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A Randomized Phase II Trial of High Dose Melatonin and Radiation Therapy for RPA Class 2 Patients with Brain Metastases (RTOG 0119)

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Abstract

Background—RTOG 0119 was a Phase II randomized trial for RTOG RPA Class 2 patients with brain metastases to determine if high-dose melatonin improves survival over historical controls, and to determine if the time of day melatonin was given affects its toxicity or efficacy.

Methods—RTOG RPA class 2 patients with brain metastases were randomized to 20 mg of melatonin given either in the morning (8-9 am) or evening (8-9 pm). All patients received radiation therapy (30 Gy in 10 fractions) in the afternoon. Melatonin was continued until neurological deterioration or death. The primary endpoint was overall survival time. Neurological deterioration as reflected by the Mini-Mental Status Exam was also measured.

Results—Neither of the randomized groups had survival distributions that differed significantly from the historic control of patients treated with whole brain radiotherapy. The median survivals of

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No conflicts of interest

All patients gave IRB approved informed consent prior to enrolling on this trial.

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the morning and evening melatonin treatments were 3.4 and 2.8 months while the RTOG historical control is 4.1 months.

Conclusion—High dose melatonin did not show any beneficial effect in this group of patients.

Keywords

melatonin; brain metastases; chronobiology; randomized trial; survival

1.0 Introduction

Melatonin, an indoleamine molecule (N-acetyl, 5-methoxytryptamine) plays an important role in a number of processes including circadian rhythm regulation, sleep disorders, seasonal reproduction, retinal physiology, immune function, intermediary metabolism (1,2) and carcinogenesis. (3) It is also a highly efficient and potent free radical scavenger/antioxidant molecule and physiological blood levels of correlate with the total antioxidant capacity of the serum. (4) Oral ingestion of microgram amounts of melatonin results in near physiological nocturnal blood levels of melatonin. (5,6) The oral bioavailability of milligram doses of oral melatonin from nutritional supplements is about 15% (7) and results in supra-physiological melatonin levels.

Numerous studies have demonstrated that physiological and pharmacological blood concentrations of melatonin inhibit tumorigenesis in a variety of *in vivo* and *in vitro* experimental models of neoplasia. (6,8,9) A preliminary study demonstrated that pretreatment of rats bearing hepatomas, for two weeks prior to a single dose of radiation administered just prior to lights off, with a non-tumor inhibiting dose of melatonin also given just before lights off, had a marked radiosensitizing effect. Pretreatment of tumor-bearing rats with AM doses of melatonin were ineffective. (10)

The great majority of human trials of melatonin for cancer treatment or supportive care have come from Lissoni at the Ospedale S. Gerardo in Monza, Italy. Two trials form the basis of the current trial. In the first trial, Lissoni randomized 50 patients who had previously had radiation therapy for brain metastases from solid tumors and subsequently had intracranial progression to either supportive care or supportive care and 20 mg/d of melatonin at 8:00 pm daily until further deterioration or death. (11) Neurological stability and survival were both higher in the melatonin arm. The second trial randomized 30 patients with glioblastoma multiforme to either radiation therapy alone (60 Gy) or radiation therapy and 20 mg/d of melatonin. (12) The survival of the patients receiving melatonin was significantly higher at one year, with 6/14 surviving in the melatonin arm and only 1/16 in the control arm ($p < 0.05$).

The RTOG developed BR-0119 based on the two Lissoni trials and the experimental cancer work showing the circadian stage dependency of melatonin's antitumor action and its anti-tumor effects. The trial was designed to compare whole brain radiation therapy alone to radiation therapy and 20 mg/d melatonin for patients with brain metastases from solid tumors. All of the previous trials gave melatonin in the evening. Pre-clinical data suggest that the timing of melatonin administration relative to the radiation therapy may be important (13). Therefore patients were randomly assigned to receive the melatonin in the morning or in the evening. Because the previous trial of melatonin given during radiation therapy for patients with glioblastoma multiforme (12) showed a marked improvement in survival, it was decided to give the melatonin concurrently with the radiation therapy. Preclinical studies also support concurrent administration (13) All patients received radiation therapy in the afternoon to eliminate time of treatment as a variable. Patients on the two arms were then compared to the RTOG's historical database of patients treated from brain metastases to determine if there was

any evidence of increased survival in either arm. If one was seen, a Phase III trial would be run to confirm it.

2.0 Patients and Methods

2.1 Eligibility and Randomization

Eligible patients were those with RPA Class 2 brain metastases (Zubrod Performance Status 0-1 and any of the following: ≥ 65 years of age, extra-cranial metastases, or uncontrolled primary). The patients were not on concurrent chemotherapy. Patients were randomized to a.m. or p.m. 20 mg melatonin according to a permuted block design, balanced by institution. The randomization was stratified by planned chemotherapy (*yes vs. no*). Patients were randomized centrally at RTOG headquarters via phone call. Patients gave IRB-approved informed consent prior to randomization.

2.2 Study Design

Eligible patients were stratified by whether chemotherapy was planned after the whole brain irradiation. Patients had to start radiation therapy within 14 days of the diagnosis of the brain metastases. The patients were randomized to receiving 20 mg melatonin (two 10 mg capsules) in the morning (between 8 a.m. and 9 a.m.) or in the evening (between 8 p.m. and 9 p.m.). If the patient missed a dose at the specified time and was within two hours of the proper time, the patient was to take the dose. Otherwise the patient was to wait until the next scheduled dose. All patients took the melatonin during radiation therapy and continued for six months or until progression of their disease. The radiation therapy was given as 30 Gy in ten fractions to the whole brain, Monday through Friday. Radiation was to be given between 2 p.m. and 6 p.m. to try to control for any chronobiological effects of the radiation therapy. (14,15)

2.3 Statistics

The primary endpoint of the trial was overall survival from time of registration. The trial was as a randomized Phase II trial with each arm being compared to the RTOG historical database for RPA Class II patients using a one-sided log-rank test with a significance level of 0.10. The primary objective of this study was to compare the overall survival of brain metastases RPA class II patients treated with radiation therapy (*RT*) and concurrent morning (*a.m.*) or evening (*p.m.*) melatonin to corresponding patients from the RTOG database. Survival was chosen for the primary endpoint because of the previous data suggesting a survival advantage (11) and because other possible endpoints, such as neurological function, do not have sufficient historical data for a Phase II analysis. For each arm, an increase in the median survival time (MST) of two months compared to the historical MST of 4.2 months was considered a meaningful improvement in survival. A sample size of 60 evaluable patients followed for 8 months was needed to provide at least 90% probability of detecting a two month (48%) improvement in MST compared to the historical control at a one-side significance level of 0.10. (16) Adjusting for an expected 95% eligibility/evaluability results in 64 patients for each arm. This study required a total sample size of 128 patients, 64 per arm. A secondary endpoint was neurocognitive deterioration as measured by the Mini-Mental Status Examination (MMSE). An age- and education-adjusted cutoff was used to define patients with possible cognitive dysfunction. (17,18) Ineligible patients and those patients who do not receive any of the experimental component of this study were removed from follow up and excluded from analysis.

2.4 Melatonin

The melatonin was obtained from Cardiovascular Research Ltd. of Concord, California The active capsules contained 10 mg of melatonin.

2.5 Patient Assessments

Prior to entry patients were to have a history and physical, contrast CT or MRI, staging of metastases, Zubrod performance status evaluation and MMSE. At the end of radiation therapy the Zubrod performance status, MMSE and optional melatonin blood collection were obtained. At 1, 2, 3, 6, 12 and 18 months after start of the radiation therapy the Zubrod performance status and MMSE were obtained.

3.0 Results

The trial opened May 21, 2002 and closed July 1, 2003. One hundred and thirty patients were accrued from 36 different institutions. One hundred and twenty six were available for analysis (62 assigned to A.M. melatonin and 64 to P.M. melatonin). Four patients were excluded from analysis: one because the patient received systemic therapy for small cell carcinoma after study entry, one was not a confirmed RPA Class II at the time of registration, one because no melatonin was given because of patient refusal, and one because no melatonin was given because the melatonin arrived after the start of radiation therapy. The results presented in this report include all data available as of May 2006.

Patient characteristics are shown in Table 1. The two arms were well balanced. The majority of patients had lung cancer. Approximately half of the patients in each arm had neurocognitive deterioration at baseline, as determined by the MMSE.

Overall the 20 mg of melatonin was well tolerated. Table 2 shows treatment adverse events, as reported as definitely, probably or possibly related to treatment. There were 11 cases with Grade 3 or 4 toxicities in the A.M. arm and 12 in the P.M. arm. The median interval between the first and last dose of melatonin was 56.5 days on the A.M arm and 38 days on the P.M. arm. Eleven patients (18%) on the A.M. arm and 8 (13%) on the P.M. arm ended melatonin greater than 140 days after their initial dose. The most common reasons for discontinuing melatonin treatment earlier than 140 days were patient withdraw or refusal (31% A.M. and 19% P.M.), death (18%, 22%), or progression (10%, 17%). Toxicity was cited as a reason in a minority of cases (8% A.M. and 5% P.M.). The most common toxicities were fatigue, rash and neurological changes.

One hundred eighteen of the 126 cases analyzed are dead. One of the censored cases withdrew from the study after 2 months of melatonin treatment and was lost; the remaining have a minimum of 12 months and a median of 29 months of follow-up Figure 1 shows the survival of the two arms as compared to historical RTOG control. The median survival of the A.M. melatonin patients was 3.4 months, of P.M. melatonin 2.8 months and of the historical controls 4.1 months. There is no significant difference in survival between either of the randomized arms and the expected survival, based on historical data from the RTOG. A randomized trial (RTOG 0118) of thalidomide for patients with brain metastases with similar entry criteria was accruing concurrently with this trial. The control arm of that trial is included to confirm that this did not bias the patient distribution onto the melatonin trial.

Additionally, patients from this study were matched to cases from the historic database on the basis of Zubrod, primary site, spread of metastases, and age (+/- 5 years) (Figure 2). One hundred twelve of the 126 cases could be so matched. There was no significant survival difference found in either comparison.

Table 3 presents the time of neurological deterioration as measured by the MMSE, for patients with no deterioration at baseline. Fifty percent of the patients underwent deterioration in the first three months with the remaining patients showing stable neurological functioning.

Serum melatonin levels were collected at approximately noon on 23 patients. The mean level was 889.3 pg/ml for the A.M. administration patients (95% confidence interval 464.8 to 1314). For the P.M. arm, the mean was 386.7 pg/ml (95% CI 341.3 to 432.2). This difference reflects the timing of administration of the melatonin in relation to blood sample collection at a single time point during midday.

4.0 Discussion

The majority of randomized trials showing the clinical efficacy of melatonin among cancer patients has come from the trials of Lissoni. (19,20,21,22,23,11,24,25,26,27,28,29,30,31,32,33) Three independent randomized trials, including this trial, have been run. (34,35) It is noteworthy that all of the trials from Lissoni and colleagues have had positive outcomes and, as of yet, there have been no confirmatory publications from outside of his group.

The difference could reflect a difference in the biological properties of the melatonin being used. Melatonin has very poor bioavailability, with approximately 15% absorption. (7) There can also be marked differences in absorption between individuals. (36) However, in a large trial such as this one and the Sarma trial, a negative trial studying the ability of melatonin to to ameliorate marrow toxicity during CHOP chemotherapy (35), such individual differences would be expected to be averaged out.

Another possibility is that the dose chosen is not optimal. No oral melatonin dose response study has been performed. If the timing within the day of melatonin is critical for its anti-cancer activity, in some tumors, the 20mg dose may be present at supraphysiologic concentrations at times of day when it should be absent.

This study did confirm several findings. One, melatonin at 20 mg is well tolerated. There was an increase in the number of patients reporting fatigue in the A.M. melatonin arm (25 vs. 17, $p = 0.10$). This also consistent with melatonin's diminishment of core body temperature and decrease in sleep latency without soporific effect. The high rate of skin reactions may have been due to radiation dermatitis, but details of the skin toxicities were not collected. Second, at baseline, overnight melatonin urinary metabolite excretion levels were higher than those obtained during daytime ($p < 0.01$). This means that despite the stress of their advanced cancer, the patients remained to some extent circadian organized *vis a vis* daily nocturnal melatonin production and urinary metabolite excretion. The third finding is the high degree of accuracy of the recursive partitioning analysis of the RTOG historical database. The predicted median survival curves of the case-control patients and the patients on the two arms correlate well.

The only neurocognitive measure in this trial was the MMSE, which is not considered a sensitive measure of neurocognitive functioning. (37). MMSE changes were followed in RTOG 9101, a randomized trial comparing standard whole brain radiotherapy to hyperfractionated radiation therapy for a similar group of patients (38). In that study, over 80% patients with a high initial MMSE score maintained a stable MMSE score at 3 months. In this study, as shown in Table 3, approximately 50% of patients with a high initial MMSE score had deterioration in their score by 3 months. Therefore there does not appear to a protective effect by melatonin for neurological functioning, at least as measured by the MMSE.

There are limitations in the trial. It is assumed that the patients were taking their melatonin, but serum monitoring was not required. It was also assumed that they were taking the melatonin at their appropriate time. Further, the length of exposure of the patients to melatonin was limited, primarily because of the short times to mental deterioration and death of the patients. However, these same limitations were in many of the Lissoni trials that did show survival advantages for patients receiving melatonin.

5.0 Conclusion

This trial does not confirm the hypothesis that 20 mg of melatonin improves survival in patients with solid tumors metastatic to the brain receiving palliative whole brain radiotherapy. This is in contrast to a previous trial of Lissoni, et al, in which 20 mg of melatonin produced a significant increase in one year survival among patients with brain metastases and neurological progression after radiation therapy (11). The cause of this difference is not apparent. Further studies of the efficacy of melatonin in advanced cancer are needed before a conclusion can be reached on the utility of melatonin in this setting.

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Figure 1.

The survival distributions of the AM melatonin (red curve) and PM melatonin (blue curve) cases failed to show improvement to the historical control (black curve) of patients from the RTOG database. Neither the AM nor PM arm was statistically significantly different from control. The green curve is the RPA class II patients from the WBRT arm of RTOG study 0118.

Figure 2.

Survival analysis by matched pairs failed to show improvement with melatonin. Fifty-seven of the 62 AM patients were able to be matched to patients from the historic database whereas only 55 of the 64 PM patients could be matched. Neither comparison showed statistically significant survival differences.

Table 1

Pretreatment Characteristics

	Melatonin Timing	
	A.M. (n=62)	P.M. (n=64)
Age		
<65	37 (60%)	33 (52%)
65+	25 (40%)	31 (48%)
Gender		
Male	30 (48%)	35 (55%)
Female	32 (52%)	29 (45%)
Chemotherapy planned after WBRT		
No	33 (53%)	35 (55%)
Yes	29 (47%)	29 (44%)
Neurological Function		
No Symptoms	22 (35%)	21 (33%)
Minor Neurologic Findings	24 (39%)	27 (42%)
Moderate Neurologic Findings	12 (19%)	14 (22%)
Major/Severe Neurologic Findings	2 (3%)	1 (2%)
Missing	2 (3%)	1 (2%)
Zubrod		
0	21 (33%)	16 (25%)
1	41 (66%)	48 (75%)
Primary Site		
Breast	6 (10%)	7 (11%)
Lung	47 (76%)	41 (64%)
Skin/Melanoma	1 (2%)	3 (4%)
Other	8 (13%)	12 (19%)
Unknown Primary	0	1 (2%)
Primary Status		
Controlled	15 (24%)	21 (33%)
Uncontrolled	42 (68%)	37 (58%)
Unknown	5 (8%)	6 (9%)
Current Spread of Metastases		
Brain Alone	23 (36%)	22 (34%)
Brain + One Additional Site	24 (39%)	23 (36%)
Bone	3	7
Liver	6	2
Lung	9	7
Other	6	7
Brain + Two Additional Sites	10 (16%)	11 (17%)
Lung + Bone	2	1
Lung + Liver	3	1

	Melatonin Timing	
	A.M. (n=62)	P.M. (n=64)
Lung + Other	4	6
Bone + Liver	0	2
Bone + Other	1	1
>Two Additional Sites	5 (8%)	8 (13%)
Baseline Clinical Deterioration† Status by Mini-Mental Status Exam (MMSE)*		
No Failure	31 (50%)	35 (55%)
Failure	29 (47%)	27 (42%)
Not assessed	2 (3%)	2 (3%)

Table 2
Treatment Adverse Events Reported as Definitely, Probably, or Possibly Related to Treatment

	Melatonin Timing							
	A.M. (n=62) Grade				P.M. (n=64) Grade			
	1	2	3	4	1	2	3	4
Allergy/immunology	1	0	0	0	0	0	0	0
Auditory/hearing	0	0	0	0	3	0	1	0
Blood/bone marrow	0	1	0	0	0	0	0	0
Constitutional Symptoms (Fatigue)	8	13	4	0	7	6	3	1
Constitutional Symptoms (Other)	3	0	0	0	1	1	1	0
Dermatology/Skin	3	14	0	0	2	8	2	0
Gastrointestinal (Nausea/Vomiting)	2	1	1	0	3	2	3	0
Gastrointestinal (Other)	4	2	0	0	0	5	2	0
Infection/febrile neutropenia	1	0	0	0	0	0	0	0
Musculoskeletal	0	0	0	0	0	1	0	0
Neurology	6	8	6	0	1	6	3	0
Ocular/visual	0	2	0	1	0	1	0	0
Pain (Headache)	3	4	0	0	3	4	0	0
Worst Non-hematologic	9	19	10	1	7	17	11	1
Worst Overall	8	20	10	1	7	17	11	1

Table 3

Time to Clinical Deterioration Determined by MMSE (Patients with no failure at baseline)

Month	<u>A.M. Melatonin</u>		<u>P.M. Melatonin</u>	
	Estimate	# at Risk	Estimate	# at Risk
0	0%	33	0%	37
1	21%	23	27%	25
2	33%	17	41%	15
3	48%	9	51%	7
4	52%	6	54%	5
Failure/Total	18/33		21/37	