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Research Letter

A phase 2 study of radiosurgery and temozolomide for patients with 1 to 4 brain metastases

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Abstract

Purpose: To determine if temozolomide reduces the risk of distant brain failure (DBF, metachronous brain metastases) in patients with 1 to 4 brain metastases treated with radiosurgery without whole-brain radiation therapy (WBRT).

Methods and materials: Twenty-five patients with newly diagnosed brain metastases were enrolled in a single institution phase 2 trial of radiosurgery (15-24 Gy) and adjuvant temozolomide. Temozolomide was continued for a total of 12 cycles unless the patient developed DBF, unacceptable toxicity, or systemic progression requiring other therapy.

Results: Twenty-five patients were enrolled between 2002 and 2005; 3 were not evaluable for determining DBF. Of the remaining 22 patients, tumor types included non-small cell lung cancer (n = 8), melanoma (n = 7), and other (n = 7). Extracranial disease was present in 10 (45%) patients. The median number of tumors at the time of radiosurgery was 3 (range, 1-6). The median overall survival was 31 weeks. The median radiographic follow-up for patients who did not develop DBF was 33 weeks. Six patients developed DBF. The 1-year actuarial risk of DBF was 37%.

Conclusions: In this study, there was a relatively low risk of distant brain failure observed in the nonmelanoma subgroup receiving temozolamide. However, patient selection factors rather than chemotherapy treatment efficacy are more likely the reason for the relatively low risk of distant brain failure observed in this study. Future trial design should account for these risk factors.

Conflicts of interest: None.

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Introduction

Brain metastases are generally managed with various combinations of surgery, radiosurgery (single fraction), and whole-brain radiation therapy (WBRT). Randomized trials have demonstrated an improved overall survival with the addition of either surgery or radiosurgery to WBRT for patients with single brain metastases[1,2] Although WBRT will reduce the risk of new brain metastases in areas distant in the brain (metachronous brain metastases) after either surgery or radiosurgery, overall survival is not improved with adjuvant WBRT.[1,3] Although controversial, WBRT has been implicated in neurocognitive toxicity and there has been clinical interest in radiosurgery alone with deferral of WBRT until progression.[1,3]

Temozolomide (Temodar, TMZ) is an oral imidazotetrazine derivative and cytotoxic alkylating agent. TMZ was developed as a potential alternative to dacarbazine in view of its demonstrated antitumor activity and better toxicity profile in preclinical testing. The efficacy of TMZ in the treatment of newly diagnosed and relapsed primary malignant brain tumors is now well established. Other studies have demonstrated activity of TMZ in the treatment of metastatic brain tumors. Abrey et al evaluated response to temozolomide in 26 patients with recurrent brain metastases. Eleven of the 26 (42%) patients had either stable disease or partial response by magnetic resonance imaging (MRI).[4] Another phase 2 trial using TMZ 150 mg/m^2 on days 1 through 5 every 28 days found either partial response or stable disease in 5/28 heavily pretreated patients with brain metastases. Antonadou et al[5] performed a small, randomized phase 2 study comparing TMZ 75 mg/m^2 during fractionated WBRT and then 200 mg/m^2 for 5 days beginning 1 month following radiation therapy. TMZ was continued for 6 months. Although only 28 patients were enrolled into this study, there was a statistically significant increase in the complete response rate with the addition of TMZ to WBRT (7/15 vs 2/13, $P = .038$). Other studies suggest that regimens containing TMZ may decrease the incidence of new brain metastases in patients with melanoma compared with regimens containing dacarbazine. Paul et al from the United Kingdom performed a retrospective case control study of patients enrolled in 3 consecutive phase 2 trials evaluating various systemic therapy regimens for stage IV melanoma that had not metastasized to the central nervous system (CNS). Only 2/19 patients receiving TMZ failed in the CNS compared with 8/21 treated with regimens containing dacarbazine. In this report, TMZ chemotherapy reduced the incidence of CNS recurrences ($P = .0167$).[6] Taken together, these early-phase studies that were done by Mikkelsen suggest that TMZ may decrease CNS progression in patients with brain metastases.[7]

In this trial, we hypothesized that systemically administered TMZ could decrease the risk of progression of microscopic to macroscopic disease in the CNS while radiosurgery would control the existing macroscopic tumor. This approach might allow for the initial deferral of WBRT in selected patients.

Because this clinical trial was designed, risk factors for distant brain failure (DBF, metachronous brain tumors) have been identified. A retrospective analysis of 100 patients by Sawrie et al identified number of brain metastases (>3), melanoma histological characteristics, and active extracranial disease as significant independent predictors of DBF.[8] The same study stratified patients without these risk factors into a low-risk group (with 1 year actuarial freedom from DBF of 83%) that can benefit only from stereotactic radiosurgery alone, while making additional stereotactic radiosurgery or WBRT a salvage therapy in case of disease progression. However, patients with the risk factors described in this study were stratified into a high-risk group (with a 1-year actuarial freedom from DBF of 26%), and were better candidates for WBRT as part of their initial treatment. Taken together, the primary endpoint of this clinical trial is the rate of DBF (metachronous brain tumors) to emphasize the role of our approach as an alternative technique to WBRT in controlling DBF.

Methods and materials

After obtaining approval from the University of Alabama at Birmingham Institutional Review Board, 25 patients with newly diagnosed brain metastases were enrolled in a single-institution phase 2 trial of radiosurgery (15-24 Gy) and adjuvant TMZ. Eligible patients included those 18 years of age or older with 1 to 4 brain metastases seen on postcontrast T1 MRI. Patients with additional metastases seen on the day of radiosurgery MRI scans were allowed to stay in the trial if all lesions could be treated with radiosurgery. Eastern Cooperative Oncology Group performance status of 0 to 1 was required for those who had not had prior chemotherapy and 0 to 2 for those who had received prior cytotoxic chemotherapy. A life expectancy of at least 12 weeks was required. Hematologic parameters included absolute neutrophil count $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9 g/dL, blood urea nitrogen/creatinine $\leq$1.5X upper limit of normal (ULN), serum glutamic pyruvic transaminase/serum glutamic oxaloacetic transaminase/alkaline phosphatase $\leq$2x ULN if documented liver metastases, and serum glutamic pyruvic transaminase/serum glutamic oxaloacetic transaminase/alkaline phosphatase $\leq$5x ULN if no documented liver metastases.

Radiosurgery was administered with either a model U or model C Gamma Knife (Leksell). Dose prescription was generally according to Radiation Therapy Oncology Group 90-05 guideline[9] (15-24 Gy to the 50% isodose line), but the treating radiation oncologist was allowed to