Interferon- α 2a and 13-*cis*-retinoic acid with radiation treatment for high-grade glioma^{1,2}

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Interferon- α (IFN- α) has been safely given concurrently with radiation therapy (RT) in treating gliomas. As single agents, both IFN- α and *cis*-retinoic acid (CRA) have produced objective tumor regressions in patients with recurrent gliomas. In vitro, IFN- α 2a and CRA enhance radiation therapy effects on glioblastoma cells more than either agent alone. This trial was conducted to determine the clinical effects of IFN- α 2a and CRA when given concurrently with radiation therapy to patients with high-grade glioma. Newly diagnosed patients with high-grade glioma received IFN- α 2a at a dosage of 3 to 6 million IU s.c. 4 times a day for 3 days per week and 1 mg/kg CRA by mouth 4 times a day for 5 days per week during the delivery of partial brain radiation therapy at 180 cGy $\times$ 33 fractions for 5 days per week for a total of 59.4 Gy during the 7-week period. Use of the antiepileptic phenytoin was prohibited after observing that the combination of IFN- α 2a, CRA, and phenytoin was associated with a high rate of dermatologic toxicity not seen in a previous study with concurrent IFN- α 2a and radiation therapy. Forty patients (26 men and 14 women) with a median age of 60 (range, 19 to 81 years) were enrolled between August 1996 and October 1998. Histopathologic diagnoses were glioblastoma multiforme or grade 4 anaplastic astrocy-

toma in 36 patients, and grade 3 anaplastic astrocytoma in 4 patients. Only 4 patients (10%) underwent a gross total resection of tumor prior to this therapy; 50% were asymptomatic when treatment was initiated. The planned 7-week course of concurrent therapy was completed by 75% of patients; 30% completed the 16-week course of IFN- α and CRA alone. At a median follow-up of 36 months, there were 37 deaths, with a median overall survival of 9.3 months and a 1-year survival rate of 42%. There was no improvement in survival compared with a similar group of 19 patients treated with concurrent IFN- α 2a and radiation therapy in a previous trial. In the high-risk group of patients in the present study, concurrent treatment with IFN- α 2a, CRA, and RT was feasible, but was not associated with a better outcome compared with a similar patient population treated with radiation therapy and IFN- α 2a, or compared with radiation therapy alone in other trials. *Neuro-Oncology* 3, 35–41, 2001 (Posted to *Neuro-Oncology* [serial online], Doc. 00-036, November 6, 2000. URL <neuro-oncology.mc.duke.edu>)

Brain tumors are the second leading cause of cancer death in children and the third leading cause of cancer death in young adults aged 15 to 34 years. In the United States, more than 18,000 new primary brain tumors are diagnosed each year, and more than 10,000 patients die each year of their disease (Laws and Thapar, 1993). Most malignant glial tumors are poorly differentiated and include anaplastic astrocytomas (grade 3 astrocytomas), which are characterized by vascular proliferation and moderate polymorphism, and glioblastomas (grade 4 astrocytomas), which are characterized by necrosis, in addition to more cellular atypia and mitosis, and by endothelial vascular proliferation (Kelly et al., 1984; Bruner, 1994). Glioblastomas and anaplastic astrocytomas constitute 40% to 60% of all primary adult CNS tumors. Historically, after surgery alone, the

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⁴Abbreviations used are as follows: CRA, *cis*-retinoic acid; IFN- α , interferon- α .

median survival for these patients was only 8 months, with a 1-year survival of 33%, and a 2-year survival of 0% (Cooper et al., 1982).

Surgery remains the mainstay of standard therapy, but advances in microsurgical techniques have had little impact on survival (Black, 1991a, 1991b; McVie, 1993). Many patients still present with gliomas that are considered inoperable or only partially resectable because of the anatomic location and/or size of their tumors. Radiation therapy is typically used in the management of gliomas, either after surgical resection or as primary therapy in patients who are not surgical candidates (Leibel et al., 1994). The best survival rates for glioma patients have been for patients who have undergone a complete resection of tumor followed by radiation therapy and chemotherapy. A meta-analysis of randomized trials of adjunctive chemotherapy determined that the 1-year survival among 884 patients treated with radiation therapy alone was 41% compared with 54% among 1,538 patients who received radiation and chemotherapy (Fine et al., 1993). Two-year survival was only 16% for radiation compared with 23% for radiation therapy plus chemotherapy. However, these trials resulted in the selection of a favorable subset of patients who were doing well enough to be considered candidates for chemotherapy after having already completed radiation therapy. Unfortunately, even for these highly selected patient populations, combination therapy with surgery, radiation therapy, and chemotherapy was associated with median survivals of less than 1 year and 2 years for no better than 15% to 25% of patients (Green et al., 1983; Werner-Wasik et al., 1996). Stereotactic radiosurgery (Loeffler et al., 1992; Morantz and Wara, 1995) has enabled more specific delivery of even higher doses of radiation, with some evidence that use of this technology may improve survival (Shrieve et al., 1999). Adding chemotherapy to the standard local treatment modalities, and even high-dose chemotherapy with autologous bone marrow stem cell rescue, has done little to enhance survival (Lesser and Grossman, 1994; Phillips et al., 1986).

The possible role of immunotherapy in the management of glioblastomas is under investigation. So far, the systemic use of interferons, interleukin-2, monoclonal antibodies, retinoids, vaccines, and adoptive cellular therapy has not been associated with improved outcomes, although phase II trials have shown that both IFN- α and CRA, an analogue of vitamin A, have some antitumor effects on gliomas (Weller and Fontana, 1995). There is a rationale for using both IFN- α and CRA in combination. Both modulate malignant cell differentiation and proliferation and have immunoregulatory, antiangiogenic, and antiviral activity. A large number of patients with a variety of advanced malignancies have been treated with the combination of s.c. IFN- α and oral CRA (Dillman et al., 1997; Lippman et al., 1992, 1993). In a randomized phase II trial involving patients with recurrent glioblastoma, the combination of IFN- β and CRA yielded a progression-free survival of 43% to 50% at 24 weeks compared with 11% to 29% for IFN- β alone (Yung et al., 1995). In vitro studies showed that both IFN- α and CRA, separately, augmented radiation-induced cytotoxicity in glioblastoma cells, but the com-

bination produced the best results (Malone et al., 1999). A previous clinical trial (CBRG 90-03) in patients with glioblastoma demonstrated that IFN- α 2a could be safely given concurrently with radiation therapy (Dillman et al., 1995). Based on this series of observations, we designed a phase II trial of IFN- α 2a plus CRA in combination with radiation therapy as part of the initial management of patients with newly diagnosed high-grade glioma.

Patients and Methods

Patient Population

Eligible patients had newly diagnosed glioblastoma or anaplastic astrocytoma and were referred for consideration of radiation therapy as part of their primary treatment plan. Grade 3 anaplastic astrocytoma or glioblastoma (grade 4 anaplastic astrocytoma) by the St. Anne-Mayo classification system (Daumas-Duport et al., 1988) was confirmed; however, there was no central review of pathology. The tumors were either totally resected, incompletely resected, or biopsied and found to be unresectable. Patients were at least 16 years old, with a life expectancy greater than 4 months. They had no prior therapy for glioma other than surgery. Corticosteroid administration was permitted as clinically indicated, but use of the lowest dose needed to control symptoms was encouraged. Written informed consent was obtained from all patients. The protocol and consent forms were approved by the Institutional Review Boards of all participating institutions.

Therapeutic Agents

Recombinant interferon- α 2a (Roferon; Hoffman-LaRoche, Nutley, N.J.) was given s.c. at a dosage of 3 to 6 million IU every other day (Monday, Wednesday, and Friday) during days of radiation therapy and for 9 weeks after completion of radiation therapy for a total of 16 weeks of treatment. *cis*-Retinoic acid (Accutane; Hoffman LaRoche) was given by mouth at a dosage of 1 mg/kg 5 days a week (Monday through Friday) during and after radiation therapy for a total of 16 weeks. IFN and CRA were started on day 1 of radiation treatment. Interruption and resumption of IFN and CRA therapy was permissible for severe, grade 3 toxicity at the discretion of the treating physician. Both drugs were to be discontinued in the face of life-threatening, grade 4 toxicity. Both drugs were donated by Hoffman-LaRoche so that ability to pay for the drugs was not a confounding variable for eligibility.

Radiation Therapy

Radiation therapy began no later than 5 weeks after the diagnostic surgical procedure. Radiation was delivered by external beam to a partial brain field as 180 cGy x 33 fractions for a total dose of 5940 cGy given over 49 days. Patients were treated with radiation delivered via megavoltage equipment with photon energies of 4 to 24 MeV delivered at a rate of at least 0.5 Gy/min with a source-

to-surface distance of at least 80 cm. Multidose field plans of radiation delivery were used as much as possible, with parallel opposed fields discouraged. If MRI was used for treatment planning, the target volume was to include the region of abnormal signal intensity on the T2-weighted image, with at least a 1.0-cm margin. If CT was used for treatment planning, the target volume included the enhancing mass with a margin of at least 3.0 cm.

Clinical Design

This study was conducted as an open label, nonrandomized trial. Patients were to receive 7 weeks of concurrent IFN, CRA, and radiation therapy, followed by 9 more weeks of IFN and CRA alone. Other concurrent chemotherapy was prohibited. Beyond 16 weeks, any type of additional treatment was at the physician's discretion; supplemental radiation and/or chemotherapy were neither proscribed nor prohibited.

Analysis

This study was designed as a phase II trial. Toxicity was graded 0 to 5 (none, mild, moderate, severe, life-threatening, lethal) using standard criteria per guidelines of the National Cancer Institute (Trotti, 2000). In the absence of acute or severe life-threatening toxicity in the first 3 patients, the next analysis occurred after 10 patients were enrolled. In view of the absence of delayed toxicity or poor disease control, a total of 40 patients were enrolled in order to get more reliable survival data with a larger study population. Because of patient variability related to surgery, and the anticipated difficulties associated with interpreting tumor response in the face of radiation treatment, no effort was made to estimate tumor response, although very few patients were totally free of radiographically detectable tumor at the time treatment was initiated. It was initially planned to use event-free survival (death or disease progression, whichever came first) as the major end point, but reliable establishment of progressive disease by radiographic criteria proved to be impossible; so overall survival became the major end point, with event-free survival a secondary end point. Disease progression was defined by the treating physician, based on his/her clinical assessment of all available subjective and objective information, including physical examination and radiographic findings. Actuarial survival was computed from the date of study registration (Kaplan and Meier, 1958). Overall survival was compared with results achieved in study CBRG 90-03 (Dillman et al., 1995) in which similar patients were treated with radiation therapy and IFN- α 2a, but without CRA.

Results

This protocol was officially activated on November 3, 1995, with 40 patients enrolled between January 8, 1996, and September 30, 1998, when the study was closed because of attainment of accrual goals. Patient characteristics are shown in Table 1. Radiation treatment was started an average of 20.4 days (range, 3-33 days)

Table 1. Characteristics of 40 patients having newly diagnosed glioma

Sex	26 men	14 women	
Age	Median 60 yrs	Range 19-81 yrs	
ECOG performance status	0 50%	1 32%	2 18%
Resection	Near total 10%	Partial 53%	Biopsy only 37%
Histology	Glioblastoma 66%	Anaplastic astrocytoma 30%	Other 4%

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

after diagnosis. One patient started radiation therapy, then declined all further therapy and died 1.6 months after study entry. Thirty patients (75%) completed 7 weeks of IFN- α 2a and CRA in conjunction with radiation therapy; 12 (30%) patients completed a full 16-week course of IFN- α 2a and CRA. The other 9 patients completed 1 to 4 weeks of IFN- α 2a and CRA, and 7 of 9 completed the prescribed radiation therapy.

The most significant toxicities associated with this treatment were mucocutaneous- and cutaneous-related. Among the first 8 patients who were treated, there were 6 episodes of pruritus and skin rash, and 2 of the 6 developed Stevens-Johnson syndrome. All of these patients were taking phenytoin (Dilantin) in addition to the study drugs. Because in our earlier trial (CBRG 90-03) only 2 of 19 patients developed a skin rash when IFN and phenytoin were given concurrently, we presumed that the presence of CRA with IFN- α 2a was enhancing sensitivity to phenytoin. For this reason, the protocol was modified effective October 1996 to exclude the use of phenytoin as an antiepileptic while IFN- α 2a and CRA were being given. There were only 4 additional episodes of cutaneous toxicity, all grade 2, in the subsequent 32 patients. Skin rash of any degree was noted in 25% of patients and pruritus in 10%. Mild elevations of serum glutamate-oxalate transaminase (SGOT) were recorded in 47%, and lactic dehydrogenase (LDH) was elevated in 30%. Elevated serum triglycerides, a potential complication of CRA, were noted in 38% of patients, but only 5% were elevated to a grade 3, and none were grade 4. Although 63% of patients had some degree of fatigue/malaise, it was rated as severe in only 5%. Alopecia was attributed to radiation therapy, and hyperglycemia to the concurrent use of dexamethasone.

Survival rates for all 40 patients enrolled in this trial are shown in Fig. 1. Median follow-up at the time of analysis was 36 months, and 37 patients died. The 3 patients still living at the time of this analysis had been followed for at least 16 months. The 2 patients who survived more than 2.5 years are summarized here. One was a 55-year-old white female who underwent partial resection of a glioblastoma located in the left temporal lobe. After protocol therapy, she also received procarbazine, CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea], and vincristine (PCV). Because of radiographic changes suggestive of recurrence, she underwent a craniotomy 11.3 months after diagnosis and was found to have extensive

Fig. 1. Event-free survival (EFS) and overall survival (OS) from date of study entry for 40 patients who had newly diagnosed high-grade glioma and were enrolled in the current trial (CBRG 95-08) of radiation therapy given concurrently with *cis*-retinoic acid and interferon- α 2a. Median EFS was 3.7 months, and median OS was 9.3 months, with a 1-year survival rate of 42% and a 2-year survival rate of 7%.

necrosis with some residual tumor cells. Gliadel wafers were inserted at the time of the craniotomy. Another craniotomy was performed 22.7 months after diagnosis at which time lymphokine-activated killer cells were placed in the operative site. She died 35.8 months after study entry. The second patient was a 36-year-old male with a high-grade anaplastic astrocytoma who underwent a partial resection. After completion of the 7 weeks of concurrent IFN- α 2a, CRA, and radiation therapy, he declined further treatment. He remained progression free and alive 33.8 months from the date of study entry.

The rationale for this trial was the potential additive and/or radiosensitizing effects of combining CRA and IFN with radiation therapy. Based on our *in vitro* observations (Malone et al., 1999), we felt this combination might induce more radiation necrosis than that typically observed with standard radiation therapy. It is interesting that several patients appeared to have progression of disease based on neurologic deterioration, but actually sur-

vived surprisingly long after a radiographic interpretation of progressive disease. This raised the question as to whether radiation necrosis, rather than tumor progression, was accounting for symptoms in some patients. Ten patients actually underwent a second craniotomy because of uncertainty regarding the etiology of neurologic and radiologic deterioration. These patients' treatment and survival are summarized in Table 2. All initially had at least a partial resection of tumor, and 2 underwent a complete resection initially. Although most of these patients did have some microscopic tumor at the time of the second craniotomy, in several cases there was extensive coagulative necrosis of the type associated with radiation therapy, with only rare residual tumor cells. As noted by others, PET was not reliable in predicting which patients had recurrent or resistant tumor and which predominantly had necrosis (Ricci et al., 1998).

Survival for patients treated in this trial (CBRG 98-08) was compared with that observed for glioma patients

Table 2. Summary of patients undergoing a second craniotomy because of worsening neurologic symptoms and radiographic findings suggesting glioma progression

Age (yrs)	Sex	Diagnosis	RT started	No. weeks RT	No. weeks IFN/CRA	Date of 2nd surgery	Pathology	Survival (mos.)
75	M	GBM	5/14/96	7	8	11/96	Extensive necrosis, residual GBM	11.1
60	F	AA ^a	6/17/96	7	4	1/16/97	Extensive RT necrosis, residual AA	10.1
55	F	GBM	10/8/96	7	24	9/17/97	Extensive RT necrosis, residual GBM	35.8
58	M	GBM	1/24/97	7	16	1/22/98	GBM and hemorrhage	16.8
45	M	GBM	3/4/97	7	14	6/10/97	Residual GBM	11.0
43	M	GBM ^a	5/6/98	7	8	10/3/98	Extensive RT necrosis, focal residual GBM	16.8
48	M	GBM	5/19/98	7	11	8/14/98	GBM, some necrosis	19.6
54	M	GBM	11/17/98	7	16	4/9/98	Extensive necrosis	14.0
46	F	GBM	3/30/98	7	16	11/12/98	Extensive necrosis, residual GBM	15.0
52	F	GBM	9/9/98	7	8	12/2/98	Residual GBM	13.7

Abbreviations: AA, anaplastic astrocytoma; CRA, *cis*-retinoic acid; GBM, glioblastoma multiforme; IFN, interferon- α 2a; RT, radiation therapy.

^aComplete resection of tumor at time of initial surgery; all others had partial resections.

Fig. 2. Comparison of overall survival of 40 patients treated concurrently with radiation therapy, interferon α -2a, and *cis*-retinoic acid, in the current study (CBRG 95-08), with survival of 19 patients treated concurrently with radiation therapy and interferon α -2a in a previous study (CBRG 90-03). Median survival was 9.3 months in CBRG 95-08 compared with 7.7 months in CBRG 90-03, and 1-year survival rates were 42% compared with 21%, respectively, although the survival curves were not statistically different ($P = 0.45$, log-rank test).

in our previous trial (CBRG 90-03) of radiation therapy plus IFN- α 2a alone (Dillman et al., 1995). That trial had similar eligibility criteria, and 19 patients were treated with IFN- α 2a plus radiation as part of their primary therapy. The patient populations in these two trials were quite similar: Median ages of 64 years (range, 24-77 years) and 60 years (range, 19-81 years), percentage of males 63% and 65%, percentage undergoing complete resection 10.5% and 10.0%, percentage undergoing partial resection 47% and 53%, percentage undergoing only a biopsy prior to therapy 42% and 37%, and percentage diagnosed as glioblastoma (grade 4 anaplastic astrocytoma) 74% and 70%, respectively for the previous and current trials. The earlier trial had an accrual goal of 20 patients. Median survival in that trial of IFN- α 2a plus radiation therapy was 7.5 months compared with 9.3 months in the current trial of IFN- α 2a and CRA plus radiation therapy. The difference in survival curves, however, was not significant (Fig. 2) even though the 1-year survival rate of 42% in the current trial was double the 1-year survival rate of 21% observed in the previous trial. The 2-year survival rate was less than 10% in both studies.

Discussion

The major conclusion from this trial is that concurrent administration of CRA plus IFN with external beam radiation therapy is unlikely to produce a survival benefit compared with that observed with radiation plus IFN or radiation therapy alone. IFN and CRA had both exhibited antitumor effects in phase II trials (Lippman et al., 1992, 1993; Dillman et al., 1997), and the combination produced enhanced radiosensitization in vitro (Malone et al., 1999). Therefore one would hope that the addition of these agents to radiation therapy would provide some additive and/or synergistic effects that result in improved survival. The median survival for patients in this trial was

9.3 months from the date of diagnosis, and the 1-year survival rate was 42%. Unfortunately, these survival figures are no better than results previously published for radiation therapy alone as primary therapy of gliomas. For instance, the median survival for radiation therapy alone in the original Brain Tumor Study Group trial was 10.5 months, but those patients had to be medically suitable to receive chemotherapy as a condition of entry into the study (Green et al., 1983). The meta-analysis of trials of radiation therapy alone in the treatment of glioblastomas disclosed a one-year survival of 41% (Fine et al., 1993). In a single arm trial it is impossible to be confident of the relative efficacy of the specific treatment approach because comparison with other trials is not reliable because of differences in the patient populations that were treated. Perhaps a more relevant comparison would be with the comparable group of patients who were treated with radiation and IFN- α 2a alone in our previous trial (CBRG 90-03), because they had to meet the same eligibility criteria and were being treated as part of the same cooperative group (Dillman et al., 1995). However, the data suggest that the addition of CRA to the regimen did not improve survival. Although this question could only be resolved with a randomized trial, without more encouraging results, such a trial is probably not worthy of pursuit. For this reason, in future trials we will pursue other therapeutic approaches rather than building on this trial.

One interesting observation from this trial is that treatment with CRA plus IFN- α 2a concurrently with radiation therapy appears to be associated with radiation necrosis. In vitro data suggest that IFN- α 2a plus CRA could enhance the radiosensitivity of glioma cells to an extent greater than radiation plus IFN- α 2a or radiation plus CRA (Malone et al., 1999). During the course of the current clinical trial, several patients experienced some worsening of neurologic symptoms that appeared to be due to an enhanced radiation effect rather than progression of tumor. Some patients had MRI scans that were

initially interpreted as disease progression with edema and central necrosis, but the scans subsequently showed no increased uptake of tracer according to PET scan (Ricci et al., 1998). Ten of the 40 patients underwent a second craniotomy later in their management, and 6 had extensive necrosis with minimal residual tumor. Three of the 10 patients underwent a craniotomy specifically to relieve pressure that was associated with what seemed to be increased edema that had not resolved with dexamethasone treatment according to MRI. Two of these patients had only necrosis, and 1 patient had only rare foci of microscopic disease detected at the time of repeat craniotomy. Although it is difficult to differentiate tumor necrosis from radiation necrosis, reports after stereotactic radiosurgery demonstrate that patients that predominantly have radiation changes in their posttreatment biopsies have a better survival than do patients that predominantly have infiltrating tumor or solid tumor (Schwartz et al., 1998). Median survival for all 40 patients was 9.3 months, but 10 patients who underwent a second craniotomy survived more than 10 months, including the 6 patients who had extensive necrosis documented at the time of surgery.

Based on this trial, IFN- α 2a and CRA can be safely given concurrently with radiation therapy during the treatment of patients with high-grade gliomas. Most of the toxicity observed was mild to moderate. However, one interesting observation in this trial was the high fre-

quency of what we concluded was phenytoin-related skin rash. Six of the first 8 patients treated experienced skin rash, and 2 also had mucositis that lead to the clinical diagnosis of Stevens-Johnson syndrome. There is a previous report of 8 cases of erythema multiforme or Stevens-Johnson syndrome occurring in patients who had intracranial tumors and were receiving phenytoin and radiation therapy (Delattre et al., 1988). However, mucocutaneous problems were uncommon when phenytoin was given concurrently with IFN- α 2a and radiation therapy in our previous brain tumor trial (CBRG 90-03), although one patient was taken off study because of skin rash (Dillman et al., 1995). We have not seen this problem in clinical trials during which CRA and IFN- α 2a were given to patients with squamous cell carcinomas (Dillman et al., 1997). This led us to postulate that CRA or the combination of CRA plus IFN- α 2a might be increasing the risk of an immune reaction to phenytoin. There was no further significant problem with mucocutaneous toxicity after we modified the protocol to exclude the concurrent use of phenytoin as an anti-epileptic.

In conclusion, this regimen of concurrent treatment with external beam radiation therapy, oral *cis*-retinoic acid, and s.c. interferon is feasible and associated with more radionecrosis than might be expected from standard radiation therapy alone. However, there did not appear to be any significant impact on survival of these patients with newly diagnosed high-grade glioma.

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