End of the road: confounding results of the CORE trial terminate the arduous journey of cilengitide for glioblastoma

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The integrin family of cell adhesion receptors has been studied extensively in cancer and is implicated in tumor cell survival, migration, proliferation, and angiogenesis.1 These transmembrane receptors, composed of dimerized α and β domains, play a crucial role in how tumor cells communicate with the microenvironment through a multiplicity of interactions with numerous extracellular ligands via an arginine-glycine-aspartic acid (RGD) peptide. Integrins are involved in the regulation of tumor cell survival, but their role is complex and incompletely understood. There is evidence that these receptors influence tumor cell survival in both ligated and unligated states in often contradictory ways. Integrins are apparently involved in the biology of glioblastoma, where αvβ3 and to a lesser extent αvβ5 integrins are expressed at increased levels at the interface of the tumor and normal tissues, including angiogenic endothelial and glioblastoma cells, where they have a putative role in invasion, angiogenesis, and growth factor–mediated cell survival.2 Furthermore, the αvβ3 ligand vitronectin is expressed in glioblastoma extracellular matrix where potential interactions with surrounding integrins can influence tumor cell survival and invasion.3

Cilengitide, a cyclic RGD peptide that inhibits both αvβ3 and αvβ5 integrins, has received rigorous and thoughtful evaluation in glioblastoma as a novel therapeutic targeting the tumor microenvironment.4 Preclinical studies have demonstrated antiangiogenic and anti-invasive activity in glioma models.5 Moreover, radiation sensitization of glioblastoma by cilengitide has been observed in glioma cells and orthotopic rat glioma xenograft models.6,7 Phase I/II studies of cilengitide alone or in combination with temozolomide in recurrent and newly diagnosed glioblastoma demonstrated that treatment was well tolerated with minimal toxicity and associated with potential antitumor activity.8,9 Most importantly a multicenter phase I/II study of cilengitide with radiotherapy and temozolomide for patients with newly diagnosed glioblastoma demonstrated improved survival compared with historical controls for the subset of patients with O6-DNA methylguanine-methyltransferase (MGMT) methylated tumors in particular, where progression-free survival (PFS) and overall survival (OS) were 13.4 and 23.2 months, respectively, compared with 3.4 and 13.1 months, respectively, in patients with MGMT unmethylated tumors.10

Based on promising preliminary survival data, a multicenter, randomized, open-label phase III trial, the CENTRIC EORTC 26071-22072 study, of radiotherapy with temozolomide and cilengitide administered at a dosage of 2000 mg intravenously twice weekly versus radiotherapy with temozolomide alone was initiated in patients with newly diagnosed MGMT methylated glioblastoma.11 A total of 3371 patients were screened to enroll 545 patients; results were disappointing, with median OS of 26.3 months in the cilengitide group and 26.3 months in the control group. As this was a registration trial, failure to demonstrate survival advantage in the patients most likely to benefit from the addition of cilengitide to standard initial therapy resulted in a decision to abandon development of cilengitide as an anticancer drug.

In this issue of Neuro-Oncology, Nabors et al report the results of a companion study to the CENTRIC phase III trial, a randomized phase II study of 2 cilengitide regimens with radiotherapy and temozolomide versus radiotherapy and temozolomide alone for patients with newly diagnosed MGMT unmethylated glioblastoma, the CORE trial.12 The genesis of this trial was based on desire to offer cilengitide to patients who failed screening for the CENTRIC trial as a consequence of MGMT methylation status but was also motivated by interest in evaluating a strategy of cilengitide dose intensification as a means of overcoming drug resistance in this poor prognosis group with few therapeutic options and dismal survival expectations. Indeed, there was preliminary evidence that dose escalation and intensification of cilengitide could improve outcome in patients with recurrent glioblastoma.13 In the CORE study, 265 patients with newly diagnosed MGMT unmethylated glioblastoma were randomized to standard cilengitide (2000 mg twice weekly until progression) or intensive cilengitide (2000 mg daily for 5 days during radiotherapy followed by twice weekly until progression) with radiotherapy and temozolomide or a control arm with standard chemoradiotherapy with temozolomide. A phase 1 component to evaluate the safety of cilengitide dose intensification during irradiation was required, and as expected, cilengitide was well

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tolerated, as it was in both arms of the phase II expansion. The results of this trial are unexpected and perplexing: the primary endpoint, median OS, was improved most in the standard cilengitide arm (16.3 mo, \(P = .032\)) versus the intensive cilengitide arm (14.5 mo, \(P = .3771\)) compared with the standard control arm (13.4 mo). Paradoxically, median PFS as assessed by an independent review committee was 5.6 months and 5.9 months in the standard and intensive cilengitide arms, respectively, versus 4.1 months in the control arm. While cilengitide has putative antiangiogenic properties, radiographic pseudoresponse did not appear to account for a slightly improved median PFS in the intensive arm; more importantly, however, while survival was modestly improved in both experimental arms, the expected dose-response outcome was not observed. Furthermore, as this was a phase II trial, it was not powered sufficiently for these survival differences to be statistically meaningful. Perhaps even more bewildering is why a survival advantage was observed in patients with unmethylated glioblastoma at all when the benefit of cilengitide was predicted to be restricted to but ultimately not realized in patients with MGMT methylated tumors.

With the publication of the CORE trial results, the evaluation of cilengitide for glioblastoma can be considered finished. The CENTRIC trial was a major disappointment in clinical neuro-oncology considering the herculean effort required to complete this study. The results of the CORE trial, while provocative, are affected adversely by the negative phase III study in MGMT methylated tumors and by contradictory dose-response survival outcomes. The modest 3-month improvement in OS in the standard cilengitide arm must be viewed with suspicion given the limited power of this trial. Additionally, the lack of a biomarker that might identify responding patients; the need for twice weekly infusions; and its impact on cost, patient compliance, and quality of life diminish the significance of this possible survival benefit.

Despite the failure of cilengitide to change the therapeutic landscape of glioblastoma, integrins likely remain important targets for which we need not only effective agents but also a deeper understanding of tumor–extracellular matrix interactions and how best to manipulate them.

### References