developing glioma, though other studies have failed to support this claim.[18] Viral antigens from the JC virus and human herpesvirus 6 have been detected in brain tumor subtypes, but it is unclear whether they have a role in tumorigenesis. Nucleic acids and proteins from human cytomegalovirus have also been found in high-grade gliomas. Intriguingly, other studies have indicated that previous infection with *Varicella zoster* may decrease glioma risk. Likewise, there seems to be an inverse association of allergic diseases (asthma, eczema, and general allergy) with glioma, further suggesting that the immune system is involved in the formation of the disease.

The possible risk of developing brain cancer from exposure to electromagnetic fields through power lines has also been investigated. To date, studies do not support any such relationship. However, there continues to be anecdotal concern regarding such matters fueled by increased exposure to radiofrequency because of the increased use of handheld phones and wireless radio devices. Again, numerous studies fail to indicate a causal relationship. In fact, a recent case-control study found no relationship between brain cancer mortality and radiofrequency exposure. Of course, the effects of long-term exposure remain to be determined.

Another area of popular concern is the possible association between head trauma and brain tumor development. To date, no correlation between head trauma and glioma has been supported. A recent study that compared adult patients with glioma and a history of head injury requiring medical attention with control patients failed to support an association during an average of 8 years of follow-up. However, there was a slight increased risk for developing a brain tumor in the first year after the injury that the authors attributed to increased detection.[19] This leaves a measure of uneasiness regarding unequivocally denying an association between head trauma and brain tumor development.

Studies of diet, vitamins, alcohol, tobacco, and environmental exposures have also revealed little information regarding the cause of glioma. Nitrate exposure from cured meats likely does not influence brain tumor development; however, reliable assessment of true exposure to nitrates is difficult because of widespread potential exposure through tobacco smoke and cosmetics, as well as endogenous digestive exposure. Although tobacco is a common environmental source of carcinogens, studies have not indicated that it causes brain tumors. Alcohol consumption does not seem to increase the risk of developing a glioma, and may actually decrease the risk. Lastly, little to no significant association has been found between developing glioma and exposure to pesticides, synthetic rubber, or agents known to be carcinogens, including vinyl chloride and petrochemicals.

Prognostic Factors and Clinical Outcome

The overall survival for patients with glioma has not improved significantly in the past 20 years. From 1975 to 1995, patients younger than 65 years with primary brain cancer made modest improvements in survival, but older patients made no such advances.[50] Glioblastoma remains the histological subtype associated with the poorest survival; less than 3% of patients with glioblastoma multiforme (GBM) survive 5 years after diagnosis. Increased mitotic activity correlates with reduced survival in patients with high-grade glioma.

Among high-grade gliomas, correct histological identification can be complicated by a high degree of inconsistency in tissue appearance and collection and interobserver variability. Such challenges can lead to errors in identification and subsequently in prognostic estimation. In contrast to this type of classification, a gene expression-based categorization is gaining favor and may assist in appropriately estimating prognosis and guiding clinically relevant treatment. A recent study demonstrated that gene expression profiling, when coupled with class-prediction methodology, classified diagnostically challenging malignant glioma in a manner that better correlated with clinical outcome than did histopathological identification. Even so, further studies and reproducible results are needed before this technique is widely used.

There is limited but increasing data on the prognostic value of molecular markers. Hegi et al.[15] found that patients with GBM containing a methylated methylguanine methyltransferase (*MGMT*) promoter benefited from radiation and temozolomide, whereas those without a methylated promoter did not have such a benefit. Patients with promoter-region methylation achieved a 2-year survival rate of 46% with concurrent temozolomide compared with 14% for those patients with an unmethylated *MGMT* gene. Thus, it seems that the methylation status of the *MGMT* promoter may be an important molecular marker for selecting temozolomide as a first-line treatment. If so, then further research on specific inhibitors of *MGMT* could be valuable.

Studies of patients with anaplastic oligodendroglioma demonstrate that certain chromosomal abnormalities also correlate with survival. Studies have shown that the loss of

chromosome arms 1p and 19q is associated with chemosensitivity and improved overall survival. Similarly, patients with GBM (without features of an oligodendroglioma) and 1p and 19q deletions also survive significantly longer than patients with GBM who do not have these deletions. In patients with anaplastic astrocytoma, loss of the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene is associated with poor survival. Additionally, epidermal growth factor receptor (EGFR) overexpression, particularly when combined with normal p53 expression, may correlate with poor survival in GBM patients younger than 55 years. Overexpression of MDM2, a p53 inhibitor, has also been found to significantly correlate with short-term survival in GBM patients. Deletions or mutations in the *p14ARF* gene, responsible for activation of p53, have been discovered in 70% of GBMs, but the prognostic value of this information is still under analysis.

Age and functional status continue to be strong prognostic indicators of survival in patients with malignant glioma. In general, age less than 45 years is associated with increased survival.[50] Stratifying patients into risk groups on the basis of age is likely to lead to better prognostic information. A recent retrospective study using recursive partitioning of 832 glioblastoma patients who were enrolled into prospective clinical trials at the time of initial diagnosis established three risk groups on the basis of age: 40 years or younger, 40 to 65 years, and 65 years and older.[25] Based on the commonly accepted idea that functional status also predicts longer survival, this study subdivided the 40- to 65-year age group by Karnofsky Performance Score (KPS) into greater than 80 or less than 80 KPS groups, resulting in the less than 80 KPS group behaving similarly to the age 65 years or older group. Mental status has also been shown to be a prognostic factor. In fact, recent publications report that baseline mini-mental status score correlates more strongly with time to progression and survival than performance status.

Tumor location, size, and extent of resection have also been studied in relation to predicting survival. Multivariate analyses have not shown tumor location or size to be significant prognostic factors.[2] The potential benefit of extensive resection continues to be debated, although most of the neuro-oncology literature testifies to the positive benefit of extensive resection, especially when compared with biopsy alone. However, these studies are retrospective and subject to selection bias. Although patients with surgically resectable tumors may survive longer than those who do not have surgically resectable tumors, it has not been shown that prognosis is necessarily improved by extensive resection. In the absence of randomized clinical trials and prospectively collected data, this question remains unanswered.

IMAGING

Magnetic resonance imaging (MRI) with intravenous contrast is the standard technique used to diagnose and monitor brain tumors before, during, and after therapy. Recent advances in imaging methods, such as diffusion-weighted imaging (DWI), perfusion imaging, and spectroscopic imaging can provide quantitative cellular, hemodynamic, and metabolic information that may enhance our understanding of brain tumor biology. Specifically, such imaging advances may improve assessment of treatment response, more accurately determine tumor activity during therapy, and differentiate between recurrent tumor and treatment-related complications.

For example, dynamic MRI techniques can measure features of vascularity in a region of interest within the brain.[17] Studies have demonstrated that relative cerebral blood volume maps correlate with the histopathological microvascularity of brain tumors and can guide stereotactic biopsy. Tumor vasculature normally has an increase in capillaries and permeability of vessels, leading to elevated cerebral blood volume, which can be measured relative to normal-appearing brain tissue.[26] In contrast to these findings, irradiated brain tissue has been found to have a dose-dependent decline in vessel density.[27] However, irradiated brain has also been found to have an increase in vascular permeability, which could obscure the differentiation between a tumor and treated brain tissue. Dynamic perfusion MRI also may suffer from a large amount of susceptibility to artifact and fail to provide any meaningful information. Magnetic resonance spectroscopy (MRS) provides supplementary information regarding the extent and nature of changes on a routine MRI scan by analyzing the presence and/or ratio of tissue metabolites, such as N-acetylaspartate (NAA), creatine, choline, and lactate.[28] Such information may be used to guide biopsies, define radiotherapy targets, and monitor patients after treatment. The ratio of choline to normal creatine level is usually significantly elevated in those areas consistent with tumor compared with those areas containing predominantly normal brain tissue or treatment effect.[20,37] Treatment effect is generally indicated by a marked depression of all of the intracellular metabolite peaks from choline, creatine, and N-acetyl compounds.

MRS alone may not be helpful in instances in which patients have mixed histological findings comprised of necrosis and tumor. Because of this heterogeneity and low spatial resolution, MRS findings of choline and NAA resonances below the normal range may indicate variable histological findings ranging from radiation necrosis, astrogliosis, and macrophage infiltration to mixed tissues that contain some regions of tumor.[9] Careful choice of voxel placement and interpretation of results in concordance with other imaging and clinical findings is critical.

Although different tumor types and grades contain characteristic MRS patterns of chemicals, at the present level of spectroscopic resolution, it is unlikely that MRS will replace biopsy as the "gold standard." Furthermore, validation studies using image-guided acquisition of tissue need to be performed to confidently correlate imaging with histopathology. The use of MRS in brain tumors is further limited by technical factors that render it unreliable for lesions less than 2 cm in diameter or for lesions close to bone, cerebrospinal fluid, or fat, because of signal contamination.

DWI is an MRI technique that measures differences in apparent diffusion coefficient (ADC).[16] Tumors with densely packed cells, such as lymphomas and medulloblastomas, show restricted diffusion compared with normal brain tissue (bright on DWI and dark on ADC maps). In contrast, greater diffusion is seen in gliomas as compared with normal brain tissue, and they, therefore, appear dark on DWI and bright on ADC maps. DWI may also be used to reliably distinguish between necrotic tumors and abscesses. The core of an abscess shows a hyperintense signal on DWI and a hypointense signal on ADC maps. In contrast, necrotic brain tumors have central areas of hypointense signal on DWI. In terms of differentiating treatment effect from tumor, ADC ratios of recurrent tumors are generally significantly lower than those of treated brain tissue. However, it should be noted that dexamethasone produces a localized reduction in the magnitude of extracellular water molecule mobility in peritumoral edematous brain tissue, which may prevent proper interpretation of results.[43]

The above imaging techniques render the greatest amount of information when used together. Research continues to be performed in this area and validation studies that correlate image-guided acquisition of tissue with histopathology are needed.

ORIGIN OF GLIOMAS

Several genetic abnormalities in genes governing growth factor-signaling pathways or cell-cycle control are evident in glioma. Discovering how and why these genetic mutations occur may lead to an improved understanding of the disease and to better treatments. The undifferentiated character of brain tumors and recent investigation into cancer stem cells have fueled debate regarding whether or not neural stem cells give rise to brain tumors via acquisition of oncogenic mutations. Until relatively recently, the adult brain was thought to be a static environment. It is now known that several regions of the brain contain cells capable of proliferation. Such cells are either stem cells (multipotent and self-renewing) or progenitor cells (self-renewing precursors capable of producing astrocytes or oligodendrocytes). Thus, either stem cells or progenitor cells, in addition to differentiated glia, could be the substrate for neoplastic transformation into brain tumors.[39]

Because stem cells already possess the machinery for self-renewal, and their longevity targets them for accumulation of genetic mutations, it is easy to see why the stem cell theory is attractive. Regions of the brain with stem cell populations are more sensitive to viral or chemical oncogenesis,[42] and it has been shown that differentiated cells in the brain can give rise to tumors when infected with activated *Ras* and *Akt* and *c-Myc* gene transfer. Additionally, the concept of cancer stem cell clonal population implies that with tumor recurrence, mutations found in the first tumor should be found in the second. However, this is not always the case.[41] It also seems that neural stem cells are recruited by brain tumors, leading to the possibility of heterogeneous and or polyclonal cell population with one tumor. Thus, the appearance of stem cells in a brain tumor may be a consequence of dedifferentiating mutations and not the cause of the tumor. Whether the transforming event(s) causing a brain tumor occurs in a stem cell or a more differentiated cell that has reacquired stem cell characteristics remains to be proven. Likely, the role of stem cells in the ontogeny of brain tumors is more complex than originally thought.

MOLECULAR BIOLOGY

A comprehensive review of what is currently known regarding cell-signaling pathways and their inter-relationships in brain tumors is beyond the scope of this chapter. A simplified discussion of cell signaling pathways and how these pathways may play a role in tumor development follows.

Gliomas commonly express molecular or genetic abnormalities that influence the growth factor-regulated signaling pathways that, in turn, regulate cell proliferation.[48] For instance, a glioma cell may overexpress EGFR, a tyrosine kinase receptor with downstream effects resulting in cell proliferation and invasion. Overexpression of EGFR occurs in approximately 10% of grade III anaplastic astrocytomas and in 40 to 50% of GBMs. Gliomas also may contain mutations of tumor-suppressor genes, such as *PTEN*.[29] These gains or losses may promote cancerous behavior and may be targets for new treatments.

Studies have also revealed that GBMs seem to originate in one of two ways. Primary GBMs occur mostly in older patients who do not have a previous history of lower-grade astrocytoma; they generally overexpress EGFR. Secondary GBMs seemingly arise from lower-grade astrocytomas, occur in younger age groups, and generally do not overexpress EGFR; instead, they generally have mutations in tumor suppressor gene p53 (*TP53*).

The most common type of EGFR mutation is known as EGFRvIII, which is constitutively active, existing in a low-level state of autophosphorylation that induces receptor signaling. It lacks an extracellular receptor domain and cannot

bind to a ligand, making it resistant to the down-regulation that occurs when a ligand activates a normal receptor.

TP53 is responsible for cell cycle control, DNA repair, and induction of apoptosis. It is mutated in approximately 50% of cancers and 30% of gliomas. Mutation of TP53 results in decreased apoptosis in response to DNA damage, thereby predisposing the cell toward neoplastic transformation.

Other glioma cell signaling pathways may also be altered and result in tumorigenesis.[48] Activation of a tyrosine kinase receptor platelet-derived growth factor (PDGF) or vascular endothelial growth factor (VEGF) by a growth-factor ligand can result in cellular proliferation via one of two pathways. First, binding of the receptor may activate the Ras pathway (membrane-associated small GTPases), causing the cell to proliferate via the mitogen-activated protein-kinase cascade (MAPK). For Ras to do this, it requires prenylation, the attachment of a farnesyl or geranylgeranyl group. Prenylation is catalyzed by farnesyl transferase. Secondly, VEGF or PDGF may activate phospholipase C, which catalyzes the formation of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3) from phosphatidylinositol 4,5-diphosphate. IP3 and DAG activate protein kinase C (PKC), which may trigger the MAPK pathway directly or through the Ras pathway.

VEGF not only causes cell proliferation, but is also involved in the pathways that determine endothelial proliferation and neovascularization. PDGF also promotes angiogenesis by inducing VEGF expression.

Ras mutations may lead to increased cell proliferation; however, they are rare in astrocytomas, and it is thought that upstream components of the Ras pathway contain mutations, e.g., PDGF receptor (PDGFR).

As more is known regarding cell signaling pathways and cell cycle control, new therapeutic agents are being created that may lead to greater efficacy in treating glioma when used alone or in combination. Some of these agents are discussed in the next section.

TARGETING CELL SIGNALING PATHWAYS

In an attempt to better improve the outcome of patients with brain tumors, several phase I and II studies and a few phase III studies of new molecular agents are ongoing. More detailed information regarding these new agents and how they may affect cell-signaling pathways may be found elsewhere.[3,30–34] Different agents work on specific targets that can influence cell growth, invasion/migration, angiogenesis, and apoptosis. What follows is a brief summary of some of the agents under current investigation for treatment of patients with recurrent high-grade gliomas.

Tyrosine Kinase Inhibitors

Several synthetic inhibitors of EGFR and PDGF have been tested in brain tumor clinical trials. Phase I studies of ZD1839 (Iressa) and OSI-774 (Tarceva) demonstrated that these agents were well tolerated by patients. Median overall survival for patients with GBM treated with Iressa at the time of first recurrence was 39.4 weeks.[7] Evaluation of other EGFR inhibitors, e.g., GW572016, as well as these agents in combination with other modalities, such as chemotherapeutic agents or other targeted therapies, is ongoing. STI-571 (Gleevec) is a PDGF tyrosine kinase inhibitor that is also being evaluated in ongoing studies of patients with recurrent malignant glioma.

Inhibitors of the RAS/MAPK Pathway

Farnesyl transferase inhibitors have been proven to inhibit the growth of multiple tumors, presumably by blocking Ras-mediated cell signals. Synthetic farnesyl transferase inhibitors, such as R111577 (tipifarnib) and SCH66336 (lonafarnib) have demonstrated positive results in preclinical studies using brain tumor models. A phase I study of R115777 demonstrated that the agent is well tolerated, and its toxicity profiles are dependent on the use of enzyme-inducing antiepileptic agents.[38]

Inhibition of the AKT/mTOR Pathway

Direct inhibitors of Akt have been difficult to develop and have not been tested in glioma clinical trials. An alternative approach has been to develop agents that inhibit downstream pathways, such as the mammalian target of rapamycin (mTOR) pathway, which is activated by Akt and involved in regulation of protein synthesis and cell growth.[5,40] Rapamycin is an mTOR inhibitor, but is relatively unstable in solution and, therefore, has not been used in many clinical trials. Instead, more soluble ester analogs of rapamycin, such as CCI-779, have been studied. CCI-779 inhibited GBM proliferation in vitro and was well tolerated in patients with recurrent malignant glioma. Two phase II studies, however, recently reported that less than 10% of patients were progression-free at 6 months, suggesting that, as a single agent, this drug has limited activity.[6,12] The challenge for developing targeted therapies is identifying which subsets of patients may benefit from them. High levels of phosphorylated p70s6 kinase in baseline tumor samples seemed to predict a patient population more likely to derive benefit from treatment with CCI-779. Other mTOR inhibitors, such as rapamycin analog drug (RAD001), are also being investigated as single agents and in combination with other targeted therapies, as well as with chemotherapy.

Anti-Angiogenesis

Increased vascularity and endothelial cell proliferation in gliomas are driven by hypoxia-induced expression of pro-angiogenic cytokines, such as VEGF.[4,22] Multiple anti-VEGF agents are being evaluated and include AZD2171, BAY 43–9006 (Sorafenib), GW86034, and, more recently,

the recombinant humanized anti-VEGF monoclonal antibody, bevacizumab (Avastin).

PKC-β is an important molecule in the induction of and signaling through the VEGF pathway, thus, making PKC-β an attractive therapeutic target.[1,21,36] Preclinical studies demonstrate the potent anti-angiogenic activity of enzastaurin—a specific inhibitor of PKC-β in tumor models**,** including glioma models.[23,47] These observations make GBM a potential target for enzastaurin, and results from a phase II study using enzastaurin in patients with recurrent high-grade gliomas demonstrated that it was well tolerated in this patient population and suggested significant antitumoral activity.[11] Future studies are planned with this agent.

Histone Deacetylase Inhibitors

Other interesting agents being evaluated are inhibitors of histone deacetylase (HDAC), an enzyme that regulates chromatin structure and gene expression. HDAC inhibitors can induce growth arrest, differentiation, and/or apoptosis of tumor cells by altering the transcription of gene expression, and are a promising approach to cancer therapy. Agents such as FK228 or depsipeptide and suberoylanilide hydroxamic acid (SAHA) or vorinostat are being evaluated in patients with brain tumors.[10]

CHEMOTHERAPY

Standard treatment of high-grade gliomas usually consists of cytoreductive surgery followed by radiation therapy. On the basis of several previous meta-analyses, adjuvant chemotherapy adds some survival benefit, but its efficacy had been disputed until recently. The work of Stupp et al.[44,45] has made radiation in combination with the oral alkylating agent temozolomide, followed by adjuvant temozolomide, the standard of care for patients with newly diagnosed GBM. This treatment regime is considered standard because of recent results of a randomized phase III trial in adults with newly diagnosed GBM, who received radiotherapy alone or radiotherapy with concurrent Temodar (an alkylating agent) followed by adjuvant Temodar for 6 months. The 2-year survival rate was 26.5% for patients treated with Temodar, but only 10% for those treated with radiation alone. Equally important, there were few adverse events associated with this combination therapy.

Although these results have led to general agreement on the initial treatment of high-grade glioma, there is no consensus regarding the most appropriate salvage agent. Regardless of this lack of accord, some patients likely benefit from additional chemotherapeutic regimens.[14] Nitrosoureas are perhaps the most commonly used second-line agents, but carboplatin, etoposide or irinotecan, or a combination of these agents are also commonly used. Research continues regarding what role targeted agents when used alone or in combination with more traditional types of chemotherapy may play in the setting of recurrent disease.

ALTERNATIVE DELIVERY STRATEGIES

The development of surgically based drug delivery strategies specific for the central nervous system in combination with drugs that target molecules specific for gliomas is an exciting area of research.[49] Such approaches may improve the delivery of effective concentrations of agents and reduce systemic complications caused by the compartmental specificity of a targeted therapy delivered locally. Additionally, such approaches may effectively contend with infiltrative tumor cells that lie beyond the surgical margin. Convection-enhanced drug delivery (CEDD) is a surgically based method that can deliver large molecules, which are soluble in the interstitial space and will have a long half-life. Such therapies deliver agents by slow, direct infusion via stereotactically placed catheters. Several compounds have been created that can be delivered in this way. These include a recombinant fusion protein (IL13-PE38QQR) composed of interleukin (IL)-13 and a mutated form of the *Pseudomonas* exotoxin, which is being studied in a multisite phase III trial, randomizing patients with recurrent GBM to convection-enhanced delivery of IL13-PE38QQR or implantation of Gliadel wafers. Other agents, such as Taxol, a recombinant chimeric protein composed of transforming growth factor (TGF)-α and a mutated form of the *Pseudomonas* exotoxin termed PE-38 (TP-38) are also being tested in clinical trials.

OTHER EXPERIMENTAL THERAPEUTIC APPROACHES

Clinical research in gene therapy using replication incompetent versus competent (oncolytic) viruses is an exciting approach that is being evaluated in patients with brain tumors. Recent progress has focused on improving gene delivery methodology, development of new delivery approaches, such as stem cells and novel viruses, and increasing transgene potency.[24] As we learn more about the properties of neural stem cells, they may potentially be used as a direct antitumor agent, or a vehicle to deliver therapeutic agents or convert prodrugs within the tumor environment. There are several immunotherapy strategies that are being evaluated in brain tumor patients. These include nonspecific activation of the immune system using cytokines, active specific therapy using vaccines, local adoptive immunotherapy with augmentation of cellular elements to enhance tumor cell kill, and passive immunotherapy approaches using antibodies directed at specific tumor antigens.

CONCLUSION

Several areas of research continue with the goal of improving the prognosis for patients with brain tumors. Epidemiological and imaging advances continue to improve

our understanding of how gliomas may behave. Stem cell research is an exciting area of investigation that may provide clues regarding how to better treat patients. The expanding amount of information on cell growth signaling pathways and the role of oncogenes and tumor suppressor genes is critical to developing new molecular-based approaches to treating brain tumors. Appropriate evaluation of the efficacy of these new imaging techniques and novel agents requires the neurooncology community to continually redefine clinical trial design and strategy. In addition, because the molecular pathogenesis of brain tumors has not been linked to a single genetic defect or target, a single molecular agent is not expected to be an effective treatment. Efforts are ongoing to determine a molecular profile of each patient's tumor, in the hope of selecting those patients who will benefit most from specific molecularly based treatments.

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