Review

Integrin Inhibitor Cilengitide for the Treatment of Glioblastoma: A Brief Overview of Current Clinical Results

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Abstract. *Glioblastoma is the most frequent primary malignant brain tumor in adults. Postoperative radiotherapy (RT) with concomitant and adjuvant chemotherapy with temozolomide is the standard treatment, however the prognosis remains poor with a median survival in the range of 12-15 months. In recent years, several targeted agents have been developed as potential inhibitors of molecular genetic and signal transduction pathways involved in gliomatogenesis, including those of vascular endothelial growth factor and its receptor, epidermal growth factor receptor, integrin, and mammalian target of rapamycin. The integrins are a family of transmembrane glycoprotein receptors that mediate cell matrix and cell-cell interactions, and are widely expressed in glioma cells and tumor vasculature. The critical role of integrins in angiogenesis, cell invasion and migration make them an attractive target for anticancer therapy. Inhibitory peptides and monoclonal antibodies to integrins are currently being investigated in clinical trials in patients with solid tumors, such as colorectal cancer, renal cell carcinoma, and melanoma. Cilengitide, a cyclized Arg-Gly-Glu(RGD)-containing pentapeptide that selectively blocks activation of the αvβ3 and αvβ5 integrins has shown encouraging activity in patients with glioblastoma as single agent, and in association with standard RT and temozolomide. In this review, we provide a brief overview of the preclinical experience and current clinical results of cilengitide therapy in patients with recurrent or newly diagnosed glioblastoma.*

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Glioblastoma is the most common malignant primary brain tumor, with an incidence rate of 2.8 cases per 100,000 person-years (1). Postoperative radiotherapy (RT) with the addition of concurrent and adjuvant chemotherapy with temozolomide is the standard of care for newly diagnosed glioblastoma, although the prognosis remains poor, with the majority of patients experiencing recurrence locally and dying within 2 years of diagnosis (2, 3).

In recent years, several targeted agents have been developed as potential inhibitors of molecular genetic and signal transduction pathways involved in gliomatogenesis. Tyrosine kinases inhibitors (TKIs) and monoclonal antibodies directed against epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and platelet growth factor receptor (PDGFR), and inhibitors of mammalian target of rapamycin (mTOR) and integrin molecular pathways have been evaluated in several randomized and prospective studies as single agents or in combination with RT and cytotoxic chemotherapy, however, with modest survival benefit (4-18).

Angiogenesis represents one of the most important therapeutic targets in glioblastoma treatment. Several antiangiogenic inhibitors directed against the VEGFR pathway, including the humanized murine monoclonal antibody bevacizumab and the VEGFR TKIs cediranib, vandetanib and vatalanib have been recently evaluated in phase I and II studies (19-27). On the basis of positive results in two prospective phase II studies (28, 29), bevacizumab was granted accelerated approval by the US Food and Drug Administration (FDA) as a single agent for recurrent glioblastoma. Promising antiangiogenic activity has been shown by inhibitors of the integrins, which are a family of heterodimeric cell adhesion molecules that play a crucial role in cell-cell adhesion and cell extracellular matrix (ECM) interaction (30-32). Cilengitide, a potent and selective inhibitor of the integrins αvβ3 and αvβ5, has been recently evaluated in phase I and II studies, with promising results (33-48).

In this short review, preclinical and clinical studies of cilengitide for the treatment of newly diagnosed and recurrent glioblastoma are summarized, and its potential role as an antiangiogenetic therapeutic agent discussed.

Integrins

Integrins are heterodimeric transmembrane glycoproteins composed of two subunits α and β, altogether forming more than 24 different proteins using 18 α and 8 β subunits, which have a crucial role in cell-cell adhesion and cell interaction with ECM. Integrins bind with specific ECM proteins, such as fibronectin, laminin, collagen, vitronectin and fibrinogen, through specific ligands that recognize the Arg-Gly-Asp (RGD) tripeptide motif (30-32).

The α subunit, consisting of approximately 1100 amino acids, is the largest and is composed of chains of different lengths held together by two disulfide bridges. The β subunit consists of about 800 amino acids, with the exception of the β4 subunit, which contains about 1750 amino acids. Both the α and β subunits have a small transmembrane region, a large extracellular domain and a small cytoplasmic tail. The cytoplasmic domain is crucial for the regulation of integrin activity. It controls the integrin affinity state and its ECM ligand-binding activity, and promotes cellular responses upon extracellular ligand binding. After activation of the cytoplasmic domain by its extracellular ligand, integrins, which lack intrinsic kinase activity, cluster to form cell membrane focal adhesion complexes. Focal adhesion kinase (FAK) is recruited and autophosphorylated at these sites, in turn activating signaling pathways through phosphatidylinositol 3-kinase (PI3K), nuclear factor kappa B (NF-kB), sarcoma tyrosine kinase (SRC) and extracellular signal-regulated kinase (ERK/MAPK) (Figure 1) (49-52). This leads to the regulation of several cellular processes, including: cell motility and invasion; remodeling of the ECM by means of localization proteases; cell growth through adhesion-dependent control of proliferation, and cell signaling by cross-talk with growth factors and cytokine receptors. In addition, integrins are involved in several steps of normal immune-cell function, including T-cell activation and lymphocyte adhesion to endothelial cells (53), and modulate apoptosis, regulating the activity of pro-apoptotic proteins, such as caspase, with a mechanism called integrin-mediated death (54). However, the exact molecular mechanisms and pathways involved in their actions remain unclear.

Endothelial integrins are very important in the physiological and pathological process of angiogenesis; they play an important role in embryonic development of blood vessels in placenta and brain, whereas fibronectin-binding integrins are essential for developmental angiogenesis (55) The integrins involved in angiogenesis comprise the heterodimers α1β1, α2β1, α4β1, α5β1, α6β1, α6β4, α9β1, αvβ3 and αvβ5 and the glial cell integrin αvβ8 (56). The αvβ3 and αvβ5 integrins are over expressed by both tumor-associated vasculature and glioma cells (57, 58), and their activation is associated with several cellular mechanisms, including proliferation, growth factor signaling, survival, invasion, and angiogenesis (59). Therefore, this class of integrins as key molecular players in multiple tumor cell processes represents an attractive therapeutic target in malignant gliomas, and potential inhibitors have been developed.

Cilengitide

Cilengitide (EMD 121974; Merck KgaA, Darmstadt, Germany), is a cyclized Arg-Gly-Glu (RGD)-containing pentapeptide that selectively blocks activation of the αvβ3 and αvβ5 integrins (60, 61). Its precursor was first synthesized in 1995 as c(RGDfV) (62), and later modified by the incorporation of *N*-methyl Val c(RGDfMetV), generating the current form of the drug. Cilengitide displays subnanomolar antagonistic activity for αvβ3 and αvβ5 (63), and is the first integrin antagonist evaluated in clinical phase I and II trials for treatment of glioblastoma and several other tumor types.

The crystal structure of the extracellular segment of integrin αvβ3 bound to cilengitide confirms that interactions between the positively charged arginine and the α-subunit, and between the anionic aspartic acid and the β-subunit, are crucial for optimal RGD sequence and integrin αvβ3 binding (64). The chemical formula of cilengitide is $C_{27}H_40N_8O_7$ and the molecular weight is 588.7 atomic mass units. The drug is formulated as a sterile aqueous solution for intravenous administration. Following intravenous administration, plasma cilengitide concentrations decline, with a mean terminal elimination half-life of 3 to 5 hours. Maximum concentrations are achieved within 60 minutes, and the drug is predominantly eliminated by renal excretion (65).

Preclinical Studies

Several preclinical studies, both *in vitro* and *in vivo*, have demonstrated that cilengitide is a potent inhibitor of angiogenesis, and inducer of apoptosis in the endothelial cells by inhibition of the interaction between integrins, especially αvβ3, and their ECM ligands (66-71).

Cilengitide-induced glioma cell death and inhibition of blood vessel formation may use different molecular mechanisms, including regulation of tumor hypoxia and activation of apoptotic pathways (72, 73). In U87 and SF763 glioblastoma cells inhibition of αvβ3 and αvβ5 integrins by cilengitide reduces glioma hypoxia and vessel density (72). In human $CD133^+$ endothelial progenitor

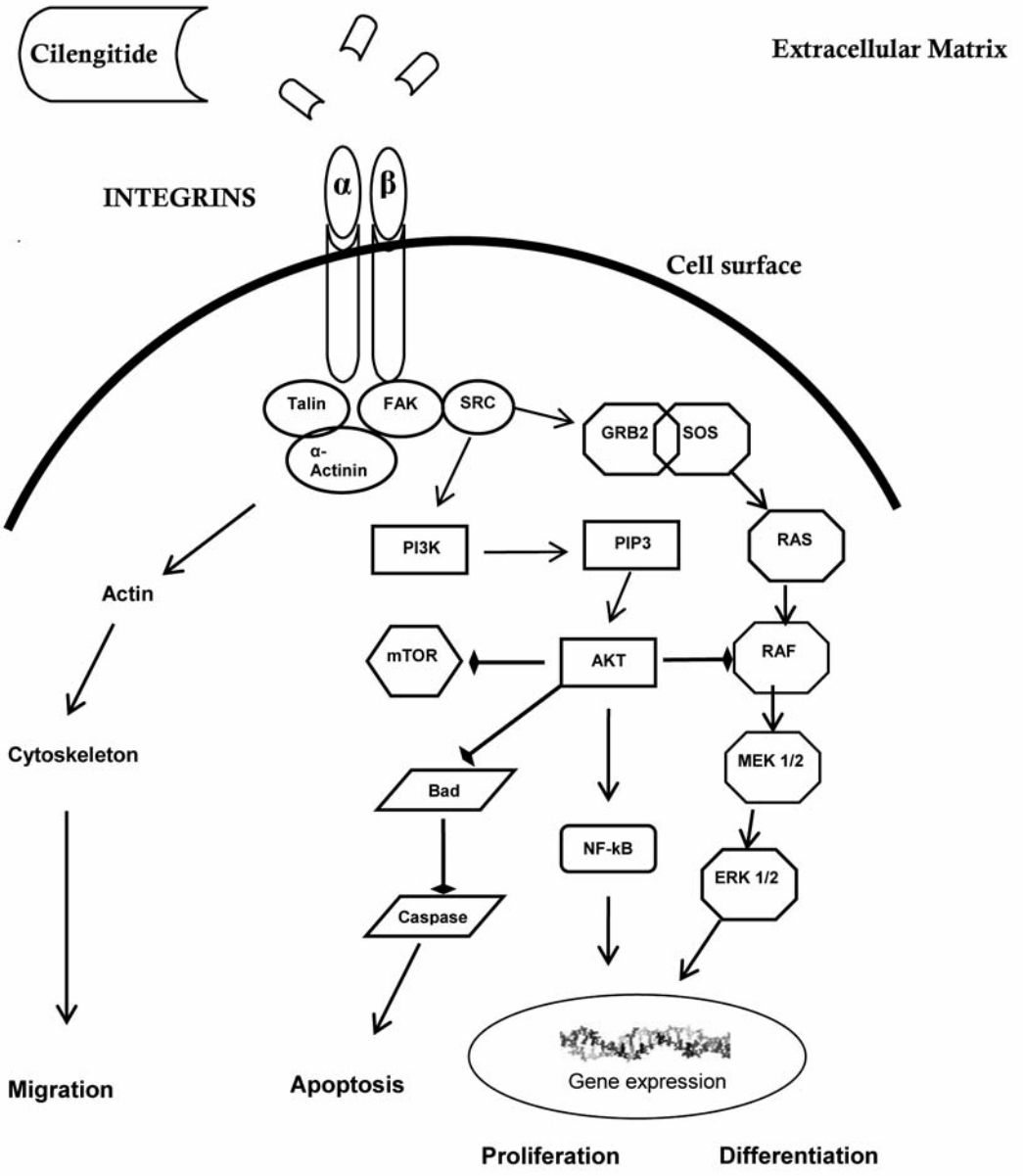

Figure 1. *Schematic representation of main signaling pathways activated by integrins. AKT, protein kinase B; BAD, Bcl2 antagonist of cell death; ERK1/2, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GRB2, growth factor receptor-bound protein 2; MEK1/2, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol triphosphate; RAF, serine/threonine protein kinase; RAS, RAS GTPase; SOS, son of sevenless; SRC, sarcoma tyrosine kinase.*

cells, which are essential in tumor angiogenesis, cilengitide inhibits cell proliferation and differentiation in a dose-dependent manner (73).

The cytotoxic effect of cilengitide may be independent of alterations of tumor vascularization. Targeting αv integrins in endothelial and glioma cells with cilengitide results in decreased proliferation by inhibition of FAK, SRC and protein kinase B (AKT) pathways which are involved in apoptosis (74). Cilengitide induces detachment and apoptosis of both brain capillary endothelial cells and brain tumor cells by preventing the interaction of αv integrins expressed on cell surface with the matrix proteins vitronectin and tenascin (75).

The anti-angiogenic and anti-tumor activities of cilengitide have been confirmed in various animal models. In a study by MacDonald *et al*. (76) nude mice with orthotopic brain tumors derived from medulloblastoma and glioblastoma cell

lines treated with cilengitide daily survived for more than 16 weeks as compared to 4-6 weeks in control animals. In contrast, the growth of brain tumor cells in the heterotypic model was not affected by the drug, suggesting that the brain environment might play a critical role in the susceptibility to cilengitide. Inhibition of cellular growth has also been demonstrated in blood vessels and human U-87 glioblastoma cells stereotactically injected into the caudate/putamen of nude mice treated with cilengitide (77). Cilengitide has also been shown to prevent metastasis formation *in vivo* in hamsters bearing amelanotic hamster melanoma A-Mel-3 (78). After 11 days, 50% of the animals treated with cilengitide were free of metastases, while all control animals developed palpable lymph node metastases.

Preclinical studies were also focused on the potential synergistic effect of cilengitide in combination with RT and/or chemotherapy with temozolomide. The role of cilengitide in increasing radiation-induced apoptosis has been suggested by using *in vitro* and *in vivo* models, although the mechanism of radiosensitization by cilengitide is still not clear. RT induces expression of αvβ3 integrins in several human cell lines, including umbilical vein endothelial cells, and H157 and H460 non small cell lung cancer cells; treatment with cilengitide followed by single doses of radiation increases apoptosis and detachment of these cell lines (79). In orthotopic rat models of human malignant glioma, concomitant chemoradiation with cilengitide dramatically amplified the effects of radiation, resulting in significant longer survival. Interestingly, a single dose of 4 mg per kg given between 4 and 12 hours prior to irradiation was sufficient to produce the same effect as that of daily injections (80). This observation suggests that, differently from classical radiosensitizers which need to be present during RT, cilengitide is able to enhance the efficacy of ionizing radiation before the radiation treatment. The suggested mechanism of radiosensitization is amplification of radiation-induced apoptosis rather than vascular normalization induced by the antiangiogenic effect of cilengitide. An enhanced apoptotic response and suppression of tumor growth were in fact found by histology at necropsy (80). Different signaling pathways may be activated in tumor by co-treatment with cilengitide and RT, including that of NF-kB, which is a recognized mediator of cellular response to radiation.

The combination of cilengitide with temozolomide has demonstrated an additive effect on inhibiting proliferation and inducing apoptosis in glioma cells with O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation (74). Interestingly, cilengitide has also shown synergistic or additive effects when combined with temozolomide in *MGMT*-deficient cells (81). The synergistic antiproliferative effect of cilengitide and temozolomide has been demonstrated in melanoma and immortalized human endothelial cells using both *in vitro* and *in vivo* models, suggesting that the combination of cilengitide and temozolomide might represent a feasible treatment option for such tumors (82).

Clinical Studies

The encouraging results of preclinical studies have led to the development of several phase I and II trials using cilengitide in either solid tumors or recurrent gliomas. Esklens *et al*. (33) reported a phase I study of 37 patients with metastatic solid tumors treated with a twice-weekly infusion of cilengitide at doses ranging from 30 to 1600 mg/m^2. No dose-limiting toxicities (DLTs) were observed and the maximum-tolerated dose (MTD) was not reached. Plasma pharmacokinetics determined at days 1 and 15 showed an apparent terminal half-life of cilengitide of 3 to 5 hours. In a phase I trial of 20 patients with advanced solid tumors who received 50 courses of twice-weekly infusion of cilengitide every 28 days at doses of 600 or 1200 mg/m^2, Hariharan *et al*. (34) reported no DLTs. Pharmacokinetics were dose dependent and revealed a terminal half-life of 4 hours. In a phase I study of 35 patients with solid tumors treated with continuous infusion of cilengitide in 4-week cycles at different dose levels up to 40 mg/h, no toxicities greater than grade 2 were reported (35). Fatigue was the most common toxic effect occurring in 17% of patients, while all other toxicites were reported in fewer than 10% of patients. Similarly to other phase I studies, the MTD was not reached. The pharmacokinetics were consistent with the results obtained using a twice-weekly infusion, suggesting that cilengitide can also be safely administered as a continuous infusion at doses of up to at least 40 mg/h.

Phase I and II studies in recurrent glioma. Cilengitide has been assessed in two phase I dose-escalation studies in adults and children with recurrent brain tumors (Table I). Nabors *et al*. (36) reported on a multi-institutional phase I trial designed to assess the toxicities and the MTD of cilengitide as single-agent in adult patients with recurrent malignant glioma. Cilengitide was administered continuously as a twice-a-week infusion at doses ranging from 120 to 2400 mg/m^2 in 4-week cycles to 51 patients. Treatment-related DLTs were one grade 3 thrombosis to doses of 120 mg/m^2, one grade 4 myalgia and arthralgia to doses of 480 mg/m^2, one grade 3 thrombocytopenia to doses of 600 mg/m^2, and one grade 3 anorexia, hypoglycemia, and hyponatriemia to doses of 1800 mg/m^2. The MTD was not reached. The median survival time was 5.6 months. Complete response was observed in two patients, partial response in three, and stable disease in 16. As for other phase I studies of cilengitide in solid tumors (33, 34), the kinetics of the drug were linear and were not affected by the concurrent administration of enzyme-inducing anticonvulsant drugs.

Table I. *Clinical trials of cilengitide*

Authors	Trial	Patients	Tumor	Cilengitide dose	Outcomes
Nabors *et al*., 2007 [36]	Phase I	51	Recurrent malignant gliomas	120 to 2400 mg/m^2	OS: 5.6 months
MacDonald e*t al*., 2008 [37]	Phase I	31	Recurrent pediatric brain tumors	120 to 2400 mg/m^2	CR: 1 patient SD: 2 patients
Reardon *et al*., 2008 [38]	Phase II	81	Recurrent malignant gliomas	500 or 2000 mg	PFS-6: 15% (2000 mg) OS: 9.9 months (2000 mg)
Gilbert *et al*., 2012 [40]	Phase II	30	Recurrent GBM	500 or 2000 mg before surgery; after: 2000 mg	PFS-6: 12% PFS: 8 weeks
Nabors *et al*., 2009 [42]	Phase I	112	Newly diagnosed GBM	500 or 2000 mg + RT + TMZ	OS: 18.9 months
Stupp *et al*., 2010 [41]	Phase I/IIa	52	Newly diagnosed GBM	500 mg + RT + TMZ	PFS-6: 69% OS: 16.1 months

GBM, Glioblastoma; OS, overall survival; PFS-6, 6-month progression-free survival; RT, radiotherapy; TMZ, temozolomide; CR, complete response; SD, stable disease.

Another phase I dose-escalation trial was performed in 31 pediatric patients with recurrent brain tumors (37). Dose escalation started at 120 mg/m^2 and continued to the final dosage of 2400 mg/m^2. Cilengitide was administered twice weekly for up to 52 weeks, starting at 120 mg/m^2 to the final dosage of 2400 mg/m^2. There were no DLTs and the MTD was not reached. A grade 3 or 4 intracranial hemorrhage occurred in three out of 13 patients treated with 2400 mg/m^2, although it was asymptomatic in two patients. Complete response was achieved in one patient with recurrent glioblastoma at the dose of 1200 mg/m^2, and two patients had stable disease for at least 22 weeks. The pharmacokinetics analyses were comparable with those from studies in adult patients, confirming the feasibility of the twice-weekly infusion.

Based on data from phase I trials demonstrating that cilengitide is well tolerated and clinically active in patients with malignant glioma, several phase II randomized studies have tested the efficacy of different treatment dosages (Table I). Reardon *et al*. (38) assessed the activity and safety of cilengitide in 81 patients with recurrent glioblastoma after standard treatment who were randomly assigned to receive the drug as single agent at either 500 or 2000 mg twice-weekly infusions. The 6-month progression-free survival rates were 15% in the 2000 mg arm and 10% in the 500 mg arm, and the respective median overall survival rates were 9.9 and 6.5 months. A partial response was achieved in 9% of treated patients, with a median duration of 17 months. Karnofsky performance score (KPS) ≥90 was the only independent variable predictive of better progression-free survival and overall survival. Grade 3-4 hematological and non hematological toxicity was similar for both arms and occurred in fewer than 15% of patients. Long-term follow-up data of the trial were reported at the 2010 ASCO Annual Meeting (39). At a median follow-up of 53 and 48 months, survival rates were 2.4% for patients receiving 500 mg and 10.0% for patients receiving 2000 mg dose, respectively.

Gilbert *et al*. (40) have recently reported on the efficacy and tumor delivery of cilengitide in 30 patients with recurrent glioblastoma who underwent tumor resection. Patients were randomized to receive three intravenous doses of cilengitide at either 500 or 2000 mg starting 8 days prior to surgery, and thereafter at a dose of 2000 mg in a twice-weekly infusion for a maximum of 2 years. The reported median and 6-month progression-free survival rates were 8 weeks and 12%, respectively. Grade 3-4 hematological adverse events were observed in nine patients, with lymphopenia being the most common.

Phase I and II studies in newly diagnosed glioma. The clinical activity of cilengitide in association with standard RT/temozolomide treatment in patients with newly diagnosed glioblastoma has been explored in few clinical trials (Table I). In a phase I/IIa study, Stupp *et al*. (41) reported on 52 patients treated with cilengitide at a dose of 500 mg twice weekly in association with RT and concomitant and adjuvant temozolomide for up to six cycles. At a median follow-up of 34 months, the 6-month progression-free survival was 69% and the median overall survival was 16.1 months, as compared to 53.9% and 14.6 months, respectively for standard treatment (2). The treatment was well tolerated and discontinuation of therapy possibly due to treatment-related toxicity occurred in 14% of patients. Adverse events were represented by thrombocytopenia, intracranial hemorrhage, neuropathy, and idiosyncratic liver toxicity. Thromboembolic events were reported in three patients and mild to moderate hypertension was observed in five patients. Pharmacokinetic studies revealed that metabolism of both temozolomide and cilengitide was not affected by their concomitant use. Interestingly, patients with methylated *MGMT* gene promoter had a significantly longer progression-free survival and overall survival as compared with those with unmethylated *MGMT*, suggesting that only patients with methylated

Table II. *Ongoing clinical trials of cilengitide.*

Trial	Estimated enrollment	Disease setting	Endpoint	Treatment	Start date	Estimated study completion date	Estimated primary completion date
Phase III CENTRIC [ClinicalTrials.gov ID: NCT00689221]	504	Newly diagnosed GBM (methylated *MGMT* promoter)	Safety and efficacy	Cilengitide (2000 mg) + RT + TMZ *vs.* RT + TMZ	September 2008	October 2016	September 2012
Phase II CORE [ClinicalTrials.gov ID: NCT00813943]	264	Newly diagnosed GBM (unmethylated *MGMT* promoter)	Safety and efficacy	Cilengitide (2000 mg) + RT + TMZ *vs.* RT + TMZ	December 2008	June 2014	March 2013
Phase II CeCil [ClinicalTrials.gov ID: NCT01044225]	108	Newly diagnosed GBM (unmethylated *MGMT* promoter)	Safety and efficacy	Cilengitide (2000 mg) or Cetuximab + RT + TMZ	September 2009	Closed prematurely	NR
Phase II ExCentric [ClinicalTrials.gov ID: NCT01124240]	48	Newly diagnosed GBM (unmethylated MGMT promoter)	Safety and efficacy	Cilengitide (2000 mg) +RT + TMZ + PCB	November 2009	January 2014	November 2012
Phase I [ClinicalTrials.gov ID: NCT00979862]	52	Progressive/ recurrent GBM	Safety and dosage	Cilengitide + Cediranib maleate	March 2010	NR	June 2012
Phase I CILENT-0902 [ClinicalTrials.gov ID: NCT01165333]	40 (children)	Diffuse intrinsic pontine glioma	Safety and PK	Cilengitide (240 to 1800 mg/m^2) + RT	July 2010	July 2015	July 2012
Phase II HGG-CilMetro [ClinicalTrials.gov ID: NCT01517776]	33 (children and adolescents)	Refractory HGG or diffuse intrinsic pontine glioma	Safety, efficacy and PK	Cilengitide (1800 mg/m^2) + metronomic TMZ	January 2012	January 2015	June 2014

GBM, Glioblastoma; MGMT, O-6-methylguanine-DNA methyltransferase; RT, radiotherapy; TMZ, temozolomide; PCB, procarbazine; PK, pharmacokinetics; HGG, high-grade glioma; NR, not reported.

MGMT are likely to have any benefit from the addition of cilengitide to temozolomide. A possible explanation could be a direct potentiation of the antitumor activity of temozolomide by cilengitide, or a greater delivery of temozolomide due to the antiangiogenic effect of cilengitide that normalizes tumor vasculature (83).

Similar encouraging data were reported in the preliminary results of a randomized phase II trial of the New Agents Brain Tumor Treatment (NABTT) cooperative group (NABTT 0306) (42). In this study, 112 patients with newly diagnosed glioblastoma were randomized to receive cilengitide at a dose of either 500 or 2000 mg twice weekly, concomitantly with standard concurrent and adjuvant RT/temozolomide treatment, and then as single agent after six cycles of temozolomide until evidence of progressive disease. Median survival and one-year survival rates were 18.9 months and 79.5%, respectively, with a more favorable trend for patients treated with the 2000 mg dose as compared with those receiving the 500 mg dose. Interestingly, overall survival was 30 months for patients who had methylated *MGMT* status, and 17.4 months for patients who had unmethylated *MGMT* status. For both studies, the reported median survival observed with cilengitide combined with standard chemoradiation was superior to that observed in the European Organisation for Research and Treatment of Cancer Brain Tumor (EORTC) trial using standard chemoradiation alone (2).

Ongoing trials. Several ongoing clinical trials are evaluating the efficacy of cilengitide in adult patients and children with recurrent or newly diagnosed malignant glioma (84); however, no preliminary data are currently available (Table II).

A phase III randomized study which started in September 2008 is investigating the efficacy and safety of cilengitide, given twice weekly (2000 mg), in combination with standard RT-temozolomide treatment *versus* standard RT-temozolomide alone to patients with newly diagnosed

glioblastoma and methylated MGMT gene promoter status (CENTRIC Study). The enrollment of 504 patients was recently concluded and a primary analysis of outcome measures is expected in September 2012 (ClinicalTrials.gov ID: NCT00689221). A similar phase II clinical trial launched in December 2008 is evaluating the efficacy and safety of two different regimens of cilengitide in combination with standard treatment *versus* standard treatment alone in newly diagnosed glioblastoma with unmethylated *MGMT* promoter (CORE Study). The study completion is estimated for June 2014, with 264 patients enrolled, and preliminary results are expected by March 2013 (ClinicalTrials.gov ID: NCT00813943).

A similar phase II study designed for patients with glioblastoma without methylation of the *MGMT* promoter gene is currently recruiting participants (ExCentric Study). Cilengitide will be administered at a dose of 2000 mg twice weekly over a period of 18 months without interruption in combination with RT and concomitant and adjuvant daily temozolomide and procarbazine, starting one week before RT. After a 4-week break, adjuvant temozolomide and procarbazine will then be given daily for a total of 6 cycles of 28 days (ClinicalTrials.gov ID: NCT01124240).

The safety and optimal dose of cilengitide in association with other cytotoxic or targeted agents in children are under investigation in few studies. A dose-escalation phase I study is investigating the safety and pharmacokinetics of cilengitide with concomitant RT in children and young adults (aged 6 months to 21 years) with diffuse intrinsic pontine gliomas (CILENT-0902 Study). This study is currently recruiting participants to a total estimated number of 40 patients (ClinicalTrials.gov ID: NCT01165333). In January 2012, a new study was launched with the aim of evaluating the efficacy and safety of a combined treatment of cilengitide (1800 mg/m^2 twice weekly) and metronomic oral temozolomide in children and adolescents (aged 3 to 17 years) with relapsed or refractory high-grade malignant gliomas or diffuse intrinsic pontine gliomas (HIT-HGG-CilMetro Study). The study is recruiting participants with an estimated enrollment of 33 patients and an estimated completion date in January 2015, with primary outcome measures in June 2014 (ClinicalTrials.gov ID: NCT01517776).

Conclusion

Anti angiogenic agents represent an important advance in cancer therapy. The integrin inhibitor cilengitide has been evaluated in clinical studies both as single agent for recurrent malignant glioma, and in association with standard RT and temozolomide in newly diagnosed glioblastoma. Preliminary data suggest single-agent activity in recurrent glioma, however the reported overall survival remains modest. Moreover, data need to be interpreted with caution, since the majority of published studies do not specify if patients who progressed on cilengitide-based therapy received further treatments that could have positively impacted on the observed survival. Future studies should try to identify molecular factors predictive of response, and the options that should be offered to patients after cilengitide failure. Most phase I and II clinical studies confirm that treatment with cilengitide is also well tolerated when given for a long time. However, despite acceptable toxicity, the twice-weekly intravenous administration of cilengitide may represent a negative factor that can affect quality of life in such patients with poor prognosis. Also this important aspect needs to be addressed in future studies.

Ongoing trials are evaluating the combination of cilengitide with standard chemoradiation and/or with other cytotoxic or targeted biological agents. Results from these studies should definitively clarify the role of cilengitide either as up-front treatment for malignant glioma, or in tumor recurrence. Interestingly, some of these trials are investigating the efficacy of cilengitide in patients without *MGMT* promoter methylation, which is known to be a negative predictive factor for response to temozolomide. If cilengitide demonstrates a survival advantage for this subpopulation, it could become a valid alternative treatment or a salvage option for this subset of patients who are unlikely to benefit from standard treatment.

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