RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-10

A PHASE II STUDY OF CONVENTIONAL RADIATION THERAPY FOLLOWED WITH RECOMBINANT INTERFERON BETA FOR SUPRATENTORIAL GLIOBLASTOMA

(NSC # 658933)

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INDEX
INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluation

5.0 Randomization

6.0 Radiation Therapy Parameters

7.0 Chemotherapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessment

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Karnofsky Performance Status and Neurologic Function Status
Appendix III - Toxicity Criteria
Appendix IV - Adverse Reaction Reporting Guidelines
Appendix V - Radiation Therapy Parameters
Appendix VI - Product Shipment Form
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SCHEMA

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
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<tbody>
<tr>
<td>S</td>
<td>1. ≥ 18 to &lt; 40</td>
<td>R</td>
<td>60.0 Gy/30 fractions x 2.0 Gy. For the first 46 Gy/23 fractions the treatment volume should include the volume of contrast enhancing lesion and surrounding edema on pre-operative CT/MRI scan plus a 2 centimeter margin. If no edema is present the margin should be 2.5 cm. After 46.0 Gy, the tumor volume should include the contrast enhancing lesion (without edema) on the pre-surgery MRI/CT scan plus a 2.5 centimeter margin.</td>
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<tr>
<td>T</td>
<td>2. ≥ 40 to &lt; 60</td>
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<tr>
<td>T</td>
<td>3. ≥ 60</td>
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<tr>
<td>R</td>
<td>Performance Status</td>
<td>E</td>
<td>Beginning 4-6 weeks after completion of radiation therapy, administer recombinant interferon beta (rhIFN-b) 6 million units IM once a day Monday, Wednesday, Friday, three times per week. Three weeks on drug and one week off drug.</td>
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<tr>
<td>A</td>
<td>1. KPS ≥ 80</td>
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<tr>
<td>A</td>
<td>2. KPS 60-70</td>
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Eligibility (See Section 3.0 for details)

- Histopathologically confirmed glioblastoma multiforme (with areas of necrosis)
- The tumor must be supratentorial in location
- Age ≥ 18
- KPS ≥ 60
- No prior radiation therapy to head or neck area, chemotherapy or radiosensitizer.
- Absolute Neutrophil count ≥ 1500, platelets ≥ 100,000, BUN ≤ 25, Creatinine ≤ 1.5, Bilirubin ≤ 2.0, Hgb ≥ 10 gm
- No malignancy (within the past five years) except non-melanomatous skin cancer or carcinoma in-situ of the cervix
- SGPT or SGOT ≤ 2 x normal range
- Signed study-specific consent form

Required Sample Size: 108

7/1/99

Institution #

RTOG 97-10

Case #
1. Does the patient have histologically confirmed supratentorial glioblastoma multiforme?
2. Is the tumor recurrent?
3. Has the patient recovered from the effects of surgery, post-operative infection or other complications?
4. Has a diagnostic contrast enhanced MRI or CT of the head been performed pre-operatively?
5. Has a diagnostic contrast enhanced MRI or CT of the head been performed post-operatively?
   If no, did the patient have only a stereotactic biopsy performed?
6. Do the patient’s laboratory values meet the criteria in Section 3.1.10?
7. Has the patient received any prior radiotherapy to the head and neck or any chemotherapy or radiosensitizer for any reason?
8. Is the patient known to have Acquired Immune Deficiency Syndrome?
9. Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma in-situ of uterus, cervix or bladder?
   If yes, has the patient been disease free for ≥ 5 years?
10. Does the patient have any detected metastases below the tentorium or beyond the cranial vault?
11. Is the patient’s KPS ≥ 60 and age ≥ 18?
12. Does the patient have an estimated survival of at least 8 weeks?
13. Does the patient have any major medical or psychiatric illness which in investigator’s opinion will prevent administration or completion of the protocol therapy?
The following questions will be asked at Study Registration:

______ (Y) 1. Has the Eligibility Checklist (above) been completed?

______ (Y) 2. Is the patient eligible for this study?

____________ 3. Date the study-specific Consent Form was signed? (must be prior to study entry)

__________________ Patient's Name
__________________ Verifying Physician
__________________ Patient ID #
__________________ Referring Institution # (if different)
__________________ Age (≥ 18)
__________________ Karnofsky Performance Status (≥ 60)
__________________ Medical Oncologist
__________________ Birthdate
__________________ Sex
__________________ Race
__________________ Social Security Number
__________________ Zip Code (9 digit if available)
__________________ Method of Payment
__________________ Will any component of the patient’s care be given at a military or VA facility?
__________________ Treatment Start Date
__________________ Treatment Assignment

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

1.1 Background

The diagnosis of malignant glioma includes tumors characterized as astrocytoma with anaplastic foci (AAF) or as glioblastoma multiforme (GBM). Despite important advances in diagnosis and therapy, malignant gliomas continue to frustrate clinical investigators in their tendency to recur and progress at or near their original location. A number of studies performed by the Brain Tumor Study/Cooperative Group (BTSG or BTCG) and the Radiation Therapy Oncology Group (RTOG) have settled several important therapeutic issues regarding malignant gliomas. At the same time these studies have raised several new questions, particularly the role of chemotherapy in the overall management of patients with glioblastoma multiforme. The major issue in the treatment of glioblastoma pertinent to this study is the role of interferon in improving time to tumor progression and survival.

1.2 Prior Studies

Two successive randomized BTSG studies, 69-01 and 72-01 demonstrated superior survival for patients with malignant glioma receiving whole brain RT to 60 Gy in single 1.8 to 2.0 Gy daily fractions with or without BCNU (69-01) or MeCCNU (72-01) as compared to either drug alone or to supportive care following biopsy or subtotal resection. An evaluation of these trials as well as BTSG 66-01 by Walker, et al. suggested that an RT dose response existed to at least 60 Gy, with an increase in median survival time observed from 28 to 42 weeks. A report from the randomized trial BTCG 80-01 demonstrated that at least the final portion of the 60 Gy can be delivered via a "coned-down" field including the primary tumor plus margin without compromise on outcome.

In RTOG 74-01 no survival difference was observed between the treatment arm using 60 Gy whole brain RT plus a 10 Gy "boost" and the treatment arm using 60 Gy whole brain without a boost. With the advent of improved neuroradiologic techniques, especially computed tomography and magnetic resonance imaging, the recent RTOG malignant glioma studies (83-02 and 86-12) have replaced whole brain RT with a large partial brain field encompassing the primary tumor and surrounding edema with margin followed by a smaller field to the tumor plus margin. This approach has the advantage of decreasing the volume of neural tissue irradiated and thereby decreasing treatment toxicity, without compromising tumor control. Based on these studies, current standard radiotherapeutic management of malignant gliomas involves delivery of 60 Gy in 1.8 to 2.0 Gy single daily fractions using the shrinking field technique described above. Two recent reports correlated the location of tumor failure of glioblastoma multiforme with pretreatment tumor and edema volumes and one of these reports observed tumor infiltration within and just beyond the peritumoral edema, confirming the need for adequate radiotherapeutic coverage of this region.

1.3 Role of Chemotherapy and Treatment Response Modifiers for Malignant Glioma

Several RTOG and BTSG/BTCG studies have confirmed that the nitrosourea carmustine (1,3-bis (2-chloroethyl)-1 nitrosourea, i.e., BCNU) confers a real but modest survival benefit to the advantage seen with RT alone in at least several patient categories. In BTSG 69-01, patients receiving BCNU + RT had an improved survival rate at 18 months compared to RT alone. While no overall survival difference was observed in RTOG 74-01 between the RT/BCNU arm and RT alone, a survival difference (p < 0.01) was observed in patients less than 60 years of age in favor of the RT/BCNU arm (median survival: 12.0 vs. 8.7 mo.).

Both cooperative groups have studied other systemic agents to improve on the modest benefit seen with BCNU. No further survival advantage was seen with MeCCNU (BTSG 72-01), MeCCNU plus dacarbazine, (RTOG 74-01), methylprednisone (BTSG 75-01), misonidazole (RTOG 79-18 and BTCG 77-02), streptozotocin (BTCG 77-02), and procarbazine, hydroxyurea, and VM-26 (BTCG 80-01). In a Northern California Oncology Group study comparing post-RT BCNU versus procarbazine, CCNU, and vincristine, (PCV), Levin et al. reported an improved survival among "adequately treated" anaplastic glioma patients treated with PCV over BCNU. This difference was less apparent when all randomized patients with anaplastic gliomas were analyzed and was not present among patients with GBM, the histology seen among 80-85% of patients enrolled on RTOG glioma trials.

Other strategies have included: (1) high dose preirradiation chemotherapy; (2) intra-arterial (IA) chemotherapy; and (3) new systemic agents. The preirradiation chemotherapy regimens have included...
high dose BCNU with autologous bone marrow transplantation,\textsuperscript{17} “eight-drugs-in-one-day” chemotherapy,\textsuperscript{18} and infusional BCNU and cisplatin.\textsuperscript{19} Despite responses, no improvement in median survival time over conventional therapy has been suggested by these pilot studies. IA chemotherapy offers the theoretical advantage of enhanced drug delivery to the tumor site while minimizing systemic side effects. While Mahaley, et al. reported a 34\% response rate among recurrent irradiated gliomas using nonstandard response criteria,\textsuperscript{20} most investigators, including the Southwest Oncology Group,\textsuperscript{21} have reported unacceptable toxicity\textsuperscript{22} and lack of improved efficacy for IA versus intravenous chemotherapy.

Interferons (IFN) are a group of naturally produced glycoproteins endowed with antiviral, antiproliferative and immunomodulatory properties. Three main classes of IFN have been identified based on cell of origin and physiochemical, antigenic and biological differences: alpha (\(\alpha\)), beta (\(\beta\)) and gamma (\(\gamma\)). Leukocytes produce interferon-alpha, fibroblasts secrete IFN-\(\beta\) and T lymphocytes produce interferon-gamma. IFN-\(\alpha\)-alpha and IFN-\(\beta\) are known collectively as type I interferons, and are inducible by viruses or polynucleotides; they are resistant both to heat and extremes of pH. Type II interferon (IFN-gamma) is induced by mitogens and antigens and is heat- and acid-labile. Type I interferons are encoded on chromosome 9 in close proximity to each other, whereas the gene for interferon-gamma is on chromosome 12. IFN-beta differs serologically and chemically from IFN-alpha and IFN-gamma. Its amino acid homology with the alpha interferons is only 30\% and with IFN-gamma a mere 1\%.\textsuperscript{23} It induces antiviral effects in some cells in vitro more rapidly than either of the other two types of interferon. Although, like IFN-alpha, it binds to the type I IFN receptor it does so with a higher affinity.\textsuperscript{24} There is some preliminary evidence that it also has its own receptor type distinct to the one it shares with IFN-alpha. The gene for classical type I receptor is located on chromosome 21 and that for the type II receptor on chromosome 6.

Interferons exert three different types of biological effects including anti-viral, anti-proliferative and immunomodulatory. The enzyme 2', 5' oligoadenylate synthetase (2', 5' OAS) is induced by interferons and causes polymerization of ATP into 2', 5' oligoadenylates, which activate an endonuclease that is capable of cleaving single stranded RNA.\textsuperscript{25} This enzyme is of interest in the clinic as a possible marker predictive of clinical response to interferon therapy.\textsuperscript{25, 26, 27} Interferons induce expression of MHC class I and II antigens on various cells.\textsuperscript{28, 29} They also induce protein kinase\textsuperscript{30} and protein 78\textsuperscript{31} which are important in mediating anti-viral and anti-proliferative activities. IFN-\(\beta\) is capable of inducing indolamine 2,3-dioxxygenase (IDO) in monocytes and macrophages but not in lymphocytes.\textsuperscript{32, 33} This enzyme plays an important role in the defense against intracellular pathogens, toxoplasma gondii, for example. It may also be important in the tumoricidal function of the macrophages. In addition to the induction/enhancement of MHC antigens, the expression of certain tumor-associated antigens (e.g. carcinoembryonic antigen) on the surface of human tumor cell lines can be regulated in vitro by all three classes of interferons.\textsuperscript{34} Interferons are also known to stimulate a variety of immune effector cells in vitro and in vivo. Hence, by augmentation of these two mechanisms, afferent and efferent, greater therapeutic effect might be achieved. All three classes of interferons are capable of up-regulating estrogen and/or progesterone receptors on tumor cells both in vitro and, in the case of IFN-\(\beta\), in the clinic.\textsuperscript{35} Additionally, IFN-\(\beta\), but not IFN-\(\alpha\), has been shown to augment the expression of glucocorticoid receptors in HL-60 cells (Sica, 1990).

IFN-beta from other sources (both natural and a recombinant product with an amino acid substitution at position 17) has so far been more extensively tested than the recombinant material and appears to be less toxic than IFN-alpha.\textsuperscript{36, 37} IFN-beta has been shown to have activity in herpetic infections,\textsuperscript{38} human papillomavirus infections,\textsuperscript{39-42} hepatitis B,\textsuperscript{43} HIV infection,\textsuperscript{44} hairy cell leukemia,\textsuperscript{45} brain tumors,\textsuperscript{46} and multiple sclerosis.\textsuperscript{47} Additionally, in hormone responsive tumors (e.g. breast and endometrial cancer), enhanced sex hormone receptor expression in response to IFN-beta has been observed both in vitro and in vivo.\textsuperscript{35} There is also some evidence that IFN-beta has greater in vitro antiproliferative activity than IFN-alpha against many solid tumor cell lines.\textsuperscript{48}

We have conducted a multicenter phase I/II trial of a human recombinant interferon beta (Betaseron) in patients with recurrent glioblastoma and anaplastic astrocytoma.\textsuperscript{49} Betaseron was given intravenously three times per week, starting at 90 x 10\(^6\) IV per dose and escalating by 90 x 10\(^6\) IV every 2 weeks up to a maximum dose of 540 x 10\(^6\) IV per treatment. All patients had failed prior radiotherapy and chemotherapy. Of 65 evaluable patients, 15 (23\%) had an objective response, and 18 (28\%) had stable
disease, with a combined response rate of 51%. The median time to progression was 24 weeks for the 33 responders, 10 weeks for the non-responders, and 23 weeks for the whole group. These results suggest that Betaseron has definite activity in recurrent gliomas, but the time to progression is short lived.

2.0 OBJECTIVES
2.1 To determine if recombinant interferon beta given intramuscularly three times per week after conventional RT may improve the median survival time of adults with newly diagnosed supratentorial glioblastoma.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility
3.1.1 Histopathologically-confirmed glioblastoma multiforme *(with areas of necrosis).*
3.1.2 Diagnosis must be made by surgical biopsy or excision.
3.1.3 The tumor must be supratentorial in location.
3.1.4 The patient must have recovered from the effects of surgery, or post-operative infection and other complications before entry into the study.
3.1.5 Therapy must begin \( \leq \) four weeks after surgery.
3.1.6 Patients must have an estimated survival of at least 8 weeks.
3.1.7 Karnofsky Performance Status of \( \geq 60. \)
3.1.8 Age \( \geq 18. \)
3.1.9 A diagnostic contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively before the initiation of radiotherapy. Preoperative and postoperative scans must be the same type.
3.1.9.1 Patients diagnosed only by stereotactic biopsy do not require the post-op scan.
3.1.10 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.

*Hematologic:* Hemoglobin \( \geq 10 \) grams

*Renal:* BUN \( \leq 25 \) mg

*Hepatic:* Bilirubin \( \leq 2.0 \) mg

3.1.11 The patient must give written study-specific informed consent prior to entry into the study. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.2 Conditions for Patient Ineligibility
3.2.1 Astrocytomas
3.2.2 Recurrent malignant gliomas.
3.2.3 Patients in whom metastases are detected below the tentorium or beyond the cranial vault.
3.2.4 Major medical illnesses or psychiatric impairments which in the investigator’s opinion will prevent administration or completion of the protocol therapy.
3.2.5 Previous radiotherapy to the head or neck.
3.2.6 Previous malignancies, except for non-melanomatous skin cancers and carcinoma *in situ* of the uterine cervix or bladder, unless disease-free for \( \geq 5 \) years.
3.2.7 Prior chemotherapy or radiation therapy.
3.2.8 Patients who cannot be regularly followed by the investigator.
3.2.9 Patients with known Acquired Immune Deficiency (AIDS).

4.0 PRETREATMENT EVALUATION
4.1 Mandatory Studies
4.1.1 Complete history and general physical examination.
4.1.2 Contrast-enhanced MRI or CT scan performed preoperatively and postoperatively prior to the initiation of radiotherapy *(mandatory for eligibility).* The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.
4.1.3 CBC with differential, platelet count, BUN, serum creatinine, bilirubin, and SGOT or SGPT.
4.1.4 Chest x-ray.
4.1.5 Detailed neurological examination and Mini-mental status exam immediately prior to beginning protocol treatment course. Request a forms pack from RTOG Headquarters in advance.

4.1.6 Steroid doses must be documented.

5.0 REGISTRATION PROCEDURES

5.1 Each institution must submit a Product Shipment Form (Appendix VI) to RTOG Headquarters prior to the registration of its first case. Institutional IRB approval of the study must be obtained before submitting this form to RTOG. Allow adequate processing time (7-10 days) before calling to register your first case.

5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY PARAMETERS

6.1 Dose Definition and Schedule

Radiotherapy must begin within 4 weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over six weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose which shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.1.2 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However if this technique is utilized the dose shall be specified at the center of the target area.

6.1.6 Other or complex treatment arrangements: at the center of the target volume.

6.2 Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up to and including 10 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy ≤ 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines secondary collimation is required. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast enhancing lesion plus a 2.5 centimeter margin.

This initial target volume will be treated to 46.0 Gy in 23 fractions. After 46 Gy the conedown tumor volume should include the contrast enhancing lesion (without edema) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

6.4 Treatment Planning
Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum. The minimum dose to the target volume should be kept within 5% of the dose at the center of the volume. The use of vertex fields require either a diagram or photograph of treatment position to be submitted to RTOG Headquarters. The maximum dose should be no higher than 5% of the dose at the center of the target volume.

6.5 Dose Limitation to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60.00 Gy, the retina of at least one eye (but preferably both) to 50.00 Gy, and the brain stem to 60.00 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

6.6 Documentation Requirements

A copy of the pretreatment CT/MRI, the treatment prescription form, treatment calculation form, simulation films and representative portal films of each initial field must be forwarded to RTOG Headquarters within two weeks of treatment start. At the completion of treatment, the following shall also be forwarded to Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the reduced fields, and the radiotherapy summary.

6.7 Acute Radiation Toxicities

6.7.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.

6.7.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation.

6.7.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the RTOG Toxicity Criteria.

7.0 DRUG THERAPY (NSC #658933, BB-INB 7732)

7.1 rhIFN-b (Interferon Beta [Biogen])

7.1.1 Chemistry

Avonex (rhIFN-beta) has been extensively characterized to demonstrate a high level of purity. Analytical studies have also confirmed that Biogen’s rhIFN-beta is essentially identical to fibroblast-derived (or natural) IFN-beta. The molecular weight of rhIFN-beta is about 23,000 daltons and identical to that of fibroblast-derived IFN-beta. The complete amino acid sequence of rhIFN-beta was determined by two different methods. The sequence of 166 amino acids is identical to that of fibroblast-derived IFN-beta and consistent with the sequence as deduced from the nucleotide sequence of the gene.

7.1.2 Pharmacodynamics and Pharmacokinetics

Results from pharmacokinetic and pharmacodynamic studies of interferon beta-1a in healthy subjects following doses of 30 mcg (6MU) through 75 mcg (15 MU) indicate that parental administration of interferon beta-1a is followed by predictable systemic absorption and dose-related biological response. Peak serum antiviral activity levels and overall systemic exposure, as measured by the area under curve (AUC), increase with dose. At the dose recommended for use in MS, 30 mcg given IM, serum levels of interferon beta-1a are slightly above detectable limits (pharmacokinetics of interferon beta-1a in MS patients have not been evaluated).

Pharmacodynamic effects of interferon beta-1a were evaluated by measuring serum levels of interferon-induced proteins: β2-microglobulin and neopterin. Biological response markers are induced by interferon beta-1a following parenteral doses of 15 mcg (3MU) through 75 mcg (15 MU) in healthy subjects and in treated patients. Biological response marker levels increase within 12 hours of dosing; peak serum levels are typically observed between 24 and 48 hours after injection.

In general, IM administration induced higher levels of neopterin and β2-microglobulin than SC or IV administration. In addition, a direct correlation between dose and biological response was observed.
following IM administration. Following a single IM injection of 30 mcg (6 MU), elevated biological response markers were observed for more than 4 days post-dose.

7.1.3 
**Toxicology**

Repeat SC administration of interferon beta-1a to rhesus monkeys for 2 to 9 weeks at doses of 1.25 mcg (0.25 MU)/kg and 5.0 mcg (1 MU)/kg caused no toxic effects directly attributable to administration. Elevated body temperature, reduced food consumption, decreased platelet counts, and decreased serum albumin and calcium concentrations were observed at the high dose tested (50 mcg[10 MU]/kg). All of these effects were reversible. This dose level yielded serum interferon beta activity 100-to 200-fold above observed therapeutic levels. After approximately 2 weeks of treatment, the monkeys developed a neutralizing antibody response to interferon beta-1a; for this reason chronic repeat dose toxicity testing was not performed.

Similar clinical signs have been reported in patients in undergoing interferon therapy. The primary side effects observed in patients and/or healthy subjects treated with interferon beta-1a include flu-like symptoms (e.g., fever, nausea); however, the clinical laboratory changes noted in monkeys, such as effects on platelets and serum albumin and calcium concentrations, were not evident in MS subjects treated with interferon beta-1a in a phase III clinical trial.

No respiratory, cardiovascular, or acute allergic reactions were evident. No overt effects on the central nervous system were noted in any of the treated animals. Interferon beta-1a was non-irritating following single IM administration.

7.1.4 
**Phase I Studies**

A phase I open label, dose-escalating study of interferon beta-1a in the treatment of subjects with recurrent gliomas was conducted to determine a maximum tolerated dose of interferon beta-1a when given intramuscularly 3 times per week. Sixteen subjects (thirteen males and three females) were entered into this study. Dose-limiting neurotoxicity was recognized at 40 mcg (8 MU)/m². At this dose level, two of three subjects developed confusion and grand mal seizure activity and were withdrawn from the study. The third subject required dose discontinuation for grade 3 thrombocytopenia but this was on a background of poor bone marrow reserve after extensive chemotherapy. In addition, two other subjects discontinued dosing at lower dose levels for adverse events: one for asymptomatic elevation in liver enzyme levels (considered probably related to interferon beta-1a) and one for non-ketotic, hyperosmolar coma complicated by a seizure and atrial fibrillation (due likely to high dose corticosteroid administration).

7.1.5 
**Pharmaceutical Data** (9/8/98)

- **How Supplied:** Interferon beta-1a is supplied as a lyophilized powder, in 30 microgram (6 million units) vials.
- **Ingredients:** Interferon beta-1a contains recombinant human interferon beta and excipient materials (Albumin Human, USP, Sodium Chloride, USP and Sodium Phosphate, USP).
- **Storage:** Interferon beta-1a dosage units must be stored at 2-8°C (36-46°F).
- **Reconstitution:** (3/17/99)
  To each vial of Interferon beta-1a, add 1.1 mL of sterile water for injection, USP preservative-free. Gently swirl until all material is dissolved. Reconstituted material may be held at 2-8°C for a period not to exceed six (6) hours.

7.1.6 
**Special Considerations**

- Reconstitute before use.
- Do not freeze the reconstituted material.
- Do not use if solution is not clear or if there is visible particulate matter.
- Do not use after expiration date unless subsequent extensions are provided by Biogen.
- Do not shake.

7.1.7 
**Drug Supply** (9/8/98, 3/17/99)

7.1.7.1 The drug will be provided and distributed by Biogen. RTOG members must submit the Product Shipping Form (Appendix VI) to RTOG at least a week prior to registering their first case to the study but after institutional IRB approval has been obtained. Biogen will distribute kits containing (4) vials of of Interferon beta-1a 30 micrograms per vial. These must be stored at 2-8°C (36-46°F). These kits are open label products and will be labeled as such.
An accessory pack will be shipped with each kit and will contain four (4) Dose Accessory Packs each including: one (1) single-use diluent vial (10 mL sterile water for injection, USP, preservative free), two (2) alcohol swabs, one (1) syringe, one (1) vial access pin, one (1) needle, and one (1) adhesive bandage. These can be stored at room temperature.

7.1.7.2 After delivery of the initial kits, additional supplies can be obtained by contacting:

Keri Lynch
Biogen, Inc.
14 Cambridge Center
Cambridge, MA 02142
(617) 679-2797
FAX (617) 679-3518

7.1.7.3 Quarterly during the study, institutions must send copies of their drug logs to RTOG HQ to the attention of Elaine Pakuris. The logs must show the receipt and dispensing of all study product received from Biogen. RTOG will send reminders (October, January, April, and July) to those institutions who have submitted the Shipping Form (Appendix VI) to Headquarters. After completion of the study, unused kits must be returned to Biogen and recorded on the institutional drug logsheets for final accountability.

7.2 Schedule

7.2.1 rhIFN-beta: Beginning 4-6 weeks after completion of radiotherapy the starting dose for rhIFN-beta will be 6 million units given intramuscularly, once a day, 3 times per week, on Monday, Wednesday, and Friday. The patient will have three weeks of drug followed by one week with no drug. The three weeks of treatment followed by a week off treatment will be considered one cycle.

7.2.2 This schedule will continue without interruption for a maximum of two years as long as there is no tumor progression and toxicity is \leq grade 3. Self administration is permitted.

7.2.3 Eight weeks (2 cycles) will be considered as one course (\leq 18 injections).

7.3 Dose Modification (3/17/99)

7.3.1 Blood counts will be monitored every two weeks during drug therapy. If the starting dose level has been associated with no toxicity greater than grade 3, dosage escalation will proceed as shown below after each course (8 weeks) of treatment.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhIFN-beta(million units per day)</td>
<td>3</td>
<td>4.5</td>
<td>6</td>
<td>9 (maximum escalation)</td>
</tr>
</tbody>
</table>

7.3.2 Dose Adjustments During Treatment: Treatment will continue without dose adjustment for the first 8-week course as long as there are no toxicities \geq grade 3. For grade 3 or greater toxicities, treatment will be withheld and the patients will be monitored weekly until toxicities resolve to grade 2 or better.

7.3.3 Dose Adjustments for the Subsequent Courses: Subsequent courses will start (as long as the treatment is beneficial) after complete resolution of toxicities to grade 2 or better. A minimum of 2-week rest period will be required if there is grade 3 or greater toxicity. Dosage for the subsequent course will be one dose level below the dose that produced toxicity. See Section 7.3.1. There will be no dose re-escalation after dose reduction.

7.3.4 A minimum of 8 weeks (1 course) shall be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients will be considered evaluable for toxicity and will be followed (per Section 12.1) after completion of treatment. Any patient who receives beta interferon or radiotherapy will be considered evaluable.

7.3.5 Progression of Disease

No beta interferon will be given if the patient experiences clinical progression and/or radiographic progression as evidenced on the post XRT/pre beta interferon MRI or CT scan. The patient will be considered progression of disease (PD), and the patient can be treated with any treatment at the discretion of the treating physician. If the patient experiences clinical progression and/or radiographic progression as evidenced on MRI or CT scan during beta interferon treatment, the patient will be considered progression of disease (PD). Beta interferon will be discontinued, the patient can be treated with any treatment at the discretion of the treating physician.

7.4 Adverse Drug Reaction Reporting Guidelines

7.4.1 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

7.4.1.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.4.1.3 Any death on study if clearly related to the commercial agent(s).
7.4.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
7.4.2 The ADR report should be documented on the FDA form 3500 (Appendix IV) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
(301) 230-2330
Telephone available 24 hours
FAX # 301-230-0159

8.0 SURGERY
The extent of surgical resection prior to protocol entry shall be documented as a) biopsy, b) subtotal resection, or c) total resection as described by the operative report and/or post operative imaging.

9.0 OTHER THERAPY
9.1 All patients should be maintained on the lowest steroid dose necessary for neurological stability.

10.0 PATHOLOGY
Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters Table

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Prior to Therapy</th>
<th>During Radiotherapy</th>
<th>Post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological Exam, H&amp;P</td>
<td>X</td>
<td>weekly</td>
<td>X^d</td>
</tr>
<tr>
<td>Steroid Dose Documentation</td>
<td>X</td>
<td>X</td>
<td>X^e</td>
</tr>
<tr>
<td>CBC and differential, Platelets</td>
<td>X</td>
<td></td>
<td>X^c</td>
</tr>
<tr>
<td>BUN, Serum Creatinine, Bilirubin, &amp; SGOT or SGPT</td>
<td>X</td>
<td></td>
<td>X^c</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td></td>
<td>X^a</td>
</tr>
<tr>
<td>Contrast enhanced Brain CT or MRI</td>
<td>X^b</td>
<td></td>
<td>X^b</td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td></td>
<td>weekly</td>
<td>X^e</td>
</tr>
</tbody>
</table>

a. As clinically indicated.
b. Both preoperatively and postoperatively prior to RT; post RT/prior to drug; then q 2 months. Post-operative scan not required if patient diagnosis was by stereotactic biopsy only.
c. Every 2 weeks during drug administration.
d. Every two months.
e. Every two weeks during drug administration, then at each followup.

Important: It is mandatory that patients are followed with the same study (CT vs. MRI) as the baseline study

11.2 Evaluation During Study
11.2.1 A neurologic examination shall be performed once a week during radiation therapy and every two months thereafter.
11.2.2 Skin within the treatment portal shall be examined at least once per week during radiation therapy.
11.2.3 The contrast-enhanced CT/MRI of the brain shall be obtained prior to surgery, post-surgery, prior to initiation of interferon therapy, then every 2 months and at the time of neurologic deterioration.
Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination.\textsuperscript{50} Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation. See Section 7.3.5.

11.2.4 While a patient is receiving interferon, blood counts are required every two weeks.

11.3 CT/MRI Review
The serial CT/MRI shall be examined at the institution by an independent reviewer, a neuroradiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.4 Overall Response

11.4.1 *Complete Response (CR)*: shall be defined as the circumstance when the tumor is no longer seen by neuroimaging provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.2 *Partial Response (PR)*: Decrease of \( \geq 50\% \) in the product of two diameters provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.3 *Minor Response (MR)*: Decrease in diameter products of \(< 50\% \) provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.4 *Stable Disease (SD)*: shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids.

11.4.5 *Progression (P)*: shall be defined as a \( > 25\% \) increase in tumor area (two diameters) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point.

11.5 Instructions For Administration of Mini-Mental Status Examination (MMSE)
The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the Mini-Mental Status Exam needs to be sensitive to when the patient shows embarrassment of their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

11.6 Criteria for Evaluation of Therapy Effectiveness

11.6.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from the first day of treatment until deterioration is documented by the individual Investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (CT or MRI).

11.6.2 Overall survival will be measured from the time of first surgery until death.

11.6.3 The quality of survival will be measured by neurological functional classification and performance status.

11.6.4 Post mortem examination of the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Data</th>
<th>When Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within two weeks of registration</td>
</tr>
<tr>
<td>On-study Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment MRI/CI scan (both pre- and post-surgery) (C1) and reports (C3)</td>
<td></td>
</tr>
<tr>
<td>Pathology report (P1)</td>
<td></td>
</tr>
<tr>
<td>Mini Mental Status Exam (MS)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within one week of treatment start</td>
</tr>
<tr>
<td>Radiotherapy prescription (T2)</td>
<td></td>
</tr>
<tr>
<td>Simulation &amp; Portal Localization films (T3)</td>
<td></td>
</tr>
<tr>
<td>Central Axis Calculations (T4)</td>
<td></td>
</tr>
</tbody>
</table>
Radiotherapy Form (T1)
Final Dosimetry Information: Within one week of completing radiotherapy
Daily Treatment Record (T5),
Isodoses (T6),
Simulation & Port films of all Fields (T8)

Study Specific Flow Sheet (SF) Monthly for first 3 mos. of drug administration
then with every F1.

Follow-up Form (F1) Every 3 months from treatment start for year 1;
Mini-Mental Status (MS) q 4 months x 1 year; q 6 months x 2 years, then
annually. Also at progression/relapse and at
death (F1 only).

Post-treatment MRI/CT (C2) and Report (C3) One month post-RT; for grade ≥ 3 RT
toxicity and for progression.

Operative reports (S2), surgical reports(S5) As applicable
(for subsequent surgery)

Autopsy Report (D3) As applicable

12.2 CT/MRI Documentation
The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins must
be submitted within two weeks of registration. A post-RT, pre-drug-therapy scan must also be submitted to
Headquarters. A MRI/CT must be done at the time of neurologic deterioration, suggestive of tumor
recurrence and not related to lowered steroid dose, unless the last MRI/CT had been done within one
month and was compatible with recurrence. Other causes of neurological deterioration, such as metabolic
imbalance, anticonvulsant or interferon toxicities, should be considered and properly investigated. The
patient should consistently be followed with the same diagnostic study. Subsequent scans and reports,
other than the pre-entry and post-RT scans, should be forwarded to RTOG Headquarters only in the event
of a suspected grade ≥ 3 RT toxicity.

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints
13.1.1 Overall survival
13.1.2 Acute and late toxicities associated with interferon and radiotherapy.

13.2 Sample Size (7/1/99)
The primary objective of this study is to estimate the median survival time (MST) for glioblastoma
multiforme (GBM) patients treated with rhIFN-b and radiotherapy. Patients enrolled onto this trial
should not be eligible for RTOG 93-05; thus, the majority of patients will have a maximum tumor
diameter greater than 4.0 cm. Historically, GBM patients with RPA class of III and IV have an estimated
MST of 12.7 months. A sample size of 60 evaluable class III and IV patients followed over 18 months
will ensure at least 80% probability of detecting a minimum of 35% improvement in MST compared to
the RTOG glioma database at the 0.20 significance level (one-sided). Based on previous RTOG GBM
studies, 67% of patients are predicted to be in class III and IV, resulting in an overall sample size of 80
evaluable patients in order to accrue 60 class III and IV patients.51,52 Furthermore, assuming a 5%
ineligibility/inevaluable rate, the total sample size required will be 84 patients.
The ineligibility/inevaluable rate on this study has been higher than expected. We had calculated the
sample size based on an expected ineligibility rate of 5%, but we find that 26% of the 57 patients who
have been on the study for at least 12 weeks (as of 6/4/99) did not receive the protocol drug (due to
progression, death, patient choice). Based on this rate, we have increased required accrual to 108
patients in order to achieve the 80 evaluable patients needed.

13.3 Inclusion of Women and Minorities
In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to
inclusion of women and minority in clinical research, we make the following observations. The recursive
partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any
treatment interaction with gender.52 The RTOG found no difference in survival of glioblastoma
multiforme patients by race.53 Since there are no publications found to support a possible interaction
between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

13.4 Patient Accrual
The patient accrual is projected to be 14 cases per month, based upon the monthly accrual for RTOG 90-06. At this rate, it will take six months to reach the required total accrual of 84 cases. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.5 Suspension of Accrual Due to Morbidity
If there is any fatal treatment morbidity, the accrual will be suspended, and all data pertaining to the event will be reviewed by the study chairman and reported to the RTOG Data Monitoring Committee (DMC) for review.

13.6 Analyses Plans
13.6.1 Interim Analyses
Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:
   a) the patient accrual rate with a projected completion date for the accrual phase;
   b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
   c) the frequency and severity of the toxicities.
Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.6.2 Analysis for Reporting the Initial Treatment Results
This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:
   a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
   b) reporting institutional accrual;
   c) distribution of important prognostic baseline variables - (age, KPS, neurologic function, extent of surgery, time from first symptom, location of primary, and site of tumor);
   d) observed results with respect to the endpoints described in Section 13.1.

The estimated median survival from this sample will be tested against the historical control presented in Section 13.2 using a one-sample test. Median survival estimates will also be calculated for patient subgroups according to the subgroups identified in Curran et al. The Brookmeyer-Crowley confidence interval for median survival will be provided for all estimates.

An improvement in MST of at least 35% dependent upon appropriately identified baseline comparison, will be encouraging for further study.
REFERENCES


APPENDIX I

RTOG 97-10

A PHASE II STUDY OF CONVENTIONAL RADIATION THERAPY FOLLOWED WITH RECOMBINANT INTERFERON BETA FOR SUPRATENTORIAL GLOI BLASTOMA

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have been diagnosed with a brain tumor called glioblastoma multiforme. Further treatment is recommended. The usual treatment in cases such as mine is radiation therapy plus chemotherapy or biological therapy. Radiation therapy is the treatment of tumors by means of x-rays. It is usually given once daily, five days per week for six to eight weeks.

Beta interferon is a natural occurring protein substance. It is now made by normal cells grown in a tissue culture laboratory. Beta interferon has been used in the treatment of patients with brain tumors such as mine. This drug together with radiation therapy may be helpful for controlling my disease.

Therefore, the purpose of this research study is to determine the effectiveness of radiation therapy given once daily with beta interferon.

DESCRIPTION OF PROCEDURES

This study involves daily radiation treatments to the tumor. Radiation treatments will be given once a day, five times a week for six weeks. Four to six weeks after the six weeks of radiation, I will get one beta interferon injection a day, three times a week (Monday, Wednesday, Friday). I will receive beta interferon for three weeks, have a week off, then will start up again for three weeks. The beta interferon will continue for a maximum of two years. The beta interferon will be stopped if it causes severe side effects or if the tumor begins to grow.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

**Risks from Radiation Therapy**: include some or all of the following side effects: scalp redness, or soreness, hair loss, which may be temporary or permanent, dry mouth or altered taste, hearing impairment, fatigue, sleepiness or temporary aggravation of tumor symptoms such as headaches, seizure, or weakness. There is a risk of injury to the eyes from radiation therapy with the possibility of blindness. Cataracts may occur, although every effort will be made to minimize the chances of this occurring. Radiation sometimes causes late side effects such as mental slowing or behavioral change. Occasionally radiation causes severe local damage to normal brain tissue. This is a condition called necrosis. Radiation necrosis can mimic recurrent brain tumor or those of a stroke and may require surgery.

**Risks from Beta Interferon** include some of or all of the following: Common side effects include headaches, flu-like symptoms, muscle and joint aches and fatigue. Less common side effects include flushing, fever, chills, heavy sweating, breathing difficulties, sore throat, and a runny or stopped up nose. Loss of appetite, taste changes, nausea, vomiting, stomach pain, upset stomach or diarrhea may occur. I may feel drowsy or dizzy and may have trouble sleeping. Patients may have liver, heart or kidney damage, as well as hormone or blood pressure changes. It may cause nervousness, difficulty in concentrating, irritability, depression, thoughts of suicide. In rare cases, it may cause severe confusion and seizures even
after treatment has stopped. Beta interferon may prevent the patient's body from making and keeping new blood cells, so while I take the drug, there may be more chance of getting a severe infection including pneumonia. The normal body makes antibodies as part of the natural disease-fighting system. Although these antibodies are not known to be harmful at this time, they may affect future treatment with beta interferon. My blood platelet count may fall and I may become anemic or have problems with bleeding. If very severe, I may need a blood transfusion. Pain, redness swelling, and bruising may occur where the needle enters the muscle?

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If I am a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), I must use adequate birth control measures to prevent pregnancy while participating in this study. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately.

CONTACT PERSONS

If injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. __________ the investigator in charge at _____________________________. In addition, I may contact ______ at _____________________________ for information regarding patients’ rights in research studies.

BENEFITS

The study treatment may keep the brain tumor from growing or may even shrink it. This may provide relief from symptoms and improve my quality of life; however, this is not guaranteed.

ALTERNATIVES

Alternatives include radiation therapy performed off-study either alone or with chemotherapy or other immunotherapy to make me feel better. These will not necessarily cure me or make my disease less. Another choice is no further therapy. This would probably result in continued growth of my tumor. My doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my outlook with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take
part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, my participation has been voluntary.

**CONFIDENTIALITY**

Records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative)  
Date
### APPENDIX II

**KARNOFSKY PERFORMANCE SCALE**

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

### NEUROLOGIC FUNCTION (NF) STATUS

<table>
<thead>
<tr>
<th>NF</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No neurologic symptoms; fully active at home/work without assistance.</td>
</tr>
<tr>
<td>1</td>
<td>Minor neurologic symptoms; fully active at home/work without assistance.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate neurologic symptoms; fully active at home/work but requires assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate neurologic symptoms; less than fully active at home/work and requires assistance.</td>
</tr>
<tr>
<td>4</td>
<td>Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.</td>
</tr>
</tbody>
</table>
APPENDIX IV

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS – DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as “known” or “unknown” toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters’ Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters’ Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD  20824
Telephone number available 24 hours
(301) 230-2330      FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working
- All deaths within 30 days of termination of the agent. As above
- All life threatening (grade 4) events which may be due to agent. As above
- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB Drug monitor and RTOG Headquarters. **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions Resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 Working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related To investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
APPENDIX V

RADIATION THERAPY PARAMETERS

The 2.5 cm margins (for the boost fields) are three-dimensional: superiorly, inferiorly, medially and laterally as well as anteriorly and posteriorly. (See Diagrams A & B)

Please note that it is important that the dose inhomogeneity be minimized particularly between the central axis dose and the tumor minimum dose. The protocol dose should be prescribed at the center of the target volume.

The inferior margin of the temporal lobe follows the outline of the sphenoid sinus. In order to encompass a 2.5 cm margin around most temporal lobe tumors, the entire temporal fossa usually needs to be included. In order to deliver a full dose to the inferior portion of the temporal fossa, the inferior border of the treatment portals should be below the bottom of the sphenoid sinus. (See Diagram B).

Diagram A

Diagram B
APPENDIX V
(continued)

Diagram 1

Diagram 1 illustrates that even with 6 MV photons utilizing parallel opposed portals, if the treatment portal encompasses the posterior occiput or the frontal region, it is obvious that without wedges the target minimum dose is 10% lower than the prescribed central axis dose, and there is a hot spot in the thinner portion that can be 10% to 15% hotter. These differences can be minimized with the use of wedges as in Diagram 2. The tumor minimum is only 2% lower than the central axis dose, and the hot spots are smaller and of lower dose. Isodose distributions are required for parallel opposed fields.

Diagram 2
APPENDIX V
(continued)

Diagram 3 is an example of a composite plan for an anteriorly located lesion with significant edema. By combining large 15 wedged parallel opposed fields to 57.60 (Diagram 4), it was possible to even out hot spots and treat the target volume to a high dose throughout with minimal gradient. Optimization of individual plans and the submission of composite plans is an essential requirement of this study.
APPENDIX VI

RTOG 97-10

INTERFERON BETA SHIPMENT FORM

Study drug kits will be shipped only to institutions who have identified a single individual associated with the investigational drug unit of the institution. This form must be completed and returned to RTOG Headquarters prior to registering any patients on study. Documentation of IRB approval must be enclosed. Allow adequate processing time (7-10 days) at Headquarters before calling to register your first patient.

SHIP TO:

Name: __________________________________________

Address: _______________________________________
(No P.O. Box numbers)

_________________________________________________________________

_________________________________________________________________

_________________________________________________________________

Telephone: _______________________________________

Fax#: ___________________________________________

RTOG Institution#: _______________________________

Institution Name: _________________________________

IRB Approval Date: ________________________________
(attach copies of IRB approval and sample consent form)

Investigator (PI) Signature __________________________ Date:__________

Investigator Name (Print) ______________________________

Investigator NCI # (Required) __________________________

Return to:

RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107

ATTN: ELAINE PAKURIS
FAX# 215/928-0153

RTOG Headquarters Approval __________________________ Date: ____________