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CLINICAL INVESTIGATION **Brain**

A PILOT SAFETY STUDY OF LENALIDOMIDE AND RADIOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

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Purpose: To define the maximum tolerated dose (MTD) of lenalidomide, an analogue of thalidomide with enhanced immunomodulatory and antiangiogenic properties and a more favorable toxicity profile, in patients with newly diagnosed glioblastoma multiforme (GBM) when given concurrently with radiotherapy.

Patients and Methods: Patients with newly diagnosed GBM received radiotherapy concurrently with lenalidomide given for 3 weeks followed by a 1-week rest period and continued lenalidomide until tumor progression or unacceptable toxicity. Dose escalation occurred in groups of 6. Determination of the MTD was based on toxicities during the first 12 weeks of therapy. The primary endpoint was toxicity.

Results: Twenty-three patients were enrolled, of whom 20 were treated and evaluable for both toxicity and tumor response and 2 were evaluable for toxicity only. Common toxicities included venous thromboembolic disease, fatigue, and nausea. Dose-limiting toxicities were eosinophilic pneumonitis and transaminase elevations. The MTD for lenalidomide was determined to be 15 mg/m^2/d.

Conclusion: The recommended dose for lenalidomide with radiotherapy is 15 mg/m^2/d for 3 weeks followed by a 1-week rest period. Venous thromboembolic complications occurred in 4 patients, and prophylactic anticoagulation should be considered. © **2009 Elsevier Inc.**

Lenalidomide, Glioblastoma, Angiogenesis, Radiotherapy, Immunomodulatory.

INTRODUCTION

Glioblastomas are the most common type of malignant primary brain tumor. Standard therapy consists of resection followed by irradiation with concurrent and adjuvant temozolomide (1). Despite advances in neurosurgery, radiotherapy, and chemotherapy, the median survival of patients diagnosed with glioblastoma remains less than 15 months (1). Therefore, new investigational agents are warranted in the treatment of glioblastoma. Preclinical studies have shown that glioblastomas are highly angiogenic, a process that is driven by hypoxia. Hypoxia leads to increased levels of hypoxia-inducible factor α and subsequent activation of many hypoxia-regulated genes (2). The resulting expression of vascular endothelial growth factor (VEGF), transforming growth factor α, platelet-derived growth factor β, basic fibroblast growth factor (bFGF), and others results in endothelial cell migration, growth, and tumor angiogenesis (3, 4). Consequently, inhibition of the VEGF and bFGF signaling pathways may have antitumor activity.

Thalidomide was one of the first oral antiangiogenic agents evaluated in patients with recurrent malignant gliomas. It has been demonstrated in murine models that thalidomide reduces the expression of potent angiogenic factors, such as bFGF, VEGF, and tumor necrosis factor-α (TNF-α) (5–8). Phase II trials with thalidomide in patients with recurrent gliomas

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produced modest responses (9), and the combination of thalidomide and chemotherapy seemed to be more active than either agent alone (10). However, thalidomide has shown only limited activity in newly diagnosed glioblastomas (11), leading to the search for similar but more effective agents.

Lenalidomide [3-(4′aminoisoindoline-1′-one)-1-piperidine-2, 6-dione] is an analogue of thalidomide with pharmacologic and biologic properties similar to thalidomide but significantly increased potency and fewer nonhematologic side effects, such as sedation and constipation (12). Lenalidomide has antiangiogenic activity through the inhibition of bFGF-induced, VEGF-induced, and TNF- α-induced endothelial cell migration (13). In addition, lenalidomide stimulates T cell proliferation and the production of interleukin (IL)-2, IL-10, and IFN-γ; inhibits IL-1-β and IL-6; and modulates IL-12 production (14). Significant activity was demonstrated in patients with myelodysplastic syndromes with a 5q deletion and in patients with multiple myeloma (15–18).

There is increasing interest in the use of antiangiogenic agents with radiotherapy. A Phase I trial was initiated in 2002 at the National Cancer Institute to investigate the toxicity of lenalidomide in treatment of recurrent gliomas (19). Preliminary results on the first 18 patients found lenalidomide to be well tolerated, with only one drug-related toxicity greater than Grade 1 (Grade 2 myelosuppression in a patient with previous bone marrow transplantation). One patient with rapidly progressive spinal hemangioblastomas and 2 patients with rapidly progressive glioblastoma experienced disease stabilization for 6, 5, and 7 months, respectively.

On the basis of these encouraging preliminary results, coupled with the improved tolerability of lenalidomide, an open-label, Phase I, multicenter clinical pilot trial was conducted to determine the efficacy and toxicity of lenalidomide in combination with radiotherapy in patients with newly diagnosed glioblastomas. Antiangiogenic therapies and radiation both target the tumor endothelium. In addition, antiangiogenic therapies may potentially increase tumor oxygenation through normalization of tumor vasculature, potentially increasing the sensitivity of tumor cells to radiation (9, 20–23). There is evidence that thalidomide may change the tumor microenvironment, increasing tumor oxygen partial pressure and radiosensitizing the tumor (24).

Hematologic toxicity was dose limiting in all prior clinical trials evaluating single-agent lenalidomide for hematologic malignancies (15, 16). Because of concerns about additive hematologic toxicity when used in combination with temozolomide, we decided to perform a pilot safety trial of single-agent lenalidomide in combination with radiotherapy and to defer combination therapy until after single-agent safety had been demonstrated.

PATIENTS AND METHODS

Patients

Twenty-three patients were enrolled between October 2005 and December 2006. Eligibility criteria included informed consent, age 18 years or older, histologically confirmed newly diagnosed supratentorial glioblastoma, and a Karnofsky performance status of $\geq$60. In addition, patients had to have adequate organ and bone marrow function. Patients were excluded if they had received prior cranial radiotherapy, Gliadel Wafers (MGI Pharma, Bloomington, MN), or had recent thromboembolic disease, ongoing cardiac or pulmonary dysfunction, and active infection, including human immunodeficiency virus. Because thalidomide is teratogenic, and lenalidomide is an analogue of thalidomide, women of childbearing potential and men had to agree to use adequate contraception before study entry and for the duration of study participation. The study was approved by the institutional review boards of the Dana Farber/Harvard Cancer Center and the University of Virginia Medical Center.

Pretreatment evaluation

Baseline evaluations included a medical history and complete physical and neurologic examinations, contrast-enhanced MRI of the brain, a complete blood count with differential, coagulation studies, biochemical profile (including thyroid-stimulating hormone, T3, T4), anticonvulsant drug levels, 12-lead electrocardiogram, chest X-ray, urinalysis, and a serum or urine pregnancy test.

Treatment and follow-up studies

Lenalidomide capsules were provided by Celgene (Warren, NJ). Treatment with lenalidomide was begun 4–7 days before the start of radiotherapy and continued thereafter in 4-week cycles. Lenalidomide was administered orally as a single daily dose for 3 weeks followed by a 1-week rest, constituting 1 cycle. The starting dose of 20 mg/m^2/d was based on the experience in patients in the National Cancer Institute Phase I trial of lenalidomide in recurrent malignant gliomas (19). In this trial, patients were treated with doses up to 20 mg/m^2/d orally once daily for 3 weeks followed by a 1-week rest (4-week cycle) without developing dose-limiting toxicity. Because data from other trials suggested that doses >40 mg/d were associated with neutropenia, the maximum total daily dose was predetermined to be 40 mg. Lenalidomide doses were rounded to the nearest 5 mg. To reduce the potential for venous thromboembolic complications, patients were given aspirin (325 mg/d) because this was shown to reduce thrombotic complications in a study of lenalidomide in patients with multiple myeloma (15).

Dose-limiting toxicity (DLT) was defined as Grade 4 hematologic toxicities, with the exception of Grade 3 thrombocytopenia and Grade 3 or higher nonhematologic toxicities occurring within the first 12 weeks of therapy. A patient's first episode of venous thromboembolic disease was not considered to be a DLT because patients with glioblastoma have a significantly increased baseline risk of developing venous thromboembolic disease (25). The Common Toxicity Criteria (version 3.0) of the National Cancer Institute were used for toxicity grading.

Treatment continued until unacceptable adverse events or documented disease progression occurred. Patients were followed until death. Patients underwent imaging with an enhanced brain CT or MRI scan 4 weeks after completion of RT and every 8 weeks thereafter. Thyroid function tests were performed every 3 months.

All patients underwent a planning MRI scan. Simulation was performed using a clinical CT simulator. Radiotherapy began within 11 days of registration and within 35 days of the surgical procedure and was administered in 200-cGy/d fractions delivered 5 days per week to a total dose of 6000 cGy. A total of approximately 4600 cGy was to be delivered to the radiographic tumor volume, consisting of the T2-hyperintense signal plus a 2-cm margin, using three-dimensional conformal radiotherapy. An