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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

lower the dose if normal tissue such as brain stem or optic apparatus was considered dose-limiting. Most patients received TMZ with radiosurgery and were administered 150 to 200 mg/m^2 by mouth each day x 5 days in 28-day cycles. TMZ was continued for a total of 12 cycles unless the patient developed DBF, unacceptable toxicity, or systemic progression requiring other therapy.

Because of the heterogeneous patient population, a matched historical control group not treated with adjuvant temozolomide or WBRT was identified matching enrolled patients ~2:1 for number of tumors, histology (melanoma vs other), and presence of extracranial disease. The risk of DBF in clinical trial patients was retrospectively compared with the match control group.

The primary study endpoint was (metachronous brain metastases).[8,10] Secondary endpoints included toxicity, overall survival, and quality of life as measured by Functional Assessment of Cancer Therapy-Brain. Clinical, MRI scans, and quality of life assessments were performed after radiosurgery at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months.

For purposes of sample size calculation, the baseline risk of DBF in patients with 1 to 4 brain metastases was estimated to be approximately 60% at 1 year as calculated by the Kaplan-Meier method.[11] Enrollment of 28 patients would have an 80% power to detect a reduction in the 1-year risk of DBF from 60% to 30%. Because Sawrie et al identified DBF risk factors after this trial activation and the trial design did not include this heterogeneous risk of DBF, these factors have significant implications in the interpretation of the results of the trial. To account for variable risk of DBF in the clinical trial patients, a post hoc matched case control comparison from the University of Alabama at Birmingham Gamma Knife database was done to account for the risk factors that have been recently identified. Clinical trial cases were matched to 2 controls matching the number of tumors, histology (melanoma vs other), and presence of extracranial metastatic tumor. The log-rank test was used to compare the risk of DBF in the clinical trial cohort and a match case control cohort. Independent factors of DBF were calculation using a Cox proportional hazards model.

Results

Twenty-five patients were enrolled between 2002 and 2005; 3 were not evaluable for determining DBF. Patient characteristics are shown in Table 1. 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 radiographic follow-up for patients that did not develop DBF was 33 weeks.

Table 1 Patient characteristics

Patient feature	No.	%
Histology/tumor type		
NSCLC	9	39
Melanoma	7	30
Breast	6	26
Colon	1	4
Extracranial metastases	11	48
Number of CNS metastases at time of radiosurgery		
Median	3 (range, 1-6)	NA
Solitary tumor	6	26
Sex		
Male	10	43
Female	13	57
Age		
Mean	56 y	NA
Range	23-80	
RPA class		
I	8	32
II	17	68

CNS, central nervous system; NA, not available; NSCLC, non-small cell lung cancer; RPA, recursive partitioning analysis.

The total number of TMZ cycles by patient is shown in Fig 1 (mean, 3.6; range, 1-12). Most patients stopped TMZ early because of DBF or extracranial progression requiring other chemotherapy. One patient discontinued TMZ because of fatigue without disease progression. Fifteen serious adverse events occurred in the overall group of 25 patients (Table 2). None of these was judged to be clearly related to TMZ.

Six patients of the 22 imaging evaluable patients developed DBF. The 1-year actuarial risk of DBF was 37% (Fig 2A). Patients with melanoma had a higher risk of DBF than other patients ($P < .001$, log-rank). Only 1/15 patients without melanoma versus 5/7 patients with melanoma developed DBF (Fig 2B). The clinical trial group receiving adjuvant temozolomide had a trend for a

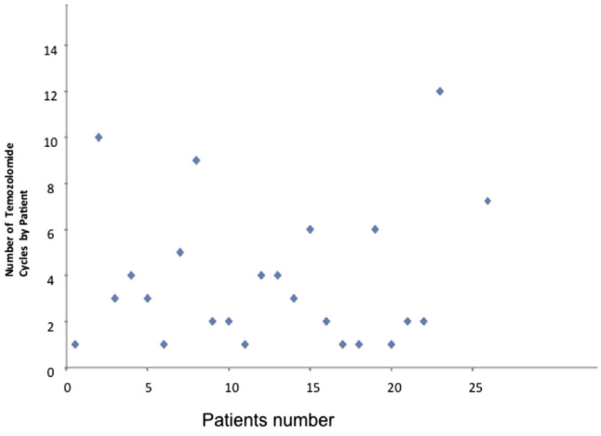

Figure 1 Number of TMZ cycles by patients.

Table 2 Number of temozolomide cycles per patient

System	Event	Days elapsed since radiosurgery	Relationship to study drug
Pulmonary	Hospitalization for ruptured diverticula and pneumonia	118	Unrelated
	Death during hospitalization from pneumonia and lung cancer	135	Unrelated
Central nervous system	Hospitalization for seizures (1 day)	105	Unrelated
	Hospitalization for craniotomy for resection of necrotic tissue	146	Unrelated
	Hospitalization for altered mental status	53	Unlikely
	Hospitalization for dizziness	17	Unrelated
G.I.T	Hospitalization for workup for new pancreatic lesion, nausea, and vomiting	64	Unrelated
	Hospitalization for heme + stool from colon cancer	10	Unrelated
Cardiovascular	Hospitalization for DVT	18	Unrelated
	Hospitalization for DVT	30	Unrelated
	Hospitalization to rule out DVT	50	Unrelated
	Hospitalization for chest pain and altered mental status	164	Unlikely
	Death at home of apparent heart attack (no autopsy)	71	Unknown
Miscellaneous	Hospitalization for broken hip	37	Unrelated
	Hospitalization for surgery	173	Unrelated

DVT, deep vein thrombosis.

lower risk of DBF than the matched controls (Fig 2, $P = .12$, log-rank test). When this relationship was further evaluated in a Cox proportional hazards model, the adjuvant use of temozolomide (clinical trial group) was not an independent risk factor for DBF. The risk stratification scheme described by Sawrie et al[8] was an independent predictor of DBF (data not shown). In the analysis of serial Functional Assessment of Cancer Therapy-Brain data in the 6 patients that developed DBF, the occurrence of DBF was not associated with a reduction in quality of life. Of these 6 patients, only 1 experienced vision and speech difficulties as well as numbness in the right hand and in the tongue at time of distant brain failure and responded well to corticosteroids.

As shown in Fig 3, the median overall survival was 31 weeks.

Discussion

Although combinations of WBRT and radiosurgery or surgery produce the highest rates of intracranial tumor control over monotherapy, there remains some controversy in how to best use WBRT in patients with brain metastases because of the presumed risk of late toxicity. A phase 3 randomized trial from Japan did not find a reduction in overall survival in patients treated with radiosurgery alone, but the risk of tumor progression at

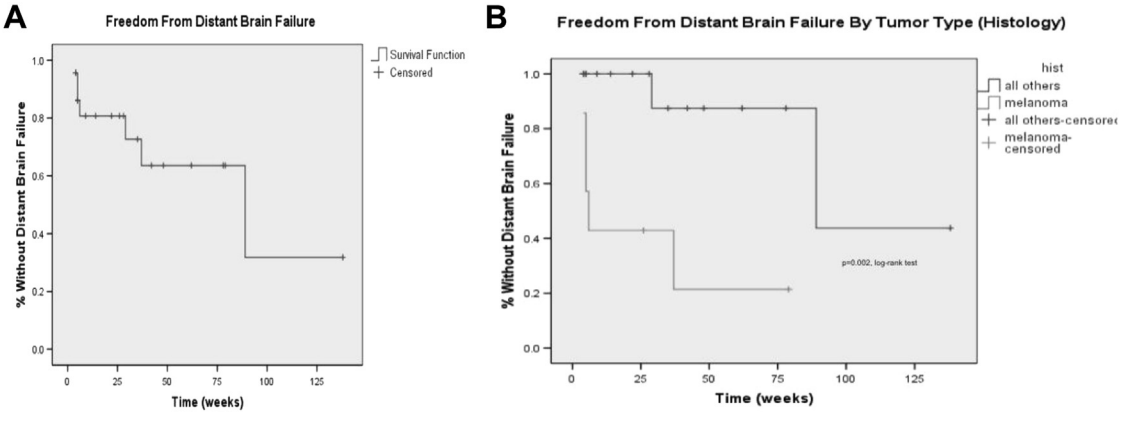

Figure 2 (A) Freedom from distant brain failure. (B) Freedom from distant brain failure by tumor type.

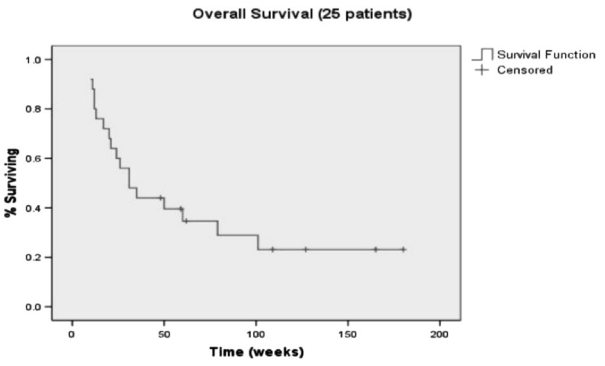

Figure 3 Overall survival.

the local tumor site and elsewhere in the brain (DBF) was greater in the patients who did not received WBRT. This lower rate of CNS control was not associated with a reduction in neurologic functional status or Mini-Mental Status Examination scores. Despite this finding, a lower dose of WBRT used as prophylactic cranial radiation was associated with toxicity in patients with small cell lung cancer. Other retrospective studies have suggested that CNS progression after radiosurgery alone is associated with symptoms in 71% of patients and neurologic deficits in 59%.[12-14] The risk of symptoms and deficits in quality of life from the late toxicity of WBRT versus those from brain progression has not been fully explored in radiosurgery randomized trials that include comprehensive neurocognitive and quality of life assessments. Such studies are ongoing in the United States (NCCTG/ACOSOG-N0574) and in Europe (European Organization for Research and Treatment of Cancer). However, such evidence does exist that better CNS control is associated with better survival and neurocognitive outcomes. In a randomized trial of WBRT with or without motexafin gadolinium, tumor regression was associated with improved survival and better fine motor skills and executive function.[15-17] Because of this observation, a strategy of treating unselected patients with radiosurgery alone may be less desirable; thus, adding a drug to radiosurgery may be an attractive clinical trial strategy. In this phase 2 clinical trial, we hypothesized that an oral chemotherapy, TMZ, may stabilize microscopic tumor in the brain and delay the development of new gross brain metastases. We have provided here a proof of the principle that WBRT can be omitted and localized radiosurgery can be used solely with systemic available agents that can cross the blood–brain barrier, paving a path for other investigator to use same principle. We aimed to increase the number of patients but because the availability of many new drugs for melanoma and non-small cell lung cancer we unfortunately could not recruit more. Despite there being a small number of patients, our results have met the aim of our approach.

This approach would potentially treat microscopic disease present at the time of radiosurgery and prevent new cells from seeding the CNS at a later date. If successful, it would allow for deferral of WBRT or additional radiosurgery.

The combination of radiosurgery followed by TMZ was well-tolerated without high grade toxicity unique to the combination treatment. Because TMZ was discontinued for any systemic progression requiring other chemotherapy, most patients received only a few cycles of TMZ. Among the 22 patients with evaluable MRI scan follow-up, only 6 (27% crude) patients developed DBF with an estimated 1-year risk of 37%. Although TMZ is often used as a frontline therapy of metastatic melanoma, these patients had a higher risk of DBF than the non-melanoma subgroup, as was found in a previous retrospective study. The melanoma patients were randomly selected without any censoring, depending on the burden of extracranial disease activity; therefore, additional strategies will be needed in melanoma patients. Only 1 of 15 non-melanoma patients developed DBF, but the use of adjuvant TMZ in this group was not an independent predictor of DBF. However, we do not know if this finding was attributed to TMZ effectiveness in controlling the disease and preventing DBF or from the non-fulminant biological property of melanoma in these patients.

Although combining radiosurgery with chemotherapy is an attractive clinical trial strategy to improve CNS control, the investigators have learned several important factors regarding the design and logistics of this type of study. First, new agents must be integrated into the standard chemotherapy regimens that are used to treat extracranial disease. In this trial, accrual was slower than expected because many patients required chemotherapy other than study drug TMZ. Phase 1 clinical trials of carboplatin and paclitaxel plus TMZ have been performed, and this might have been a better choice for non-small cell lung cancer patients if they had active extracranial disease.[17] Similar studies have been described for erlotinib plus TMZ (clinicaltrials.gov: NCT00249964, NCT00268684). Second, enrichment of the study population should be considered through limiting enrollment to a given tumor type or through molecular profiling. Finally, the risk of DBF varies greatly by number of tumors, histology, and presence of extracranial tumor. These factors need to be included in the design of future studies.

In conclusion, although the use adjuvant use of TMZ after radiosurgery was associated with a lower than expected risk of DBF, especially in non-melanoma patients. This was likely the result of patient selection factors in this study rather than TMZ efficacy.

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