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Brain Metastases From Melanoma:

Is There a Role for Concurrent Temozolomide in Addition to Whole Brain Radiation Therapy?

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Abstract

Objectives—This study was performed to evaluate the addition of temozolomide (TMZ) to whole brain radiotherapy (WBRT) for brain metastases from melanoma.

Methods—Seven patients with brain metastases from melanoma were treated on a North Central Cancer Treatment Group (NCCTG) trial (N0274) of TMZ plus WBRT. TMZ was given orally in doses of 200 mg/m² for 5 days every 4 weeks for up to 8 cycles. WBRT was started on the first day of TMZ and included the delivery of 3750 cGy in 15 fractions. In addition, separately analyzed was a cohort of 53 patients treated at the Mayo Clinic who received WBRT alone (39 patients) or WBRT plus TMZ (14 patients).

Results—The median survival of the 7 patients treated on N0274 was 3.6 months with 2 of 7 (29%) failing in brain and 5 of 7 (71%) failing elsewhere. For the other cohort of 53 patients, the median survival was 3.8 months with WBRT alone compared 4.3 months for WBRT plus TMZ ($P = 0.5$).

Conclusions—Patients did not appear to benefit from the addition of TMZ to WBRT for the treatment of their brain metastases. Further improvements in outcome will require research to discover more effective systemic therapy and RT techniques.

Keywords

brain metastases; melanoma; whole brain radiotherapy; temozolomide; combined modality therapy

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Melanoma has increased in incidence and was estimated to have caused 8420 deaths in the United States during 2008.¹ Of the patients who die of this disease, 50% to 75% will develop brain metastases.² Additionally, approximately one-half of patients with brain metastases will die as a direct result of these lesions.

Survival from brain metastases is generally measured in months and appears related to various prognostic factors including patient age, performance status, and the presence of extracranial metastatic disease.^{3,4} There has been little progress in developing effective treatment for patients with multiple brain metastases because of melanoma. The most commonly administered treatment is whole brain radiotherapy which has been associated with improvement in neurologic signs and symptoms. However, the median survival of patients with brain metastases because of melanoma treated with whole brain radiotherapy alone is approximately 3 months.⁵ In an attempt to improve the results of therapy for patients, we initiated a trial (N0274) through the auspices of the North Central Cancer Treatment Group. This trial included the administration of concurrent temozolomide (TMZ) with whole brain radiotherapy (WBRT) for patients with brain metastases because of melanoma. TMZ demonstrates comparable activity to the current standard treatment, dacarbazine, with the additional benefit of being a convenient oral treatment that penetrates the blood-brain barrier.⁶ This combination was thought to have the potential to improve the survival of patients with brain metastases from melanoma.

MATERIALS AND METHODS

Trial N0274 enrolled patients at least 18 years of age with histologically confirmed stage IV melanoma. Patients were required to have measurable disease by RECIST criteria, unresectable disease involving the CNS, adequate blood counts and chemistries (CBC, Creatinine, Liver function studies), Karnofsky Performance Score of 70, Recursive Partitioning Analysis class I or II, and the ability to provide consent. Exclusion criteria included: prior TMZ, meningeal carcinomatosis, uncontrolled or current infection, or other prior therapy during the past 4 to 6 weeks. Women who were pregnant or breast-feeding were not eligible for this study.

This study was approved by the participating institutions' IRB and each patient provided written consent. Prior to treatment, all patients had magnetic resonance imaging (MRI) or computed tomography (CT scans) of the head, chest radiographs, blood work (CBC, liver function studies, and serum creatinine), history, and physical examinations.

Treatment was to commence within 1 week of registration. TMZ was given orally in daily doses of 200 mg/m² for 5 days every 4 weeks for up to 8 cycles. The first cycle of TMZ was given within 1 hour prior to WBRT. WBRT was started on the first day of TMZ. WBRT included the delivery 3750 cGy in 15 fractions with mega-voltage x-rays utilizing opposed lateral fields and custom blocking to protect the facial structures.

Patients were evaluated every 4 weeks during treatment and, then, every 8 weeks following completion of TMZ until progression. This included history and physical examination, tumor evaluation (CT or MRI scan), monitoring of progression in extra-CNS sites, review of

steroid use, blood chemistries, and toxicity assessment using the NCI-CAE criteria (see Table 1 for sites of initial metastases in the N0274 patients).

The original primary end point of this trial was tumor response proportion defined as the number of eligible patients whose disease met the RECIST criteria for complete response (CR) or partial response (PR) on 2 consecutive evaluations divided by the total number of eligible patients who began treatment. A 2-stage Simon phase II clinical trial design with the significance level of 0.10 was chosen so that the power to detect that the true response rate is greater than 5% when it is at least 20% would be 90%. Specifically, 12 eligible patients were to be enrolled on the first stage. If none of these patients had a confirmed CR or PR without excessive toxicity, the regimen would have been considered ineffective and the study closed. Otherwise, an additional 25 eligible patients were to be enrolled. If at least 4 of the 37 eligible patients enrolled had a confirmed CR or PR without excessive toxicity, the regimen would be considered for further testing in this patient population.

The distribution of progression-free survival and overall survival times were estimated using the Kaplan-Meier method. Patients were followed until death.

We also retrospectively evaluated a cohort of 53 patients with brain metastases from melanoma treated at Mayo Clinic with either WBRT alone or in combination with concurrent TMZ. This was done to evaluate a larger cohort of patients and compare the results of WBRT alone to WBRT and TMZ. Patients were included in this cohort if they received WBRT for the diagnosis of brain metastases because of melanoma regardless of the number of brain metastases, performance status, or presence of extracranial metastases. This cohort included 40 males and 13 females with ages ranging from 30 to 84 years (median: 58 years). The number of brain metastases ranged from 1 to >10 (median: 4). Of the 53 patients, 46 (87%) had no extracranial metastases at the time of therapy. Refer Table 2 for characteristics of the 53 Mayo Clinic patients.

All patients provided informed consent prior to therapy. WBRT included the delivery of 20 Gy in 5 fractions to 45 Gy in 18 fractions (median: 30 Gy in 10 fractions). TMZ was given concurrently with WBRT in 14 patients at the dose of 200 mg/m² orally for 5 days every 4 weeks for up to 8 cycles. Survival and failure rates were calculated using the Kaplan-Meier Method with differences between groups determined using the log-rank test.

RESULTS

All of the 7 patients treated on N0274 had extracranial metastases and received WBRT and TMZ. Of these 7 patients, 3 (43%) had grade 3 or greater (3+) toxicity related to therapy. No patients died of complications related to therapy. The median survival was 3.6 months with a range of 1 to 7 months. Disease progression occurred at a median of 1 month with a range of 0.3 to 4.7 months. The toxicity and initial patterns of failure are described for each patient on Table 1. Of the 7 patients, 2 (29%) were found to have radiographically or clinical evidence of brain progression. The study was modified after the first 7 patients were enrolled because of rapid progression of extracranial disease which occurred in 5 (71%) patients. The eligibility criteria were changed to include patients with brain metastases because of

melanoma but no evidence of metastases elsewhere. However, there was no further accrual because of a lack of eligible patients and the trial was closed.

Because the N0274 cohort was so small, firm conclusions could not be made and we subsequently retrospectively reviewed a larger cohort of 53 patients treated at Mayo Clinic. The median survival of this cohort of 53 patients was 4 months. The median survival of the 14 patients who received concurrent TMZ and WBRT was 4.3 months compared with 3.8 months for the 39 patients who received WBRT alone ($P = 0.5$, Fig. 1). The median time to brain failure in the 14 patients who received concurrent TMZ and WBRT was 3 months compared with 5 months for the 39 patients who received WBRT alone ($P = 0.1$). The median time to nonbrain failure in the 14 patients who received concurrent TMZ and WBRT was 3 months compared with 12 months for the 39 patients who received WBRT alone ($P = 0.4$). Toxicity (grade 1 or greater) was noted in 9 of the 14 (64%) who received WBRT + TMZ compared with 1 of 39 (3%) who received WBRT alone ($P < 0.0001$). These included dermatitis, fatigue, hair loss, anorexia, and hematologic toxicity. None were noted to be severe (grade 3 or greater). Quality of life was not assessed.

We examined the following potential prognostic factors in the 53 Mayo patients: gender, age, performance status, presence of non-CNS metastases, number of sites outside the brain, number of brain metastases, size of the largest brain metastasis, total RT dose, and RT dose-fractionation. None of these factors was significantly associated with patient survival.

DISCUSSION

Metastatic melanoma has been a very challenging disease with few major advances occurring within the past several years. Additionally, distressing is the fact that the incidence of this disease has increased over time. Brain metastases are especially challenging. Melanoma is generally described being “radio-resistant.” This should not be misconstrued as radio-untreatable or radio-incurable. Radiobiologic laboratory data has revealed that the majority of melanoma cell lines tested were as radiosensitive as other cancer cell types.⁷ Additionally, radiation therapy has been used successfully as an adjuvant therapy after resection, for primary therapy for ocular or other melanomas in poor surgical candidates, and for the palliation of metastases.^{8–11}

Whereas progress in the treatment of brain metastases has been slow, there have been some breakthroughs. Of 3 phase III trials, 2 have shown that resection followed by WBRT yielded better survival than WBRT alone for patients with solitary brain metastases.^{12–14} Additionally, radiosurgery plus WBRT resulted in better survival than WBRT for those with solitary lesions.¹⁵ Thus far, there are no studies which clearly show a significant survival benefit for the addition of systemic therapy for brain metastases. Resection or radiosurgery are viable treatments for solitary brain metastases and radiosurgery is often used for patients with just a few brain metastases. However, for the majority of patients who present with multiple brain metastases from melanoma, WBRT remains the most commonly administered therapy. WBRT alone results in median survival ranging from 3 to 6 months which is similar for patients with brain metastases from melanoma or other primary tumors.¹⁶ This is also very similar to the survival of patients receiving palliative radiotherapy for symptomatic

metastases from melanoma at non-CNS sites.¹⁰ The median survival of our previously evaluated cohort of patients, treated with palliative RT for non-CNS metastases from melanoma was 3.7 months after RT. There was a relationship between patient survival and both overall dose and biologically effective dose ($BED = nd(1 + d/(\alpha/\beta))$) in these patients with non-CNS metastases. The median survival was 8 months for patients who received either an overall dose of >30 Gy or a BED of >39.0 Gy₁₀ compared with 2 months for those who received lesser doses ($P < 0.0001$). Rades et al. reported a series of 51 patients with brain metastases from melanoma. At 6 months, the survival rates were 27% after 10×3 Gy and 50% after higher doses ($P = 0.009$).¹⁷ Thus, this data suggests that there may also be room for improvement in patients with brain metastases from melanoma with a modest increase in the overall dose administered.

Other investigators have used TMZ in combination with RT. Hoffman et al treated 35 patients with unresectable brain metastases from melanoma. The median survival time was 5 months for patients who received TMZ alone, 9 months for patients with concurrent TMZ plus stereotactic radiotherapy, and 7 months with concurrent TMZ plus whole brain radiotherapy.¹⁸ Conill et al reported 4 month median survival for patients with brain metastases from melanoma who received either 30 Gy in 10 fractions of WBRT or 20 Gy in 5 fractions of WBRT in conjunction with TMZ.¹⁹

Margolin et al also reported on WBRT (30 Gy in 10) plus TMZ (75 mg/m²/d) for brain metastases because of melanoma.¹⁶ The median survival was 6 months and the investigators concluded that the combination had limited antitumor activity. Verger performed a randomized trial of TMZ (75 mg/m²/d) plus WBRT (30 Gy in 10 fractions) versus WBRT alone in patients with brain metastases from multiple primary tumor types. The overall survival was similar in both arms.²⁰ Adkins et al employed WBRT (30 Gy in 10 fractions) with both TMZ (75 mg/m²/d), and thalidomide (100 mg/d).²¹ The median overall survival was 4 months which is similar to the results of the present study.

Agarwala et al administered TMZ alone for brain metastases. The goal was to assess safety and efficacy of TMZ in patients with brain metastases from melanoma who did not require immediate radiotherapy. The median survival was 3.5 months for patients without previous therapy and 2.0 months for those who received previous therapy.²²

The combination of TMZ and WBRT is frequently employed in patients with brain metastases from melanoma. Unfortunately, the finding that TMZ does not appear to significantly impact on survival in patients with brain metastases should not be entirely unexpected. To date, no systemic therapy program (including TMZ) has significantly improved the survival of patients with metastatic melanoma. One promising recent study was a phase II North Central Cancer Treatment Group Trial reported by Perez et al. This study treated patients with non-CNS metastatic melanoma with carboplatin, paclitaxel, and bevacizumab which resulted in a relatively favorable median time to progression of 163 days (5.5 months).²³

Whereas progress has been modest, it appears that resection and specialized RT boost techniques have been associated with improved survival in select patients with brain

metastases. There may be room for further improvements by increasing the biologically effective dose of radiotherapy as was seen in patients with metastases from melanoma treated with palliative radiotherapy and those with solitary brain metastases of various types treated with radiosurgery.^{10,15,17} Although systemic therapy can result in tumor response, there have not been major gains reported in patient survival.

Based on our experience and that of the literature, there appears to be no clear disease control or survival benefit conferred on patients with brain metastases from melanoma with the addition of TMZ to WBRT. Fortunately, there are newer targeted agents that are just starting to yield better results with metastatic melanoma.²³ Future improvements in outcome will require further research to discover more effective systemic therapy and RT techniques.

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FIGURE 1.
Patient survival.

TABLE 1

Summary of Outcome for Patients on N0274

Patient	Sites of Metastatic Disease	Sites of Progression	Total Doses of TMZ Administered	Completed RT	Grade 2 + Toxicities Reported*	Time to Progression (d)	Survival Time (d)
1	Lung and brain	Clinical deterioration vs. CNS progression	5	Yes	Grade 4: leukocytopenia, neutropenia, and thrombocytopenia Grade 3: anorexia, confusion, and fatigue Grade 2: weight loss	41	109
2	Subcutaneous tissue, nodes, lung, soft tissue, and brain	Trunk and lower extremities	5	Yes	None	30	99
3	Subcutaneous tissue, lung, and brain	Trunk, adrenal gland, subcutaneous tissue, and interabdominal nodes	8	Yes	Grade 3: RT-related pharyngeal dysphagia Grade 2: anorexia and fatigue	61	158
4	Subcutaneous tissue, lung, soft tissue, and brain	Lung and subcutaneous tissue	8	Yes	Grade 3: fatigue Grade 2: anorexia and vomiting	141	209
5	Lung, lymph nodes, and brain	Trunk	5	Yes	None	14	53
6	Lung, liver, spleen, brain	Brain	5	No	Grade 2: fatigue	14	28
7	Lung and brain	Pulmonary	5	Yes	Grade 2: insomnia and fatigue	26	218

* Attribution: possibly, probably, or definitely related to treatment.

TABLE 2

Characteristics of 53 Mayo Clinic Patients Treated With Whole Brain Radiotherapy (WBRT) or WBRT + Temozolomide (TMZ)

Characteristic	WBRT: No. Patients (% of Patients)	WBRT + TMZ: No. Patients (% of Patients)	<i>P</i>
Age >58 yr (median = 58 yr)	17/39 (44%)	12/14 (86%)	0.004
Female gender	11/39 (28%)	2/14 (14%)	0.3
ECOG PS >2	13/39 (33%)	3/14 (21%)	0.4
Non-CNS metastases present	34/39 (87%)	11/14 (79%)	0.3
>3 Brain metastases present	35/39 (90%)	14/14 (100%)	0.3

Eastern Cooperative Oncology Group Performance Score (ECOG PS).