

Symposium

Current concepts and newer developments in the treatment of malignant gliomas

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Abstract

Primary malignant brain tumors account for only 2% of all adult cancers but they cause a disproportionately high cancer-related disability and death. Survival of malignant glioma patients has changed only modestly over the past three decades despite the emergence of new treatment strategies for these tumors. In this review, we describe the standard treatment modalities for malignant glioma, which include surgery, radiation therapy and chemotherapy, as well as the status of novel therapies that have been developed to target various aspects of glioma cell biology. We also address this issue of drug delivery as a factor limiting the efficacy of systemic administration of therapeutics and attempts to overcome this barrier. Further progress towards a cure for malignant gliomas will require a greater understanding of the underlying mechanisms driving the growth, and resistance to therapy, of these challenging tumors.

Key words : Glioma, surgery, chemotherapy, radiation therapy, experimental therapy, convection enhanced delivery, blood brain barrier

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Introduction

Primary malignant brain tumors account for only 2% of all adult cancers, but they cause disproportionately high cancer-related disability and death. The annual incidence of primary malignant brain cancer from 1997 to 2001 was 7.3 per 100,000 person-years.^[1] The median survival of patients with glioblastoma, as the most common form of glioma, was 14.6 months with chemoradiotherapy.^[2] Survival of malignant glioma patients has changed only modestly over the past three decades, despite the emergence of new treatment strategies for these tumors.^[3,4]

Current "Standard" Treatment in the United States - An Overview

Most high-grade glioma patients usually undergo multimodality treatments after histological diagnosis, including surgical resection, radiation, and chemotherapy. It is thought that maximal surgical resection of gliomas significantly improves survival, although there is scant level 1 evidence supporting this practice.^[5] While a complete resection of the contrast enhancing tumor is the usual goal for surgery,

it is also widely accepted that the surgeon must simultaneously minimize the risk of producing a new neurological deficit as a result of the disruption of functional pathways. There are more extensive, prospective, randomized data supporting the use of radiation therapy (RT) for the management of gliomas^[6] and the shrinking field technique of radiotherapy has been the standard for more than a decade.^[7] On the other hand, the survival benefits of adjuvant chemotherapy have been debated and are, at best, modest, compared to those seen in other solid cancers^[8] More recently, Stupp *et al.*^[9] and Taphoorn *et al.*^[10] demonstrated that concurrent chemotherapy during radiation therapy can increase the median and two-year survival rates of patients with GBM without degrading their quality-of-life.

Current Therapeutic Modalities

Surgery

The first-line treatment for malignant gliomas is surgery. Maximizing the extent of resection with preservation of neurologic function is the main goal in the initial management of patients with malignant gliomas.^[11-13] Gliomas have long been considered surgically incurable

because of early infiltration of tumor cells into areas of an apparently normal brain. It has been suggested that the survival benefit for patients whose surgery is effective is, relieving mass effect, reducing tumor volume remaining to be treated with other modalities, and removing the necrotic tumor core, which may be poorly accessible to circulating chemotherapy.^[14]

Surgery is also offered to patients with recurrent malignant gliomas who have good performance status, local mass effect symptoms, and accessible tumors, which are distant from the eloquent areas. Surgical resection may also be used to reduce mass effect, in order to buy time for additional therapeutic options. It has also been shown that maximizing surgical debulking may improve response to chemotherapy. Keles *et al.* have found that patients with recurrent GBM, in whom the volume of residual postoperative disease is less than 10 cm³ at the start of chemotherapy, have had a six-month, progression-free survival rate of 32% compared with 3% for patients who have had a volume of residual disease larger than 15 cm³.^[15-17]

Radiotherapy

Survival benefit for postoperative whole brain radiotherapy (WBRT) for malignant glioma was demonstrated in studies going back three decades ago. Median survival increased from 17 weeks in patients treated with conventional measures to 37.5 weeks in patients treated with postoperative WBRT.^[17,18] Subsequent advances in radiotherapy (RT) techniques have used improved imaging of the tumor and focused on RT techniques that maximize treatment to the tumor, while minimizing radiation to normal brain tissue. Focal external beam RT, termed involved field RT (IFRT) has replaced WBRT as the standard approach. Some types of IFRT include 3D-conformal RT and intensity modulated RT.

Although the essence of these techniques has remained unchanged, there have been numerous attempts to tailor RT to obtain lowest toxicity and maximum effect. The rationale for limiting the RT field is based on the observation that recurrent astrocytoma following WBRT develops within 2 cm of the original tumor site in 80 to 90% of the cases; while fewer than 10% are multifocal.^[19-21] To include the potentially infiltrating tumor cells into the target area, the RT dose (typically 60 Gy) is usually delivered to the tumor plus a margin of apparently normal tissue.^[22]

The shift from WBRT to IFRT has not changed the pattern of treatment failure or altered the percentage of patients with multifocal failures. As an example, in a series of 42 patients with recurrent AA or GBM

following IFRT, all recurrences were within 2 cm of the original tumor site, while two patients had a second lesion both inside and outside the 2 cm margin and two patients had a distant second lesion.^[23]

Intensity-modulated RT (IMRT) is another technique that relies upon software and modification of the standard linear accelerator output, to vary the radiation intensity across each treatment field. IMRT provides particular advantages when the target is critically close to the radiation-sensitive structures, as the dose to these structures can be minimized without affecting the dose to the tissue that needs to be treated.^[22,24]

Radiosurgery

Because the majority of malignant gliomas recur in close proximity to the original tumor and multifocal or disseminated disease is uncommon, there is great interest in maximizing the radiation dose to the tumor bed without increasing radiation exposure to the surrounding brain. Stereotactic radiosurgery (SRS) is a technique of external irradiation that uses multiple convergent beams to deliver a high single dose of radiation to a small (< 4 cm), discrete treatment volume. Radiosurgery can be performed with high-energy x-rays produced by a linear accelerator (multiple devices), with gamma radiation from Co⁶⁰ sources (Gamma Knife®), and with charged particles such as protons produced by cyclotrons, which are used less frequently. Stereotactic radiation techniques produce a rapid falloff of dose at the edge of the target volume. This feature creates a clinically insignificant radiation dose to the normal, nontarget tissue. Initial, small, single institution studies have revealed positive effects of SRS for newly diagnosed gliomas, but a prospective, multicenter trial showed no survival benefit after the addition of SRS to the standard therapy for GBM.^[17,25] SRS has also been used in the setting of recurrence; however, no randomized studies have been performed to date.^[17,22]

Interstitial Brachytherapy

Interstitial brachytherapy consists of the intraoperative placement of radioisotope seeds into a tumor or resection cavity. Brachytherapy permits the delivery of a large radiation dose to the tumor volume, with rapid fall-off in the surrounding tissues. Sublethal damage fails to get repaired with continuous rather than intermittent dose delivery and this increases tumor susceptibility, as the cells progress into a sensitive phase of the cell cycle. Despite the theoretical, dosimetric, and radiobiological advantages of brachytherapy, randomized clinical trials have shown marginal or negligible benefit from the use of brachytherapy in the treatment of malignant gliomas.^[22,26,27]

Chemotherapy

For decades, chemotherapy for malignant gliomas did not produce results comparable to those seen in other areas in oncology. Combination chemotherapy regimens failed to show any meaningful effect. Despite these negative results, the procarbazine, lomustine, and vincristine regimen (PCV) was widely used prior to the development of temozolomide.^[22,28]

Temozolomide

Temozolomide, an oral alkylating agent, is now the preferred agent for concurrent and adjuvant chemotherapy in patients with malignant gliomas. The benefit of concurrent and adjuvant temozolomide was demonstrated in a phase III trial in which 573 newly diagnosed patients with GBM were randomly assigned to postoperative involved-field RT (60 Gy in daily 30 fractions) versus the same RT plus concomitant temozolomide (75 mg/m² daily up to 49 days) followed by up to six cycles of adjuvant temozolomide.^[2,22]

Adjuvant temozolomide was associated with significant improvements in median progression-free survival (6.9 versus 5.0 months without temozolomide), overall survival (14.6 versus 12.1 months), and two-year survival (26 versus 10%). This improvement in survival was achieved with no detrimental effect on the quality of life of the patients.^[10,22] It is important to note that benefits from adjuvant temozolomide were observed in all patient subsets, even though the benefits of adjuvant temozolomide were most pronounced in patients with relatively favorable prognostic characteristics.^[29,30]

In spite of these promising results, resistance to treatment remains a major barrier to effective therapy. O(6)-alkylguanine-DNA alkyltransferase (AGT) is a DNA repair protein encoded by the (6)-methylguanine-DNA methyltransferase (MGMT) gene on chromosome 10. It effectively removes alkyl groups from the O6 position of guanine, thereby, reversing the cytotoxic lesion created in the DNA by nitrosourea and temozolomide. Epigenetic silencing of MGMT by promoter methylation is associated with loss of MGMT expression (and consequently less cellular AGT), diminished DNA repair, and increased tumor chemosensitivity.^[31] Response to temozolomide and overall survival has also been shown to correlate with MGMT promoter methylation status.^[32] Median survival among patients in the above-described phase III trial who had methylated tumors was 18.2 months, compared with 12.2 months among those whose tumors were not methylated; MGMT promoter methylation status was a more significant predictor of the outcome than the treatment assignment.^[32]

MGMT depletion has been investigated as a method used to increase the sensitivity of gliomas to chemotherapy. O6-benzylguanine (O6BG) is an AGT substrate that irreversibly inhibits this enzyme, and has been shown to deplete AGT in high-grade gliomas when administered to patients before surgery.^[33] In a phase I study, however, myelosuppression necessitated significant dosage reductions of BCNU when combined with O6BG^[34] leading to abandonment of this combination strategy.

Carmustine polymer wafers — Gliadel wafers represent a local delivery approach to the use of chemotherapy in malignant gliomas. Recurrence of malignant gliomas is often local, suggesting a role for intracavitary therapy. Gliadel wafers contain carmustine (BCNU) embedded in a biodegradable matrix, which is designed to release this agent over a two- to three-week period. After a gross total resection of the enhancing tissue, the wafers are placed on the surface of a tumor bed. Gliadel was originally approved as an adjunct to surgery for patients with recurrent GBM, based on the results of a randomized study showing benefit compared to placebo control.^[35] The indication for use of these wafers was then expanded to cover its use for patients with newly diagnosed malignant glioma, based on the results of a second phase III trial. In this trial 240 newly diagnosed adults undergoing resection of a malignant glioma were randomly assigned to placement of up to eight carmustine wafers or a placebo, followed by standard RT. Patients receiving carmustine polymer had a statistically significant increase in median survival (13.9 versus 11.6 months).^[22,36,37]

New and Developing Therapies for Malignant Gliomas

Targeted Therapies

New understanding of the molecular mechanisms of signal transduction via cell surface receptors, angiogenesis, and cell growth in malignant gliomas, has led to the development of a number of agents that specifically target mediators of these functions. Although the histological and molecular genetic variability exists within malignant gliomas, there are alterations in specific cellular signal transduction pathways or cellular functions which are common in most gliomas. This finding has led to trials of novel molecularly targeted therapeutic agents alone, and in various combinations, for patients with malignant gliomas. As with all CNS therapies, the successful development of targeted therapies for gliomas must include attention to the important subject of adequate delivery, specificity to tumor cells or tumor-associated endothelial cells, relative to normal cells.^[8]

Signal Transduction Inhibitors

Growth factors and their respective receptors mainly regulate proliferation and survival pathways.^[37] A promising target for anticancer therapy is the Epidermal Growth Factor (EGF). It has been shown to be involved in the pathogenesis of different types of human cancers.^[38] Furthermore the EGF receptor (EGFR) is found to be amplified and overexpressed in approximately half of the glioblastomas.^[39,40] In addition, upregulation of EGFR is positively related to aggressiveness of GBM tumors, and radiation resistance may be caused by changes in EGFR signaling.^[37] Inhibition of tyrosine kinases and associated growth factor pathways were the main foci of investigations by targeted molecular therapies in GBM. Gefitinib (Iressa®; Astra-Zeneca Pharmaceuticals, Wilmington, DE) is a selective, small-molecule inhibitor of the EGFR.^[41] In a phase II study, using gefitinib monotherapy, 13% of the patients with recurrent GBM remained progression-free for a minimum of six months.^[42] Another phase I/II study conducted by the North American Brain Tumor Consortium (NABTC) has shown partial responses after previous RT in five of 38 patients with GBM.^[43] Erlotinib (Tarceva®; OSI Pharmaceuticals, Inc., Melville, NY) is another small-molecule inhibitor of the EGFR that also inhibits the active mutant EGFRvIII found in approximately 40% of GBMs.^[39,40,44] Initial clinical trials with erlotinib have produced mixed results. Therefore, the potential role of erlotinib in the treatment of patients with GBM remains to be determined.^[45] Recent data suggest that detection of phosphorylated protein kinase B, may predict lack of response to EGFR inhibitors. Dual tyrosine kinase inhibitor studies are also under way, which include early clinical trials on lapatinib (GW-572016; GlaxoSmith-Kline, Philadelphia), an EGFR and ErbB-2 inhibitor; and AEE788 (Novartis Pharmaceuticals Corporation, East Hanover, NJ), an EGFR and vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor, aiming to overcome this resistance potential.^[40] Lapatinib has revealed preliminary evidence of biological and clinical activity in ErbB-overexpressing tumors,^[46] and AEE788 has antiproliferative and antiangiogenic activity in *in vitro* and *in vivo* experiments and is under investigation in phase I clinical trials.^[47]

In addition to the upregulation of EGFR signaling, the PDGF receptor (PDGFR) pathway upregulation is also found in GBM (36). Imatinib mesylate (Gleevec®; Novartis Pharmaceuticals Corporation) is a potent small-molecule inhibitor of the Bcr-Abl receptor, tyrosine kinase. It has inhibitory effects on PDGFR. Although it has poor penetration across the blood-brain barrier, imatinib mesylate has been shown to be active in recurrent GBMs, in the phase II trials.^[48] Imatinib

mesylate has been seen to enhance the cytotoxic effect of ionizing radiation in a human glioblastoma cell line.^[49] CP-673,451 (Pfizer Pharmaceuticals, New York), another inhibitor of the PDGFR pathway, has been seen to inhibit PDGFR- β in an *ex vivo* glioblastoma tumor model.^[50] The role of these agents in the treatment of GBM is promising, but needs to be revealed with additional studies.

Other potential tyrosine kinase targets that are worth mentioning include the inhibition of Ras/mitogen-activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K) / Akt pathways, farnesyltransferase, rapamycin, histone deacetylation, insulin-like growth factor receptor (IGFR), cell cycle components, transforming growth factor beta (TGF- β), and heat shock protein 90.^[30,40]

Anti-Angiogenesis Agents

Malignant gliomas are highly vascularized tumors. The growth and survival of these tumors is dependent on an adequate blood supply. A complex interaction of many angiogenic factors, including VEGF, basic fibroblast growth factor (bFGF), and PDGF orchestrate the formation of new blood vessels.^[40] Targeting factors and pathways actively participating in angiogenesis is a potentially effective approach. The anti-angiogenic therapy option offers several theoretical advantages, compared to conventional chemotherapeutic agents, in the treatment of malignant brain tumors. The tumor cell itself is targeted with conventional chemotherapy. For this reason, the efficacy in successfully destroying brain tumors with conventional chemotherapy is limited by its low drug penetration of the blood-brain and blood-tumor barriers, decreased drug delivery into the tumor interstitium and into the invasion border zone caused by antagonistic diffusion and convection pressures within the tumor and the brain, and the notorious genetic instability of glioma cells leading to chemoresistance. In contrast, the endothelial cell is the primary target of an anti-angiogenic therapy. Endothelial cells are in direct contact with blood so anti-angiogenic compounds reach their target much easier than conventional chemotherapeutic drugs, without the need for crossing the blood vessel wall. Being genetically more stable than tumor cells, endothelial cells are not prone to develop a resistance mechanism against the therapy. On the other hand, the cytostatic character of anti-angiogenesis has important clinical implications, in that it should be planned as a life-long maintenance therapy. In some patients, the latter may augment ischemic diseases.^[51,52] Due to the cytostatic character of this strategy, the standard radiological criteria for evaluating drug efficacy in clinical trials may not be efficient to assess the benefits of anti-angiogenic strategies in future. Instead,

clinical criteria like progression-free survival and overall survival will be of more value in making the assessment of efficacy. Angiogenesis depends on multiple different pathways, and targeting only one signaling pathway may fail due to activation of alternative pro-angiogenic pathways. Therefore use of combination antiangiogenic therapies may be justified.^[53-57]

Bevacizumab (Avastin®, Genentech) is a monoclonal antibody that binds VEGF and prevents its interaction with the VEGF receptors on the cell surface.^[22] Phase II results indicate that the combination of bevacizumab plus irinotecan, which is a potent topoisomerase inhibitor, may be effective against recurrent malignant gliomas. The results revealed that the six-month, progression-free survival among all patients was 46%. The six-month overall survival was 77%.^[58] In another study aiming to predict the clinical and radiographical responses to the combination of bevacizumab plus irinotecan using PET, patients showing positive imaging response to treatment had a significantly prolonged overall survival of 10.8 versus 3.4 months.^[59] These results reveal that the bevacizumab plus irinotecan combination is a promising weapon and may lead to a new generation of targeted therapies.^[60]

Immunotherapy

Interest in the use of immunotherapy to treat gliomas has increased over the last three decades. These approaches have included adoptive immunotherapy (the passive administration of sensitized immune cells, largely abandoned in recent years), passive immunotherapy (target-specific exogenous antibodies), and active immunotherapy with tumor vaccines. Immunotherapy faces several major challenges within the CNS, including the absence of a lymphatic system, the presence of a blood-brain barrier, the paucity of tumor-specific antigens, and the secretion by gliomas of immunosuppressive factors, including transforming growth factor (TGF)- β 2 and interleukin (IL)-10. Several promising strategies are undergoing evaluation in clinical trials. One passive immunotherapy approach involves the use of radioactive iodine-labeled monoclonal antibodies to tenascin (an extracellular matrix protein) being delivered into a tumor resection cavity.^[61-63] Active immunotherapy approaches typically use dendritic cells, which are potent antigen-presenting cells that can be loaded with tumor lysates or peptides.^[62-65] Another approach has been to vaccinate the immune system, to recognize the EGFR vIII variant; of course, this approach may only be useful in the 30-40% of the patients expressing this variant.^[66-68]

Gene Therapy

Another biological treatment strategy for high-grade

gliomas is the option of genetic therapy. Herpes simplex virus-thymidine kinase (HSV-tk) gene therapy has been the pioneering and most commonly used application. Since the first trials, gene delivery has been most commonly performed using direct delivery methods, involving either stereotactic intratumoral injection or intraoperative injections into the margins of the tumor cavity. The most commonly used strategy of gene transfer has been through the use of adenoviral particles as vehicles. Some studies have shown efficacy in adenovirus-mediated HSV-tk gene therapy against glioblastoma.^[69] The disadvantages of gene therapy have included, low tumoricidal effect *in situ* and a limited distribution of the transgenes and / or vectors to tumor cells, localized peripherally from the main tumor mass. In addition virus-derived vectors may have the potential to create damaging immunological reactions by immune-mediated toxicity, especially in the presence of circulating antibodies, to the virus vectors^[69-71] or by triggering immune reactions to self or transgene antigens.^[69,72,73]

Challenge of Delivery of Therapeutics to the Brain

The brain is a privileged organ protected with a very effective blood brain barrier (BBB). In most primary brain tumors the BBB is disrupted in a heterogeneous fashion and there may still be residual barrier function in the blood-tumor-barrier (BTB). The BBB may still be completely intact in areas of the brain that are infiltrated by the invading malignant glioma cells and where contrast enhancement has not yet occurred.^[74,75] Therefore, it is crucial to develop a strategy to allow drug delivery around the BBB.

Convection Enhanced Delivery

One way to overcome the BBB is to use direct delivery strategies. One of which is convection enhanced delivery (CED). CED of an agent through the interstitial space of the brain provides a means of achieving therapeutic drug concentrations within the CNS parenchyma on a regional basis, without the limitations imposed on delivery by the BBB. A potential advantage of this method is the ability of the agent to reach cells that have invaded the peritumoral region and beyond, thus making it potentially possible to reduce (if not halt) the spread of the disease.^[76] It is possible to achieve much higher concentrations of drug in the brain by CED, into the parenchymal space, substantially reducing the systemic drug concentrations.^[77] Several key features exist which affect the distribution of solutes delivered using CED, including: infusion rate, cannula size, infusion volume, interstitial fluid pressure, and tumor tissue structure. In addition, the physical characteristics of particles to be delivered are important. For example, particle negative charge and size are shown to be

important factors in creating the distribution profile of drugs and molecules used in CED.^[77,78] Clinical trials involving CED of a variety of therapeutic agents including viral vectors, chemotherapeutic agents, and targeted molecules have been performed.^[79] CED of paclitaxel, a taxane with no potential of penetration to CNS with conventional delivery, was tried in patients with recurrent malignant gliomas and was shown to have a high anti-tumor response rate; on the other hand, it was also associated with a significant incidence of treatment-associated complications.^[80] CED of a novel nanoparticle liposome containing topotecan (Ls-TPT) has been studied in rat models of experimental brain tumors. This study concluded that the delivery of the novel nanoparticle Ls-TPT using CED was effective in treating experimental brain tumors, but that it was necessary to perfuse all of the tumor tissue with the therapeutic agent in order to observe efficacy (use reference 85). An iron-loaded human transferrin conjugated to a genetically modified diphtheria toxin termed 'cross-reacting material 107' (Tf-CRM107) exhibits cytotoxicity *in vitro* against mammalian cells expressing the transferrin receptor with activity at picomolar concentrations. A Phase I clinical trial using Tf-CRM107, delivered via CED, showed evidence of activity in malignant gliomas, which was refractory to conventional therapy, and without significant toxicity.^[81] However, a Phase III trial of this agent was terminated early due to lack of apparent efficacy. A completed Phase III study involved Cintredekin Besudotox (CB), which is a recombinant cytotoxin consisting of interleukin-13 and truncated *Pseudomonas* exotoxin that binds selectively to interleukin-13R[alpha]2 receptors, which are overexpressed by a large percentage of malignant gliomas. Unfortunately, the trial failed to show superior efficacy to Gliadel, but this failure may have been due to imperfect technology for achieving widespread tissue distribution of the therapeutic agent via CED.^[45] Ongoing research in the field of CED is focused on improving the ability to reliably deliver the drug along with the use of imaging techniques to document its distribution.

Conclusions

Although our understanding of the biology of malignant gliomas has improved, survival rates are improving only marginally. Surgery and radiotherapy have not lost their importance and a recent advance in the use of concurrent chemo-radiation has improved survival in a large fraction of patients. A variety of new treatment modalities are undergoing development and hold promise for further survival gains in the near future.

References

1. CBTRUS Statistical Report, Central Brain Tumor Registry of the United States 2004: Primary Brain Tumors in the United States, 1997-2001.
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *Engl J Med* 2005;352:987-96.
3. Avgeropoulos NG, Batchelor TT. New treatment strategies for malignant gliomas. *Oncologist* 1999;4:209-24.
4. Huncharek M, Muscat J. Treatment of recurrent high grade astrocytoma: Results of a systematic review of 1415 patients. *Anticancer Res* 1998;18:1303-11.
5. Lacroix M, Abi-Said D, Fournay DR, Gokaslan ZL, Shi W, DeMonte F, *et al.* A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. *J Neurosurg* 2001;95:190-8.
6. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. *Cancer* 1983;52:997-1007.
7. Liang BC, Thornton AF Jr, Sandler HM, Greenberg HS. Malignant astrocytomas: Focal tumor recurrence after focal external beam radiation therapy. *J Neurosurg* 1991;75:559-63.
8. Sathornsumetee S, Rich JN. New approaches to primary brain tumor treatment. *Anticancer Drugs* 2006;17:1003-16.
9. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-96.
10. Taphoorn MJ, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ, *et al.* Health-related quality of life in patients with glioblastoma: A randomised controlled trial. *Lancet Oncol* 2005;6:937-44.
11. Dinapoli RP, Brown LD, Arusell RM, Earle JD, O'Fallon JR, Buckner JC, *et al.* Phase III comparative evaluation of PCNU and carmustine combined with radiation therapy for high-grade glioma. *J Clin Oncol* 1993;11:1316-21.
12. Black PM. Brain tumors. Part 1. *N Engl J Med* 1991;324:1471-6.
13. Shapiro WR, Green SB, Burger PC, Mahaley MS Jr, Selker RG, VanGilder JC, *et al.* Randomized trial of three chemotherapy regimens and two radiotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma: Brain Tumor Cooperative Group Trial 8001. *J Neurosurg* 1989;71:1-9.
14. Grossman SA, Batara JF. Current management of glioblastoma multiforme. *Semin Oncol* 2004;31:635-44.
15. Keles GE, Lamborn KR, Chang SM, Prados MD, Berger MS. Volume of residual disease as a predictor of outcome in adult patients with recurrent supratentorial glioblastomas multiforme who are undergoing chemotherapy. *J Neurosurg* 2004;100:41-6.
16. Barker FG 2nd, Chang SM, Gutin PH, Malek MK, McDermott MW, Prados MD, *et al.* Survival and functional status after resection of recurrent glioblastoma multiforme. *Neurosurgery* 1998;42:709-20.
17. Norden AD, Wen PY. Glioma therapy in adults. *Neurologist* 2006;12:279-92.
18. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, *et al.* Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: A cooperative clinical trial. *J Neurosurg* 1978;49:333-43.
19. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology* 1980;30:907-11.
20. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1989;16:1405-9.
21. Choucair AK, Levin VA, Gutin PH, Davis RL, Silver P, Edwards MS, *et al.* Development of multiple lesions during radiation therapy and chemotherapy in patients with gliomas. *J Neurosurg* 1986;65:654-8.
22. Batchelor T, Supko JG. Experimental treatment approaches for malignant gliomas. In: Rose BD, editor. *UpToDate*, Waltham, MA; 2008.

23. Liang BC, Thornton AF Jr, Sandler HM, Greenberg HS. Malignant astrocytomas: Focal tumor recurrence after focal external beam radiation therapy. *J Neurosurg* 1991;75:559-63.
24. Narayana A, Yamada J, Berry S, Shah P, Hunt M, Gutin PH, *et al.* Intensity-modulated radiotherapy in high-grade gliomas: Clinical and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006;64:892-7.
25. Tsao MN, Mehta MP, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, *et al.* The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma. *Int J Radiat Oncol Biol Phys* 2005;63:47-55.
26. Sneed PK, Lamborn KR, Larson DA, Prados MD, Malec MK, McDermott MW, *et al.* Demonstration of brachytherapy boost dose-response relationships in glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 1996;35:37-44.
27. Selker RG, Shapiro WR, Burger P, Blackwood MS, Arena VC, Gilder JC, *et al.* The Brain Tumor Cooperative Group NIH Trial 87-01: A randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery* 2002;51:343-55; discussion 355-7.
28. Huncharek M, Muscat J, Geschwind JF. Multi-drug versus single agent chemotherapy for high grade astrocytoma: Results of a meta-analysis. *Anticancer Res* 1998;18:4693-7.
29. Mirimanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, *et al.* Radiotherapy and temozolomide for newly diagnosed glioblastoma: Recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol* 2006;24:2563-9.
30. Reardon DA, Wen PY. Therapeutic advances in the treatment of glioblastoma: Rationale and potential role of targeted agents. *Oncologist* 2006;11:152-64.
31. Gerson SL. Clinical relevance of MGMT in the treatment of cancer. *J Clin Oncol* 2002;20:2388-99.
32. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, *et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005;352:997-1003.
33. Friedman HS, Kokkinakis DM, Pluda J, Friedman AH, Cokgor I, Haglund MM, *et al.* Phase I trial of O6-benzylguanine for patients undergoing surgery for malignant glioma. *J Clin Oncol* 1998;16:3570-5.
34. Friedman HS, Pluda J, Quinn JA, Ewesuedo RB, Long L, Friedman AH, *et al.* Phase I trial of carmustine plus O6-benzylguanine for patients with recurrent or progressive malignant glioma. *J Clin Oncol* 2000;18:3522-8.
35. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, *et al.* Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas: The Polymer-brain Tumor Treatment Group. *Lancet* 1995;345:1008-12.
36. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, *et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003;5:79-88.
37. Jendrossek V, Belka C, Bamberg M. Novel chemotherapeutic agents for the treatment of glioblastoma multiforme. *Expert Opin Investig Drugs* 2003;12:1899-924.
38. Kuan CT, Wikstrand CJ, Bigner DD. EGF mutant receptor vIII as a molecular target in cancer therapy. *Endocr Relat Cancer* 2001;8:83-96.
39. Benjamin R, Capparella J, Brown A. Classification of glioblastoma multiforme in adults by molecular genetics. *Cancer J* 2003;9:82-90.
40. Kesari S, Ramakrishna N, Sauvageot C, Stiles CD, Wen PY. Targeted molecular therapy of malignant gliomas. *Curr Neurol Neurosci Rep* 2005;5:186-97.
41. Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, *et al.* Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000;18:708-15.
42. Rich JN, Reardon DA, Peery T, Dowell JM, Quinn JA, Penne KL, *et al.* Phase II trial of gefitinib in recurrent glioblastoma. *J Clin Oncol* 2004;22:133-42.
43. Lieberman FS, Cloughesy T, Fine H, *et al.* NABTC phase I/II trial of ZD-1839 for recurrent malignant gliomas and unresectable meningiomas. *J Clin Oncol* 2004;22:1510.
44. Haas-Kojan DA, Prados MD, Tihan T, Eberhard DA, Jelluma N, Arvold ND, *et al.* Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib. *J Natl Cancer Inst* 2005;97:880-7.
45. Kunwar S, Westphal M, Medhorn M, Ram Z, Sampson J, Byrne R, *et al.* Results From Precise: A Randomized Phase 3 Study In Patients With First Recurrent Glioblastoma Multiforme (GBM) Comparing Cintredekin Besudotox (CB) Administered Via Convection-Enhanced Delivery (Ced) With Gliadel Wafers (GW). Abstracts for the Twelfth Annual Meeting of the Society for Neuro-Oncology (SNO). November 15 -18, 2007
46. Spector NL, Xia W, Burris H 3rd, Hurwitz H, Dees EC, Dowlati A, *et al.* Study of the biological effects of lapatinib: A reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol* 2005;23:2502-12.
47. Traxler P, Allegrini PR, Brandt R, Brueggen J, Cozens R, Fabbro D, *et al.* AEE788: A dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. *Cancer Res* 2004;64:4931-41.
48. Raymond E, Brandes A, Van Oosterom A. Multicentre phase II study of imatinib mesylate in patients with recurrent glioblastoma: An EORTC: NDDG/BTG Intergroup Study. *J Clin Oncol* 2004;22:1501.
49. Holdhoff M, Kreuzer KA, Appelt C, Scholz R, Na IK, Hildebrandt B, *et al.* Imatinib mesylate radiosensitizes human glioblastoma cells through inhibition of platelet-derived growth factor receptor. *Blood Cells Mol Dis* 2005;34:181-5.
50. Roberts WG, Whalen PM, Soderstrom E, Moraski G, Lyssikatos JP, Wang HF, *et al.* Antiangiogenic and antitumor activity of a selective PDGFR tyrosine kinase inhibitor, CP-673. *Cancer Res* 2005;65:957-66.
51. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
52. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
53. Tuetttenberg J, Friedel C, Vajkoczy P. Angiogenesis in malignant glioma: A target for antitumor therapy? *Crit Rev Oncol Hematol* 2006;59:181-93.
54. Bello L, Carrabba G, Giussani C, Lucini V, Cerutti F, Scaglione F, *et al.* Low-dose chemotherapy combined with an antiangiogenic drug reduces human glioma growth in vivo. *Cancer Res* 2001;61:7501-6.
55. Erber R, Thurnher A, Katsen AD, Groth G, Kerger H, Hammes HP, *et al.* Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *FASEB J* 2004;18:338-40.
56. Farhadi MR, Capelle HH, Erber R, Ullrich A, Vajkoczy P. Combined inhibition of vascular endothelial growth factor and platelet-derived growth factor signaling: Effects on the angiogenesis, microcirculation, and growth of orthotopic malignant gliomas. *J Neurosurg* 2005;102:363-70.
57. Reardon DA, Quinn JA, Vredenburgh JJ, Gururangan S, Friedman AH, Desjardins A, *et al.* Phase 1 trial of gefitinib plus sirolimus in adults with recurrent malignant glioma. *Clin Cancer Res* 2006;12:860-8.
58. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, *et al.* Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722-9.
59. Chen W, Delaloye S, Silverman DH, Geist C, Czernin J, Sayre J, *et al.* Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: A pilot study. *J Clin Oncol* 2007;25:4714-21.
60. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, *et al.* Friedman bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722-9.
61. Hockaday DC, Shen S, Fiveash J, Raubitschek A, Colcher D, Liu A, *et al.* Imaging glioma extent with 131I-TM-601. *J Nucl Med*

- 2005;46:580-6.
62. Reardon DA, Akabani G, Coleman RE, Friedman AH, Friedman HS, Herndon JE, *et al.* Phase II trial of murine (131I)-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. *J Clin Oncol* 2002;20:1389-97.
 63. Wheeler CJ, Das A, Liu G, Yu JS, Black KL. Clinical responsiveness of glioblastoma multiforme to chemotherapy after vaccination. *Clin Cancer Res* 2004;10:5316-26.
 64. Yu JS, Luptrawan A, Black KL, Liu G. Mahaley Clinical Research Award: Chemosensitization of glioma through dendritic cell vaccination. *Clin Neurosurg* 2006;53:345-51.
 65. Mellinger IK, Wang MY, Vivanco I, Haas-Kogan DA, Zhu S, Dia EO, *et al.* Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med* 2005;353:2012-24.
 66. Cavaliere R, Wen PY, Schiff D. Novel therapies for malignant gliomas. *Neurol Clin* 2007;25:1141-71.
 67. Heimberger AB, Crotty LE, Archer GE, Hess KR, Wikstrand CJ, Friedman AH, *et al.* Epidermal growth factor receptor VIII peptide vaccination is efficacious against established intracerebral tumors. *Clin Cancer Res* 2003;9:4247-54.
 68. Hussain AE, Blakley BW, Nicolas M, Balderston J. Assessment of the protective effects of amifostine against cisplatin-induced toxicity. *J Otolaryngol* 2003;32:294-7.
 69. Pulkkanen KJ, Hertzuala SY. Gene therapy for malignant glioma: Current clinical status. *Mol Ther* 2005;12:4.
 70. Wood MJ, Byrnes AP, Pfaff DW, Rabkin SD, Charlton HM. Inflammatory effects of gene transfer into the CNS with defective HSV-1 vectors. *Gene Ther* 1994;1:283-91.
 71. Thomas CE, Schiedner G, Kochanek S, Castro MG, Löwenstein PR. Peripheral infection with adenovirus causes unexpected long-term brain inflammation in animals injected intracranially with first-generation, but not with high capacity, adenovirus vectors: Toward realistic long-term neurological gene therapy for chronic diseases. *Proc Natl Acad Sci U S A* 2000;97:7482-7.
 72. Dewey RA, Morrissey G, Cowsill CM, Stone D, Bolognani F, Dodd NJ, *et al.* Chronic brain inflammation and persistent herpes simplex virus 1 thymidine kinase expression in survivors of syngeneic glioma treated by adenovirus-mediated gene therapy: Implications for clinical trials. *Nat Med* 1999;5:1256-63.
 73. Zermansky AJ, Bolognani F, Stone D, Cowsill CM, Morrissey G, Castro MG, *et al.* Towards global and long-term neurological gene therapy: Unexpected transgene dependent, high-level, and widespread distribution of HSV-1 thymidine kinase throughout the CNS. *Mol Ther* 2001;4:490-8.
 74. Flawers A, Levin V. Chemotherapy for brain tumors. In: Kaye H, Laws ER, editors. *Brain Tumors*. New York: Churchill Livingstone; 2001.
 75. Leary SP, Liu CY, Apuzzo ML. Toward the emergence of nanoneurosurgery: Part III-nanomedicine: Targeted nanotherapy, nanosurgery and progress toward the realization of nanoneurosurgery. *Neurosurgery* 2006;58:1009-26.
 76. Raghavan R, Brady ML, Rodríguez-Ponce MI, Hartlep A, Pedain C, Sampson JH. Convection-enhanced delivery of therapeutics for brain disease and its optimization. *Neurosurg Focus* 2006;20:E12.
 77. Huynh GH, Deen DF, Szoka FC Jr. Barriers to carrier mediated drug and gene delivery to brain tumors. *J Control Release* 2006;110:236-59.
 78. MacKay JA, Deen DF, Szoka FC Jr. Distribution in brain of liposomes after convection enhanced delivery: Modulation by particle charge, particle diameter, and presence of steric coating. *Brain Res* 2005;1035:129-53.
 79. Vogelbaum MA. Convection enhanced delivery for the treatment of malignant gliomas: Symposium review. *J Neurooncol* 2005;73:57-69.
 80. Lidar Z, Mardor Y, Jonas T, Pfeffer R, Faibel M, Nass D, *et al.* Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: A phase I/II clinical study. *J Neurosurg* 2004;100:472-930.
 81. Weaver M, Laske DW. Transferrin receptor ligand-targeted toxin conjugate (Tf-CRM107) for therapy of malignant gliomas. *J Neurooncol* 2003;65:3-13.

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