

RADIATION THERAPY ONCOLOGY GROUP

RTOG 79-03

A PHASE I/II PROTOCOL FOR THE EVALUATION OF
 MISONIDAZOLE COMBINED WITH NEUTRON
 RADIATION IN THE TREATMENT OF PATIENTS
 WITH MALIGNANT GLIOMA

closed

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Schema

Record	Treatment					
	Neutron radiotherapy + misonidazole					
Tumor location						
Size						
Stage						
Extent of resection						
Grade						
Performance status						
Week	1	2	3	4	5	6
Neutron x RT 300 rad x 6	+	+	+	+	*	*
Misonidazole 2.5 g/m ² x 6	+	+	+	+	+	+
		*reduced field				

Eligible: Patients with biopsy proven malignant gliomas age > 18 < 70; Karnofsky \geq 50; no previous radiation to brain or chemotherapy.

Radiotherapy: 300 rad (neutrons) to entire brain in single weekly fraction x 4 plus two 300 rad fraction to the reduced volume.

Misonidazole: 2.5 g/m² 4-6 hours before radiotherapy x 6 doses. Total dose 15 g/m².

Patients must be registered with RTOG Headquarters (215) 574-3191, 9:00 a.m. - 5:00 p.m., EST prior to beginning radiotherapy. Submit drug request forms (NIH 986) to RTOG Headquarters for approval.

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1.0 INTRODUCTION

1.1 Disease Specific Background

The malignant gliomas are rarely controlled by any treatment and are almost uniformly fatal. Survival following conventional neurosurgical intervention and radiotherapy can be measured in terms of months and reported survival frequencies are in the range of 55-67% at 6 months, 27-39% at 12 months, and 8-20% at 24 months. Relentless local growth of tumor rather than metastases kills the patient.

Considerable effort has been made by investigators in recent years to search for newer avenues of approach, including higher doses of conventional photon radiation, combination of chemotherapy and photon radiation, and high LET radiations.

The RTOG and ECOG have a joint current protocol (RTOG 74-01) which tests standard whole brain radiation using photons to a total dose of 6,000 rad against the same radiation dose with a 1,000 rad boost added, or the addition of chemotherapy using BCNU or methyl CCNU + DTIC. Over 600 patients have been randomized. The study was closed in March, 1979, and preliminary analysis shows no difference among the four treatment randomizations. These preliminary findings are consistent with the early reports of the Brain Tumor Study Group investigation of radiation alone versus radiation plus BCNU.

Inasmuch as there are theoretical biological bases for better responses of the tumors to high LET radiation, pilot studies with fast neutron whole brain radiotherapy were undertaken and some initial observations are available.

Thirty-three patients treated at the University of Washington in Seattle and 35 patients treated at Hammersmith, England, showed excellent tumor control with autopsy data showing better than 90% of the patients with gross tumor replaced by

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coagulation necrosis and only reactive astrocytes in the region. However, diffuse gliosis and demyelination suggested that the RBE for neutrons in the brain may be nearly 4 rather than 3. Dosage was reduced 20% which resulted in no observable brain damage, but patients died of persistent, viable tumor.

A current RTOG protocol (RTOG 76-11) is evaluating the combination of photon radiation to 5000 rad with a neutron boost of 500 rad (approximately equivalent to 1500 photon rad). Although this study is still accruing patients and has yet to mature, a dramatic gain has not been demonstrated in the preliminary results of the first sixty patients.

1.2 Misonidazole Background

Hypoxic cells are known to be present in solid tumors in man and animals, and are known to be more resistant to the effects of ionizing radiation than aerated cells. Whether or not the radioresistance of such cells is a limiting factor in the local control of solid tumors treated with radiotherapy is the subject of the current study. Attempts to improve the killing of hypoxic cells have involved the use of hyperbaric oxygen, high-linear-energy-transfer irradiation and hypoxic cell sensitizers. Of the compounds tested to date as hypoxic cell sensitizers, the nitroimidazoles appear to have the greatest potential because of their superior pharmacologic properties and greater effectiveness in mammalian cells. Among these, metronidazole (Flagyl) and misonidazole (Ro-07-0582) have proven to be active in animal model systems and are now in early clinical evaluation in several countries (1). Initial clinical pharmacologic and toxicologic evaluation of misonidazole by Dische et al. in England (2), by Urtusan et al. in Canada (3), and by Wasserman et al. in the United States (4) provides some qualitative and quantitative data on these drug properties for single dose and some multiple dose schedules. Pharmacologic studies using ultraviolet spectrophotometric (UV) and high-pressure liquid

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chromatographic (HPLC) assays have established that peak serum levels of misonidazole occur 1-4 hours after the given dose with serum half lives ranging between 9 and 17 hours. Peak serum levels in mg/ml were slightly higher than drug dose administration in mg/kg. A good percentage of serum levels has been detectable in tumor biopsies and in the cerebrospinal fluid (CSF). Acute toxicity of the oral formulation has been expressed by nausea and vomiting. Multiple-dose schedules revealed the dose-limiting toxicity to be peripheral neuropathy, with the incidence apparently related to total drug dose given, dose frequency, and size of each individual drug dose.

The RTOG has completed a Phase I evaluation of misonidazole administered once and twice per week for 3 and 6 weeks and administered three times per week for 2 weeks and daily for 5 and 7 days. A total of 104 patients have been entered into this study. The results on the first 40 patients were presented to the American Society of Therapeutic Radiologists, November 1978, and the publication is in press (5).

This study established the maximum tolerated dose for one dose/week for 3 weeks as $4 \text{ gm/m}^2/\text{dose}$ or a total of 12 gm/m^2 in three weeks. At this dose approximately 50% of the patients will have measurable peripheral neuropathy, but this neuropathy will rarely exceed Grade II, i.e., sensory only of a moderate degree.

This study also established that for weekly administration for 6 weeks, 15 gm/m^2 was the maximum tolerated dose. At this dose level over this time period also, approximately 50% of patients experienced peripheral neuropathy of a Grade I-II nature with only occasional patients experiencing more severe neuropathies. More severe neuropathies were always associated with advanced age, marked dehydration, excessively high blood levels, or a pre-existing severe neuropathy such as from vincristine.

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Subsequent to this publication by Wasserman, et al, an additional 64 patients have been treated on multiple doses/week schedules. With administration twice per week a dose of 1.5 gm/m^2 was given to 6 patients for 6 weeks or 12 doses. Two patients died during the study and one withdrew. Of the three patients completing treatment, one had a Grade II, one a Grade III, and one a Grade IV neuropathy with encephalopathy. It was assumed that this was too high a dose. Fourteen patients were then given 12 doses of 1.25 gm/m^2 over 6 weeks. Of these only one died during treatment and one withdrew. No drug related deaths were noted. Three patients experienced Grade I neuropathies and four Grade II neuropathies with no neuropathies of a more severe nature. It was thus determined that the maximum tolerated dose in 6 weeks, with 12 doses was 1.25 gm/m^2 or a total of 15 gm/m^2 . Thus, the total dose could not be increased by dividing it into two rather than one administration per week.

Thus, it would appear that fractionation of the drug dosage has no effect on drug tolerance as related to neuropathy. Smaller incremental doses do, of course, markedly reduce nausea and vomiting. The maximum tolerated dose, regardless of fractionation, appears to be approximately 8 gm/m^2 in one week, 10.5 gm/m^2 in 1.5 weeks, 12 gm/m^2 in 2-3 weeks and 15 gm/m^2 in 6 weeks.

There has been no unusual adverse reaction to radiation in terms of either normal-tissue acute reactions, or at this point, with one year of observation, late radiation damage. All of the patients studied in the Phase I trial have had advanced disease and thus tumor control has not been easily assessable. It is a general conclusion that the drug used at the recommended maximum tolerated doses is reasonably safe with only occasional neuropathies more severe than Grade II. Most of these have appeared to be avoidable by adequate

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hydration and careful monitoring of the blood levels and the neurologic condition. It is clear from the responses seen to date that the drug warrants further clinical evaluation in a larger patient population in order to establish whether the recommended doses will indeed be tolerated and whether the radiation fractionation schemes will be acceptable in this type patient with these doses of misonidazole.

1.3 Fractionation Schedule Background

Significant plasma levels are required for reasonable enhancement of sensitivity in hypoxic cells. Dische, Saunders, Lee, and Adams (2) have published a curve combining data for V79 cells in culture and human skin.

McNally et al have recently published additional information concerning the relationship of drug concentration and the enhancement ratio in hypoxic tumor cells (6). They found that the in vivo radiosensitizing effect of the drug at concentrations ranging from 25-250 ug/gm of tumor tissue was at least as good as that published at lower concentrations. Enhancements with photons of up to 1.5 were seen for concentrations of approximately 40 and 50 ug/ml. Enhancement ratios with photons of about 1.75 were seen for 100 ug/ml, about 1.8 for 200-250 ug/ml.

The Phase I RTOG study, including cases from both the single weekly dose series and the multiple dose series, yields information on the relationship between drug dose given and mean 4-6 hr. serum level. With doses of 1.25 gm/m^2 the mean serum level is 46 ug/ml including both Ro-07-0582 and Ro-05-9963, the primary metabolite. Since Ro-05-9963 seems to be as active a sensitizer as the parent compound it has been included in the total levels and is indeed measured as part of the total level with UV spectrometry. At 1.5 gm/m^2 a mean level of 54 ug/ml was seen, at 2 gm/m^2 , 76 ug/ml and at 2.5 gm/m^2 , 98 ug/ml.

Since the curve relating enhancement ratio to misonidazole concentration is steep in its initial portion and then bends over, there is little gain in increasing concentration much above 100 ug/ml. Levels above this have also been associated with higher risks of severe neuropathy.

Because of the maximum tolerated doses expressed in Section 1.2 it is obvious that misonidazole cannot be administered daily with 20 or 30 fractions. On the other hand, it is clear that up to 12 adequate doses may be administered over 6 weeks.

1.4 Study Rationale.

While the OER for photons is 3.0, that for neutrons is approximately 1.6. Animal experimentation data suggests that the OER for neutrons can be reduced from the 1.6 level to nearly 1.0 by using the hypoxic cell sensitizers. This phase I/II study is proposed to evaluate the feasibility and toxicity of giving six neutron treatments at weekly intervals preceding each treatment by misonidazole 2.5 gm/m^2 , 4 hrs. prior to the neutron treatment. The incremental neutron dose will be 300 neutron rad. The first five doses will include the whole brain while the sixth dose will be delivered to a reduced boost volume. Allowing for the differences in beam energy, methods of dose measurement, and treatment schedule, this dose should be similar to 1300 Hammersmith rad.

2.0 OBJECTIVES

- 2.1 To lay the basis for a randomized phase III of misonidazole and neutron radiation versus misonidazole and photon radiation.
- 2.2 To determine the tolerance of the unusual radiation fraction scheme proposed in this protocol in terms of acute and late normal tissue reaction and damage.
- 2.3 To establish that the tumor clearance rate, disease-free interval and local tumor control rate are within the expected ranges for malignant gliomas.

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3.0 SELECTION OF PATIENTS AND ELIGIBILITY CRITERIA

3.1 Eligibility criteria.

- 3.1.1 Histologically confirmed malignant glioma, grade III or IV.
- 3.1.2 Tumor must be supratentorial in location.
- 3.1.3 All patients in this study will be over age 18 but less than age 70.
- 3.1.4 Life expectancy of at least four months.
- 3.1.5 Karnofsky Performance status equal to or greater than 50% (see Appendix I).
- 3.1.6 Patients must have a post-surgical, preradiotherapy CT scan for identification of extent of residual tumor.
- 3.1.7 Signed informed consent indicating awareness of the investigational nature of the study. The consent form must be in keeping with the policies of the institution and the National Cancer Institute (see Appendix II).
- 3.1.8 Functional Class I, II, or III (see Appendix V).
- 3.1.9 Patients must have an acceptable neurologic and metabolic status for ambulatory treatment at the neutron facility.
- 3.2.0 Renal function must be adequate with BUN values equal to or less than 25 and creatinine equal to or less than 1.5.

3.2 Ineligibility criteria.

- 3.2.1 Glioma, grade I and II.
- 3.2.2 Tumor which is infratentorial in origin.
- 3.2.3 Prior radiotherapy to the brain.
- 3.2.4 Any active malignancy in another body site.
- 3.2.5 Performance status less than 50 on the Karnofsky scale; Functional Class IV (see Appendix V).
- 3.2.6 Age less than 18 or over 70.

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- 3.2.7 Prior or concurrent chemotherapy. Pre-existing vincristine neuropathy or other severe drug related neuropathies. Concomitant neuropathies of central nervous system changes which would preclude the evaluation of misonidazole effects.

4.0 PRETREATMENT EVALUATION

4.1 General Evaluation.

- 4.1.1 A complete history and physical, including the documentation of all measurable disease is necessary. Special attention should be directed to a careful neurologic examination, including cranial nerves, mental status, visual status, peripheral reflexes, peripheral sensation, motor activity and cerebellar function.

4.2 Mandatory Imaging Procedures.

- 4.2.1 CT brain scan done post surgery but prior to the start of radiation.
- 4.2.2 Necessary imaging and/or contrast studies to optimally define the location and extent of the tumor including brain scan, CT scan, echogram, cerebral arteriography and/or air studies, i.e., ventriculogram, pneumoencephalogram.

4.3 Mandatory Laboratory Procedures.

- 4.3.1 CBC including platelets.
- 4.3.2 Serum alkaline phosphatase, SGOT, LDH, total protein, albumin, BUN, creatinine, bilirubin, calcium, sodium, potassium, phosphorus, total protein, uric acid, or other tests to assure acceptable liver and renal function.
- 4.3.3 Complete urinalysis.

- 4.4 Neurologic examination will include functional classification of status as per RTOG (see Appendix V).

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5.0 REGISTRATION

5.1 There will be no formal stratification as long as eligibility and ineligibility criteria are met (see 3.1 and 3.2).

5.2 The following information on each patient will be recorded in detail for future analysis:

5.2.1 Patient Name;

5.2.2 Institution;

5.2.3 Physician;

5.2.4 Location - frontal, parietal, temporal, occipital, central;

5.2.5 Size - volume in mm^3 estimated on CAT scan;

5.2.6 Number of lobes and hemispheres involved;

5.2.7 Extent of resection - biopsy only, partial extirpation, radical extirpation;

5.2.8 Grade III or IV, histology;

5.2.9 Performance status (see Appendix I).

5.3 Patients must be registered prior to starting therapy.

A patient will be entered into the study by calling the RTUG Headquarters (215) 574-3191 from 9:00 a.m. - 5:00 p.m., EST. After eligibility is verified, the patient will be assigned a project case number which will be confirmed by mail.

6.0 TREATMENT

6.1 Radiation Therapy.

6.1.1 Patients will be treated in the currently active neutron research facilities using the treatment distances and energies currently available at each of the installations.

6.1.2 Specific simulation is required to insure that the entire cranial contents are included in the treatment volume. The treatment portals should cover the cranial contents with a 1 cm margin. A film of each lateral portal must be obtained and provided to RTOG Headquarters. Appropriate head

holding or other immobilization devices should be used in order to insure reproducibility. The last two treatments are to a reduced volume including the gross disease with a 1 cm margin.

6.1.3 Doses will be specified along the central axis in the midplane of the skull.

6.1.4 Isodose curves, correction for inhomogeneities and off axis corrections are not required. The portals shall be opposing lateral portals covering the cranial contents but avoiding the orbit. Each portal must be treated at each treatment session, except for the boost.

6.1.5 Dose definition and schedule.

6.1.5.1 Treatment will be 1 fraction per week, 300 neutron rad at the midplane of the skull delivered with equal components from each lateral field (for the first four fractions). The final boost may be delivered from one or both sides depending on tumor location.

6.1.5.2 The total number of fractions shall be 4 to the whole brain plus two boosts.

6.1.5.3 The treatment shall be delivered in no more than six weeks. The total dose shall be 1200 neutron rad whole brain plus 600 rad boost.

6.1.6 No time dose modifications are permitted. Occasional delays because of equipment malfunction or transportation difficulties will permit the extension of the overall time to six weeks from five if one fraction is logistically not feasible.

6.1.7 Documentation requirements. After study entry, the radiotherapy prescription and a copy of the radiotherapy portal film, central axis calculations and treatment prescription must be forwarded to RTOG Headquarters within one week. At the completion of therapy, the radiotherapy flow sheet and a copy of the boost film must also be submitted.

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6.1.8 Institutional requirements. Only neutron facilities affiliated with the RTOG are eligible. A laboratory calibrated to measure misonidazole levels must be available to participants.

6.2 Chemotherapy Program.

6.2.1 Misonidazole.

6.2.2 Misonidazole - Ro-07-0582 (1-2 nitro-1 imidazolyl-3-methoxy -2- propanol) is a 2 nitroimidazole manufactured by Hoffman LaRoche Inc., Nutley, New Jersey and obtained through the National Cancer Institute, Division of Cancer Treatment, (NSC #261037). Drug request forms (NIH 986) must be submitted to RTOG Headquarters for approval. The drug is available as 500 and 100 mg capsules to be taken orally after a light meal.

6.2.2.1 Stability: The drug is stable for months.

6.2.2.2 Pharmacology: The assay for the drug in the blood is a spectro-photometric assay or HPLC assay as outlined in Appendix III. All participating institutions must have a reliable assay which has been calibrated against a standard curve before patient entry.

6.2.3 Dose Modification and Toxicity.

6.2.3.1 The dosage of misonidazole employed in this protocol may induce nausea and in occasional cases, vomiting. This can be minimized by administration of the drug within one-half to one hour following a light meal. If nausea is experienced symptomatic treatment can be administered in the form of antiemetic medications, so long as the dose and nature of these medications is documented on the study form. A compazine suppository (25 mg inserted 2 hrs. before drug

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administration) is usually effective. If a patient does experience vomiting, the time after the drug dose should be recorded, and whether or not drug is lost during the vomiting episode. Nausea and vomiting should be rated on a scale of 0-4 with the rating scale defined as follows:

- 0 = No vomiting or nausea.
- 1 = Slight nausea-no vomiting.
- 2 = Nausea-occasional vomiting.
- 3 = Nausea-vomits 1-3 times per day.
- 4 = Nausea severe and continuous with continuous vomiting requiring hospitalization.

Care must be taken to see the patients do not become dehydrated because of nausea ratings 3 or 4, since this may augment the neurologic toxicity of the misonidazole. Dehydration must be corrected with appropriate fluids or misonidazole must be stopped.

6.2.3.2 Neurologic toxicity. Patients may experience peripheral neurologic toxicity as a secondary effect due to misonidazole. The toxicity should be rated on the following scales:

6.2.3.2.1 Peripheral nervous system toxicity scale.

- 0 = none measurable.
- 1 = Decreased DTR's.
 - mild pain.
 - mild paresthesia.
 - mild constipation.
- 2 = Absent DTR's.
 - detectable or moderate weakness.
 - moderate paresthesia.
 - moderate constipation.

- 3 = Severe weakness, paresis; cannot squat or sit up in bed unassisted.
Severe pain.
Severe paresthesia.
Severe obstipation, manageable without surgery.
- 4 = Paralysis.
Transverse myelitis.
Obstipation requiring surgery.

6.2.3.2.2 Central nervous system toxicity scale.

- 0 = None measurable.
- 1 = Transient alteration in mental status and/or minimal lethargy.
Mild or transient alteration in cerebellar functions.
- 2 = Alteration of mental status > 50% of the time or of function.
Alteration of motor or cerebellar functions, > 50% decrement of baseline capabilities. Seizure disorder which is transient or satisfactorily controlled by medical therapy.
- 3 = Alteration of mental status \leq 50% of the time or of function.
Alteration of motor or cerebellar functions, \leq 50% decrement of baseline capabilities. Seizure disorder not controlled by medical therapy.
- 4 = Comatose.
Paralysis.
Confinement to bed due to cerebellar dysfunction.
Status epilepticus.

6.2.3.2.3 Ototoxicity. (Appendix IV for baseline values).

0 = \leq 25 db hearing loss.

No difficulty with faint speech.

1 = 25-40 db hearing loss.

Difficulty with faint speech only.

2 = 41-55 db hearing loss.

Frequent difficulty with faint speech.

3 = 56-70 db hearing loss.

Frequent difficulty with loud speech.

4 = \geq 71 db hearing loss.

Understands only shouted or amplified speech, if any.

6.2.4 Documentation of Toxicity. All toxicity must be rated as above and recorded on the sensitizer form. The time in relation to drug administration of the onset of these toxicities must be recorded. The amount of any analgesic medication required because of peripheral neuropathy as opposed to other pain must be recorded. All major drugs administered must be recorded with their doses in particular dexamethazone, phenytoin sodium and any other anticonvulsant.

6.2.5 Dose Modification. The dose of misonidazole indicated in the protocol should not be reduced for nausea or vomiting. At the first sign of any central nervous system effects thought due to misonidazole, or signs of ototoxicity due to misonidazole of any grade, the misonidazole must be stopped. Radiation should continue as per the protocol and the patient will remain on study. At the development of any Grade 2 or greater peripheral neuropathy, misonidazole administration should be discontinued, but the patient

continued in the protocol as above. If the patient is withdrawn from misonidazole administration because of the above, call Dr. Lawrence Davis, Associate Chairman, (215) 574-3180, or the sensitizer Co-Chairman for toxicity, Dr. Todd Wasserman. His number is (314) 454-3381. If they cannot be reached inform Dr. Theodore L. Phillips, at (415) 666-4815.

- 6.2.6 Details of drug administration. The drug shall be given at a dose of 2.5 g/m^2 once per week 4-6 hours before the neutron treatment for a total of 6 doses. Drug shall be given after a light meal. A compazine suppository of 25 mg shall be inserted 2 hours before drug administration unless the patient has a known allergy or reactivity to compazine. The total dose of drug administered under this protocol should not exceed 15 g/m^2 .
- 6.2.7 The number of radiation fractions and the number of misonidazole doses required by this protocol must be administered unless unacceptable toxicity as listed previously is encountered. Additional misonidazole will not be given beyond that specified by the protocol. Patients not responding well should not be removed from the study prior to administration of the prescribed radiation and misonidazole dosage unless unacceptable toxicity is encountered, or the patient refuses.
- 6.2.8 A minimum of two blood levels are required. Initial blood levels should be obtained 4-6 hours after the drug administration (at the time of radiation) and a second blood level should be obtained 24-28 hours after drug administration. If the 4-6 hour blood level varies from the mean by more than two standard deviations per the table below, then a repeat of the measurement after the next dose of Misonidazole must be made. If the 24-28 hour concentration is greater than 25% of the 4-6 hour concentration, then a repeat of both measurements with the next dose of Misonidazole must be made. If the repeat measurements confirm the initial variation of either the 4-6

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hour or the 24-28 hour concentrations, then the Cochairman for sensitizers should be called for the appropriate dose reduction of Misonidazole.

Relationship of Dose to Mean 4-6 Hour Serum Level

Dose = 2.5 gm/m²

	<u>Phase I</u>	<u>Phase II</u>
No. of Doses (Determinations)	43	324
Mean 4-6 Hr. Serum Level ug/ml	98	83
+/- Standard Deviation	23	29
Observed Range	35-148	4-165

7.0 PATHOLOGY

Does not apply to this study.

8.0 PATIENT ASSESSMENTS

8.1 Patient assessment will include the following:

8.1.1 Study Parameters.

	<u>Pre-Treatment</u>	<u>During Treatment</u>	<u>Each Follow-up</u>
History and Physical (including neurological assessments)	x	x	x
Karnofsky Status	x	a	x
Neurological Functional Classification	x	x	x
CT Scan	x		b
CBC, platelets	x	a	b
Urinalysis	x		
BUN, creatinine, uric acid	x	a	b
Alkaline Phosphatase, LDH, SGOT, bilirubin	x	a	b
Electrolytes	x	a	
Total Protein, Albumin	a	a	
Misonidazole Serum level		a	

- a) If receiving misonidazole (see Appendix V for additional assessments).
- b) If indicated.

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- 8.1.2 Misonidazole Toxicity: The frequency, duration and grade of nausea and vomiting occurring in the patient will be recorded and evaluated.
- 8.1.3 The incidence and degree of peripheral and central neurologic toxicity and ototoxicity will be recorded and evaluated as a function of the number of drug administration, total drug dose, and plasma levels.
- 8.1.4 Mean plasma (4-6 hour) blood levels will be recorded for each drug administration and correlated with the observed frequency and severity of gastrointestinal and neurologic toxicity as well as the drug dose administered in terms of mg/m^2 and mg/kg .
- 8.1.5 Reactions to radiotherapy, both acute and late, will be recorded and included in the complete toxicity evaluation (Appendix IV). Toxicity occurring in any organ will be recorded, as will the location of the organ (within or outside of the radiation treatment volume).
- 8.1.6 Late normal tissue reactions should be recorded at the time of each follow-up according to the scale in Appendix VII.

8.2 Criteria for Tumor Response.

- 8.2.1 All neurological exams and CT scans are graded by comparing the results of the current test with the most recent preceding test. The scale below is to be followed:
- | | | | |
|----|-------------------------------------|----|-----------------------|
| -3 | Marked Deterioration | +3 | Marked Improvement |
| -2 | Definite Deterioration | +2 | Definite Improvement |
| -1 | Suspected Deterioration | +1 | Suspected Improvement |
| 0 | No change since previous evaluation | | |

- 8.2.2 Response is defined as definite (+2) improvement in at least one of these two parameters: neurological examination and CT scan, provided that the patient is on a stable or decreasing dose of steroids. A concomitant increase in steroid dose will rule out a "response" designation at this point. Suspected (+1) improvement will not designate response.

8.2.3 Conversely, progression is defined as definite (-2) deterioration in at least one of these two parameters: neurological exam and CT scan, provided that the patient has not had his/her dose of steroids decreased since the last course of therapy. A concomitant decrease in steroid dose will rule out a "progression" evaluation at that point. Suspected (-1) deterioration will not designate progression.

8.2.4 Stabilized disease (no change) is defined as stability or suspected (+1 or -1) changes in the test parameters, or improvement in one of the parameters, and deterioration in one parameter.

8.2.5 Follow-up assessments are to be done midway through treatment, upon completion of radiotherapy, then every three months until death. Patients receiving misonidazole are to have assessments done prior to each treatment according to misonidazole study parameters (Appendix VI). Every attempt should be made to obtain an autopsy for confirmation of tumor types and for studying radiation-sensitizer effects on normal brain.

8.3 Measurement of Specific End Points.

8.3.1 Relapse free interval will be measured from the first day of treatment until deterioration is documented as defined in 8.2.

8.3.2 Overall survival will be measured from the first day of radiotherapy until death.

9.0 DATA COLLECTION

9.1 The forms to be utilized will be the standard RTOG on study form, completion of treatment and follow-up forms of the glioma studies. A study specific flow sheet for the recording of drug administration, doses, blood levels and tumor levels are to be used. Since this is an ongoing flow sheet, it should be copied and forwarded to RTOG Headquarters according to the specified schedule. The completed form will be forwarded when all of the required entries have been made at the scheduled times and upon termination of the study.

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9.2 Data Submission.

<u>Form</u>	<u>Due</u>
On Study Form Radiotherapy prescription, Calculations, localization film	Within one week of commencement of treatment
Radiotherapy Form Treatment Record Boost film	Within one month of completion of treatment
Follow-up Form Sensitizer flow sheet	Midway through treatment, at completion of treatment, then every 3 months and at death.

9.3 The individual laboratories at the participating institutions measuring blood levels by ultra-violet spectrophotometry of high pressure liquid chromatography will have their laboratories calibrated by a sample specimen or set of specimens to be provided by Dr. Wolfgang Sadee at the University of California, San Francisco. Dr. Sadee's laboratory will act as a reference laboratory for this study and will review the ability of the individual laboratories to reproduce drug level measurements. The laboratories of affiliate members will be calibrated by the laboratory of the full member with whom they are associated.

9.4 The radiologic physics center will have reviewed the dosimetry of each participant in the study. All neurologic reactions of Grade III or IV will be reviewed by Dr. Victor Levin, the General Neurological consultant to the project.

9.5 Case histories and copies of neurologic examinations recorded by the local neurologists should be forwarded to RTOG Headquarters to be reviewed by Dr. Levin in situations in which patients experience a Grade III or IV peripheral or central nervous system neuropathy.

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10.0 STATISTICAL CONSIDERATIONS

- 10.1 This study is a non-randomized Phase I/II evaluation of the combination of misonidazole and neutron radiation for malignant glioma.
- 10.2 In general, 25 patients will be entered into the protocol although termination or dose modification may occur earlier if undue toxicity occurs or if response is completely beyond the limits expected. The protocol will be open to all members who have approved laboratories for the measurement of misonidazole levels and who have access to neutron treatment facilities.

With this sample size we have a 93% chance of seeing any complication that occurs one time out of ten. Furthermore, we have over a 90% chance of accepting the treatment for further testing if the actual local control rate of the new treatment is 45% at one year and less than 25% chance of further testing if the actual control rate at one year is 25%.

11.0 ADDITIONAL TREATMENT

- 11.1 Patients must have all necessary general medical supportive care. In particular, care must be taken that patients do not become dehydrated due to vomiting or diarrhea and that their serum electrolytes remain within acceptable limits.
- 11.2 Infections: Infections are not generally a problem under misonidazole administration.
- 11.3 Analgesia: Patients should be administered analgesic treatment as needed but this should be recorded, particularly when related to peripheral neuropathy.
- 11.4 Patients shall be removed from the study at any time if they develop unacceptable side effects that cannot be controlled with other agents (e.g. antiemetics). Should deterioration in hematologic or chemical parameters occur, this can be considered grounds for removal from the study and cessation of drug administration. Drug neurotoxicity as described previously in Class III or IV shall require that the patient receive no further drug and be observed for the course of toxicity. However, follow-up assessments must be submitted, as required, until death.

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11.5 Any patient shall be removed from the study if his overall condition, in terms of general functional status, should deteriorate without obvious explanation. The drug shall be stopped in such patients and they shall be evaluated individually. The time of cessation of drug and reasons therefore should be recorded carefully. Follow-up assessments must be submitted until death.

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APPENDIX I

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some sign or symptoms of disease.
70	Cares for self, unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated, although death not imminent.
20	Very sick; hospitalization necessary; active support treatment is necessary.
10	Moribund; fatal process progressing rapidly.
0	Dead.

APPENDIX II

CONSENT FORM FOR NEUTRON RADIOTHERAPY AND MISONIDAZOLE PROTOCOL

I understand that my diagnosis is malignant glioma, a brain tumor, and that further treatment is recommended. The standard therapy in the management of cases such as mine would be radiotherapy with or without chemotherapy. Radiotherapy is the treatment of tumors by means of x-rays. Chemotherapy is the treatment of tumors by means of chemicals which selectively destroy tumor tissue.

A new type of radiation called neutrons may improve the chance of controlling the tumor although the side effects of treatment may be more severe.

Misonidazole is a drug which has been found to possibly enhance the effect of radiotherapy in patients with brain tumors such as mine. This drug is therefore considered to be potentially helpful for controlling my disease.

Side effects which may occur are nausea and vomiting. These can frequently be controlled by anti-nausea medications. In patients treated with Misonidazole some developed weakness, numbness and tingling in the arms and legs. Although these side effects may not occur with the dosages to be given to me, I understand these side effects are possible. These side effects are usually mild and reversible.

I understand that Misonidazole has been approved for investigational use in human beings by the Food and Drug Administration. No guarantee or assurance has been made as to the results that may be obtained, since investigational results cannot be fully foreseen.

As part of the evaluation of Misonidazole and my therapy, I will permit my doctors or their designated nurses to withdraw samples of my blood during the Misonidazole course. Possible side effects include minimal discomfort from venipuncture and possible hematoma ("black and blue" mark). On the days of Misonidazole ingestion two samples of blood will be required. Each sample will amount to less than 2 teaspoons.

Neutron radiotherapy in the doses and schedule to be given to me have been modified to take best advantage of the effects of Misonidazole. Side effects include hair loss, reddening of the skin, possible nausea, headaches and fatigue.

I understand I will be treated with neutron radiotherapy and Misonidazole. I understand that the possible benefits are shrinkage and control of my tumor and prolongation of life.

This hospital and institution where I am being treated does not provide compensation for any treatment disability incurred as a result of participating in this research.

I have discussed the above information with _____ and he/she has agreed to answer any questions I may have concerning this treatment program and the methods available for treatment of my disease. I understand alternate forms of therapy include conventional radiotherapy alone or conventional radiotherapy and chemotherapy.

I have reviewed the foregoing statements and understand them. I understand that I am free to withdraw from this treatment program at any time without penalty or prejudice. I agree to participate in this treatment evaluation.

(Physician's signature)

(Patient's signature)

(Date)

(Date)

(Witness's signature)

(Responsible party if patient
is unable to give consent)

(Date)

(Date)

(Relationship)

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APPENDIX III

UV SPECTROPHOTOMETRY METHODS

A. Whole Blood

1. Blood is drawn in a red top tube and allowed to clot.
2. A hematocrit must be performed on the specific blood sample for use in future correction of the results.
 - a. 1 cc of whole blood at room temperature is placed in 9 cc of ethanol and allowed to stand for 15 minutes.
3. The mixture is centrifuged at 2500 x g for 10 minutes.
4. The optical density of the supernatant is measured at 318-325 nm. The exact value should be established for each laboratory at the peak of spectrophotometric absorption of a standard sample.
5. The reading for a control blood sample handled in the same manner is subtracted from it.
6. Using this method, a standard curve is set up by placing various quantities from 50 to 1000 M of Ro-07-0582 in the blood prior to preparation. The readings of the standard curve are then compared to the reading of the unknown to determine the quantity of Ro-07-0582 in the sample.
7. Since the hematocrit will somewhat change the reading, a correction curve for the hematocrit of the blood used must be generated, and this correction applied if the hematocrit of the standard is different from that of the test sample. This can be avoided if a sample of the patient's blood is available just before drug administration for use as a control.

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B. Tissue Determinations

1. Samples of 0.5 to 1 gm of tissue are minced with scissors in 9 (or 4.5) cc of ethanol. As much blood as possible should be allowed to drain from the sample before preparation; then loose blood should be blotted from the surface.
2. Samples should be allowed to stand for one to two hours.
3. Samples are then centrifuged at 2400 x g for 10 minutes.
4. The optical density of the supernatant is measured at 318-325 nm. The exact value should be established for each laboratory at the peak of spectrophotometric absorption of a standard sample.
5. The background reading of a control tissue sample is subtracted from the reading.
6. A standard curve is set up in the manner similar to that for blood and used to determine the exact level in the unknown sample.

APPENDIX IV

RT06 TOXICITY CRITERIA --- RADIOSENSITIZERS

RT06 TOXICITY CRITERIA - CONTINUED

GRADE

TOXICITY CRITERIA	GRADE				
	0	1	2	3	4
a) Hemorrh. None	Minimal	Mod-Mot debilitating	Debilitating	Life threatening	
b) Infection None	Fever during treatment, No organism recovered.	Localized infection (e.g. cystitis, pneumonia)	Bacteremia	Septic shock	
a) Protein Neg.	Micro-Cult 0	2+ - 3+ Gross-Cult 0	4+ Gross 5 Clots	± obst uropathy	
b) Hematuria Neg.	None	None	Micro-Cult 0	Hepatic coma	
URIN	None	None	Hemorrhagic cystitis	Cystectomy required	
a) Nausea & Vomiting None	Slight nausea - no vomiting	Nausea-occasional vomiting	Nausea - Vomiting (1-3 times per day)	Nausea - Severe and continuous vomiting. Requires hospitalization	
b) Diarrhea Normal movements; No medication	Severe diarrhea; Medication; antispasmodics	Watery and frequent movements (more than 3-4 per day)	Watery and frequent movements (more than 3-4 per day)	Hemorrhagic diarrhea. Requires hospitalization	
c) Oral Toxicity No oral ulceration	Faint pinkish erythema	Patchy necrotic; brisk erythema	Fibrinous mucositis confluent	Ulcerative mucositis; Necrosis. Requires hospitalization	
a) Radiation pneumonitis None	1-ray changes. Minimal or no symptoms	Moderate symptoms; No specific rx. required	Severe Sx. Corticosteroid rx. initiated	Irreversible. Severe disability	
b) PFT None	25-50% decr. in Dec or VC	> 50% decrease in Dec or VC	Severe Sx-Intermittent O2	Assisted vent or continuous O2	
c) Clinical None	Mild Sx	Moderate Sx	Severe Sx-Intermittent O2	Severe or refract CHF ventricular tachy	
ECG	ST-T changes Sinus tachy > 110 at rest	Atrial arrhythmias Multifocal PVC's PEP/LVET > 42	Pericarditis	Myocardial infarction	
ECG	Slight erythema; Dry desquamation	Brisk erythema	Moist desquamation	Necrosis	
ECG	Slight erythema; Dry desquamation	Brisk erythema	Moist desquamation	Ulceration	
ECG	Minimal pigmentation	Predominant depigmentation mild fibrosis	Falangectasis atrophy Severe, symptomatic fibrosis	Necrosis ulceration	
ECG	Decreased DTR's	Absent DTR's	Detectable or moderate weakness	paralysis transverse myelitis	
ECG	No Change	Moderate pain Moderate parasthesia	Severe pain Severe parasthesia	Obtipation requiring surgery	
ECG	Mild constipation	Moderate constipation	Severe obstipation without surgery		

THE TOXICITY GRADE SHOULD REFLECT THE MOST SEVERE DEGREE OCCURRING DURING THE EVALUATED PERIOD, NOT AN AVERAGE. WHEN TWO OR MORE CRITERIA ARE AVAILABLE WITHIN A TOXICITY CATEGORY, E.G. NEURO-PH CODES, THE ONE RESULTING IN THE MORE SEVERE TOXICITY GRADE SHOULD BE USED. TOXICITY GRADE - 5 IF THAT TOXICITY CAUSED THE DEATH OF THE PATIENT. REFER TO DETAILED TOXICITY GUIDELINES IN THE PROTOCOL OR TO STUDY CHARTERS FOR TOXICITY NOT COVERED ON THIS TABLE.

WADSWORTH SCALE

100 - Normal; no complaints, no evidence of disease
 90 - Able to carry on normal activity; minor signs or symptoms of disease
 80 - Normal activity with effort; some signs or symptoms of disease
 70 - Care for self, unable to carry on normal activity or to do active work
 60 - Requires occasional assistance but is able to care for most of his needs
 50 - Requires considerable assistance and frequent medical care
 40 - Disabled; requires special care and assistance
 30 - Severely disabled; hospitalization is indicated, although death not imminent
 20 - Very sick; hospitalization necessary, active supportive treatment necessary
 10 - Moribund; fatal processes progressing
 0 - Dead

NEUROLOGIC STATUS
 1 - No evidence of disease
 2 - Equivocal evidence of disease
 3 - Partial regression since last
 4 - Partial regression since last
 5 - No response since last
 6 - Progression since last measurement

NEUROLOGIC STATUS
 1 - No evidence of disease
 2 - Equivocal evidence of disease
 3 - Partial regression since last
 4 - Partial regression since last
 5 - No response since last
 6 - Progression since last measurement

Relationship of Dose to Mean 4-6 Hour Serum Level

Dose mg/m ²	No. of Doses (Determinations)	Mean Serum Level (ug/ml)	Standard Deviation (0.582 x 9963)	Observed Range
1.0	17	30	17.8	21-57
1.25	116	46	17.6	31-61
1.5	78	60	17.18	16-95
1.75	18	70	17.18	39-107
2.0	99	76	17.14	51-120
2.5	43	98	17.23	35-148
3.0	25	116	17.26	38-155
4.0	6	125	17.56	83-230
5.0	7	183	17.60	91-245

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APPENDIX VI
MISONIDAZOLE PHASE II PROTOCOLS

Study Parameters to be Recorded on Flow Sheet

Parameter	On Study	At each dose Misonidazole	At last dose Misonidazole	At each Follow-up visit
Date	X	X	X	X
Weight	X	X	X	X
Karnofsky Scale	X	X	X	X
Radiation Dose	-	X	X	-
Size Indicator Lesion	X	X	X	X
Clinical Diagram or Photo	X	X	X	X
Local Disease Status	X	X	X	X
Total Disease Status	X	X	X	X
Nausea & Vomiting	X	X	X	X
Neurotoxicity	X	X	X	X
Antiemetics	X	X	X	X
Analgesics	X	X	X	X
Peak Serum Level	-	a	-	-
HCT/Hgb	X	X	X	b
WBC	X	-	X	b
Platelets	X	-	X	b
Ca+	X	-	X	b
BUN	X	-	X	b
Uric Acid	X	-	X	b
Total Protein	X	-	X	b
Albumin	X	-	X	b
Bilirubin	X	-	X	b
Alkaline Phosphatase	X	-	X	b
LDH	X	-	X	b
SGOT	X	-	X	b
Creatinine	X	-	X	b
Na+	X	-	X	b
K+	X	-	X	b

a. After first misonidazole dose.

b. If indicated or every 6 months.

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APPENDIX V

FUNCTIONAL CLASSIFICATION

- Class I Able to work or to perform normal activities.
- Class II Able to carry out normal activities with minimal difficulty. Neurologic impairment does not require nursing care or hospitalization.
- Class III Seriously limited in performing normal activities. Requiring nursing care or hospitalization. Patient confined to bed or wheelchair, or has significant intellectual impairment.
- Class IV Unable to perform even minimal normal activities, requires constant nursing care and feeding. Patient unable to communicate or in coma.

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Appendix VII

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Organ/Tissue	0	1 Mild	2 Moderate	3 Severe	4 Life Threatening	5*
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patchy atrophy Moderate telangiectasia Total hair loss	Marked atrophy Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture (< 10% linear reduction)	Severe induration and loss of subcutaneous tissue Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANES	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucus	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness Poor response on stimulation	Complete dryness No response on stimulation	Necrosis	
SPINAL CORD	None	Mild L'Hermite's syndrome	Severe L'Hermite's syndrome	Objective neurological findings at or below cord level treated	Mono or para quadriplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headache Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or Paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panophthalmitis Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever. Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency Continuous oxygen Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion and ST changes Sinus tachycardia > 110 (at rest)	Moderate angina of effort Mild pericarditis Normal heart size Persistent abnormality T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade Severe heart failure Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilatation required	Necrosis Perforation, Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping. Bowel movement < 5 times daily. Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement > 5 times daily. Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation, Fistula	
LIVER	None	Mild lassitude, nausea dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis Hepatic coma or Encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine Clearance > 75%	Persistent moderate albuminuria (2+) Mild hypertension. No related anemia. Moderate impairment renal function Urea > 36-60 mg% Creatinine 2.5-4.0 mg% Creatinine Clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (< 10g%) Severe renal failure Urea > 60 mg% Creatinine > 4.0 mg% Creatinine Clearance < 50%	Malignant hypertension Uremic coma Urea > 100 mg%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity (< 150 cc)	Necrosis Contracted Bladder (capacity < 100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Retardation of growth Irregular bone sclerosis	Severe pain or tenderness Complete arrest bone growth Dense bone sclerosis	Necrosis Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis Complete fixation	

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