Randomized, double-blind, placebo-controlled trial of marimastat in glioblastoma multiforme patients following surgery and irradiation

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Summary

Purpose: Because raised matrix metalloprotease (MMP) levels are associated with glioma invasion and angiogenesis, we tested the efficacy of marimastat (MT) an orally active drug that can reduce MMP levels, in patients with gliomas.

Patients and Methods: A total of 162 patients with intracranial glioblastoma multiforme or gliosarcomas who had undergone surgery and radiotherapy participated in this multicenter, double-blind, placebo-controlled, parallel group study conducted at 20 institutions. Seventy-nine patients (57 male, 22 female, median age 58 years) were randomized to receive placebo (PB), and 83 patients (51 male, 32 female, median age 57 years) were randomized to receive MT, 10 mg orally twice daily, until tumor progression.

Results: This intention-to-treat efficacy analysis showed no statistically significant difference between MT and PB groups with respect to survival ($P=0.38$, log rank test). The median survival time from protocol initiation was 37.9 weeks for the PB group and 42.9 weeks for the MT group, with a hazard ratio of 1.16 (95% CI 0.83 to 1.60). There were no statistically significant differences in quality of life between the PB and MT groups, as assessed by the FACT-BR questionnaire. Musculoskeletal toxicities led to dose modification or withdrawal in 20% of MT-treated and 1.2% of PB-treated patients.

Conclusion: MT does not improve survival in patients with glioblastoma or gliosarcoma following surgery and radiotherapy. Therefore, single-agent MT appears unwarranted; however, MT in combination with cytotoxic chemotherapy may be warranted, as suggested by observations in our study and other studies.

Introduction

Glioblastoma multiforme (GBM) is the most commonly diagnosed malignant primary brain tumor in adults. Despite the use of multiple aggressive treatment modalities (i.e., surgery, radiation therapy [RT], and chemotherapy), the outcomes for patients with GBM remain poor, with an overall median survival time for patients newly diagnosed with GBM of 42–59 weeks [1,2]. The failure of these therapies to substantially improve survival for GBM patients underscores the urgent need for new chemotherapy approaches.

One potential target of therapy for gliomas are matrix metalloproteases (MMPs), which are upregulated in malignant gliomas and correlate with malignant progression [3–5]. By blocking neoangiogenesis [6] MMP inhibitors (MMPIs) have been shown to inhibit tumor growth and dissemination in various animal cancer models, including glioma models [7]. Preclinical studies in animal models of malignancy further demonstrated that MMPIs restricted the growth and regional spread of solid tumors, inhibited metastatic spread, and blocked neovascularization. These collective findings pointed to a potential role for MMPIs in the treatment of GBM and GS.

Marimastat (MT) is a low-molecular-weight (331.4 Da) peptidomimetic inhibitor of the MMP family of enzymes, achieving 50% inhibition of these enzymes, including collagenase, gelatinase, and stromelysin. In preclinical
studies, MT was found to inhibit collagenase by 90% at a plasma concentration of 40 ng/mL.

At the time this study was planned, MT had been tested in 12 separate phase I/II studies in patients with melanoma and ovarian, colorectal, pancreatic, prostate, head and neck, breast, gastric, and lung cancers. The most common dose-limiting toxicities were musculoskeletal and consisted of pain and tenderness in the muscles, tendons, and joints. At a dose of 10 mg twice daily, however, the side effects were generally milder and less frequent [8].

To investigate its place in the treatment of gliomas, MT was administered to patients with GBM or GS after first-line treatment with surgery and RT.

Patient eligibility

Patients were at least 18 years of age with a life expectancy greater than 12 weeks. All patients had surgical resection when appropriate and biopsy when resection was not possible. Study entry required only that the patient have a histologically confirmed GBM or gliosarcoma (GS). Patients had to have completed conventional single, daily fractionated external-beam RT no more than 4 weeks prior to study randomization and could not have received chemotherapy except for hydroxyurea if given during RT. Patients were required to have a Karnofsky performance status (KPS) score of ≥70%. Patients showing increased contrast enhancement of their tumor following RT remained eligible. Before starting therapy, patients were required to have adequate bone marrow function (absolute granulocyte count >1500/μl and platelet count >100,000/μl, and adequate liver function (serum glutamic-oxaloacetic transaminase or serum glutamic pyruvic transaminase <3 times greater than normal limit). Additional required laboratory values were alkaline phosphatase and bilirubin <2 times normal and adequate renal function (blood urea nitrogen or creatinine <1.5 times normal limit). Other eligibility requirements included contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) performed within 4 weeks of enrollment. Pregnant patients and those with active infections were excluded. This study was approved by the Institutional Review Board at each institution in which patients were entered into the study and also under the Food and Drug Administration Investigation New Drug Application #47220. Written informed consent was obtained before enrollment. A complete medical history and physical and neurologic examination was performed on each patient prior to enrollment.

Objectives

The primary objective of the study was to compare the effect of MT vs. placebo (PB) on overall survival (OS) in patients with GBM or GS who had completed conventional first-line treatment with surgery and RT. The secondary study objectives were to compare the effects of MT and PB on progression-free survival (PFS), quality of life, and safety.

Study design and methods

This was a multicenter, randomized, double-blind, PB-controlled, parallel group study conducted in patients with GBM or GS following completion of conventional first-line treatment with surgery and conventional external-beam RT (nominal dose of 60 Gy delivered in 30–33 fractions) between September 4, 1996, and October 17, 1999, from 20 institutions in the United States and 4 Canada (Table 1). Histologic confirmation of GBM or GS was required prior to patient randomization. Central neuropathology review was conducted by Gregory Fuller, MD, PhD, at The University of Texas M. D. Anderson Cancer Center, Houston, Texas, to confirm the diagnosis of GBM or GS using the classification scheme outlined by Burger et al. [9,10].

Following study entry, patients were treated with MT or PB at 10 mg orally twice daily. Therapy was continued until study termination or early withdrawal. Patients were then evaluated for disease progression, quality of life, and adverse events. All patients were followed up for disease progression and survival. Patients who experienced disease progression discontinued MT/PB and were withdrawn from the study or, at the discretion of the investigator, could elect to continue to receive MT or PB with the addition of procarbazine, CCNU, and vincristine (PCV) chemotherapy. Patients who did not receive PCV at their first progression were not allowed to continue receiving PB or MT. Further evidence of disease progression was cause for discontinuing PB or MT treatment. Data analysis was planned for 18 months after randomization of the last patient to the trial or when 90% of the patients in one study arm were dead, whichever occurred sooner. This time point is referred to as study termination.

Efficacy evaluation

The secondary endpoints were time to disease progression and quality of life. The time to first disease progression was viewed as being equivalent to PFS, the key secondary endpoint of interest, and was defined as the time from study entry to the time when disease progression was first documented by Gd-DPTA MRI or contrast-enhanced CT. Time to second disease progression was to be analyzed separately in the subset of patients whom the investigators considered appropriate candidates for PCV combination therapy at the time of progression. The time to second disease progression was defined as the time from the start of PCV chemotherapy plus MT/PB to the time when disease progression was next documented by Gd-DPTA MRI or contrast-enhanced CT. Patient numbers were expected to be low, and no formal comparative analysis between the two groups was anticipated.

Tumor status, as evaluated by MRI or CT, KPS, weight, and total and subtotal FACT-BR scores were to be tabulated at each assessment time point [11,12]. Total FACT-BR scores were obtained during single-agent