Featured Article

A Phase I Study of Topical Tempol for the Prevention of Alopecia Induced by Whole Brain Radiotherapy

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ABSTRACT

Purpose: **Complete alopecia is a universal complication of whole brain radiation therapy which contributes to patient anxiety over treatment. Tempol, a nitroxide radioprotector, has been shown to protect against radiation-induced alopecia in an animal model. This phase Ib study was designed to evaluate the safety and side effect profile of topical Tempol in patients with brain metastases being treated with whole brain radiotherapy.**

Experimental Design: **Twelve patients with metastatic cancer to the brain were enrolled in the study between October 2000 and February 2003. Tempol (70 mg/ml concentration solution) was applied topically to the scalp 15 minutes before and washed off immediately after the completion of each of 10 fractions of whole brain radiation. Pharmacokinetic studies to evaluate the systemic absorption of Tempol were performed. Patients were assessed for toxicity before, during, and after Tempol administration. A secondary end point of the study, hair retention, was also scored.**

Results: **Eleven patients were treated with topical Tempol. Adverse events that were considered possibly, probably, or definitely related to Tempol, included asymptomatic grade 2 (two patients) and grade 1 (one patient) hypoglycemia, grade 1 forehead skin redness (one patient), grade 1 dry scalp (one patient), and grade 1 tingling sensation on the scalp (one patient). Tempol was not detected in blood samples from more than 50% of the patients. Mean maximum Tempol levels for individual patients at any time point varied from 0.4 to 3.1 μmol/L. Hair retention was localized to the base of the scalp where the Tempol solution pooled after application in the first four patients on the study. Subsequently, full scalp hair retention was seen in three of final five evaluable patients after gauze had been wrapped around the head to hold the solution against the scalp.**

Conclusions: **This study demonstrates that topical application of Tempol to the scalp before whole brain radiation is safe and well tolerated. Evidence of protection against radiation-induced alopecia was observed. A phase II study that uses a gel formulation to increase the exposure of scalp to Tempol has been initiated.**

INTRODUCTION

Alopecia is a common complication of whole brain radiotherapy (1–3). Although this complication is not life-threatening, alopecia does contribute to patient anxiety regarding cancer diagnosis and treatment (2, 3). There have been relatively few studies evaluating the effect of radioprotective agents on alopecia. One of the major concerns has been the systemic absorption of topically applied radioprotectors leading to the possibility of systemic toxicity or tumor radioprotection (4).

The nitroxides Tempol and Tempo have been shown to protect against radiation-induced alopecia (5, 6). The nitroxides are a class of stable free-radical compounds that have *in vitro* antioxidant activity, protecting mammalian cells against hydrogen peroxide, superoxide, and *t*-butyl hydroperoxide cytotoxicity (7, 8). Tempol has also been shown to protect mammalian cells against aerobic radiation cytotoxicity (9). *In vivo* Tempol radioprotection has also been demonstrated for whole body radiation in a murine model (10). In this study, the maximally tolerated dose, whole blood pharmacology, and radioprotective properties of Tempol were described in C3H mice.

Using a guinea pig model, we showed in additional studies that Tempol could protect against radiation-induced alopecia without absorption in blood or brain tissue (5, 6). Additional unpublished studies have been performed in miniature swine that demonstrated the safety of repeated applications of Tempol.[4] Overall, there appear to be no serious cutaneous or systemic toxicities associated with the topical application of Tempol to pig skin. One pig did develop hypoglycemia temporally that was not related to Tempol administration and was thought to be related to a viral infection.

This phase I study of Tempol was designed to evaluate the toxicity of the topical application of Tempol before whole brain radiation. Other end points of the study were to determine the systemic uptake of Tempol when applied to the scalp and to determine the effectiveness of topically applied Tempol for the prevention of radiation-induced alopecia.

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[4] Mitchell, J. Unpublished observations.

MATERIALS AND METHODS

Trial Design. From October 2000 to February 2003, 12 patients were enrolled on this trial at the Hospital of the University of Pennsylvania. All of the patients signed an informed consent document. One patient withdrew from the trial before Tempol administration. The trial was performed under an investigator-sponsored investigational new drug application (held by S. Hahn) from the United States Food and Drug Administration. Trial approval was obtained from the University of Pennsylvania institutional review board and from the University of Pennsylvania Cancer Center Clinical Trials and Scientific Monitoring Committee. Approval to perform measurements of Tempol levels in the Radiation Biology Branch of the National Cancer Institute was given by the institutional review board of the Clinical Center, National Cancer Institute.

Toxicity was evaluated with the CTEP (Cancer Therapy Evaluation Program) Common Toxicity Criteria (CTC) version 2.0 software. Significant toxicity was defined as grade 2 or greater toxicity as defined by the CGCTC (Cooperative Group Common Toxicity Criteria) that could not be ascribed to radiotherapy or to the patient's underlying cancer. After the first five patients were treated, the study was temporarily held to review the Tempol blood levels and toxicities. Stopping rules for the study were as follows: If Tempol was not detected in blood and there were no grade 2 Tempol-related toxicities, the study was to continue. If Tempol levels was detected in blood and there were no grade 2 Tempol-related toxicities, serial blood samples would be taken to determine whether residual Tempol was detectable. A sequential stopping rule for unacceptable toxicity was used. If 3 to 11 patients were treated and 3 patients developed an unacceptable toxicity, it was to be concluded with 99% power that the toxicity rate was $>15\%$ and the study should be stopped.

Patient Evaluation. Patients with metastatic cancer to the brain for whom whole brain radiotherapy was recommended and who were over the age of 18 and willing to sign an informed consent document were eligible to participate in the study. A histologic diagnosis of cancer was required, but a biopsy of the brain metastases was not. Patients were not permitted to have chemotherapy-induced alopecia at the time of whole brain radiotherapy. Prior chemotherapy was permitted, however. Patients were not allowed to receive concurrent chemotherapy, nor could they have planned chemotherapy likely to cause alopecia for 6 weeks after the administration of whole brain radiotherapy. Prior whole brain radiotherapy was not permitted. Prior radiation to other sites was allowed.

Patients with severe liver disease including cirrhosis, grade 3 to 4 elevations in liver function studies, or bilirubin in excess of 1.5 mg/dl were excluded. Patients with a white cell count less than 3500/μL, platelet count less than 100,000/μL, a serum creatinine equal to or greater than 2.5 mg/dl, known HIV disease, or preexisting alopecia (*i.e.*, male pattern baldness) were also excluded. Pregnant patients or any woman of childbearing potential or man unwilling to use a medically approved form of birth control were excluded. Patients who underwent a craniotomy to resect a brain metastasis or brain metastases were not excluded from this study.

All of the patients underwent a complete history and physical examination. Screening laboratory studies included a complete blood count (CBC) with differential, platelet count, electrolytes, glucose, blood urea nitrogen, creatinine, liver function tests, and a pregnancy test (female patients). A magnetic resonance imaging or computed tomography of the brain demonstrating brain metastases was required. A baseline hair score on the scalp was performed in each patient (11–14).

Patients were to be seen weekly during radiation, 1 to 2 weeks after the completion of radiation, and at 4 weeks and 6 weeks after the completion of radiation. Patients who experienced what the investigator determined to be severe alopecia were not followed further with the exception of the 3-month visit. Patients who did not receive chemotherapy likely to cause alopecia were evaluated for hair loss and hair regrowth 3 months after the completion of radiotherapy as well. At each visit, the following were performed: (*a*) history and physical exam; (*b*) photographs of scalp; and (*c*) grading of hair loss. Grading of hair regrowth was only performed in those patients who were seen 3 months postradiation. A complete blood count and liver function tests were performed weekly during radiation treatments as well as 1 to 2 weeks after the completion of radiation. Electrolytes, glucose, blood urea nitrogen, and creatinine testing were performed two times per week during radiation and 1 to 2 weeks after the completion of radiation.

During the initial phase of the study, low blood glucose values were identified in two asymptomatic patients. Initially, this hypoglycemia was scored as possibly related to Tempol administration. It was subsequently discovered that the blood samples in question had not been processed in the laboratory for a number of hours after being drawn from the patients raising the possibility of spurious laboratory results. Daily fingerstick blood glucose measurements were then instituted to more accurately assess the patients for hypoglycemia. Each day before Tempol administration, a fingerstick blood glucose value was obtained. On days that the patient also had study-associated blood studies, the blood glucose level was tested from the drawn blood sample.

Tempol Administration. Tempol was manufactured by Starks Associates, Inc. Buffalo, NY, as a light orange crystalline solid under contract from the National Cancer Institute, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis, and Centers (Bethesda, MD). Tempol was reconstituted in a 70% EtOH solution at a concentration of 70 mg/mL.

Tempol was administered topically to the scalp by the research nurse (D. S.) or the principal investigator in a patient care room in the Department of Radiation Oncology. Health care providers wore gloves while applying Tempol. One hundred milliliters of Tempol (70 mg/mL) in 70% EtOH was applied uniformly to the patient's scalp 15 minutes before each fraction of radiation. At each application, the principal investigator or research nurse verified that the solution had dried on the patient's scalp before radiation delivery. Tempol was washed off after the completion of the daily radiation fraction. The Tempol remained on the scalp for $\sim 30-45$ minutes each day. The patient's temperature, blood pressure, and heart rate were documented before Tempol application; 5, 10, and 15 minutes after Tempol application; at the completion of radiation; and after washing Tempol off the scalp.

Radiation Therapy. Radiation was administered at the Hospital of the University of Pennsylvania, Department of Radiation Oncology. A total dose of 3,000 cGy was delivered in fractions of 300 cGy/d. Patients received radiation 5 d/wk for a total of 10 treatment days. Opposed lateral fields, equally weighted, were used, and both portals were treated during each treatment session. Radiation therapy was delivered via a linear accelerator with 6 to 15 MV photons. A simulation was not required. The treatment field included the entire cranial contents, with a beam fall-off of at least 1 cm. The eyes were excluded from the beam either by field arrangement or shielding. Doses were specified at the central axis at the midplane of the brain.

Tempol Blood Measurements. Blood samples for the detection of Tempol were drawn just before drug application to the scalp as well as 15 minutes, 1 hour, and 24 hours after drug application on the 1st, 5th, and 10th (final) last day of Tempol application. Five milliliters of whole blood samples were stored at −20°C. When a sufficient number of samples were collected, the blood was delivered on dry ice to the Radiation Biology Branch, National Cancer Institute. Because nitroxides are reduced in tissues to an electron paramagnetic resonance-silent compound (15), an aliquot of whole blood thawed on ice was mixed with the oxidizing agent potassium ferricyanide (final concentration 1 mmol/L) to determine the sum of the oxidized and reduced forms. Separate samples were assayed without potassium ferricyanide to determine the concentration of the oxidized form. After mixing, 100 μL of the sample was drawn by a syringe into a gas-permeable teflon capillary tube of 0.8 mm inner diameter and 0.025 mm wall thickness (Zeus Industrial Products Inc., Raritan, NJ). Each capillary tube was folded twice and inserted into a quartz tube that was open at both ends (2.5-mm inner diameter.), and then placed vertically into the EPR cavity. EPR spectra were recorded on a Varian E4 (or E9) X-band spectrophotometer with the field set at 3357 Gauss modulation, frequency 100 KHz, modulation amplitude 1 Gauss, and nonsaturating microwave power. Tempol concentration was measured in arbitrary units of EPR signal intensity. The EPR signal intensity was converted to absolute Tempol concentration with a standard curve. The limit of detection of EPR spectroscopy is 100 nmol/L.

Evaluation of Alopecia. The grading system for hair loss involved identifying a 1-cm^2 scalp study area that was tattooed before the initiation of radiation therapy. Macrophotographs were taken at a fixed distance from the study area before treatment and during follow-up. This distance sometimes varied among patients based on the ability to count hairs. Hair counts of nonvellus hair were obtained from these photographs as described previously (11–14). Several end points were followed as described below. At baseline, each patient had an assessment of hair density by way of actual counts (number of hairs/cm^2), as well as subjective evaluation by the principal investigator. To

Table 1 Demographics of all enrolled patients

Case no.	Age	Sex	Race	ECOG status	Disease type/site	Craniotomy
1	55	M	A	1	Unknown primary	Yes
2	44	F	C	1	Lung	No
3	51	F	C	1	Breast	No
4	32	F	C	1	Melanoma	Yes
5	83	M	C	0	Melanoma	No
6	59	M	C	1	Lung	No
7	69	F	C	1	Lung	Yes
8	51	F	C	0	Lung	No
9	46	F	C	1	Lung	No
10	70	F	C	1	Lung	No
11	38	F	C	1	Breast	Yes
12	54	F	C	1	Unknown primary	Yes

Abbreviations: A, African American; C, Caucasian.

Table 2 Reported serious adverse events possibly related to Tempol

Toxicity	Grade 1	Grade 2	Grades 3–5
Skin redness (forehead)	1		
Hypoglycemia	1	2	
Scalp dryness	1		
Scalp tingling	1		

Table 3 Reported serious adverse events that were not thought to be related to Tempol

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4–5
Periorbital swelling		1		
Right scalp swelling at incision		1		
Humerus fracture			1	
Hyperglycemia		4	2	
Hypoglycemia	1		1	
Hypokalemia	3			
Anemia	4	4		
↓ WBC	1	1		
Thrombocytopenia	1			
Hypocalcemia	3	2		
Hyponatremia			1	
Transaminases increased	3			
Alkaline phosphatase increased	3			
Hypoalbuminemia	3	1		
Acidosis	1			
Hematuria		1		
Fatigue	3	2		
Weakness		1		
Anorexia		1		
Nausea	3	2		
Vomiting		2		
Blurry vision	1	1		
Seizures			1	
Flashing lights (vision)	1			
Temporary paralysis (<10 s)		1		
Partial thromboplastin time increased	1			
Dyspnea		1		
Dry mouth	1			
Oral thrush		3		
Scalp hyperpigmentation	1			
Rash 2° dilantin		1		
Headache		3		
Memory loss	1			
Taste disturbance	1			
Scalp tingling				
Occasional cough	1			
Death, cardiovascular				1

Table 4 Vital signs

Parameter	Temperature (°F)	Blood pressure (diastole/mm Hg)	Blood pressure (systole/mm Hg)	Heart rate (BPM)
Pretreatment (n = 10)	97.7 ± 0.5	70.6 ± 8.3	128.2 ± 21.5	76.7 ± 13.5
During treatment				
Average value*	97.6 ± 0.5	71.3 ± 8.0	128.4 ± 21.2	77.1 ± 13.4
Change from pretreatment	−0.10 ± 0.4	0.64 ± 3.7	0.33 ± 3.1	0.39 ± 1.9
Postradiation				
Actual value	97.7 ± 0.4	71.9 ± 6.2	131.4 ± 23.2	74.3 ± 12.0
Change from pretreatment	−0.01 ± 0.4	1.31 ± 3.6	2.97 ± 4.4	−2.23 ± 3.6
After Tempol removal				
Actual value	97.8 ± 0.4	73.1 ± 5.8	133.4 ± 22.6	76.6 ± 12.8
Change from pretreatment	0.05 ± 0.5	2.45 ± 4.7	5.13 ± 5.6	−0.4 ± 3.7

NOTE. Mean ± unit provided.
Abbreviation: BPM, beats per minute.
* A mean was derived from measurements taken 5, 10, and 15 minutes after applying Tempol for each patient.

perform this latter assessment, a part was made in the middle of the scalp, and a visual scale of hair density from 1 to 7 was used. Examples of each level of hair density were made available to the investigator at the time of the assessment.

Subjective assessments of hair loss (12) by both investigator and patients were made at 1 to 2 weeks, 4 weeks, and 6 weeks after the completion of radiotherapy with the following scale: (*a*) minimal-hair-loss to definite-hair-loss but without substantial thinning; (*b*) moderate-hair-loss to definite-hair-loss with partial thinning; and (*c*) severe-hair-loss to nearly complete or complete hair loss. The principal investigator also made an objective assessment of hair density by measuring the hairs per squared centimeter. Subjective assessment of hair regrowth was made 3 months after the completion of radiotherapy in those patients who did not receive any other agents expected to cause alopecia. The principal investigator and patient made subjective assessments of hair regrowth within the scalp study area as follows: (*a*) minimal growth to definite growth without substantial covering of the thinning area**;** (*b*) moderate growth to new growth that partially covers the thinning area; and (*c*) dense growth to full coverage of thinning areas with hair density similar to baseline evaluation.

Statistical Analysis. Descriptive statistics were generated on all study parameters, with quantitative variables being described by means and SDs and qualitative variables by frequencies and proportions. All of the observed toxicities were graded, tabled, and summarized by frequencies. A one-sided 95% exact confidence interval for the rate of grade 2 or higher, treatment-related toxicity was calculated. The upper bound of the one-sided confidence interval was used to estimate the highest true grade 2 toxicity rate possible for Tempol based on this pilot study. Tempol blood levels were characterized by scatter plots and by means and SDs at each time point.

RESULTS

Twelve patients were enrolled in the study, and 10 completed Tempol treatment. One patient withdrew from the study before the application of Tempol because of concerns over the frequency of blood draws on the study. One patient died because of an unrelated cardiac event after four treatments with radiation therapy and Tempol. Table 1 shows the demographics of the 12 patients enrolled in the study. The mean age of the patients enrolled in the study was 54.3 years (range, 32–83 years). The majority were female (70%) and nearly all were Caucasian (92% *versus* 8% African American). The most common diagnosis was lung cancer (50%), followed by breast cancer (17%), melanoma (17%), and unknown primary tumor (17%). Five patients (42%) underwent a craniotomy with surgical resection of the metastasis before radiation therapy. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (17%) or 1 (83%).

A total of 89 adverse events were reported for the 11 patients treated with Tempol; the most common were laboratory abnormalities such as anemia, hyperglycemia, hypoglycemia, and hypoalbuminemia. Table 2 shows the adverse events that were initially scored as being possibly, probably, or definitely related to Tempol. Table 3 shows the adverse events that were unlikely or unrelated to Tempol. Six adverse events were initially considered possibly, probably, or definitely related to Tempol exposure, including three episodes of asymptomatic

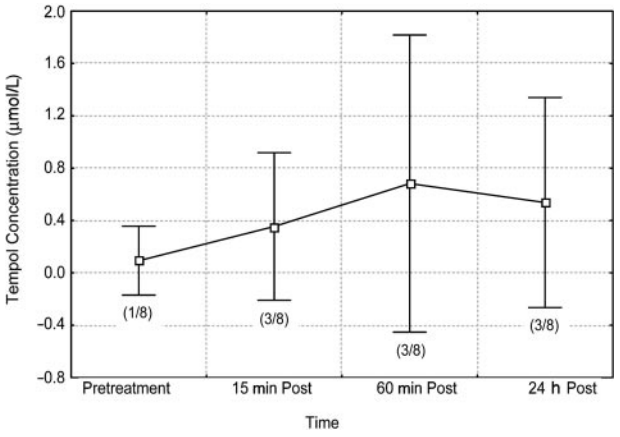

Fig. 1 Mean Tempol blood levels on treatment days 1, 5, and 10, at four times: pretreatment and at 15 and 60 minutes, and 24 hours after treatment (*15 min Post*, *60 min Post*, and *24 h Post*. *Number in parentheses*), the number of patients (in eight) who had measurable Tempol at each time point. *Bars*, ±SD.

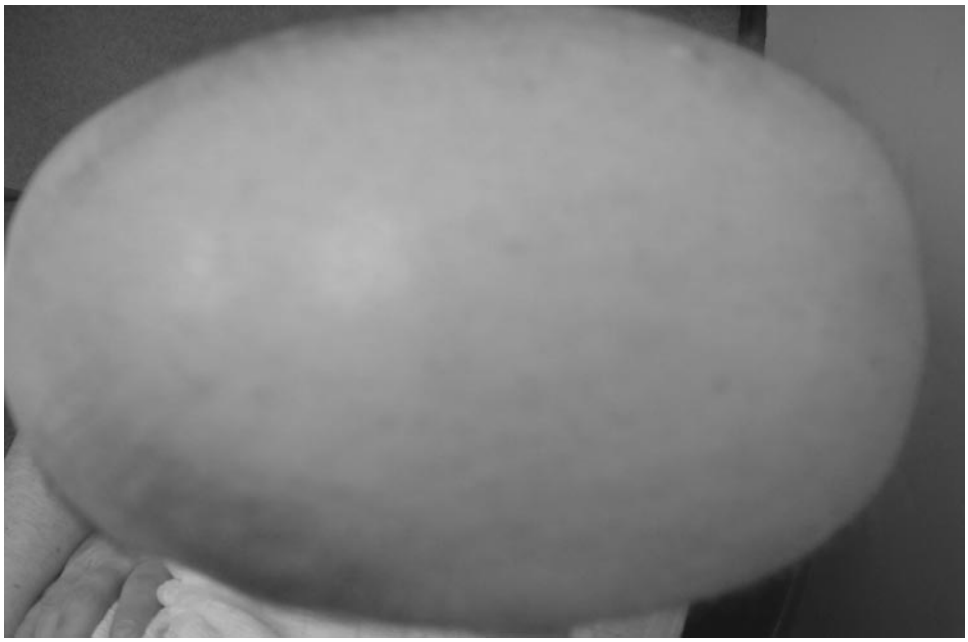

Fig. 2 Typical alopecia associated with whole brain radiation therapy

hypoglycemia, and one episode each of skin reddening, dry scalp, and a tingling sensation of the scalp (Table 2). For the three hypoglycemia events, there was one grade 1 event (glucose level 60 ng/dl) and two grade 2 events (glucose levels of 53 mg/dl and 56 mg/dl). As a safety measure and to evaluate the possibility that the hypoglycemia was related to spurious laboratory values, daily fingerstick glucose measurements were made. These fingerstick blood glucose measurements failed to demonstrate any hypoglycemia in subsequent patients. Although there were subsequent laboratory results that showed hypoglycemia, simultaneous fingerstick measurements confirmed that these values were spurious. In one instance, laboratory results showed grade 1 episode of hypoglycemia with a simultaneous fingerstick glucose measurement of 92 mg/dl. Therefore, the two additional instances of hypoglycemia shown in Table 3 were scored as unrelated, in relation to Tempol administration. To further confirm our assessment that hypoglycemia was not related to Tempol application, there was no detectable Tempol in the blood samples at any time point in the patient who had the lowest laboratory blood glucose value (34 mg/dl).

Other events thought unlikely to be related to Tempol administration included orbital swelling, seizures, and weakness (Table 3). Vital signs measured 5, 10, and 15 minutes after

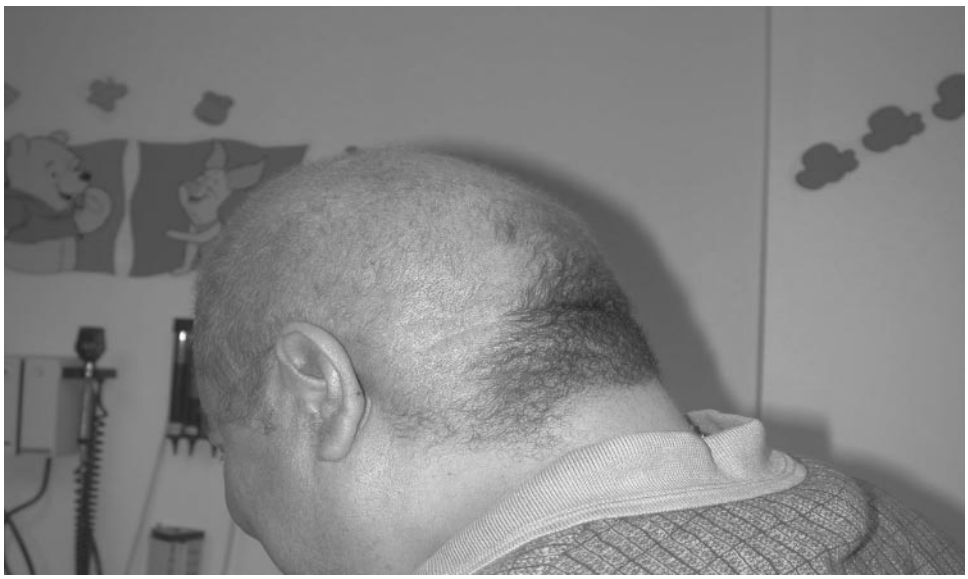

Fig. 3 Protection of hair at base of posterior scalp where towel was placed to prevent Tempol from running onto clothes

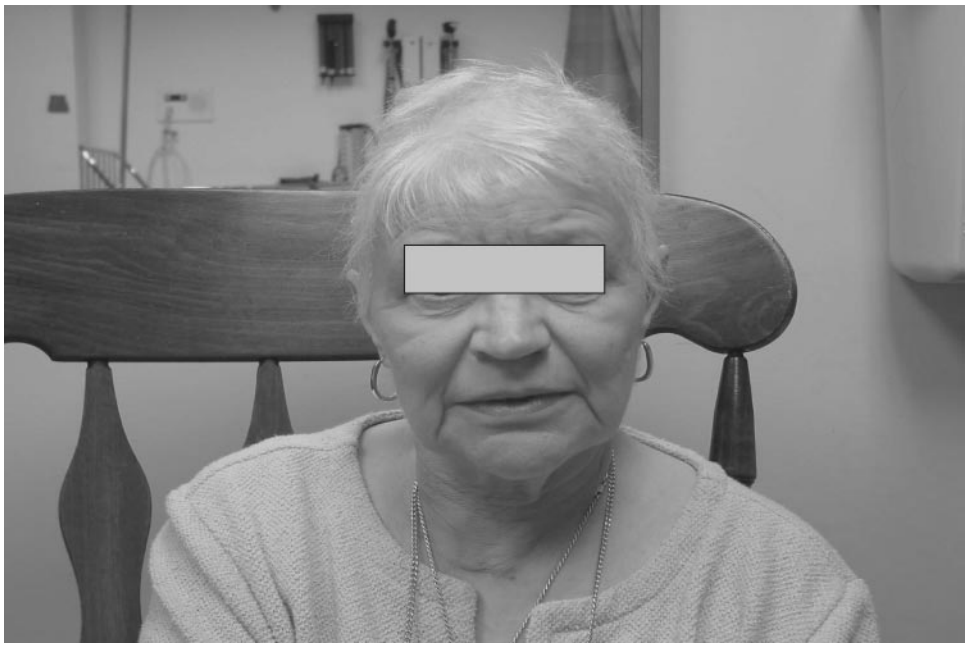

Fig. 4 Prevention of complete alopecia after gauze was used to hold Tempol against entire scalp

Tempol application were not substantially changed in comparison with baseline values. No significant vital sign changes were observed after radiation therapy or Tempol removal (Table 4). No other clinically significant laboratory abnormalities were observed other than the blood glucose levels discussed above (data not shown).

Overall, systemic absorption of Tempol into blood was minimal. Blood concentrations of Tempol blood levels averaged from 0.4 to 0.7 μmol/L at each of the three postapplication time points. Mean maximum levels for individual patients at any time point varied from 0.4 to 3.1 μmol/L. Tempol was not detected in more than 50% of the patients (Fig. 1). The patient with the highest Tempol level had a seroma in the craniotomy site that may have served as a reservoir for Tempol entry into the systemic circulation.

The first four patients enrolled on this study had severe alopecia with near complete hair loss as expected from whole brain radiation therapy (Fig. 2**)**. On review of the photographs of these patients, it was noted that hair was retained at the base of the posterior scalp and the anterior scalp line (Fig. 3). Hair retention was located where a towel had been placed to keep the liquid Tempol solution from running on the patients clothes or into the eyes. At this point, the protocol was modified to wrap gauze on the head of each patient to hold the Tempol solution against the scalp before radiotherapy. Of the next eight enrolled patients, six were evaluable for assessment of hair loss (one patient died as described above and one patient withdrew from the study before Tempol application). Of these six evaluable patients, three patients had substantial hair retention with only moderate hair loss **(**Fig. 4**)**. There was no change in the side effect profile after the change in application of Tempol.

Hair loss/growth data scored by the investigator are shown in Table 5. Minimal hair loss was observed over the first 2 weeks of the study (which includes the 10-day Tempol/radiation treatment period). Minimal to moderate hair loss was observed at week 3, and moderate to severe hair loss was observed over the next 3 weeks.

Long-term follow-up in this study was limited in many patients because of progressive systemic disease and death before the 3-month evaluation point. Of the 10 patients who completed radiation with Tempol administration, 4 (40%) completed the full study with 3-month follow-up evaluation. In two of these patients, hair regrowth was substantial with rapid recovery of hair. In the other two patients, hair regrowth was not observed. Of note, both of these patients had only moderate alopecia at the initial 6 week assessment. Of the remaining

Table 5 Hair loss/growth data

Variable	No. of patients	Mean ± SD
Investigator		
Week 1	9	1.0 ± 0.0
Week 2	9	1.0 ± 0.0
Week 3	7	1.4 ± 0.5
Week 4	5	2.8 ± 0.5
Week 5	3	2.3 ± 0.6
Week 6	2	2.5 ± 0.7
Month 3	4	1.3 ± 0.5
Patient		
Week 1	9	1.0 ± 0.0
Week 2	9	1.0 ± 0.0
Week 3	8	1.9 ± 1.0
Week 4	4	2.8 ± 0.5
Week 5	3	2.3 ± 0.6
Week 6	2	2.5 ± 0.7
Month 3	4	1.3 ± 0.5

NOTE. Variables are for investigator and patient assessment of hair loss (weeks 1–6) scored as minimal (1), moderate (2) or severe (3), or assessment of hair growth (month 3) scored as minimal (1), moderate (2) or dense (3).

patients, five (50%) did not have complete 3-month follow-up data, and one (10%) died.

DISCUSSION

Topical application of Tempol to the scalp in patients undergoing whole brain radiation was well-tolerated in this study. Six adverse events were initially scored as possibly, probably, or definitely related to treatment with this nitroxide compound (Table 3). Three of these adverse events were grade 1 or 2 hypoglycemia. Although, the low laboratory blood glucose values were initially scored as possibly related to Tempol therapy, a subsequent evaluation of simultaneous fingerstick glucose measurements with blood draws indicated that the hypoglycemia was likely a spurious laboratory value. The absence of serious Tempol-related adverse events or anomalous vital sign-blood chemistry/hematology measurements is encouraging and consistent with the finding that the majority of evaluable patients had Tempol blood levels below the detection limits of the assay used for assessment (Fig. 1).

A tertiary end point of this study was the prevention of radiation-induced alopecia. The results demonstrate that protection against radiation-induced alopecia was observed in some patients. As reported above, the first four patients experienced near complete alopecia except for regions at the edge of the scalp where a towel was applied to keep the Tempol solution from running into the patients eyes or onto their clothes. After the protocol was modified to hold the Tempol against the scalp with gauze, considerable hair retention was noted. In fact, 3 of the 5 evaluable patients treated with modified Tempol application method had only moderate hair loss.

After reviewing the photographs from the study, it was clear that the data generated from hair counts on a specific tattooed area of the scalp were not a reliable measure of hair retention. The alopecia induced by radiation can be patchy and the photographs often gave an unreliable assessment of hair retention. For example, a patient could have near complete alopecia and a small patch of hair at the tattooed area of the scalp, thereby giving a false indication that the patient had evidence of Tempol protection. Likewise, the patient could have clinically considerable hair retention, with a patch of alopecia in the tattooed area providing an inaccurate assessment. Hair retention was easily documented with front and overhead photos.

The possible mechanisms of Tempol radioprotection include oxidation of reduced transition metals, superoxide dismutase (SOD)-like activity, and scavenging of oxy- and carbon-based free radicals. Although systemic Tempol administration has been shown to provide whole body radioprotection to C3H mice (10), one concern has been that the nitroxides might also protect tumors against radiation-induced cytotoxicity. A study has been performed to evaluate tumor protection by using the murine tumor RIF-1 (16). In this study, Tempol did not decrease tumor control of the RIF-1 tumor in C3H mice. It has been speculated that the protection of normal tissues without protection of the RIF- I tumor may be the result of differential bioreduction of nitroxide in the tumor *versus* normal tissues (16). Although assessment of Tempol administration on tumor response to radiation was not an end point of this study, no deleterious effect of Tempol on tumor control was observed in this small trial.

In summary, the topical application of the nitroxide Tempol before fractionated whole brain radiotherapy in this phase I study was very well tolerated. Moderate protection against radiation-induced alopecia was observed in this study. Given the suggestion of activity and the absence of considerable toxicity, a phase II study of Tempol for the prevention of radiation-induced alopecia has been initiated with a new gel formulation to increase the delivery of drug to the scalp.

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