[Frontiers in Bioscience 10, 2645-2668, September 1, 2005]

CHEMOTHERAPY AND NOVEL THERAPEUTIC APPROACHES IN MALIGNANT GLIOMAS

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1. ABSTRACT

Glial neoplasms represent 0.5-1% of all cancers in most Western countries. Malignant gliomas are among the most devastating cancers, leading to death in most cases. They present unique challenges due to their location, aggressive biological behavior and diffuse infiltrative growth. Notwithstanding the development of new surgical and radiation techniques in the last thirty years, a cure for malignant gliomas remains elusive. In this article, we will review the standard and new therapies used for malignant gliomas. As standard therapies, surgery, radiation therapy and systemic chemotherapy, are in a continuous process of evolution. Multiple chemotherapies have been used in malignant gliomas, as single agents, in combination, or with different modes of administration, including high-dose chemotherapy with stem cell rescue and intra-arterial chemotherapy. The last decade has been noticeable for the advent of a better understanding of the biology of malignant gliomas. This has stimulated active research in multiples areas and the advent of new treatment strategies. Techniques to circumvent the resistance mechanisms to chemotherapy have been evaluated, tyrosine kinase inhibitors have shown activity in malignant primary brain tumors and radioimmunotherapy remains an area of active research. In this article, we review the past, present and future treatments of malignant gliomas with a special interest on chemotherapy, resistance mechanisms and tyrosine kinase inhibitors.

2. INTRODUCTION

Although primary tumors of the central nervous system (CNS) are uncommon with glial neoplasms representing approximately 0.5-1% of all cancers in most Western countries (1), malignant gliomas are among the most devastating cancers. Malignant brain tumors produce profound and progressive disability and lead to death in most cases. The incidence of malignant glioma peaks in children and again at age 50-60 years (2). These tumors are therefore a major cause of mortality in a young population, and improvement of survival by even a moderate amount could potentially result in many years of saved life (3). Gliomas present unique challenges due to their location, aggressive biological behavior and diffuse infiltrative growth. The treatment, but mostly the tumor itself, often results in profound changes in quality of life.

Notwithstanding the development of new surgical and radiation techniques in the last thirty years, a cure for malignant gliomas remains elusive. Thus far, only partial control of tumor growth for a brief period of time has been possible. Median survival time is limited to approximately 10-15 months for glioblastoma multiforme and 24 to 36 months for anaplastic astrocytomas (4-6). Several reasons exist for poor response of these tumors to conventional therapies including their infiltrative and rapidly aggressive nature, acquired and de novo mechanisms of therapy resistance, heterogeneity within the tumors and delivery limitations posed by the blood-brain and blood-tumor barriers.

3. STANDARD THERAPIES

3.1. Surgery

Multiple treatment modalities have been developed to try to eradicate these tumors. The first treatment modality remains surgery. The primary goals of surgery are to confirm pathological diagnosis and to improve symptoms rapidly, allowing a better quality of life for the patient and a reduction in glucocorticoids dosage (7, 8). Because malignant gliomas are histologically heterogeneous (9), it is preferable to obtain as much tissue as possible to allow an accurate diagnosis. Also, debulking surgery reduces the number of cancer cells requiring treatment and often removes the hypoxic core of the tumor that is relatively resistant to radiation and inaccessible to chemotherapy. Most experienced clinicians agree that maximal resection of malignant gliomas without causing neurologic deficits should be attempted, even if the impact on survival is controversial (10). If a gross total resection is not possible, secondary to the location of the tumor or the functional status of the patient, then a biopsy or partial resection remains indicated.

3.2. Radiation therapy

In the late 1970s and early 1980s, postoperative irradiation was established as standard therapy for patients with high-grade gliomas. Intensification of external beam radiotherapy beyond a standard course of 60 Gy over 6 weeks has been extensively investigated, but has failed to report a significant improvement in survival (1). In Phase II trials, high dose temporary brachytherapy for newly diagnosed glioblastoma has failed to show any benefit (11, 12). A phase III trial has also shown that radiosurgery for malignant gliomas to not provide any significant survival advantage for glioblastoma patients when used after surgery and prior to external irradiation (13). It is now felt that benefits observed in early studies using brachytherapy and radiosurgery are explained by selection bias (14). Inevitably, patients treated solely with radiation therapy recur. Therefore over the past several years a variety of chemotherapy agents have been tested in small clinical trials. In a large meta-analysis of adjuvant chemotherapy for malignant gliomas, the results of 16 randomized adjuvant clinical trials involving more than 3000 patients over the past 15 years demonstrated that the addition of chemotherapy to radiation improved 1-year survival by 10% and 2-year survival by 8.6%, with relative survival increases of 23% and 52% at 1 and 2 years, respectively (15).

3.3. Chemotherapy

Chemotherapies are treatment modalities that are being used to control and ideally eradicate infiltrative tumor cells. Many consider the CNS as a pharmacologic sanctuary because drug delivery to the brain via systemic administration is often difficult and incomplete due to the blood-brain barrier (BBB). It is recognized that the BBB is disrupted in many malignant brain tumors. In these tumors, blood vessels have abnormal tight junctions and disrupted endothelial surface, which allow water-soluble contrast agents to cross into the tumor and hence appear enhancing on magnetic resonance imaging (MRI). This brain-tumor barrier (BTB) tends to be more permeable than normal brain tissue, however the breakdown of the BBB in the area of tumor is variable, and large areas exist where the BBB remains intact. In those areas, the amount of drug reaching the tumor continues to be severely restricted (16, 17). In addition, the brain adjacent to tumor (BAT) is the area around the tumor that contains infiltrating tumor cells. These sites may be associated with an intact BBB, and drug delivery to this area is difficult. Finally, although most brain tumors tend to be highly vascular, the aberrant tumor-induced angiogenic process tends to create abnormal vessels such as blind loops and arteriolar-venuole shunts, making parenchymal drug delivery even more inefficient. In fact, the passage of substances across the BBB depends on their size, lipid solubility, and ionization state (18). Most hydrophilic substances and large lipophilic substances (which include many chemotherapeutic compounds) are restricted from entering the CNS.

The nitrosoureas were the first single agent therapy used to treat gliomas because they readily

cross the BBB due to their small size, non-ionized state and high lipid solubility (19). BCNU became the most commonly used single-agent chemotherapy for recurrent disease and was moved to the adjuvant setting after a randomized trial (BTSG 69-01) demonstrated BCNU and radiotherapy superior to radiotherapy alone (20). Similar results were obtained in studies using CCNU (21, 22). A recent meta-analysis suggests that nitrosourea-based adjuvant chemotherapy has a modest benefit for patients with anaplastic gliomas and a smaller benefit for those with glioblastoma.

Procarbazine and its metabolites also cross the BBB, with rapid equilibrium between plasma and CSF (23). As a single agent, procarbazine has been compared to IV BCNU, methylprednisolone, and IV BCNU with methylprednisolone, in patients with malignant glioma. The overall median survival was similar for the procarbazine and BCNU groups, but long-term survival at up to 24 months was superior in the procarbazine group (24).

Nitrosourea-based combination chemotherapy regimens (PCV: procarbazine, CCNU, vincristine) were developed in the 1980s and showed promise. PCV was compared to single-agent BCNU as postradiation therapy in a randomized trial (25). There was no significant difference in overall survival (OS) or time-to-tumor progression (TTP) for the group as a whole. However, in the subset of patients with anaplastic gliomas (rather than glioblastoma), there was a significant difference in TTP and survival for the group receiving PCV. A recent retrospective analysis of the Radiation Therapy Oncology Group (RTOG) database, including more than 400 patients with anaplastic gliomas, revealed no survival advantage for patients treated with postradiation PCV versus BCNU (26).

Temozolomide is an oral agent, which crosses the BBB. It is an imidazotetrazine derivative of dacarbazine, which spontaneously hydrolyses to its biologically active form, MTIC. The mechanism of antitumor actions is the disruption of DNA replication via methylation at specific residues including 06 position of guanine, N7 position of guanine and N3 position of adenine. One of the first studies demonstrating anti-glioma activity of temozolomide was a large multicenter phase II trial involving 162 patients with anaplastic astrocytoma or grade 3 oligoastrocytomas treated with temozolomide at first relapse following surgery and radiotherapy (27). Objective responses were observed in 35% of the patients (8% complete remission and 27% partial remission). An additional 26% of patients had stable disease. Overall, 46% of patients achieved the primary end point of 6-month progression-free survival (PFS) and 24% remained progression free at 12 months. Median overall survival was 13.6 months and 12-month survival was 56%. Importantly, there was no significant difference between 6-month PFS in patients who had received prior chemotherapy (nitrosourea-based) versus chemotherapy naive patients (44% vs 50%). Clinical trial results of temozolomide for recurrent glioblastomas are equally promising. A large randomized phase II study completed by the Temodal Brain Tumor Group compared temozolomide to procarbazine in glioblastoma multiforme at first relapse (28). In total, 225 patients were treated including 112 with temozolomide and 113 with procarbazine. Progression-free survival at 6 months and overall 6-month survival were significantly better in temozolomide-treated patients than with procarbazine (21% vs 8% ($p<0.008$), and 60% vs 44% ($p<0.019$)). Temozolomide was also demonstrated effective for patients with newly diagnosed malignant glioma (29). Among 33 patients with glioblastoma, complete responses occurred in three patients, partial responses occurred in 14 patients, stable disease was seen in four patients, and 12 patients developed progressive disease. Toxicity included infrequent grades 3 and 4 myelosuppression, constipation, nausea, and headache.

A recent phase III trial conducted by the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group compared radiotherapy with concomitant and adjuvant temozolomide for newly diagnosed glioblastoma versus radiotherapy alone (30). Five hundred and seventy-three functional, newly diagnosed and previously untreated patients with glioblastoma, between 18 and 70 years, were enrolled in the study. In all, 286 patients received a standard radiotherapy dose of 60 Gy over six weeks, and 287 patients received the same radiotherapy regimen plus 75 mg/m2 of temozolomide orally daily (7 days a week) during radiotherapy, followed by up to 6 cycles of adjuvant temozolomide (150-200 mg/m2/d on days 1-5, given every 28 days). Patients receiving temozolomide received prophylactic treatment against Pneumocystis carinii pneumonia during the concomitant radiochemotherapy period. Radiotherapy was delivered as prescribed to 93% of patients and concomitant temozolomide was given without interruption to 76% of patients. Eleven percent of patients required temporary interruption of temozolomide and temozolomide was prematurely discontinued in 12%. Overall, 88% of patients randomly assigned to treatment with temozolomide and radiotherapy received over 90% of the planned concomitant temozolomide doses. Adjuvant temozolomide was given to 76% of patients on the temozolomide arm and 36% of these patients completed all 6 cycles. The median PFS was 6.9 months for the radiotherapy plus temozolomide group compared to 5 months for the radiotherapy alone group ($p<0.0001$). At 1 year, only 9% of the patients who received radiotherapy alone had not progressed, compared with 27% of patients treated with radiotherapy and temozolomide ($p<0.0001$). The median OS rate for radiotherapy alone was 12.1 months, compared with 14.6 months for

radiotherapy plus temozolomide ($p<0.0001$). Ten percent of patients who received radiotherapy alone were alive at 2 years, compared with 26% of patients who received temozolomide in addition to radiotherapy ($p<0.0001$). Hematologic toxicities in patients receiving the combination were mostly minor, consisting of grade 1 and 2 anemia, leukopenia, and neutropenia. Grade 3 and 4 hematotoxicity occurred in 7% of patients during concomitant treatment with radiotherapy and temozolomide and in 16% of patients during adjuvant temozolomide. The most common grade 1and 2 nonhematologic toxicities were fatigue, rash, and nausea/vomiting; only rare grade 3 and 4 non-hematologic toxicities were seen. The promising results of this study have been interpreted by most neuro-oncologists as establishing a new, albeit modestly improved, standard of care for patients with newly diagnosed GBM. Temozolomide is now being evaluated in multiple new clinical trials in combination with wide variety of additional therapeutic agents including other chemotherapeutic agents, cell signaling inhibitors, anti-angiogenic agents therapeutics designed to overcome mediators of chemotherapy resistance.

Irinotecan, also known as CPT-11, is a camptothecin derivative. It is a prodrug that requires deesterification by carboxylesterases to yield its active metabolite, SN-38, which is 1,000 times more potent at inhibiting topoisomerase I (23). Topoisomerase I plays a critical role in DNA transcription, replication and repair. In early trials of this agent, some responses were documented in patients with progressive, persistent, or recurrent malignant glioma (31, 32). In a phase II trial involving 60 patients with histologically confirmed GBM receiving CPT-11 weekly (125mg/m² per week +4, then off 2 weeks (1 cycle/6 weeks)), 15% of patients had a partial response and 55% achieved a best response of stable disease lasting more than 12 weeks (31). However, it was noted that levels of CPT-11 and its metabolites were only 25-40% of those achieved among colon cancer patients treated with the same dosing schedule of CPT-11. This finding is likely related to the increased excretion rate of CPT-11 in patients on concomitant hepatic enzyme-inducing dexamethasone and anticonvulsants. A phase I trial to define the maximum tolerated dose (MTD) for patients receiving cytochrome p450-inducing anticonvulsants, specifically phenobarbital, carbamazepine, and phenytoin (EIAC) was conducted by the National Cancer Institute. In this study, the MTD of irinotecan was 410 mg/m² administered weekly for 4 weeks followed by a 2-week break among patients who were concomitantly treated with EIAC. In a similar phase I study, the North American Brain Tumor Consortium (NABTC) recommended a phase II CPT-11 dose of 750 mg/m² when administered every 3 weeks in patients receiving stable doses of EIAC (33). The promising early results with CPT-11 lead to the exploration of a number of new combinations with BCNU, temozolomide, and other active agents. Preclinical studies demonstrated that the efficacy of CPT-11 against CNS tumors is enhanced when combined with alkylators such as BCNU in a schedule-dependent manner (34). It was therefore sought to determine whether the antitumor activity of CPT-11 could be enhanced by BCNU in patients with malignant gliomas. First, a phase I study established the MTD of CPT-11 administered weekly for 4 consecutive weeks of each 6-week cycle in combination with a fixed dose of BCNU (100 mg/m² administered on day 1 of each cycle) to be 225 mg/m² for patients on EIAC and 125 mg/m² for patients not on EIAC (35). In the phase II extension of this phase I study, BCNU (100 mg/m²) was administered on day 1 of each 6-week cycle. CPT-11 was administered on days 1, 8, 15, and 22 at 225 mg/m² for patients receiving CYP3A1- or CYP3A4-inducing anticonvulsants and at 125 mg/m² for those not on these medications. Newly diagnosed patients received up to 3 cycles before radiotherapy, while recurrent patients received up to 8 cycles. Seventy-six patients were treated, including 37 with newly diagnosed tumors and 39 with recurrent disease. Five newly diagnosed patients (14%) achieved a radiographic response (1 CR and 4 PR). Five patients with recurrent disease also achieved a response (1 CR and 4 PR; 13%). More than 40% of both newly diagnosed and recurrent patients achieved stable disease. Median time to progression was 11.3 weeks for recurrent glioblastoma multiforme patients and 16.9 weeks for recurrent anaplastic astrocytoma/anaplastic oligodendroglioma patients (36). A synergistic effect of CPT-11 combined with temozolomide has also been reported in preclinical studies (37). We recently completed a phase I study of temozolomide plus CPT-11 in patients with recurrent malignant glioma. Patients in this study received temozolomide at a dose of 200 mg/m2 on days 1-5, and intravenous CPT-11 over 90 minutes on days 1, 8, 22, and 29 of a 6-week cycle. The MTD of CPT-11 for this drug combination has been determined for the non-EIAC stratum at 125 mg/m², and at 325 mg/m² for the EIAC stratum (38).

Topotecan is a water-soluble camptothecin analogue with excellent CNS penetration that binds directly to topoisomerase I without activation (23). A phase II trial for adults with newly diagnosed or recurrent malignant gliomas has demonstrated 3 PR (12%) and 10 SD (40%) in 25 newly diagnosed patients and 3 PR (8%) and 10 SD (26%) in 38 patients with recurrent disease (39). Activity in pediatric patients with low- and high-grade gliomas, medulloblastoma, and brainstem gliomas was not demonstrated in a phase II study (40).

Etoposide is highly lipophilic but does not readily cross the BBB due to its large size. Etoposide has been demonstrated to have minimal activity as a single agent in some patients with malignant gliomas (41, 42). The use of oral etoposide at 50 mg/m²/day for 21 days, followed by 14 day rest period and an additional 21 days of oral etoposide (50 mg/m²/day) was demonstrated effective and feasible by

Chamberlain (43). Of 12 evaluable patients with recurrent brainstem gliomas, 1 presented complete response, 3 partial responses and 2 stable disease, for a median duration of response of 8 months.

Cisplatin and carboplatin are water-soluble and penetrate the BBB poorly. Cisplatin demonstrated variable activity against a wide range of tumors, including anaplastic astrocytoma, glioblastoma multiforme, medulloblastoma/primitive neuroectodermal tumor (PNET), CNS lymphoma, and germ cell tumors (44-46). In combination with CCNU or cyclophosphamide plus vincristine, cisplatin also is effective against high-risk and recurrent medulloblastomas (47). Carboplatin is a cisplatin analogue with a similar activity profile and comparable cytotoxicity *in vitro.* As a single agent, carboplatin has demonstrated efficacy in pediatric patients for both low-grade gliomas and recurrent malignant primary brain tumors (48, 49). In adults, single-agent carboplatin has shown minimal activity for the treatment of recurrent malignant gliomas (50).

Oxalipatin, like cisplatin and carboplatin, is a platinum-based cytotoxic agent. However, unlike other platinum-based agents it does not appear to cause ototoxicity, nephrotoxicity, cardiac toxicity, or alopecia in adults. Data for malignant gliomas are limited to nine patients with recurrent glioblastomas (51). A phase II trial of neoadjuvant oxaliplatin will commence in the near future.

Vincristine is a water-soluble molecule that penetrates the BBB poorly (52). Despite its limited CNS penetration, vincristine is said to show activity as part of multiagent regimens against low-grade gliomas, oligodendrogliomas, and anaplastic astrocytomas (53-55). However, vincristine has never been rigorously evaluated as a single agent for primary brain tumors.

Paclitaxel is an agent that inhibits microtubule disassembly. It binds to the N-terminal amino acids of the b-tubulin subunit of microtubules and induces polymerization, resulting in cytotoxicity due to the disruption of normal microtubular function during cell division. As a single agent in phase I and II studies, paclitaxel demonstrated an overall stabilization rate of 35 % in patients with recurrent gliomas although there were essentially no objective radiographic responses most of the responses have been in patients with AA or oligodendroglial features (56, 57). Minimal response has been observed in glioblastoma multiforme (56-59).

3.4. High-dose chemotherapy

High-dose chemotherapy, followed by autologous bone marrow transplantation or peripheral blood stem cell rescue, has been used with the rationale that increased delivery of chemotherapeutic agents across the BBB will occur secondary to higher serum levels. Several studies have evaluated this modality of treatment for newly diagnosed or recurrent anaplastic gliomas (60). These regimens have included high-dose BCNU (61), high-dose BCNU plus intra-arterial cisplatin (62); or some combination of BCNU, carboplatin, etoposide, and thiotepa (63, 64). High-dose chemotherapy has shown encouraging results, primarily for pediatric patients with relapsed medulloblastomas and intracranial germ cell tumors. It has also been used in young children to avoid the toxic effects of craniospinal radiation (65). High-dose chemotherapy with autologous stem cell rescue has been significantly less promising for adults with malignant glioma. In general, response rates and overall survival have not been impressive, and toxicity has been substantial (66). A single pulse of high-dose chemotherapy may not achieve a high enough exposure to have an effect. The major problem with high-dose chemotherapy is the increased systemic toxicity. Although myelosuppression may be treated with infusion of stem cells, other toxicities are then unveiled, including neurotoxicity associated with high-dose thiotepa, renal and ototoxicity associated with carboplatin, cardiovascular toxicity associated with cyclophosphamide, mucositis associated with etoposide, and pulmonary and hepatic toxicities associated with the nitrosoureas (65). The potential benefit of high-dose chemotherapy must be balanced against the 5% to 20% reported incidence of toxic deaths and the potential for delayed neurotoxicity from high-dose BCNU or thiotepa.

3.5. Intra-arterial chemotherapy

Intra-arterial infusion of chemotherapy can provide a several fold delivery advantage over the same drug dose given systemically in terms of peak drug concentration in the tumor and the total area under the curve drug exposure. There are numerous published trials of intra-arterial chemotherapy for newly diagnosed or recurrent malignant gliomas, most of which are small phase II studies (67). Nitrosoureas theoretically are well suited for intra-arterial infusion because of their lipid solubility and high extraction fraction (first-pass effect) in the brain. A large phase III trial comparing intra-arterial BCNU to intravenous BCNU in newly resected malignant glioma adult patients demonstrated that the intra-arterial BCNU group actually had a lower survival rate than patients treated with intravenous BCNU. The reason for the decreased survival rate was unclear, but serious toxicity, including irreversible encephalopathy and blindness, was observed in the intra-arterial group (68). Intra-arterial nitrosoureas have been studied for recurrent tumors, but there are no direct comparisons of the response rate or duration of response with intra-arterial versus intravenous administration. Cisplatin and carboplatin theoretically do not provide as much delivery advantage as nitrosoureas with intra-arterial infusion, but they have been studied either as single agents or in combination regimens. There are no published randomized studies comparing intra-arterial versus intravenous cisplatin or carboplatin. No large randomized trial has yet demonstrated that intracarotid administration of chemotherapy is more advantageous than systemic administration (6, 68). The dose-limiting

toxicity of intra-arterial chemotherapy is neurotoxicity, inducing seizures, vision loss, worsening neurologic deficits, and rarely cerebral herniation occurring within 48 hours after infusion. Superselective infusion of chemotherapy into major intracerebral arteries increases the drug delivery advantage and reduces the risk for vision loss but probably increases the risk for other neurotoxicities. The major unanswered questions regarding intra-arterial chemotherapy for gliomas are whether intra-arterial administration is truly more effective than systemic administration and whether any improvement in efficacy outweighs the potential for serious neurotoxicity.

4. NEW STRATEGIES

4.1. Resistance to chemotherapy

Resistance to chemotherapy remains the central reason for the failure to cure patients with cancer. Malignant gliomas display marked de novo or acquired drug resistance with ultimate lethal growth. A series of preclinical studies conducted predominately, but not exclusively, for non-CNS tumors has demonstrated that resistance to alkylnitrosourea-based chemotherapy is mediated in part through the DNA repair protein O^6-alkylguanine-DNA alkyltransferase, AGT (29, 69-74). AGT removes chlorethylation or methylation damage from the O^6 position of DNA guanines before cell injury and cell death.

The high incidence of AGT activity in human CNS tumors (75), as well as recent clinical trials that shows an inverse relationship between response or survival and AGT levels in patients with malignant glioma who received alkylnitrosoureas therapy (76-79), provides the rational for strategies designed to deplete tumor AGT levels while receiving therapy with alkylnitrosoureas.

O^6-benzylguanine (O^6-BG) is an AGT substrate that inactivates AGT and enhances the cytotoxicity of alkylnitrosoureas both *in vitro* (80-82) and *in vivo* (29, 69, 70, 83-91). A phase I trial by Friedman *et al.* (29) demonstrated that 100 mg/m2 of O6-BG can maintain tumor AGT levels less than 10fmol/mg protein for a least 18 hours after treatment, a time interval in which bis(2-chloroethyl)nitrosourea(BCNU)-induced chloroethyl adducts are fully converted into interstrand cross-links. The use of O6-benzylguanine induces a chemosensitization of tumor cells, but also induces toxicity secondary to the concurrent drug sensitization of hematopoietic stem cells as well as systemic organ cells, which have a high AGT concentration. The significant dose reduction of BCNU necessary when this agent is combined with O^6-BG probably explains why trials (92, 93) evaluating the combination of BCNU (Carmustine) plus O^6-BG have failed to demonstrate tumor regression. Combination studies of O^6-BG with temozolomide are underway. In a phase I trial patients received a 1-hour infusion of O^6-BG at 120 mg/m² followed by a continuous infusion at 30 mg/m^2/day for 48 hours plus the administration of temozolomide as a single dose at the end of the 1-hour infusion of O^6-BG, treatment cycles were repeated at 28-day intervals. It was demonstrated that the MTD of temozolomide when given in combination with O^6-BG is 472 mg/m^2 (94). A phase II study combining temozolomide with O^6-BG is now underway among patients with temozolomide resistant malignant glioma. Preliminary results indicate that for 30 assessable patients with glioblastoma multiforme (GBM), 1 partial response and 8 stable diseases were observed for more than 8 weeks. Among 28 patients with anaplastic astrocytomas or anaplastic oligodendrogliomas (AA/AO), one patient demonstrated a complete response, 3 a partial response, and 7 a stable disease for more than 8 weeks. Thirty-eight patients (21 GBM and 17 AA/AO) had progressed at the 8-week evaluation. Toxicities were limited to hematologic events (95).

4.2. Tyrosine kinase inhibitors

The recent success of small-molecule inhibitors of signal transduction pathways in other cancers has propelled rapid development of similar therapies in the treatment of patients with malignant gliomas. Several molecular targets are particularly attractive in glioblastomas, including growth factor receptors and critical intracellular signaling mediators. A variety of specific inhibitors have been developed in recent years. Cancer cells display a significantly greater dependency on the effects of tyrosine kinases than non-transformed cells, a characteristic termed oncogene addiction, which has prompted significant efforts in cancer drug development to block particular tyrosine kinases with high selectivity and specificity. Interest has recently been raised by the remarkable success of some small-molecule tyrosine kinase inhibitors (TKIs) in selectively inhibiting tumor growth. To date, the most prominent growth factor pathways in glioma biology have been the epidermal growth factor (EGF), the platelet-derived growth factor (PDGF) ant the vascular endothelial growth factor (VEGF) families. Each family contains multiple ligands and receptors that variably pair to activate intracellular signaling mediators. Upon ligand binding, receptors become dimerised and transphosphorylated, which promotes the recruitment and activation of intracellular signaling mediators, including mitogen-activated protein kinase (MAPK) and Akt/protein kinase B (PKB). Growth factor pathways regulate numerous cellular behaviors – proliferation, resistance to apoptosis, motility and elaboration of angiogenic factors – that act to increase tumor malignancy. Therefore, growth factor receptors are attractive glioma targets, as they satisfy many requirements for ideal therapeutic targets – frequent expression in tumors, large differential in expression levels between tumor and normal cells, contribution to the tumor phenotype and normal cells, contribution to the tumor phenotype and localization to the cell surface.

EGFR TKIs inhibit glioma cellular proliferation, increase sensitivity to radiation and chemotherapy, decrease matrix metalloproteinase expression and invasion, and decreases VEGF (96-98). Gefinitib (ZD1839, Iressa; AstraZeneca) is a novel, oral, low-molecular weight ATP mimetic of the anilinoquinazoline family that reversibly inhibits the tyrosine kinase activity associated with EGFR. We recently completed an open-label, single-centre phase II trial of gefitinib in recurrent glioblastomas (99), in which gefitinib was well tolerated with modest efficacy. The six-month event-free survival rate was 13% (seven out of 53 patients). However, 17.3% (9 patients) received at least six cycles of therapy and two patients (4%) remain on therapy after 10 and 17 cycles. This trial included surgery prior to study enrollment on all patients with characterization of EGFR and EGFRvIII expression measurements. Interestingly, EGFR expression patterns did not correlate with either treatment responses or resistance. In a second phase I/II study in patients with recurrent malignant glioma gefitinib did not prolong TTP compared to historical controls (100). The mean TTP observed for glioblastoma patients was eight weeks, and 15 weeks for anaplastic gliomas. The six-month progression-free survival was 9% for glioblastoma patients and 33% for anaplastic glioma patients. A phase I/II trial of gefitinib in combination with external beam radiation for newly diagnosed glioblastoma patients has found this combination well tolerated with the toxicity limited to infrequent transaminase elevations (101). Expansion to the phase II component is underway for patients who are not on EIAC. A phase II trial of patients with newly diagnosed glioblastomas did not show increased survival compared to historical controls, and no relationship to EGFR expression (102).

Erlotinib (OSI-774, Tarceva; OSI Pharmaceuticals) is an orally active quinazoline derivative that inhibits EGFR-specific tyrosine phosphorylation and has demonstrated antitumor efficacy similar to that of gefinitib in preclinical studies. In addition, erlotinib has shown activity in a phase I trial either as monotherapy or in combination with temozolomide in patients with glioblastomas or anaplastic gliomas (103). In pharmacokinetic studies, concurrent EIAC use reduced both erlotinib and active metabolite levels by 50-75%. Of 25 evaluable malignant glioma patients, six had partial responses, two had minor responses, and three patients had stable disease. A phase II trial trial of erlotinib in patients with recurrent or progression glioblastoma has shown that three of 10 patients achieved partial responses, with one patient each achieving a mixed tumor response and stable disease (104). One response was durable, with duration of over seven months. In a four institutions phase II trial of erlotinib for glioblastoma multiforme in first relapse, a response rate of 6.4% and a median time to progression of 8 weeks were observed (105).

The toxicities of gefitinib and erlotinib in brain tumor patients are the similar to those reported in other types of cancer patients – prominently rash and diarrhea – but pulmonary fibrosis has not been reported. Other EGFR TKIs are at earlier stages of development for the treatment of malignant gliomas.

The role of PDGF in gliomagenesis is well recognized. The v-*sis* oncogene isolated from cells transformed by the simian sarcoma virus is the cellular homologue of the PDGF-B ligand. Injection of simian sarcoma virus into primates induces glioma formation (106). Recent studies have shown that the expression of PDGF-B by retrovirus induces malignant gliomas in mice (107, 108). Gliomas of all grades express PDGF ligands and receptors, and contribute to the malignancy of gliomas (109, 110). Additional roles of the PDGF signaling axis in cancers is derived from the roles that PDGF has been shown to play in regulating the survival of pericytes associated with tumor vasculature (111) and regulation of interstitial fluid pressure (112).

Imatinib mesylate (STI571, Glivec, Gleevec; Novartis) is an oral, small-molecule ATPmimetic that inhibits the kinase activity of several oncogenes, including BCR-ABL, c-ABL, c-KIT and PDGF receptors. Several studies have been undertaken to evaluate imitanib mesylate in patients with recurrent malignant gliomas. A phase I/II study performed in 39 patients with malignant gliomas was associated with two grade 5 toxicities (intracerebral hemorrhage and pneumocystis pneumonia) and four patients with grade 4 toxicity (113). Fourteen out of 31 evaluable patients experienced stable disease, with four patients having more than six months of stability. Another recent study combined imitanib mesylate and the chemotherapeutic drug hydroxyurea in the treatment of patients with glioblastomas resistant to nitrosoureas and temozolomide (114). Of 26 evaluable patients, one experienced a complete response, four had partial responses, and nine had stable disease (median 12 months). No patients experienced grade 3 or 4 toxicities.

The formation of new blood vessels is a hallmark of malignant glioma pathology. This process, called angiogenesis, rarely occurs in adults under normal circumstances. As tumors begin to grow, they secrete angiogenic factors that promote the formation and stabilization of the new or cropted blood vessels essential to tumor growth. VEGF, also known as vascular permeability factor (VPF), is a major regulator of angiogenesis. The expression of both VEGF ligands and receptors is increased in malignant gliomas (115, 116). The expression of VEGF correlates with tumor grade, as glioblastomas have the highest levels of expression (117). Preclinical evaluations of anti-VEGF therapies have shown that they inhibit malignant glioma xenograft tumor growth (118, 119). Additional interest in antiangiogenic therapies for glioma therapy has been generated by the potential to avoid delivery challenges, as endothelial cells are the primary targets. Endothelial cells also

Table 1. Current combination therapies in evaluation

BCNU	**Topotecan**
BCNU	CPT-11
Imitanib mesylate (Gleevec)	Hydroxyurea
PTK787/ZK222584	Temozolomide or lomustine
Radiation therapy	High dose Tamoxifen
Radiation therapy	Topotecan
Radiation therapy	Imitanib mesylate
Radiation therapy	Capecitabine
Temozolomide	Pegylated liposomal doxorubicin
Temozolomide	Celecoxib
Temozolomide	Lomustine
Temozolomide	Etoposide (VP-16)
Temozolomide	Imitanib mesylate (Gleevec)
Temozolomide	CPT-11
Thalidomide	Cyclophosphamide
ZD1839 (Iressa)	Temozolomide

retain genomic instability, thus limiting the development of resistance.

PTK787/ZK222584 is a novel oral small-molecule ATP mimetic inhibitor of VEGF receptors that has shown antitumor activity in preclinical studies on several cancer types. A phase I multi-institutional trial of PTK787 as monotherapy found that the agent was well tolerated, with dose-limiting toxicities of deep vein thrombosis, liver enzyme elevation, insomnia, cerebral edema, fatigue and nausea/vomiting (120). One partial response was noted in 31 evaluable patients, with 20 patients (65%) having stable disease, 7 of them remained stable for more than 120 days. Another phase I trial of PTK787 is currently examining its use in combination with either temozolomide or lomustine in patients with recurrent glioblastomas, with evidence of radiographic response in a subset of patients (121). A preliminary analysis of the PTK787 plus temozolomide arm revealed that 3 patients achieved PR and 21 achieved SD among 34 evaluable patients. Two of the patients with partial responses had been previously treated with temozolomide monotherapy without response. Of 20 evaluable patients in the lomustine and PTK787 arm, one patient achieved a partial response and 13 had stable disease. Dose expansion is continuing.

In general, monotherapy with tyrosine kinase inhibitors has achieved modest activity thus far in recurrent glioblastoma multiforme. Currently tyrosine kinase inhibitors are being evaluated in several ongoing trials in combination with other treatments, such as concurrent radiation, chemotherapy, or other small molecule inhibitors (table 1).

4.3. Radioimmunotherapy

Immunotherapy with armed or unarmed monoclonal antibodies targeting tumor-specific antigens has emerged in the last two decades as a novel potential adjuvant treatment for all types of neoplasia. Results from ongoing Phase I/II clinical trials are encouraging, as disease stabilization and patient survival prolongation have been observed. Advances in preclinical and clinical research indicate that treatment of brain tumors with monoclonal antibodies can be increasingly adjusted to the characteristics of the targeted tumor and its environment. This aspect relies on the careful selection of the target antigen and corresponding specific monoclonal antibody, and antibody format (size, class, affinity), conjugation to the appropriate toxin or radioactive isotope (half-life, range), and proper compartmental administration. Our group has established the efficacy and tolerance of iodine-131-labeled antitenascin monoclonal antibody 81C6 (^{131}I-m81C6) when injected into the surgically created resection cavity of patients with newly diagnosed and recurrent malignant brain tumors. Our current approach involves administering a ^{131}I-m81C6 dose to deliver 44Gy to the 2-cm resection cavity perimeter and is based on dosimetry analyses demonstrating that a 44 Gy boost dose by ^{131}I-m81C6 achieved optimal tumor control while minimizing toxicity (122). In our phase II study, 20 patients with newly diagnosed malignant gliomas (14 GBM, 6 AA) received ^{131}I-m81C6 administered to achieve a 44 Gy boost. Grade 3/4 toxicities were limited to hematotoxicities with three leukopenias, one neutropenia and one thrombocytopenia. A median survival of 93.6 weeks was observed for glioblastoma multiforme, it has not been reached yet for anaplastic astrocytomas.

5. PERSPECTIVE

Active research has failed thus far to identify a therapeutic approach, which can cure malignant gliomas. Patients with anaplastic astrocytoma and anaplastic oligodendrogliomas with good prognostic factors: gross total resection, young age, and good performance status, can now expect a more prolonged survival. However, the prognosis of patients with glioblastoma multiforme remains dismal.

The results of a recent trial seems to suggest that a regimen of 60 Gy of radiotherapy over six weeks combined with 75 mg/m2 of temozolomide orally daily (7 days a week) during radiotherapy, followed by up to 6 cycles of adjuvant temozolomide (150-200 mg/m2/d) on days 1-5, given every 28 days) will be the new standard for patients with newly diagnosed GBM. Although this is an important step forward in that data now exists to confirm that chemotherapy can improve the outcome for patients with these devastating tumors, we must keep in mind that this new "standard of care" is associated with a PFS of only 6.9 months and a median OS of only 14.6 months. Clearly better therapies for both newly diagnosed and recurrent patients continue to be desperately needed. One promising approach involves a combination of new surgical techniques with intratumoral delivery of therapeutic molecules via convection enhanced delivery (CED). It is likely that a multimodality approach will be required to most effectively treat primary malignant brain tumors.

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Key Words: Tumor, Cancer, Glial cells, Malignant, Gliomas, Brain, malignant gliomas, radiation therapy, chemotherapy, tyrosine kinase inhibitors, Review

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