Cilengitide

- CD51 Promotes Gastric Cancer Stemness via Blocking Numb-Mediated Notch1 Degradation
- Thyroid hormones contribute to JAK/STAT pathway abnormal activation promoting T-cell lymphoma dissemination
- Inside a Metastatic Fracture: Molecular Bases and New Potential Therapeutic Targets
- Fibroblast Activation Protein (FAP)⁺ cancer-associated fibroblasts induce macrophage M2-like polarization via the Fibronectin 1-Integrin α5β1 axis in breast cancer
- Collagen V regulates renal function after kidney injury and can be pharmacologically targeted to enhance kidney repair in mice
- New insights on the protection of endangered aquatic species: Embryotoxicity effects of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) via integrin-mediated oxidative stress and inflammatory pathways in Siberian sturgeon, Acipenser baerii
- Spheroid Invasion Assay of Melanoma Cells by Hanging Drop Technique
- Targeted inhibition of integrin αVβ3 induces cytotoxicity and suppresses migration ability in ovarian cancer cells and tumor spheroids

Cilengitide is a cyclic RGD (arginine-glycine-aspartic acid) peptide that acts as an integrin inhibitor.

Cilengitide specifically targets integrins, inhibiting their function, and has been studied in the context of cancer treatment, particularly glioblastoma.

Here are key points about Cilengitide:

Mechanism of Action: Cilengitide works by inhibiting integrins, specifically αvβ3 and αvβ5 integrins. These integrins are involved in angiogenesis (the formation of new blood vessels) and are often overexpressed in certain types of cancer, including glioblastoma.

Clinical Trials in Glioblastoma: Cilengitide has been investigated in clinical trials for the treatment of glioblastoma. The rationale behind its use is to disrupt the formation of new blood vessels within the tumor (anti-angiogenic effect) and inhibit the adhesion and migration of cancer cells.

Combination Therapy: Cilengitide has been studied both as a monotherapy and in combination with standard treatments for glioblastoma, such as radiation and chemotherapy (temozolomide). The hope is that targeting integrins may enhance the effectiveness of these treatments.

Challenges and Limitations: While cilengitide showed promise in preclinical studies, the results from clinical trials have been mixed. It has faced challenges in demonstrating significant improvement in overall survival or progression-free survival in some studies. The complexity of glioblastoma and its resistance to treatment contribute to the difficulties in finding effective therapies.

Flies et al. assessed radiological progression in MGMT promoter-methylated glioblastoma treated with standard-of-care chemoradiotherapy with or without the integrin inhibitor cilengitide according to the modified RANO criteria of 2017.

Patients with ≥3 follow-up MRIs were included. Preliminary PD was defined as a ≥25% increase of the sum of products of perpendicular diameters (SPD) of a new or increasing lesion compared to baseline. PD required a second ≥25% increase of the SPD. Treatment-associated changes require stable or regressing disease after preliminary PD.

Of the 424 evaluable patients, 221 patients (52%) were randomized into the cilengitide and 203 patients (48%) into the control arm. After chemoradiation with or without cilengitide, preliminary PD occurred in 274 patients (65%) during available follow-up, and 88 of these patients (32%) had treatment-associated changes, whereas 67 patients (25%) had PD. The remaining 119 patients (43%) had no further follow-up after preliminary PD. Treatment-associated changes were more common in the cilengitide arm than in the standard-of-care arm (24% vs. 17%; relative risk, 1.3; 95% confidence interval, 1.004-1.795; p=0.047). Treatment-associated changes occurred mainly during the first six months after RT (54% after three months vs. 13% after six months).

With the modified RANO criteria, the rate of treatment-associated changes was low compared to previous studies in MGMT promoter-methylated glioblastoma. This rate was higher after cilengitide compared to standard-of-care treatment. Confirmatory scans, as recommended in the modified RANO criteria, were not always available reflecting current clinical practice [1)].

The addition of cilengitide to temozolomide chemoradiotherapy did not improve outcomes; cilengitide will not be further developed as an anticancer drug. Nevertheless, integrins remain a potential treatment target for glioblastoma [2)].

The main objective was to improve median overall survival, which is currently between 9 and 12 months, with a good quality of life, measured by the ability to carry out daily life activities [3)].

Cilengitide, a cyclized arginine-glycine-aspartic acid-containing pentapeptide, potently blocks αvβ3 and αvβ5 integrin activation. Integrins are upregulated in many malignancies and mediate a wide variety of tumor-stroma interactions. Cilengitide and other integrin-targeting therapeutics have preclinical activity against many cancer subtypes including glioblastoma (GBM), the most common and deadliest CNS tumor. Cilengitide is active against orthotopic GBM xenografts and can augment radiotherapy and chemotherapy in these models. In Phase I and II GBM trials, cilengitide and the combination of cilengitide with standard temozolomide and radiation demonstrate consistent antitumor activity and a favorable safety profile. Cilengitide is currently under evaluation in a pivotal, randomized Phase III study (Cilengitide in Combination With Temozolomide and Radiotherapy in Newly Diagnosed Glioblastoma Phase III Randomized Clinical Trial [CENTRIC]) for newly diagnosed GBM. In addition, randomized controlled Phase II studies with cilengitide are ongoing for non-small-cell lung cancer and squamous cell carcinoma of the head and neck. Cilengitide is the first integrin inhibitor in clinical Phase III development for oncology [4)].

Cilengitide is highly effective in suppressing blood vessel growth, thereby controlling the orthotopic growth of a glioblastoma cell line [5)].

In clinical trials for recurrent GBM, single-agent cilengitide has antitumor benefits and minimal toxicity. Among newly diagnosed GBM patients, single-arm studies incorporating cilengitide into standard external beam radiotherapy/temozolomide have shown encouraging activity with no

increased toxicity and have led to a planned randomized Phase III trial [6].

Mikkelsen et al. found that a single dose of cilengitide (4 mg/kg) given between 4 and 12 hr prior to radiation was sufficient to produce the same effect. Our results demonstrate that blockade of alphav integrins mediates an unanticipated rapid potentiation of radiation, and suggests possible clinical translation for glioma therapy [7].

A protocol about the temozolomide combined with radiotherapy treatment with glioblastoma was researched by Roger Stupp in 2005

The addition of concomitant and adjuvant cilengitide to standard chemoradiotherapy demonstrated promising activity in patients with glioblastoma with MGMT promoter methylation [8].

The combination therapy of cilengitide with belotecan presented more cytotoxic effects compared to the monotherapy of either drug in vitro and in vivo. This combination protocol may serve as an alternative treatment option for glioblastoma [9].

The use of novel therapeutic agents in combination with the Stupp protocol were all shown to be superior than the Stupp protocol alone for the treatment of newly diagnosed glioblastoma, ranked as follows: cilengitide 2000mg/5/week, bevacizumab in combination with irinotecan, nimotuzumab, bevacizumab, cilengitide 2000mg/2/week, cytokine-induced killer cell immunotherapy, and the Stupp protocol. In terms of serious adverse effects, the intervention group showed a 29% increase in the incidence of adverse events compared with the control group (patients treated only with Stupp protocol) with a statistically significant difference (RR=1.29; 95%CI 1.17-1.43; P<0.001). The most common adverse events were thrombocytopenia, lymphopenia, neutropenia, pneumonia, nausea, and vomiting, none of which were significantly different between the groups except for neutropenia, pneumonia, and embolism.

All intervention drugs evaluated in our study were superior to the Stupp protocol alone when used in combination with it. However, we could not conclusively confirm whether cilengitide 2000mg/5/week was the optimum regime, as only one trial using this protocol was included in our study [10].

Meningioma

Monotherapy with cilengitide is not likely to achieve major responses in rapidly growing malignant meningiomas, although brain invasion may be reduced because of the strong antimigratory properties of the drug. The combination with radiotherapy warrants further attention [11].

1)

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