A PHASE II TRIAL TO EVALUATE THE USE OF TRENTAL AND VITAMIN E FOR PROPHYLAXIS OF RADIATION NECROSIS

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1. Aims
   1.1. The goal of this single arm Phase II study is to evaluate the prophylactic use of Trental and vitamin E for its efficacy in reducing radiation necrosis after radiosurgery.

2. Background and Significance
   2.1. Hypothesis:
      2.1.1. Vitamin E and Trental are commonly used in combination to treat cerebral radiation necrosis after radiosurgery. Use of these drugs after radiosurgery may serve as prophylaxis for and reduce the incidence of radiation necrosis.
   2.2. Background:
      2.2.1. Radiation Necrosis Review:
         2.2.1.1. Radiosurgery is widely used in the treatment of various intracranial disorders such as metastatic brain tumors, meningiomas and arteriovenous malformations (1-3). However, the use of radiosurgery is limited by the risk of injury to adjacent brain. Although technological advances have considerably enhanced the safety and efficacy of radiosurgery, radiation necrosis continues to be a serious complication of treatment. A recent study at our institution showed that 14% of metastatic lesions treated with radiosurgery exhibited imaging characteristics consistent with radiation necrosis (4). Several other studies have confirmed this observation and have shown that radiographic changes can be present in up to 46% (5-7). Typically, radiation injury is categorized into acute, subacute and chronic stages based upon the time between radiation treatment and onset of symptoms (8). Imaging characteristics are variable and can range from T2 FLAIR abnormalities to areas of contrast enhancement and frank necrosis. Clinical symptoms can be associated with these radiographic changes and can range from mild headaches to progressive neurologic deterioration. Steroids are a commonly used form of treatment for radiation induced injury. However, patients who progress despite steroid treatment are often candidates for oral therapy with Trental and vitamin E. This combination has been widely used to treat radiation induced injury and will often reverse both clinical and radiographic effects (9-16). A recent randomized controlled trial showed that this combination is effective in the treatment of superficial radiation induced fibrosis over the chest, in patients receiving radiotherapy for breast cancer (13). Also, a recent study suggested that the combination may be effective in the treatment of radiation induced brain injury (14). The goal of this study is to determine whether this commonly used treatment for radiation necrosis can be used prophylactically to prevent, delay and/or reduce the severity of cerebral radiation necrosis after radiosurgery.

3. Investigator Experience
   3.1. Dr. Warnick is a board-certified neurosurgeon who has undergone fellowship training in neurosurgical-oncology at the University of San Francisco. He has published extensively in the field of neurosurgical oncology and currently has an academic neurosurgical practice with an active oncology component. He has also had extensive experience in the diagnosis and treatment of central nervous system radiation necrosis.
   3.2. Dr. Breneman is a board-certified radiation oncologist. He has published extensively in the field of radiation oncology and currently has an academic radiation oncology practice. He has also had extensive experience in the diagnosis and treatment of central nervous system radiation necrosis.

4. Experimental Design and Methods
   4.1. Patient Registration:
      4.1.1. Only patients who meet eligibility requirements may be registered.
      4.1.2. Once an eligible patient is identified by the treating physician, informed consent for participation in the study is obtained.
      4.1.3. A baseline evaluation form and enrollment form (See Appendix B) is completed.
   4.2. Pretreatment Evaluation:
      4.2.1. Prior to initiation of treatment, a complete history and physical with a detailed neurologic examination is required.
      4.2.2. Evaluation of further metastatic disease may be performed as clinically indicated.
   4.3. Treatment Phase:
      4.3.1. Patients will receive a combination of Trental 400 mg TID and Vitamin E 400IU BID starting the first day after the last radiosurgery treatment. This regimen is then continued on a daily basis for a period of 6 months after the last radiosurgery treatment.
      4.3.2. Patients will be monitored with regular clinic visits and MRIs performed at 3 month intervals. A follow up form (Appendix B) will be filled out by the treating physician at each visit.
      4.3.3. All patients will be followed for an appropriate duration as clinically indicated.
      4.3.4. Enrolled patients that require additional radiosurgery will discontinue Trental and Vitamin E for the two weeks prior to the additional radiosurgery and resume treatment the day after. These patients will remain on study, but the new site disease will not be followed in the necrosis analysis.
   4.4. Data Analysis and Monitoring
      4.4.1. Study Endpoints:
         4.4.1.1. Primary
            4.4.1.1.1. Incidence of symptomatic radiation necrosis
            4.4.1.1.2. Incidence of asymptomatic radiation necrosis
         4.4.1.2. Secondary
            4.4.1.2.1. Change in volume of contrast enhancement
            4.4.1.2.2. Change in volume of necrosis

4.4.1.2.3. Change in volume of T2 edema
4.4.1.2.4. Steroid usage

4.4.2. Results of the Data analyses will be reported over all as well as by stratifying with respect to:
4.4.2.1. Radiation prescription dose
4.4.2.2. Lesion volume
4.4.2.3. Presence of comorbidities: Hypertension, Diabetes

4.4.3. As per the design, at the first stage we would evaluate the results by identifying when we have 8 lesions with necrosis. If at that stage, we have 52 or more lesions in the study then that would confirm we should continue to complete the study with all 134 lesions. At that stage, if we find 14 or less lesions with radiation necrosis, we would then claim that the study has met its objective of a 50% reduction in incidence of radiation necrosis (from 15% to 7.5%). (see Appendix A)

4.4.4. Summary of Data Submission (See Appendix B)

4.4.4.1.	Enrollment Form (EF)	Within 2 wks of registration
4.4.4.2.	Initial Evaluation Form (IF)	Within 2 wks of registration
4.4.4.3.	Treatment Form (TF)	At the end of radiosurgery
4.4.4.4.	Follow Up Form (FF)	Every 3 months for 1 year
4.4.4.5.	Follow MRI Form (MF)	Every 3 months for 1 year

4.4.5. Treatment Form (TF) will be completed by treating physician.

4.4.6. MRI documentation

4.4.6.1. The contrast-enhanced MRI performed pre-radiosurgery and every 3 months post-radiosurgery will be evaluated by the investigators: REW, JB, LI. Form MF will be completed by investigator LI.

4.4.6.2. Radiation necrosis will be defined as previously reported by Blonigen et al. (4):

> A combination of criteria will be used including appearance on serial MRI scans, MR Spectroscopy and histology (when available). It will be further described as the following: (1) patient with radiographic changes with a requirement of steroid therapy, (2) 2 consecutive scans with persistent MRI changes consistent with radiation necrosis, (3) findings suggestive of radiation necrosis on MR Spectroscopy, or (4) histological evidence of radiation necrosis.

4.4.6.3. Once radiation necrosis is identified by the treating physician, parameters will be quantified using standard radiation oncology software tools by an investigator: LI. The volume of contrast enhancement, T2 edema and necrosis will be quantified.

4.5. Data storage and confidentiality

4.5.1. Data will be maintained in a password protected database and will only be accessed by the listed investigators. The information gathered will not be used or disclosed for any other purpose other than this specific research project.

5. Estimated period of time to complete the study.
   5.1. It is estimated that the patient recruitment period will be 2 years and the follow up period will be one year. Total estimated time to complete the study is 3 years.

6. Human Subjects: Describe the characteristics of the research population:
   6.1. Subjects will include patients receiving or planning to undergo single fraction or five fraction radiosurgery for a metastatic brain tumor.
   6.2. The demographics of the study population are expected to reflect the general population with intracranial metastatic tumors. Only adults $\geq$ 18 years of age will be included in the study.
   6.3. Recruitment:
      6.3.1. Patients seen at the University of Cincinnati Brain Tumor Center will be directly recruited by the treating physician.
   6.4. This study is estimated to require 49 patients. In a recently published study performed at the University of Cincinnati (4), patients recruited to the study had an average of 2.75 metastatic lesions. Each lesion was treated independently when analyzing the incidence of radiation necrosis. Using this same method, a total of 134 lesions are necessary to show a 50% effective reduction in radiation necrosis with our supplement. This would be estimated to require 49 patients.
   6.5. Inclusion Criteria:
      6.5.1. Patients about to undergo or currently receiving single or five fraction radiosurgery for a metastatic brain tumor.
      6.5.2. Diagnosis of a metastatic brain tumor may be accomplished by histologic confirmation or by clinical confirmation by the treating physician based on MR Imaging characteristics in the setting of a known history of cancer.
      6.5.3. Availability for follow up
      6.5.4. Ability to give informed consent.
      6.5.5. Age $\geq$ 18 years
      6.5.6. Patients who have had partial or total resection of a metastatic tumor are eligible.
   6.6. Exclusion Criteria:
      6.6.1. Known sensitivity to vitamin E or Trental
      6.6.2. Pregnant or nursing women.
      6.6.3. Recent intracranial bleed or retinal hemorrhage
      6.6.4. Major medical or psychiatric illness which in the investigators opinion will prevent administration or completion of the protocol therapy and/or interfere with followup.
      6.6.5. Treatment with a non-approved or investigational drug within 30 days before day 1 of study treatment.

      6.6.6. History of Avastin treatment.
      6.6.7. Anticipated need for treatment with Avastin.
      6.6.8. Patients currently on vitamin E or Trental are ineligible.
      6.6.9. History of bleeding disorder
      6.6.10. Patient who is on Warfarin, Lovenox, NSAIDS, or aspirin. Low dose (81 mg) of daily aspirin is acceptable.

6.6.11. History of liver disorder
6.6.12. Intolerance to methylxanthines such as caffeine, theophylline, and theobromine.

7. Risk/Benefit Assessment.
   7.1. The combination of vitamin E and Trental is a commonly used treatment for radiation induced injury to the brain as well as other body organs (9-14).
   7.2. Vitamin E (α-tocopherol):
      7.2.1. It is thought that the therapeutic benefits in combating radiation induced injury are due to its antioxidant properties and its inhibition of TGF-β and collagen production (15,16). As a common component in over the counter multivitamins, the toxicity profile of vitamin E is low and the dosage of 400 IU BID used for the study presents minimal risk to the patient.
   7.3. Trental (Pentoxyfilline):
      7.3.1. Several mechanisms of action have been proposed for the potential benefits of Trental in radiation induced injury. However, the exact mechanism is unclear. Trental may decrease the inflammatory response and formation of oxygen radicals (2,9). The dosage of Trental used in this study is typically well tolerated and presents minimal risk to the patient. Common side effects of Trental include gastrointestinal effects such as nausea, vomiting, dyspepsia; nervous system effects such as headache, dizziness, insomnia and cardiovascular effects such as palpitations, flushing and angina. While typically minor, side effects have necessitated discontinuation of Trental in approximately 3% of treated patients.
   7.4. The benefits of this study include the possibility of providing a prophylactic regimen for the prevention of radiation necrosis.

8. Payment
   8.1. None

9. Subject Costs:
   9.1. All tests and procedures involved in this study are considered standard of care and would be the responsibility of the patient and/or insurance. Vitamin E is available over the counter and trental is available by prescription.

11. Literature Cited

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Appendix A

Two-Stage Clinical Trials Sample Size (Results are in the form of NON-RN as success)

TO DETECT RN REDUCTION FROM 15% (HISTORICAL) to 10% (a 33.3% reduction)

Possible Designs For P0=0.850, P1=0.900, Alpha=0.050, Beta=0.200

N1	R1	PET	N	R	Ave N	Alpha	Beta	Constraints Satisfied
124	106	0.598	288	254	189.88	0.047	0.198	Optimum

In the first stage, we need to see 124 lesions on supplement and if we find 106 or less lesions RN-free, the trial stops. If you find 107 or more lesions RN free, the trial continues and we go all the way to 288 lesions. If we find 255 or more lesions RN free (in other words- 33 or fewer RN), we have proven that the trial succeeded in reducing the RN incidence from 15% to 10% by giving them supplement.

TO DETECT RN REDUCTION FROM 15% (HISTORICAL) to 7.5% (a 50 % reduction)

Possible Designs For P0=0.850, P1=0.925, Alpha=0.050, Beta=0.200

N1	R1	PET	N	R	Ave N	Alpha	Beta	Constraints Satisfied
52	44	0.528	134	120	90.69	0.047	0.200	Optimum & Minimax

FOR A REDUCTION OF RN FROM 15% to 5% (a 66.7% reduction)

Possible Designs for P0=0.85, P1=0.950, Alpha=0.050, Beta=0.200

N1	R1	PET	N	R	Ave N	Alpha	Beta	Constraints Satisfied
13	11	0.602	65	59	33.71	0.049	0.200	Optimum

You can interpret similarly as above for a reduction of RN from 15% to 5%.

References

Simon, Richard. 'Optimal Two-Stage Designs for Phase II Clinical Trials', Controlled Clinical Trials, 1989,
Volume 10, pages 1-10.

Report Definitions

N1 is the sample size in the first stage.
R1 is the drug rejection number in the first stage.
PET is the probability of early termination of the study.
N is the combined sample size of both stages.
R is the combined drug rejection number after both stages.
Ave N is the average sample size if this design is repeated many times.
Alpha is the probability of rejecting that P<=P0 when this is true.
Beta is the probability of rejecting that P>=P1 when this is true.
P0 is the response proportion of a poor drug.
P1 is the response proportion of a good drug.

Summary Statements

The optimal two-stage design to test the null hypothesis that P<=0.850 versus the alternative
that P>=0.950 has an expected sample size of 33.71 and a probability of early termination of
0.602. If the drug is actually not effective, there is a 0.049 probability of concluding that it is (the target for this value was 0.050). If the drug is actually effective, there is a 0.200 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 13 lesions in the first stage, the trial will be terminated if 11 or fewer respond. If the trial goes on to the second stage, a total of 65 lesions will be studied. If the total number responding is less than or equal to 59, the drug is rejected.

Appendix B

A PHASE II TRIAL TO EVALUATE THE USE OF TRENTAL AND VITAMIN E FOR PROPHYLAXIS OF RADIATION NECROSIS

Enrollment Form

Name:_____ **DOB**:_____ **MRN**:_____

Date:_____

Yes	No	
☐	☐	Patient is about to undergo single or five fraction radiosurgery for a metastatic brain tumor.
☐	☐	Able to give informed consent.
☐	☐	Age $\geq$ 18 years
☐	☐	Patient has no known sensitivity/allergy to vitamin E, Trental, caffeine, theophylline, or theobromine.
☐	☐	Patient is not pregnant or nursing.
☐	☐	Patient has not had a recent intracranial bleed or retinal hemorrhage or history of a bleeding disorder.
☐	☐	Patient has no major medical or psychiatric illness which in the investigators opinion will prevent administration or completion of the protocol therapy and/or interfere with followup.
☐	☐	Patient has not had treatment with a non-approved or investigational drug within 30 days prior to day 1 of study treatment.
☐	☐	Patient is not a current smoker.
☐	☐	Patient has no history of Avastin treatment.
☐	☐	Patient has no anticipated need for treatment with Avastin.
☐	☐	Patient is not currently on vitamin E or Trental

Answer to each of the above questions must be "Yes" in order for patient enrollment

Signature:_____ Date: _____

A PHASE II TRIAL TO EVALUATE THE USE OF TRENTAL AND VITAMIN E FOR PROPHYLAXIS OF RADIATION NECROSIS

Initial Evaluation Form

Name:_____ **DOB**:_____ **MRN**:_____
Date:_____

Location:	**Size**
_____	_____
_____	_____
_____	_____
_____	_____

HPI:_____
_____
_____
_____
_____

ROS : ☐ Headaches ☐Visual Changes ☐ Hearing Changes ☐ Sensory Changes
☐ Seizure ☐Memory loss ☐ Weakness ☐ Cognitive Changes
Other:_____

PMH: ☐ Diabetes ☐ Hypertension ☐Prior Radiotherapy Other:_____
PSH: _____

KPS: _____ **ECOG**: _____

EXAM:

Mental Status	☐ Normal	_____
Language	☐ Normal	_____
CN 2-12	☐ Normal	_____
Motor	☐ Normal	_____
Sensation	☐ Normal	_____
Reflexes	☐ Normal	_____

Medications: ☐ Dexamethasone dose: _____
☐ Anticonvulsant:_____
☐ Aspirin dose: _____
☐ NSAIDS daily dose: _____

☐ Anticoagulants: _____
Other Meds: _____

Signature:_____ Date: _____

A PHASE II TRIAL TO EVALUATE THE USE OF TRENTAL AND VITAMIN E FOR PROPHYLAXIS OF RADIATION NECROSIS

Follow Up Form

Name:_____ **DOB**:_____ **MRN**:_____
Date:_____

Radiation Necrosis Evaluation: Defined as 1) patient with radiographic changes with a requirement of steroid therapy, 2) 2 consecutive scans with persistent MRI changes consistent with radiation necrosis, 3) findings suggestive of radiation necrosis on MR Spectroscopy, or 4) histological evidence of radiation necrosis.

Location:

_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**
_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**
_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**
_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**
_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**
_____	☐ **Radiation Necrosis**	☐ **Sx**	☐ **ASx**

S:_____
_____
_____
_____

ROS : ☐ Headaches ☐Visual Changes ☐ Hearing Changes ☐ Sensory Changes
☐ Seizure ☐Memory loss ☐ Weakness ☐ Cognitive Changes
Other:_____

Trental SE:☐ GI Upset ☐ Headache ☐Dizziness Other:_____
Vitamin E SE:☐Blurred Vision ☐Bruising ☐ Skin Changes Other: _____

KPS: _____ **ECOG**: _____

EXAM:

Mental Status	☐ Normal	_____
Language	☐ Normal	_____
CN 2-12	☐ Normal	_____
Motor	☐ Normal	_____
Sensation	☐ Normal	_____
Reflexes	☐ Normal	_____

Medications: ☐ Dexamethasone dose: _____
☐ Keppra dose:_____ ☐ Dilantin dose: _____
☐ Other Anticonvulsant dose:_____
☐ Compliant with Trental and Vitamin E
☐ Aspirin dose: _____
☐ NSAIDS daily dose: _____
☐ Anticoagulants: _____
Other Meds: _____
_____

Disease Status:

Response	☐ yes	☐ no
Necrosis	☐ yes	☐ no
Recurrence	☐ yes	☐ no

Overall Clinical Picture: _____
_____

Signature:_____ Date: _____