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Clinical Report

Long Term Responses with Cetuximab Therapy in Glioblastoma Multiforme

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ABSTRACT

Glioblastoma multiforme (GBM) is responsible for most of the deaths associated with primary brain tumors. Standard treatment includes maximal surgical resection followed by chemotherapy and concomitant radiotherapy. Most patients, however, recur shortly after treatment. Second line treatment has little efficacy and the majority of patients die soon from the disease. Recent advances in molecular biology have implicated the epidermal growth factor receptor (EGFR) signaling pathways in the progression and resistance to standard therapies for GBM. This has prompted the evaluation of EGFR tyrosine- kinase inhibitors with encouraging results. Cetuximab is a monoclonal antibody targeted against the extra cellular domain of the EGFR with activity against different tumor types, either alone or in combination with chemotherapy and/or radiation therapy. Here we describe three patients with recurrent, heavily pretreated, EGFR expressing GBM who responded to treatment with single agent cetuximab.

Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumor in adults. Current treatment includes maximal surgical resection followed by adjuvant treatment with chemotherapy, starting with low dose followed by full dose of temozolomide for six months, combined with radiotherapy. In a phase III trial, this strategy resulted in a median survival of 14.6 months and a 26.5% two-year survival. However, only 10.7% of patients remained progression free at two years, reflecting an elevated rate of recurrence[1] and most patients with disease progression die shortly thereafter. New treatment strategies are therefore urgently needed in this setting.

Recent advances in molecular biology have implicated the EGFR signaling pathways in the progression and resistance to standard therapies in GBM.[2] Overexpression of this receptor is present in 40% of patients with GBM and preclinical models have suggested the potential role for EGFR targeted therapies for this condition.[3] In fact, the EGFR tyrosine-kinase inhibitors gefitinib and erlotinib are being evaluated in ongoing clinical trials in this disease. The impact of this strategy in overall survival remains, however, unclear.[4] Recent data with EGFR kinase inhibitors suggest a protein profile associated with responsiveness to these drugs.[5] However, coexpression of EGFRvIII (a pathological variation of EGFR that lacks the extracellular domain) and PTEN are needed to effectively predict clinical and radiological responses in progressive GBM patients. No correlation was observed with wild-type EGFR expression. Probably, disparate results reported with EGFR kinase inhibitors are correlated with the absence of this protein profile. In addition, GBM progression is associated with VEGFR pathway, which is not inhibited by these small kinase inhibitors.

Cetuximab is a monoclonal antibody that targets the extracelullar domain of the EGFR. In preclinical studies, the agent exerts antitumor and radiosensitizing effect in GBM. Furthermore, in intracranial GBM models, systemic administration of cetuximab has shown to be an effective treatment.[6] Furthermore, cetuximab has shown high activity in tumors expressing EGFR and it is capable to induce VEGFR pathway inhibition.[7,8] Indeed, preclinical data suggest that cetuximab binds to and internalizes EGFRvlll. This internalization induces an 80% reduction in active forms of EGFRvIII.[9] Therefore, cetuximab therapy was a rational strategy for the treatment of tumors that express EGFR and EGFRvIII. At the present time, there is no available clinical data of cetuximab in patients with GBM.

A 47-year-old white male was diagnosed with GBM located at the right frontal lobe in September 2003 after an episode of seizure treated with phenytoin and steroids. The patient underwent complete surgical resection with residual microscopic positive margins. Surgery was followed by radiotherapy to a total of 45 Gy in four weeks and con-

comitant treatment with temozolomide (75 mg/m^2) for five consecutive days every 28 days. This was followed by temozolomide (200 mg/m^2) for five consecutive days every 28 days until March 2004. In July 2004 a cranial MRI evidenced progressive disease according RECIST criteria and irinotecan (250 mg/m^2 every 15 days) was started. After two months of treatment, the patient condition deteriorated with worsening of a left hemiparesis and motor aphasia as well as radiological progression. The tumor was stained with EGFR antibodies targeted against extracellular EGFR domain and was found to be strongly positive with membranous and cytoplasmatic patterns. In September 2004, after informed consent was obtained, treatment with cetuximab, loading dose of 400 mg/m^2, followed by a weekly dose of 250 mg/m^2, was initiated.

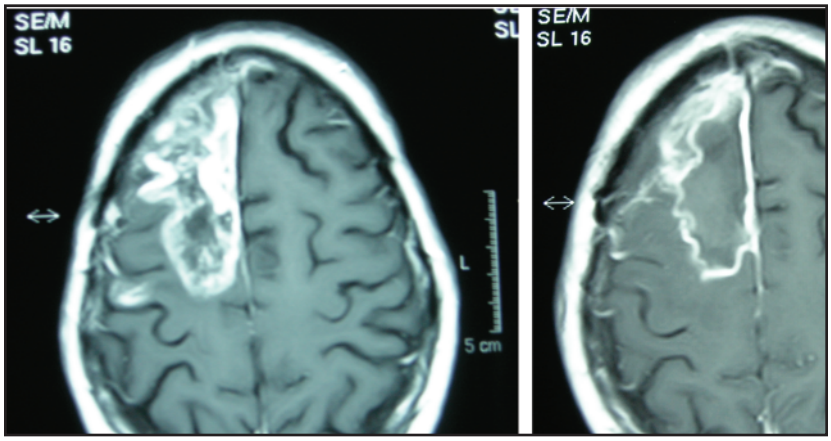

Figure 1 (A.) Baseline MRI. (B.) MRI after eight weekly doses of cetuximab.

After four weeks of treatment, patient symptoms began to improve (ECOG 4 to ECOG 1). A MRI scan performed eight weeks after treatment demonstrated a partial response in the tumor and considerable improvement in the surrounding edema (Fig. 1). Therefore, steroids were progressively tapered to a maintenance dose of 2mg/day of dexamethasone. The patient remained clinically and radiologically stable with weekly cetuximab until November 2005, when clinical and radiological worsening was detected (time to disease progression: 14 months).

Two additional patients, a 65-year-old male and a 42-year-old female, with primary EGFR positive GBM, located respectively at the right parietal lobe and the left occipital lobe, were consecutively treated. Both patients underwent maximal surgical resection (more than 90% tumoral mass), adjuvant temozolomide concomitant with radiotherapy and second line therapy with irinotecan. Then, progressive disease was diagnosed and they were treated with the same cetuximab schedule described above until progression. Clinical improvement and radiological stabilization was maintained for more than eight months (11 months and 13 months respectively). Only, phenytoin was administered as anticonvulsivant when needed.

The principal toxicities observed in these patients were, as expected, moderate asthenia and skin rash (grade 1-2 CTC-NCI v2.0), similar to those described in colorectal cancer studies.[10] Although cross-reactivity with normal CNS antigens could be an inherent risk for cetuximab in this clinical setting, no new neurological symptoms, other than those related to the underlying disease, were observed in these patients.

We believe that the natural history of GBM in these three patients was clearly modified by cetuximab. Preclinical data demonstrating that EGFR blocking is an encouraging treatment strategy for patients with high-grade gliomas supports our results in this group of patients. Two potential mechanisms may be involved in this observation. First, cetuximab exerts a direct cytotoxic effect mediated by the blocking of EGFR in in vitro and in vivo studies.[6] Second, blockage of EGFR by cetuximab induces an antiangiogenic effect inhibiting the vascular endothelial growth factor (VEGF) secretion as a consequence of a reduction of cellular level of hypoxia-inducible factor1-α.[7,8]

Several factors limit the interpretation of these data. First, and most important, a clinical trial is required to confirm the responses observed in these three patients. The data, however, suggest a clear improvement in survival when compared with historical series.[1,11] Second, the ability of a bulky monoclonal antibody to reach the CNS is not known. Several reports suggest that the blood brain barrier is presumably disrupted in patients with gadolinium-enhancing brain tumors. Although preclinical studies show that cetuximab crosses the blood brain barrier, it is unlikely that the cytotoxic effects of the antibody against the glioma cells are responsible for the entire clinical response observed.[6] In this regard, other immunological mechanisms might be implicated.[12] It is well described that secondary GBM have a better clinical course and could explain the survival observed in our patients. In this regard, all tumor samples were reevaluated by an expert neuro-pathologist and none of them presented the typical features of a secondary low-grade derived GBM. Other prognostic factors could be implicated in the evolution of our patients. All our patients were less than 60 years old at diagnosis. A retrospective analysis suggests a median survival of 43 weeks for this group.[13] So, we consider that this prognosis factor has little influence in our results. Good performance status is correlated with improved survival in patients diagnosed with GBM. However, when cetuximab therapy was started, every patient has a bad performance status (ECOG 3-4) and the worst biological situation (second line was ineffective). Thus, it is questionable that performance status had any impact over our final data. Finally, the delay between the discontinuation of irinotecan and cetuximab initiation could be a confounding factor that limits our results. However, we consider that the rapid worsening (two months until progression) and the subsequent improvement of the clinical situation when cetuximab therapy was initiated do not support this hypothesis.

To the best of our knowledge, these are the first clinical and radiological responses reported for cetuximab in the treatment of human EGFR expressing GBM. In spite of these data, the effect of cetuximab remains indeterminate in the absence of a clinical trial. So, we have now initiated a phase II study evaluating the efficacy of this therapy in this patient population.

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