Potential Usefulness of Radiosensitizers in Glioblastoma

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KEYWORDS

• Radiosensitizers • Glioblastoma • Cancer • Chemotherapy

KEY POINTS

- Concurrent use of radiation with a range of sensitizing agents, including various chemotherapeutic drugs, can augment treatment efficacy through several well-defined biologic pathways.
- Mechanisms of radiosensitization include spatial cooperation, cytotoxic enhancement, biologic cooperation, temporal modulation, and protection of normal tissues.
- Temozolamide is the only chemotherapeutic agent that has been shown to provide a survival advantage when included with standard radiation therapy as an initial adjuvant approach for glioblastoma, an effect that has been associated with radiosensitization.
- Several agents, including angiogenesis inhibitors, are currently being studied for potential use in radiosensitization.

INTRODUCTION

In spite of recent success in the treatment of various forms of systemic cancer, glioblastoma multiforme (GBM) remains resistant to most current therapies. Various tumor characteristics have contributed to this resistance, including diffuse infiltration at the time of diagnosis, significant cellular heterogeneity (both intratumor and intertumor), and the role of tumor stem/progenitor cells in reestablishment of resistant disease following cytotoxic treatments. Current standard treatment of GBM consists of the regimen established by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group (NCIC) in a landmark phase III trial published in 2005. Following maximal surgical resection, patients are treated with 60 Gy involved-field radiation therapy (IFRT), in which the involved field is defined as the radiographically evident tumor along with a margin of 2 to 3 cm. Treatment is administered in 30 fractions of 2 Gy each over 6 weeks with concurrent daily doses of the alkylating chemotherapeutic agent temozolomide (TMZ) at 75 mg/m^2. This standardized chemoradiation therapy is followed by TMZ alone at 200 mg/m^2 for 5 days every 4 weeks for a total of 6 months.[1]

The development of this combined adjuvant approach stemmed from several decades of clinical effort to improve outcomes for patients with GBM. Early studies in the 1970s had shown median survival for patients with malignant glioma, treated with surgical resection alone, to be less than 4 months.[2,3] A growing experience with postoperative radiation therapy to the brain was initiated in the late 1960s and early 1970s. The survival benefit of whole brain radiation (WBR) to greater than 50 Gy was shown through a large trial performed at the Montreal Neurology Institute in 1966 and confirmed by studies from the Brain Tumor Study Group within the National Institutes of Health in the 1970s.[4] Higher dosing strategies were explored by Salazar and colleagues in the 1970s, who concluded that doses of 70 to 80 Gy

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were well tolerated by patients but did not eradicate tumor and did not significantly improve survival compared with the 60-Gy dose. Based on histologic changes seen in autopsy specimens of the patients receiving 70 to 80 Gy, they cautioned that higher doses than this would likely involve significant risk for extensive tissue necrosis.[5]

By the mid-1970s, there was increasing interest in application of IFRT to high-grade glioma, based on increasing understanding from clinical experience that most tumors are localized and that focal treatment allows minimization of the complications of radiation.[6] It was also during this time that early reports of successful stereotactic radiosurgery suggested that precise localization of radiation was both technically possible and could be of clinical benefit. The rationale for IFRT was validated by Hochberg and Pruitt,[7] who reviewed autopsy and imaging data for patients with GBM. They concluded that microscopic disease was limited to a 2-cm margin of the primary tumor in 29 out of 35 patients examined, and that 90% of recurrences also occurred in this margin. Further, multifocal disease occurred in only 4% of untreated patients, and was always identified on imaging.[7] Ramsey and Brand[6] in 1973 randomized 34 patients to WBR versus limited-field radiation, and showed that there was a survival benefit to higher dose (60 Gy) IFRT versus lower dose (40 Gy) WBR. These results have been validated in numerous subsequent studies and, in conjunction with technical improvements such as the introduction of multileaf collimators and associated planning algorithms for linear accelerators, have become the standard of care.[4]

There has similarly been a long history of correlative adjuvant therapy in GBM through the addition of chemotherapeutic agents. Temozolomide, a second-generation DNA alkylating agent, has been the only chemotherapeutic agent to show a clear survival benefit in combination with radiotherapy (RT). The recent EORTC/NCIC study, which established the current standard of treatment, compared surgical resection plus RT versus surgical resection plus RT plus temozolomide. Median survival for patients aged 18 to 70 years was 12.1 months for surgery and RT alone to 14.6 months for surgery and RT combined with temozolomide. In a 5-year follow-up to this initial study, the benefit of the addition of temozolomide durable throughout the period of follow-up.[8] A recent review of all patients with GBM in the United States in the SEER (Surveillance, Epidemiology and End Results) database comparing 2 years before the institution of the EORTC/NCIC regimen as standard care (2002–2004) with 2 years after (2005–2007) shows a gain in median survival from 11.5 to 12.5 months in the same age group,[9] confirming that the additive effects of TMZ are mild in terms of clinical efficacy.

New therapeutic approaches are needed to provide a significant survival advantage for patients with GBM. The potential usefulness of radiosensitizing agents has been an intriguing possibility for these purposes and is the topic of this article.

RADIOSENSITIZATION: A CONCEPTUAL BASIS

Radiosensitizers are agents that are broadly defined as those that enhance the efficacy of radiation. In response to the increasing combination of radiation and chemotherapeutic agents available for the treatment of cancer in the late 1970s, Steel and Peckham[10] described 4 exploitable mechanisms of radiosensitization derived from the interaction of various therapeutic modalities. Their system was recently updated by Bentzen and colleagues[11] to provide further clinical relevance and take into account the effects of newer chemotherapeutic agents that are not directly cytotoxic. This more recent system of classification consists of 5 mechanisms of radiosensitization, which are summarized in this article.

Spatial Cooperation

The purpose of radiation therapy is locoregional control of disease, whereas chemotherapeutic agents target systemic disease that may or may not be clinically apparent. This approach allows for intensification of treatment via radiation in tissues with the greatest disease burden. Because this effect is spatial, it does not require concurrent administration of the 2 modes of therapy, and sequential treatment is generally preferred to minimize toxicity. This strategy has been effectively used in the context of various types of metastatic disease.

Cytotoxic Enhancement

The primary mechanism through which cytotoxicity is induced by ionizing radiation is the formation of free radicals within target tissues, which subsequently lead to DNA damage. Cytotoxic enhancement refers to the ability of a chemotherapeutic agent, given concurrently with radiation, to enhance DNA damage in the irradiated tissue by facilitating damage or by inhibiting repair. This approach may include inhibition of DNA replication, inhibition of mitosis, or induction of redox stress.

Biologic Cooperation

Although cytotoxic enhancement includes targeted effects of radiation and a chemotherapeutic agent on a common cell population, biologic cooperation refers to the presence of synergistic

effects exerted by the chemotherapeutic agent through either different effector mechanisms and/or the activity of different cell populations. Commonly cited examples of agents showing biologic cooperation are antiangiogenic agents (eg, bevacizumab [BEV]) and bioreductive agents.

Temporal Modulation

Temporal modulation is the enhancement of the so-called 4 R effects of radiation dose fractionation through concurrent administration of a chemotherapeutic agent. The Rs consist of (1) preferential repair of DNA in normal tissues, reducing the toxicity of radiation if administered in a single fraction; (2) reoxygenation of previously hypoxic, and therefore radioresistant, central portions of tumor following the killing of the well-vascularized peripheral portions of tumor; (3) treatment by successive fractions of tumor repopulation following cytotoxic insult; and (4) redistribution of surviving tumor cells through the cell cycle to the more radiosensitive G2 and M phases. Agents targeting DNA repair mechanisms may be involved in both temporal modulation and cytotoxic enhancement.

Protection of Normal Tissue

This mechanism refers to minimization of acute or late radiation toxicity through the administration of a systemic agent. An example is a free radical scavenger with preferential cytoprotective effects in normal tissues.

Through the aforementioned mechanisms, a variety of agents have been proposed to have radiosensitizing properties in clinical use for malignant glioma (outlined in **Table 1**). The remainder of this article provides a brief overview of several of these agents, focusing on proposed mechanism of action as well as initial clinical experience with their use.

INHIBITION OF DNA REPLICATION

Temozolomide

Temozolomide (TMZ) is currently the only radiosensitizing agent used for GBM with class I evidence of benefit. TMZ was developed in the 1980s under the sponsorship of the Cancer Research Campaign in the United Kingdom (now Cancer Research UK) and entered clinical use in the late 1990s, with accelerated US Food and Drug Administration (FDA) approval for use in anaplastic astrocytoma granted in 1999.[29] It is a second-generation alkylating agent that is provided as a prodrug. Following administration through the enteral route, it undergoes hydrolysis in physiologic pH to its active form methyltraizeno-imidazoleoarboxamid (MTIC). The main mechanism of action of MTIC, as with other alkylating agents, is to transfer a methyl group to the middle guanine in a GGG sequence to convert it to O6-methylguanine. Chakravarti and colleagues[30] showed that, in combination with radiation, TMZ exhibits cytotoxic enhancement by increasing the number of double-strand breaks and subsequently causes a greater number of the treated cells to undergo apoptosis. Hirose and colleagues[12] showed that there is also a temporal modulation effect, increasing radiosensitivity in the tumor by causing G2/M cycle arrest.

Based on the EORTC/NCIC data, Hegi and colleagues[31] showed that patient response to TMZ, as with other alkylating agents, was dependent on O6-methylguanine-DNA methyltransferase (MGMT) activity. MGMT is a DNA repair protein that reverses the O6-guanine methylation and therefore directly counteracts the action of alkylating agents. Hegi and colleagues[31] showed prolonged survival in patients in whom MGMT had been epigenetically silenced via hypermethylation of the MGMT promoter. Because MGMT is consumed in the process of performing this function, some approaches to depleting MGMT have been attempted. These approaches have included manipulation of dosing schedules of TMZ,[32] locally increased TMZ delivery to the tumor resection bed in biodegradable polymer wafers,[33] and administration of competing MGMT substrate O6-benzylguanine before TMZ administration.[34,35] A difficulty with these approaches has been the rapid de novo synthesis of MGMT and restoration of function within hours of depletion.[36]

Nitrogen Mustards

Carmustine or bis-chloroethylnitrosourea (BCNU) is a nitrogen mustard that, like temozolomide, is an alkylating agent and therefore similarly susceptible to reversal of its effect by MGMT. A recent retrospective study suggests that BCNU in biodegradable polymer wafers placed at the resection site before the current EORTC/NCIC protocol confers survival benefit compared with BCNU and radiation alone.[13]

Topoisomerase I Inhibitors

Camptothecin was first isolated from the deciduous tree *Camptotheca acuminata* in the screening program for cytotoxic plant-based substances at the Cancer Chemotherapy National Service Center (CCNSC) under the National Cancer Institute. Its discovery and antitumor activity were first described in 1966. However, it was not until 1985 that its mechanism of action via inhibition of topoisomerase I was elucidated.[14]

Table 1
Agents that have been proposed to have radiosensitizing properties in clinical use for malignant glioma

Class	Agent	Mechanism
Inhibition of DNA replication		
Alkylating agents	Temozolomide	Covalent transfer of alkyl group to guanine, increased apoptosis, and G2/M cell cycle arrest[12]
	Carmustine	Covalent transfer of alkyl group to guanine, increased apoptosis[13]
Topoisomerase I inhibitors	Camptothecin	Stabilization of topoisomerase I–DNA complex, inhibition of DNA religation[14,15]
	Topotecan	Stabilization of topoisomerase I–DNA complex, inhibition of DNA religation[15]
	Irinotecan	Stabilization of topoisomerase I–DNA complex, inhibition of DNA religation[15]
Topoisomerase II inhibitors	Doxorubicin	Stabilization of topoisomerase II–DNA complex, inhibition of DNA religation[15]
Inhibition of mitosis		
Microtubule stabilizers	Paclitaxel	Disruption of microtubule organization during mitosis
Microtubule destabilizers	Vinca alkaloids	Disruption of microtubule organization during mitosis
	Verubulin	Disruption of microtubule organization during mitosis
Augmentation of redox stress		
Nitroimidazoles	Metronidazole	Depletion of free radical scavengers
	Misonidazole	Depletion of free radical scavengers
Novel agents	Tirapazamine	Depletion of free radical scavengers
	Motexafin gadolinium	Depletion of free radical scavengers
Inhibition of angiogenesis		
Thalidomide derivatives	Lenalidomide	Inhibition of migration of endothelial cells[16]
Novel VEGF Inhibitors	Bevacizumab	Monoclonal antibody against VEGF-A[17]
	Aflibercept	VEGFR mimic, competes with VEGFR-1 and VEGFR-2[18]
Receptor tyrosine kinase inhibitors	Cediranib	Inhibits PDGFR, c-kit, all subtypes of VEGFR[19,20]
	Vandetanib	Inhibits EGFR, RET kinases, VEGFR-1, VEGFR-2[21,22]
	Sorafenib	Inhibits BRAF, PDGFR-β, c-Kit, RAS, p38 α, VEGFR-1, VEGFR-2[23]
	Cabozantinib	Inhibits VEGFR-2 and MET[24]
	Dasatinib	Inhibits BCR-Abl and Src family tyrosine kinases[25]
Adnectins	CT-322	Inhibits VEGFR-2[26]
Integrin inhibitors	Cilengitide	Inhibits signaling initiated by contact of cell with extracellular matrix[27]
Alternate signal pathway inhibition		
Receptor tyrosine kinase inhibitors	Erlotinib	Inhibition of EGFR[28]

Abbreviations: EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; RET; receptor tyrosine; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Topoisomerase I binds covalently to 1 strand of the double-stranded DNA, cuts the other strand to relax supercoils, then religates the strand before disengaging the DNA. The primary action of camptothecin and its derivatives are S-phase specific, by reversibly binding the topoisomerase I–DNA complex and stabilizing it, specifically inhibiting the religation step. A collision of the camptothecin–topo-I-DNA complex with the replication fork during DNA replication leads to irreversible arrest of the replication fork followed by RNA polymerase during transcription. This collision is thought to result in a DNA double-strand break that, if unrepaired, leads to cell death.[14] Clinical trials with camptothecin in the 1970s were not pursued beyond a small phase 2 study because of toxicity. Since that time, 2 derivatives, topotecan and irinotecan, have been developed and are in clinical use.

As radiosensitizing agents, topoisomerase I inhibitors exhibit cytotoxic enhancement by targeting S-phase cells, which are radioresistant. There are currently multiple studies in progress examining the effectiveness of these agents as adjuncts to the EORTC/NCIC protocol.

Topoisomerase II Inhibitors

Doxorubicin, an anthracycline antibiotic, acts by intercalating DNA. Its main mode of action is in inhibition of the religation action of topoisomerase II, leading to double-strand breaks. Topoisomerase II, in contrast with topoisomerase I, forms double-strand breaks before religation, allowing it to not only relax supercoils but also to perform catenation-decatenation as well as knotting-deknotting. Doxorubicin not only exhibits cytotoxicity during replication but also during transcription.[15] Although doxorubicin was known to have activity against GBM cells in vitro, it had not seen clinical use because of its poor penetration of the blood brain barrier (BBB). Following recent availability of pegylated liposomal doxorubicin (PLD), there have been trials to assess its usefulness in GBM. A recent phase II study of postradiation administration of PLD within the EORTC/NCIC protocol has shown no clear benefit.[37]

MICROTUBULE STABILIZERS/DESTABILIZERS

Microtubule stabilizers and destabilizers cause mitotic arrest in dividing cells. Both the microtubule stabilizer paclitaxel and microtubule destabilizing vinca alkaloids have previously been susceptible to development of resistance through upregulation of efflux pumps. Verubulin (MPC-6827) is a recently introduced microtubule destabilizer binding the same site on β-tubulin as colchicine. In contrast with vinca alkaloids, verubulin is not susceptible to multidrug resistance efflux pumps. A phase I dose escalation trial has been completed,[38] and phase II trials of verubulin in conjunction with standard therapy are under way. Similarly, there has been renewed interest in paclitaxel, a first-generation microtubule stabilizing agent, which is being studied with new delivery methods that are less susceptible to cellular efflux. However, there are no current studies examining paclitaxel with radiation.

AUGMENTATION OF REDOX STRESS

Trans-Sodium Crocetinate

Radiation causes DNA damage in target tissues through the action of reactive oxygen species (ROS) with unpaired, highly chemically reactive electrons in their outer shells, such as superoxide, hydrogen peroxide, hydroxyl radical, and singlet oxygen. In the presence of molecular oxygen, this leads to formation of DNA organic peroxides that cannot be reversed, thereby fixing the damage. In the absence of oxygen, it forms DNA free radicals that can be reversed by the action of antioxidants, typically through reaction with an -SH group.[39]

Early attempts at radiosensitization of hypoxic tissues with nitroimidazoles such as metronidazole and misonidazole seemed promising in vitro but failed to show any clinical effect,[4] and have largely been abandoned with recent interest focused on their use in imaging of hypoxia.

More recently, tirapazamine, a bioreductive prodrug shown to significantly enhance radiation response in an animal model,[40] was studied as a radiosensitizing agent. In hypoxic tissues, it is reduced to reactive radical forms by intracellular reductases, leading to DNA single-strand and double-strand breaks. In the presence of oxygen, it is rapidly oxidized back to its inactive prodrug form, limiting its effect to tissues with low oxygen tension.[41] A phase II trial of tirapazamine given at 2 dose levels in conjunction with radiation showed no benefit compared with historical controls.

Motaxefin Gadolinium

Motexafin gadolinium (MGd) is a redox-active compound consisting of a porphyrinlike aromatic macromolecule complexed with gadolinium (III). In vivo in the presence of oxygen, it first accepts an electron from compounds with sufficient reduction potentials to form a radical, then subsequently transfers that electron to molecular oxygen to form a superoxide in a process known as redox cycling. The reducing agents are substances such as nicotinamide adenine dinucleotide (NADH)/nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), glutathione, and ascorbic acid that act

as antioxidant agents.[42] By depleting these cellular free radical scavenging mechanisms, MGd confers radiosensitization through cytotoxic enhancement. Recent literature suggests that reduction of MGd by NADPH may be catalyzed by thioredoxin reductase, which participates in various cellular functions via its protein disulfide reductase activity. In addition, MGd may have a direct inhibitory effect on ribonucleotide reductase, which is necessary for the reduction of all ribonucleotides to deoxyribonucleotides.[43]

A phase I dose escalation study of MGd with radiation in newly diagnosed GBM showed promising results, with median survival of 16.1 months in the treatment group versus 11.8 months in case-matched historical controls receiving radiation only.[44] A separate phase I dose escalation study of MGd with radiation in newly diagnosed pediatric pontine glioma has been completed,[45] and a phase II study of MGd plus TMZ and radiation is ongoing.

INHIBITION OF ANGIOGENESIS

Microvascular proliferation has long been known to be one of the histologic hallmarks of GBM, in large part because of increased expression of vascular endothelial growth factor (VEGF) in response to the hypoxic and acidotic tumor microenvironment. VEGF binds to a tyrosine kinase receptor (VEGF receptor [VEGFR]) that then initiates various signaling cascades. Of the VEGF subtypes, VEGF-A, in particular, is known to stimulate both angiogenesis and vasculogenesis as well as increase endothelial permeability and breakdown of the BBB.[46]

Inhibition of angiogenesis is thought to exert radiosensitizing effects on 2 levels. Prevention of the development of new capillaries between radiation fractions is thought to prevent the repopulation and tissue invasion response of the tumor to a cytotoxic insult, an example of biologic cooperation. Second, Jain and colleagues[46] introduced the concept of vascular normalization that may occur in neoadjuvant administration of antiangiogenic agents. The abundant vasculature in GBM is known to have various structural abnormalities, including poor organization, excessive tortuosity, and lack of an intact BBB. Flow through this abnormal vasculature has been noted in animal models to be heterogeneous with areas of poor or static flow. The increased VEGF levels constitute one possible mechanism, and anti-VEGF agents are thought to correct this abnormality and restore structurally and functionally more normal vasculature, providing cytotoxic enhancement via the reduction of hypoxic radioresistant regions within the tumor.[46]

Thalidomide Derivatives

Thalidomide was among the first-generation agents known to inhibit angiogenesis. Because of toxicity, various derivatives with improved tolerance have been developed, among them lenalidomide. The mechanism of the antiangiogenic effects of these agents is not clearly understood. A phase II study of thalidomide and topoisomerase I inhibitor irinotecan (CPT) in both newly diagnosed and recurrent GBM was performed before the establishment of the EORTC/NCIC standard. Six-month progression-free survival (PFS-6) was 40% and 19% in the newly diagnosed and recurrent groups, respectively.[47] A phase II trial of thalidomide administered during and following radiation in pediatric GBM and brainstem gliomas in a small cohort showed no clear benefit.[48] A phase II study of lenalidomide and radiation in newly diagnosed GBM has been published.[49] The corresponding phase II study has been completed and is awaiting publication of results.

VEGF Inhibitors

An antiangiogenic agent currently of interest is BEV, a humanized monoclonal antibody against VEGF-A. Because of previous success in treating colorectal cancer with the combination of BEV and CPT, this combination has been used in many phase II studies of high-grade glioma. In a recent prospective randomized trial comparing BEV with BEV plus CPT in recurrent GBM, PFS-6 was 42.6% in the BEV group and 50.3% in the BEV plus CPT group, compared with 15% for salvage chemotherapy and CPT alone.[17] There are currently multiple studies examining the use of BEV in a neoadjuvant or concurrent dosing with the radiation in the EORTC/NCIC protocol.

A second strategy for inhibition of VEGF has been the use of a VEGF receptor (VEGFR) mimic that reversibly competes with VEGFR for binding of VEGF, effectively reducing the concentration of available VEGF. Aflibercept (VEGF-Trap), a fusion protein consisting of extracellular domains of both VEGFR-1 and VEGFR-2 bound to the Fc region of human immunoglobulin G. In contrast with the VEGF-A–specific BEV, VEGF-Trap binds VEGF-A, VEGF-B, and placental growth factor (PlGF), also implicated in GBM angiogenesis, with high affinity. A recently published phase II trial showed no clear benefit and moderate toxicity of aflibercept monotherapy in recurrent GBM.[18] There is an ongoing study examining aflibercept with TMZ and radiation in both newly diagnosed and recurrent BM.

Another approach targets VEGF signaling. Small molecule receptor tyrosine kinase inhibitors (RTKI) compete for adenosine triphosphate (ATP) binding

sites and subsequently prevent phosphorylation of the tyrosine kinase. This approach, as with VEGF-Trap, has the benefit of having multiple targets of activity. Cediranib has pan-VEGFR activity, as well as activity against platelet-derived growth factor (PDGF) and c-kit.[19,20] A phase II trial of cediranib monotherapy in recurrent GBM showed promising results with a median PFS-6 of 25.8% versus historical controls of 15%, and overall survival of 227 days versus 175 days in controls. Vandetanib has activity against VEGFR-1, VEGFR-2, epidermal growth factor receptor (EGFR), and receptor tyrosine (RET) kinases. Phase I trials in recurrent GBM have shown good tolerance of vandetanib in combination with radiation.[21,22] Sorafenib is active against VEGFR-2 and VEGFR-3, as well as BRAF, PDGF receptor-β (PDGFR-β), c-Kit, RAS, and p38-α. A recent trial examining administration of sorafenib after radiation within the EORTC/NCIC protocol showed no clear benefit, but there was a large drop-out rate before the initiation of sorafenib because of early disease progression.[23] There are also 2 newer tyrosine kinase inhibitors with few previous data in GBM: cabozontinib targeting VEGFR-2 and MET,[24] and dasatinib, targeting BCR-Abl and Src family tyrosine kinases.[25] There are ongoing trials examining all of these agents administered concurrently with radiation within the EORTC/NCIC protocol for newly diagnosed GBM.

A recently introduced class of target-binding proteins, adnectins, are currently being studied in GBM. These are proteins based on the 10th type III domain of fibronectin with its binding redirected to various targets. CT-322, an adnectin active against VEGFR-2, has been shown to be well tolerated in a phase I trial,[26] and is currently undergoing phase II evaluation.

SIGNAL PATHWAY INHIBITION

Epidermal Growth Factor Signaling

EGFR amplification is a hallmark in the pathogenesis of primary GBMs. EGFR is a tyrosine kinase receptor belonging to the human endothelial growth factor receptor (HER) family and is known to be involved in differentiation, proliferation, and migration of cells in the central nervous system during development.[50] In primary GBM, it is amplified in approximately 40% and overexpressed in greater than 60% of tumors.[51] Inhibition of the EGFR pathway may confer temporal modulation by inhibiting repopulation of the tumor between radiation fractions.

Tyrosine Kinase Inhibitors

One of the signaling pathways activated by EGFR and other receptor tyrosine kinases is the PI3K/AKT/mTOR pathway, which is involved in cell growth, survival, and proliferation.[52] Agents targeting various points along this pathway are currently under investigation, and could potentially act as radiosensitizers in the same ways as the EGFR inhibitors. Simultaneously targeting multiple levels of a single pathway may yield synergistic effects. Clinical trials of these agents administered with radiation are pending.

FUTURE DIRECTIONS

In spite of improved understanding of the biology of many tumors in recent decades, there has been only modest improvement in prognosis for GBM associated with treatment. The combination of surgical resection, radiation, and temozolomide has been shown to provide a survival benefit. However, as understanding of the role of MGMT in therapeutic response shows, the era of 1-size-fits-all therapy is ending. As understanding of the signaling pathways involved in tumorigenesis continues to improve, a shift toward rationally tailored treatment based on tumor biomarkers can be expected to maximize the additive and synergistic effects of chemotherapy with radiation.

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