A Phase I Open-Label, Dose-Escalation, Multi-Institutional Trial of Injection with an E1B-Attenuated Adenovirus, ONYX-015, into the Peritumoral Region of Recurrent Malignant Gliomas, in the Adjuvant Setting

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ONYX-015 is an oncolytic virus untested as a treatment for malignant glioma. The NABTT CNS Consortium conducted a dose-escalation trial of intracerebral injections of ONYX-015. Cohorts of six patients at each dose level received doses of vector from $10^7$ plaque-forming units (pfu) to $10^{10}$ pfu into a total of 10 sites within the resected glioma cavity. Adverse events were identified on physical exams and testing of hematologic, renal, and liver functions. Efficacy data were obtained from serial MRI scans. None of the 24 patients experienced serious adverse events related to ONYX-015. The maximum tolerated dose was not reached at $10^{10}$ pfu. The median time to progression after treatment with ONYX-015 was 46 days (range 13 to 452 + days). The median survival time was 6.2 months (range 1.3 to 28.0 + months). One patient has not progressed and 1 patient showed regression of interval-increased enhancement. With more than 19 months of follow-up, 1/6 recipients at a dose of $10^9$ and 2/6 at a dose of $10^{10}$ pfu remain alive. In 2 patients who underwent a second resection 3 months after ONYX-015 injection, a lymphocytic and plasmacytoid cell infiltrate was observed. Injection of ONYX-015 into glioma cavities is well tolerated at doses up to $10^{10}$ pfu.

Key Words: glioma, brain tumor, clinical trial, ONYX-015, gene therapy, oncolytic virus, experimental therapy, virotherapy, adenovirus, conditionally replicating adenoviruses

INTRODUCTION

Current therapies such as surgery, radiotherapy, and chemotherapy have had only limited success in treating patients with malignant gliomas [1], and thus their prognosis remains grim [2]. Novel treatment strategies are needed [3–5]. Oncolytic viral therapy is one such strategy [6,7]. This consists of the use of replication-conditional viruses, genetically altered to render their replication selective for tumor cells. An example of a replication-conditional virus is ONYX-015, an adenovirus mutant that is thought to replicate more efficiently in cells with disruptions in the p53 tumor suppressor pathway (such as tumor cells) [8], although this mechanism remains controversial since other mechanisms of replicative selectivity may be operative [9]. ONYX-015 has been tested in clinical trials for a variety of cancers, including head and neck, ovarian, prostate, and lung [10–23].

The standard therapy for patients with a suspected malignant brain mass is surgical excision, if possible. Resected tissue is analyzed and a diagnosis of glioma is made dependent on the presence of histologic features. The histologic features of the more malignant forms of glioma include nuclear atypia, endothelial proliferation, necrosis, and mitoses. Based on how many of these features are present, further classification of a malignant glioma into an anaplastic astrocytoma (World Health Organization grade III astrocytoma), an anaplastic oligo-
dendroglioma (World Health Organization grade III oligodendroglioma), or a glioblastoma multiforme (World Health Organization grade IV astrocytoma) is made. Because these tumors are characterized by extensive infiltration of single and multiple cells throughout the brain, which obviously cannot be resected, further treatment of patients with radiation is started 2 weeks after surgical excision. A total of 5400–6000 cGy is delivered to the tumor cavity and to the margins over a period of 6 weeks. At the end of this treatment, addition of chemotherapy with alkylating agents, such as BCNU, may provide additional therapeutic benefit. Throughout this time, patients are usually maintained on corticosteroids to reduce brain edema and anticonvulsants to reduce the incidence of seizures. Almost all tumors will recur during or after the above treatments, usually locally at the margin or site of the previous resection or, less often, at a distance from the main tumor mass. Generally, phase I/II experimental therapies are reserved for this group of patients.

The objectives of our study were to determine the safety and evaluate the efficacy of multiple injections of escalating doses of an E1B-attenuated adenovirus, ONYX-015, into the margins of a recurrent malignant glioma that has been resected in adult patients. We found that injection was very well tolerated without evidence of toxicities attributable to ONYX-015, up to a dose of $10^{10}$ plaque-forming units (pfu). Although previous trials of direct, stereotactic injection of replicating, tumor-selective herpes simplex viruses into the malignant gliomas of patients were reported\[24–26\], this study provides the first demonstration that injections of a replicating, tumor-selective virus into brain tissue, adjacent to a freshly excised glioma, are well tolerated. This provides justification for additional studies of such modalities in patients with malignant gliomas.

### RESULTS

Twenty-four patients were enrolled in the study between January 2000 and May 2002. All twenty-four patients were treated and all included in the intent-to-treat population. Patient characteristics are shown in Table 1.

A summary of the adverse events that occurred during the treatment period is shown in Table 2. Ten of the 24 patients experienced one or more adverse events. None of the adverse events were judged as possibly related to ONYX-015 treatment, since other etiologies provided more likely explanations. This judgment was made by the clinicians involved in the care of these patients and was reviewed by the Data Safety Monitoring Board after each enrollment into each cohort was completed. This judgment was based on the likelihood that additional etiologies for the adverse events were more likely than the injection of ONYX-015. For instance, dyslexia, dyscalculia, and dysgraphia in the postoperative period after resection of a tumor near eloquent cortex responsible for such function was more likely due to the trauma of surgery than to ONYX-015 injection.

One patient in the high-dose ($10^{10}$) cohort, whose on-study histology was anaplastic astrocytoma, has not progressed (stable disease). The remaining 23 patients have progressed. However, it should be noted that 1 of the patients who had been declared to have progressed because of increased enhancement on the MRI scan was found to have decreased enhancement on a subsequent scan (Fig. 1). This episode of increased enhancement with subsequent decreased enhancement occurred again a few months later, as detailed in the legend to Fig. 1. Median time to progression of disease after ONYX for all patients was 46 days with a range of 13 to 452 + days.

### TABLE 1: Baseline demographic and clinical characteristics for all patients and stratified by on-study diagnosis

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 24)</th>
<th>GBM (n = 17)</th>
<th>Other (AA, AO) (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>17 (71)</td>
<td>11 (65)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Race, white</td>
<td>24 (100)</td>
<td>17 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Age, years</td>
<td>52 (35–70)</td>
<td>55 (37–70)</td>
<td>38 (35–61)</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td>90 (60–100)</td>
<td>90 (60–100)</td>
<td>90 (70–100)</td>
</tr>
<tr>
<td>Prior chemotherapy(a)</td>
<td>22 (92)</td>
<td>16 (94)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Anticonvulsant therapy</td>
<td>18 (75)</td>
<td>11 (65)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Original diagnosis histology(b)</td>
<td>()</td>
<td>()</td>
<td>()</td>
</tr>
<tr>
<td>Glioma</td>
<td>1 (4)</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 2 glioma</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>5 (21)</td>
<td>0 (0)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>16 (67)</td>
<td>16 (94)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

\(\text{Median (range)} \, \text{or } N(\%)\) is shown.

\(\text{a}\) All patients had prior surgery and XRT.

\(\text{b}\) Refers to the histology at initial presentation of the patient with disease. Patients then underwent conventional, standard treatment. At re-presentation with a recurrence, this histology was either the same or had progressed to a more malignant grading (the histology at recurrence is textually described under Results).
Twenty patients have died due to tumor progression, 1 died of non-tumor-related events (ruptured intestine), and 3 remain alive. Of the survivors, 1 belongs to the $10^7$ pfu cohort, and 2 belong to the $10^8$ pfu cohort. Median survival time for all patients was 6.2 months (range 1.3–28.0 months). On-study histology for the patients by cohort was 6/6 glioblastoma multiforme (GBM) for the $10^7$ pfu cohort, 4/6 GBM and 2/6 anaplastic astrocytoma (AA) for the $10^8$ pfu cohort, 5/6 GBM and 1/6 AA for the $10^9$ pfu cohort, and 2/6 GBM, 3/6 AA, and 1/6 anaplastic oligodendroglioma (AO) for the $10^{10}$ pfu cohort. For the 3 surviving patients, 2 patients had histologies of AA and the other had AO. The Kaplan–Meier survival curve for GBM and non-GBM (AA and AO) patients is shown in Fig. 2. Median survival for the GBM patients was 4.9 months, and for AA and AO patients it was 11.3 months.

We obtained serum from all of the patients prior to the introduction of ONYX-015 and again on day 42 to assess for antibodies to adenovirus. Of the 24 patients, only 2 patients tested positive for adenovirus antibodies before inoculation. After delivery of ONYX-015, 2 patients seroconverted from negative to positive for adenovirus antibodies. One patient belonged to the $10^9$ cohort and the other patient belonged to the $10^{10}$ cohort.

One patient in the $10^{10}$ cohort (maximum dose) and one patient in the $10^7$ cohort had a recurrent mass 3 months after inoculation with ONYX-015. On MRI scans these masses were manifested as increases in gadolinium enhancement (Fig. 3). Because of their good performance status, these patients thus underwent reoperation for resection. On histologic examination of the recurrent tumor, profound lymphocytic and plasmacytoid cellular infiltrates in perivascular locations were noted within the tumor but not in the surrounding brain parenchyma in both cases (Fig. 4).

**DISCUSSION**

The primary objective of this study was to determine if injection of an oncolytic virus (i.e., a virus that can still replicate in a relatively selective fashion in tumor cells) into human brain that surrounds a resected malignant

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**TABLE 2: Serious adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy–motor</td>
<td>3/4</td>
<td>2</td>
</tr>
<tr>
<td>Dyslexia, dyscalculia, dysgraphia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal PT</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>3/4</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal SGPT</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Ten of the 24 patients experienced one or more serious adverse events. *The relationship to treatment was coded as unlikely for all serious adverse events.*
glioma would be tolerated. We determined that the treatment was well tolerated by all patients even at the highest dose of ONYX-015 that was available.

This study was conducted as a phase I dose-escalation trial in six different institutions that belonged to the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. The major novelty in this trial is that for the first time a tumor-selective virus that maintains replication was injected into brain that surrounds a surgically resected glioma. Previous trials with another oncolytic virus (based on the HSV-1 viral mutant designated G207 and another HSV-1 mutant designated 1716) have tested the viral vector via stereotactic intratumoral administration [24,26]. Other trials have involved injections of a replication-defective adenovirus vector, and not of a replication-conditional virus such as ONYX-015, to deliver p53 or the herpes simplex virus thymidine kinase gene [27–30]. Although these trials did not see evidence of toxicity until doses of 10^{12} viral particles, a very appropriate concern relates to the possibility that an oncolytic virus may still provoke clinically significant damage to brain if its action was not confined to a tumor. In fact, reports have shown evidence of cerebral inflammation in animals whose brains were inoculated with replication-defective adenoviral vectors [31–34]. It has been suggested that this may represent an immune-mediated reaction to adenoviral gene products/proteins and/or antigens released from dying tumor cells. By injecting this oncolytic adenovirus directly into human brain tissue that surrounded a resected glioma, we have demonstrated that ONYX-015 is unlikely to cause clinically significant disease in humans at doses up to 10^{10} pfu. We did not detect clinical or radiologic evidence of neurologic or systemic injury and the maximum tolerated dose was not reached at 10^{10} pfu. However, in two patients whose recurrent tumors were available for analyses we did find evidence of lymphocytic and plasma cell infiltrates that would be relatively unusual for this patient population.

![FIG. 2. Kaplan–Meier survival curve for patients treated with ONYX-015 (n = 24). Kaplan–Meier survival curves for GBM (n = 17) and other histology (n = 7) patients treated with ONYX-015.](image)

![FIG. 3. Serial MRIs with representative findings of trial. In (A), a left temporal lobe recurrence of a malignant glioma was observed and confirmed intraoperatively. (B and C) Immediate postoperative scans (following resection and margin injection of 10^{10} pfu of ONYX-015) reveal gross total resection of tumor. Approximately 3 months later, probable recurrence of glioma was visualized in resection cavity infiltrating the brain. Histological findings from the resection of this tumor are presented in Figs. 4A and 4B.](image)
and that would be consistent with the aforementioned animal studies.

No definite anti-tumor efficacy could be demonstrated in this trial. All but one patient experienced progression of disease, as determined by >25% increase in gadolinium enhancement. One patient showed evidence for increased enhancement approximately 1 year after treatment, which decreased on a subsequent scan. This episode of increased enhancement, which then decreased, had also occurred postoperatively. The postoperative changes in enhancement could be attributed to postoperative gliotic reactions, but the changes that occurred 1 year later would be more difficult to explain on this basis. Although no histologic data are available, one can speculate that it may represent an episode of transient breakdown of the blood–brain barrier due to a waxing and waning inflammatory reaction to recurrent tumor and/or residual replicative virus, in agreement with the histologic findings of the recurrent tumors described above.

The finding that such an inflammatory event may occur within a glioma that is recurring several weeks after ONYX-015 injection calls into question the current criterion of using an increase in gadolinium enhancement to decide whether there is progression of a glioma treated with such biologic agents. Although it still remains likely that observed >25% increases in gadolinium enhancement were due to tumor progression, we cannot exclude that a very localized inflammatory reaction within the injected tumor bed could have been partially responsible for such radiologic images.

Only two patients displayed evidence of seroconversion. Such a low number was likely due to the relatively immunocompromised state of this patient population, which is on steroid medication and has been treated with radiation and chemotherapy, and to the injection within the brain, an organ that is relatively immunoprivileged.

Although survival and time to progression evidence were relatively encouraging for four patients, three of these had diagnoses other than glioblastoma multiforme. It is known that patients with anaplastic astrocytomas and oligodendroglioma display more favorable average survival rates than patients with glioblastoma multiforme and thus the result of this trial should be judged in this context. It was encouraging, though, that one of the patients with glioblastoma multiforme remained alive for over a year after treatment.

In conclusion, this trial has shown the relative safety of injection of ONYX-015 into brain surrounding a resected malignant glioma. Further studies to determine a maximum tolerated dose and potential for efficacy are warranted.

**PATIENTS AND METHODS**

Approval of the trial was accomplished at each institution’s Institutional Review Board, in accord with an assurance filed with and approved by the Department of Health and Human Services. Informed consent was obtained from each subject. The following NABTT institutions participated: Massachusetts General Hospital (Boston, MA, USA), Wake Forest University (Wake Forest, NC, USA), Henry Ford Hospital (Detroit, MI, USA), Emory University (Atlanta, GA, USA), Moffitt Cancer Center (Tampa, FL, USA), and University of Alabama (Birmingham, AL, USA).
Inclusion and Exclusion Criteria

Patients were 18 years or older and had to have a histologically documented supratentorial malignant glioma (glioblastoma multiforme, anaplastic astrocytoma, or anaplastic oligodendroglioma) that had progressed after initial external beam radiation therapy. Radiation therapy had to have been between 5400 and 6700 cGy delivered in 180-to 200-cGy fractions. Patients had to have recovered from toxicity of prior therapy. An interval of at least 3 months had to have elapsed since the completion of the most recent course of radiation, while at least 3 weeks had to have elapsed since the completion of a non-nitrosourea-containing chemotherapy regimen and at least 6 weeks since the completion of a nitrosourea-containing chemotherapy. They may not have received more than two prior chemotherapy regimens. They had to have been eligible for resection of a portion of the recurrent tumor that was at least 1 cm in greatest dimension. There must have been no anticipated physical connection between the postresection tumor cavity and the cerebral ventricle. A Karnofsky performance status (KPS) of at least 60, a life expectancy of at least 3 months, and the ability to provide informed consent were required. Criteria for baseline organ function determined within 2 weeks prior to treatment on this protocol led to exclusion. Known diagnosis of Li-Fraumeni syndrome or known germ-line defect in the p53 gene was grounds for exclusion. Pregnant or lactating females were not included. Women of child-bearing potential were required to practice birth control for the duration of the treatment. Men were advised to use barrier protection for the duration of treatment. This exclusion was based on the potential risks of adenoviral encephalitis to the fetus and newborn. Finally, patients with gliomatosis cerebri were excluded.

Description of ONYX-015

ONYX-015 was manufactured under contract to Onyx Pharmaceuticals, Inc., by MAGENTA Corp. (currently BioReliance, Inc., Bethesda, MD, USA) in compliance with Good Manufacturing Practice Regulations. It was distributed to the individual trial sites by the Cancer Therapy Evaluation Program/National Cancer Institute. The purified virus was stored frozen below –60°C in aliquots. Prior to release for clinical use, each lot was tested to ensure that it met the following criteria: (1) sterility, (2) bacterial endotoxin <10 EU/ml, (3) general safety, (4) adenovirus titer in HEK293 cells for low-dose vials >2 × 10⁸ pfu/ml, (5) adenovirus titer in HEK293 cells for high-dose vials >2 × 10¹⁰ pfu/ml, (6) E1B deletion confirmed by PCR assay, and (7) selective replication in p53-deficient cells confirmed.

The product was formulated as a sterile viral solution in Tris buffer (10 mM Tris, pH 7.41; 1 mM MgCl₂; 150 mM NaCl; 10% glycerol). The product was supplied frozen in a single-use, plastic screw-cap vial. Prior to use, vials were thawed at room temperature. The appropriate dilution was admixed using aseptic procedures and transported on ice to the operating room in a sealed package. Injections were performed within a 4-h time frame after the virus was thawed. The injection protocol is described below (dose-escalation scheme). All injections were performed with a clinical lot, before the date of expiration. Although a standard for replication-defective vectors is to provide the viral particle to plaque-forming unit ratio and to provide doses as viral particles per milliliter, this was not a required release criterion for ONYX-015 and regulatory agencies did not require this release criterion.

Treatment

Pretreatment testing. All pretreatment testing/evaluations were conducted within 2 weeks of treatment and consisted of: (1) a complete history (disease history and prior oncologic therapies); (2) a physical examination including vital signs (heart rate, respiratory rate, blood pressure, temperature, and pulse), height and weight, KPS, and neurologic exam; (3) laboratory exams including CBC with differential and platelet count, serum electrolytes (Na⁺, K⁺, Cl⁻, bicarbonate), BUN, creatinine, glucose, total protein, calcium, phosphorous, magne-
sium, AST, ALT, total bilirubin, alkaline phosphatase, PT/PTT, CD3, CD4, CD8, total lymphocyte counts, serum antibody to group C adenovirus (total and neutralizing), serum pregnancy test within 72 h of treatment (for all premenopausal women with childbearing potential), and urinalysis with microscopy; (4) an EKG (12 lead); (5) a chest X-ray (PA and Lat) (within 6 weeks); (6) an MRI of the brain with and without gadolinium.

**ONYX-015 administration, schedule, and dose escalation.** Four cohorts of six patients each were treated. The number of patients per cohort was selected based on the estimate that between one-third and one-half of patients may have a mutation in the p53 tumor suppressor gene or a defect within the p53 tumor suppressor pathway [1]. Each patient received 10 injections (volume of 100 µl per injection) into the cavity wall after resection of the recurrent tumor. A period of 4 weeks (28 days) was allowed to elapse after treatment of the last patient at each dose level before escalation to the next higher dose level. At the end of each cohort study, the Data Safety Monitoring Committee (DSMC) evaluated administration methods, dosages, and overall treatment plan. The DSMC was composed of Drs. Chiocca and Barker (Massachusetts General Hospital), Dr. Stuart Grossman (Johns Hopkins University), Drs. James Zwiebel and Rick Kaplan (NCI/CTEP), Dr. Philip Gutin (Memorial Sloan-Kettering), and Dr. Michael Walker (NCI/NIH). The starting dose of ONYX-015 consisted of 10^7 pfu inoculated into the resected tumor cavity (as 10 single doses into 10 separate locations). Dose levels were successively escalated by a factor of 10 in subsequent cohorts. The selection of peritumoral injection sites was left to the judgment of the operating neurosurgeon, with the sites had to be separated by a least 1 cm. Injections were performed slowly, usually over a period of a few minutes, to avoid spillage. The depth of injection did not exceed 1 cm (length of the needle of the tuberculin syringe). The sites were selected by the neurosurgeon to avoid injections into adjacent motor or speech cortex or the cerebral ventricle or spillage into the subarachnoid space. After the injections, the wound was closed as per routine. Postoperatively, the patients were admitted to the Intensive Care Unit. Postoperative care followed standard neurosurgical practice and it included a brain MRI ± gadolinium at day 3, followed by one at day 14, one at day 42, and then every 6 weeks after. A postoperative serum sample for adenovirus antibodies was obtained on day 42.

**Toxicity Assessment**

A dose-limiting toxicity was defined as any one of the following: (1) NIH Common Toxicity Criteria (CTC; version 2.0) grade 4 toxicity for flu-like symptoms (fever, fatigue, myalgia) attributed to ONYX-015 or (2) CTC grade 3 toxicity for neurologic symptoms or for symptoms in other organ systems lasting longer than 5 days and attributed to ONYX-015. Because in the CTC (version 2.0) the grading for neurosurgical oncologic complications, such as cerebral edema, hydrocephalus, seizures, and hemorrhages, was not available or was unclear, we devised a supplemental table of neurosurgical toxicity criteria that was followed by the six participating institutions in addition to the CTC (Table 3).

**Table 3: Supplemental table of toxicities for neurological/neurosurgical disease employed in trial**

<table>
<thead>
<tr>
<th>Grade of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade I</strong></td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
</tbody>
</table>
Assessment of Response

Neurosurgical resections did not have to be gross total resections for ONYX-015 injection to occur. The scan done postoperatively was to assess the tumor configuration after injection and evaluate the extent of tumor resection. It was not used to determine response. However, it was this postoperative scan, not the scan obtained prior to surgery, that was used as the “baseline scan.” The scan obtained at day 42 was compared with the postoperative scan to determine response. Responses to ONYX-015 were determined at this 42-day time and every 6 weeks thereafter. The area of contrast enhancement was determined on each slice and the total was then multiplied by slice thickness to obtain a total volume. Response criteria were: (1) Complete Response, complete disappearance of all tumor on MR/CT scan and not taking glucocorticoids, with a stable or improving neurologic exam for at least 6 weeks; (2) Partial Response, greater than or equal to 50% reduction in tumor size on volumetric MR/CT scan, on a stable or decreasing dose of glucocorticoids, with a stable or improving neurologic exam for at least 6 weeks; (3) Progressive Disease, progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia) or a greater than 25% increase in the volume of the tumor by MRI/CT scan. Responses were determined at the 42-day time and every 6 weeks thereafter until documented tumor progression or another treatment was started.

Statistical Considerations

Survival distributions were estimated using the product limit method. The analysis was intention-to-treat and included all eligible patients. SAS software version 9 (SAS Institute, Cary, NC, USA) was used to perform analyses.

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REFERENCES


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