

Randomized trial of radiotherapy versus radiotherapy plus metronidazole for the treatment metastatic cancer to brain

A Southwest Oncology Group study

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Summary

One hundred sixteen eligible patients with metastatic cancer to the brain were randomized to receive either radiotherapy 3000 rad/10 fractions (treatment 1) or the same radiotherapy plus metronidazole 6 gm/m² (treatment 2). One hundred eleven patients were either fully or partially evaluable. The response rates (CR + PR) and survival showed no significant differences between treatments. Treatment 1: CR + PR 24%, median survival 14 weeks, Treatment 2: CR + PR 27%, median survival 12 weeks. There were no differences observed in response rates based on primary tumor site, neurologic performance status, or extent of metastatic disease. Metronidazole therapy was associated with substantial nausea and vomiting but no neurotoxicity was observed. Oral metronidazole given every other day during radiation therapy provided no clinical benefit for patients with brain metastases compared to radiotherapy alone.

Introduction

Improvements in cancer therapy have resulted in longer survival in many patients with various forms of malignancy. An unfortunate consequence of this improved survival has been the observation of an increase in metastatic disease to the brain (1-3). Autopsy studies have shown that as many as 18-22% of patients dying of cancer have intracranial metastases representing over 80 000 patients per year in the USA (4-6).

Treatment of metastatic cancer to the brain presents an important palliative problem that has yet to result in substantial survival benefit to the patient (7). Several retrospective studies (8, 9, 10) and three prospective randomized trials reported by the Radiation Therapy Oncology Group (11, 12) have demonstrated the value of whole brain irradiation. There also may be some value in resecting solitary

lesions prior to irradiation (6, 13).

Even with adequate brain irradiation, 50-60% of patients with brain metastases still die from this complication (11, 12). Thus, more effective treatment is needed. Brain metastases are frequently large masses with areas of necrosis and presumably contain a large fraction of hypoxic cells which are relatively radioresistant. Electron-affinic radiosensitizers, such as metronidazole, have been shown both in vitro and in vivo to enhance radiation sensitivity of hypoxic cells relative to euoxic cells (14). In a randomized trial, radiation plus metronidazole was found to be superior to radiation alone in the treatment of glioblastoma multiforme (15). Based on that experience the Southwest Oncology Group (SWOG) conducted a controlled clinical trial evaluating the effectiveness of metronidazole as a radiosensitizer in the treatment of brain metastases.

Materials and methods

Between July 1978 and May 1982, 25 SWOG institutions entered 127 patients on study 7811. Eligibility requirements included the following: histologic proof of malignancy, clinical documentation of brain metastases by isotope or CT brain scan, neurological symptoms, no prior cranial radiation therapy, expected survival of at least 4 weeks, and informed consent in accordance with institutional policy. All patients were adults. Systemic chemotherapy with agents known to cross the blood brain barrier such as nitrosoureas, procarbazine, DTIC, or high dose methotrexate was not allowed.

Patients were stratified according to the following: site of primary cancer (breast, lung, other); concomitant chemotherapy (yes or no); neurologic status (1 & 2 vs 3 & 4); measurable or nonmeasurable intracranial disease and extent of metastases. They were randomly assigned to either radiation therapy alone treatment 1 or radiation therapy plus metronidazole, treatment 2.

Treatment

To control for the known palliative benefit of corticosteroids, all patients were given dexamethasone 10 mg/m²/day in divided doses during the course of radiotherapy. The drug was then tapered and discontinued. If it was necessary to begin steroid therapy again, it was recorded on the data sheets.

Radiation therapy

All patients were given whole brain radiation through lateral ports encompassing the entire intracranial contents with both ports treated each day. The total dose of 3000 rads calculated at the midplane along the central axis was given in 10 daily fractions using megavoltage equipment or ⁶⁰Co units.

Metronidazole

Patients assigned to metronidazole received 6 gm/m² (maximum dose 10 gm) in a single dose on

treatment days 1, 3, 5, 7 and 9. The drug was given orally 1–4 hours preceding radiation therapy and at least 2–3 hours following the last meal for more dependable absorption. Anti-emetics were given prior to the metronidazole to control nausea and vomiting.

Study parameters and criteria for response

All patients were followed weekly by history and physical examination to determine neurologic function and performance status. In addition, complete blood counts and chemistry tests including electrolytes, renal function, and liver function were monitored. All patients also had a pre- and post-radiotherapy brain isotope or CT scan. These tests were repeated every 4–8 weeks during follow-up. All patients remained on study until death and an attempt was made to determine if death was due to the brain metastases or systemic disease.

The patients were evaluated for response according to the following criteria:

Complete response: complete disappearance of intracranial disease on isotope or CT brain scan; improvement of neurologic function by at least 1 level and discontinuation of steroids.

Partial response: reduction by 50% or more of the product of perpendicular diameters of the metastatic disease measured by isotopes or CT brain scan; stable or improved neurologic function and reduced or discontinued steroids.

Stable disease: no significant change in size of brain metastases or change in neurologic function.

Progressive disease: increase in size of brain metastases and deterioration of neurologic function.

Statistical analyses

Survival curves were estimated by the Kaplan-Meier technique (16) and compared by the two-tailed Gehan's tests (17) and logrank tests (18). Response rates and patient characteristics were compared using ordinary chi square tests.

Results

One hundred twenty-seven patients were entered on this study. Of these, 116 were eligible with 111 fully or partially evaluable. The non evaluable cases included 6 with inadequate data submission; 8 who were found unacceptable violations at radiation therapy evaluation; and 2 with failure to receive metronidazole. The patient characteristics of the fully and partially evaluable patients are shown in Table 1. No evidence of statistically significant im-

balance in the assignment of patients to treatment was found.

The complete response and partial response rates were similar for both treatments (CR + PR p value = .958). There was no statistically significant association between the response rates (CR + PR) and the primary site, neurologic function, metastatic extent age or sex. Patients with breast cancer had a higher CR rate but this was not quite statistically significant (p -value = .067). These data are listed in Table 2.

Although the median duration of the responses (CR + PR) was 18 weeks for radiation plus metronidazole compared to 11 weeks for radiation alone, the overall response duration analyses showed no significant difference (Gehan p -value = .442). The four responding patients with breast cancer had a longer duration of response (30 weeks median) than those with lung cancer (10 weeks median) (Gehan p -values .063). Patients with brain metastases only had no significantly longer response durations than those with both brain and systemic metastases. There were so few patients (5) with poor neurologic function (class 3 + 4) that responded that the comparison of response duration versus neurologic function is less valid but those with severe impairment had a median response duration of only 7 weeks compared to 18 weeks for neurologic classes

Table 1. Patient characteristics.

Characteristics	Radiation (Treatment 1)	Radiation + metronidazole (Treatment 2)
Patient no.	54	57
Age < 60 years	29	39
60 or more years	25	18
Sex M/F	30/24	33/24
Primary site		
Breast	5	8
Lung	36	33
Other	13	16
Neurologic function 1-2	44	46
3-4	10	11
Metastatic extent		
Brain only	27	28
Systemic + brain	27	29

Table 2. Response rate and duration.

Characteristic	No. patients	CR/PR (%)	Total	P -value	Remission	
					Median duration (weeks)	P -value
Treatment						
Radiation	54	7 17	24	.958	11	.442
Radiation + metro.	57	9 18	27		18	
Age						
Under 60	68	10 21	31	.133	23	.047
60 or more	43	5 12	17		9	
Primary site						
Breast	13	23 8	31		30	
Lung	69	4 20	24	.886	10	.063
Other	29	10 14	24		18	
Neurologic function						
1 + 2	81	8 18	26	.857	18	.347
3 + 4	19	10 14	24		7	
Metastatic extent						
Brain only	55	5 22	27	.784	10	.710
Systemic + brain	56	11 13	24		20	

1 + 2. There was a marked difference in remission duration based on age with those under 60 years having longer response durations (Gehan p -value = .047). These data are also listed in Table 2.

The survival of patients treated with radiation alone was not significantly different from those treated with radiation plus metronidazole. These survival curves are illustrated in Fig. 1. Survival based on primary site of malignancy did show a significant difference emerging after about 13 weeks when patients with breast cancer were compared to those with lung cancer (Logrank p -value = .048). This is shown in Fig. 2. Patients with minimal neurological impairment (neurologic class 1 + 2) had some advantage in survival when compared to those with marked symptoms (neurologic class 3 + 4) but this difference was not statistically significant (Logrank p -value = .171) (Fig. 3). Regarding the relation of survival duration and extent of metastatic disease no significant difference was observed between patients with only brain metastases and those with brain plus systemic metastases (Gehan p -value = .470) as is seen in Fig. 4. Fifty patients (45%) were judged by the investigators to have died secondary to their brain metastases. Forty seven (42%) died from systemic malignancy and 14 (13%) from both or unknown reasons. Patients aged under 60 years survived significantly longer than those age 60 years or more (Gehan p -value = .037) as shown in Fig. 5.

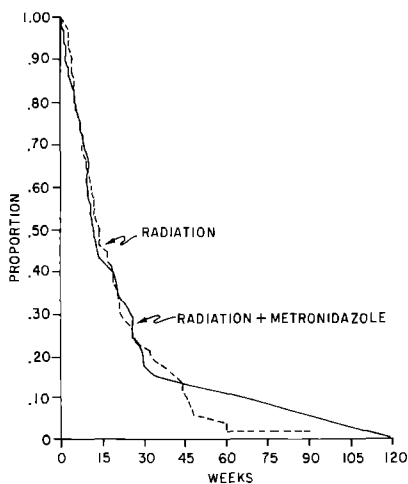


Fig. 1. Survival time for all evaluable patients. Treatment 1-radiation only, Treatment 2-radiation plus metronidazole. No significant difference is observed (P -value = .802).

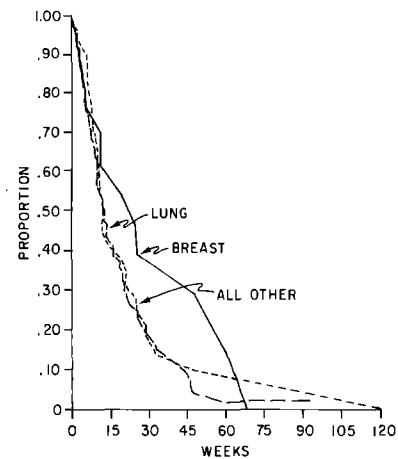


Fig. 2. Survival time based on primary site for all evaluable patients regardless of treatment. There is a significant difference based on the Logrank analysis for breast primary versus lung primary (P -value = .048).

All patients developed alopecia and some radiation scalp reaction was noted. These were not significantly worse in patients receiving metronidazole. The major toxicity observed was moderate to severe nausea and vomiting in patients receiving metronidazole. Eighty-two percent of the 57 patients evaluated on treatment 2 were recorded as completing all the prescribed metronidazole. The other ten patients completed 3 or 4 of the 5 doses. The nausea and vomiting was poorly controlled

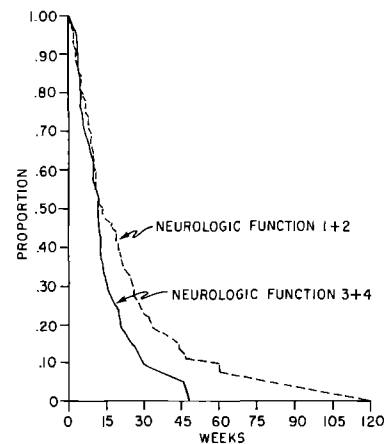


Fig. 3. Survival time for all evaluable patients based on entering neurologic function. No significant difference is observed (P -value = .171).

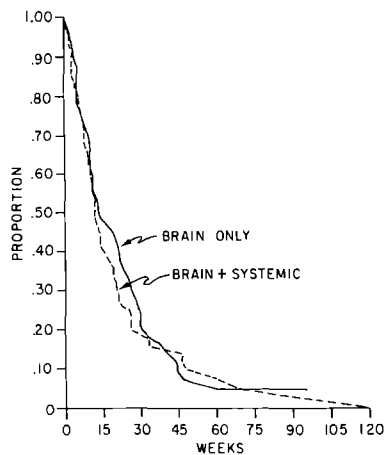


Fig. 4. Survival time for all evaluable patients based on extent of metastases. No significant difference is observed (P -value = .470).

with anti-emetics and clearly is dose limiting with the oral route for this agent. This was limited in time to the day of therapy and did not persist beyond the treatment course. No peripheral neuropathies were seen in the group receiving metronidazole. No other adverse effects were detected. Toxicity data are shown in Table 3.

Discussion

Metastatic disease to the brain is an ominous occurrence. Almost all patients become sympto-

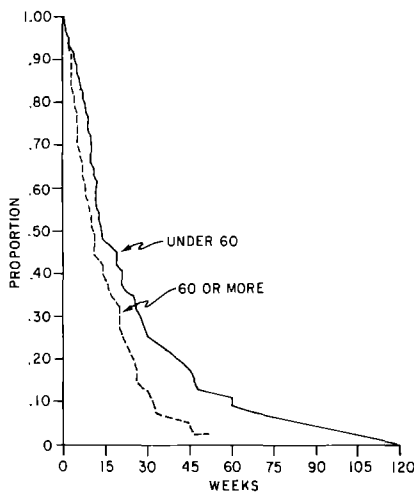


Fig. 5. Survival time for all evaluable patients based on age. Patients less than 60 years survived significantly longer than those 60 years or older (P -value = .037).

Table 3. Toxicity.

Toxicity	Radiation	Radiation plus metronidazole
Nausea/vomiting	3.2%	51%
Myelosuppression*	12.9%	0%
Neuropathy	3.2%	0%

* Some patients received concomitant chemotherapy with cyclophosphamide, vincristine, and fluorouracil.

matic from it and irregardless of current therapies, the majority will die from this complication within 3–4 months. It is clear that conventional radiotherapy can result in palliative benefit but that it will not result in long term disease control for the majority of patients (7–12). Clearly new therapies are needed.

This randomized clinical trial demonstrates that oral metronidazole given every other day was not of any value when combined with conventional radiation 300 rad fractions in 10 treatments for treatment of brain metastases compared to radiation alone. Unfortunately other clinical trials using misonidazole have also failed to have significant impact on survival (19, 20).

The dose of metronidazole used in this trial resulted in moderate to severe nausea and vomiting which was significant enough to be disabling and dose limiting. If further studies using this agent are undertaken with higher dose some alternate schedule or route of administration will be necessary such as intravenous therapy.

Other ideas under investigation for the treatment of brain metastases such as intra-arterial chemotherapy (21), surgical resection (13), hyperthermia (22), blood brain barrier disruption (23) followed by chemotherapy may be of benefit and should be pursued. One other possible approach to this problem would seem to be prophylaxis such as is used with programs designed for small cell lung cancer and leukemia.

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