Treatment of Recurrent Malignant Gliomas with High-Dose 13-cis-Retinoic Acid

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ABSTRACT
Malignant gliomas account for more than 60% of all primary brain tumors in adults. Adjuvant chemotherapy in addition to radical surgery and radiation therapy has provided only a modest increase in survival. Retinoic acid has been shown to have growth-inhibitory activity against glioma cells in culture. This provides the rationale for a Phase II study using 13-cis-retinoic acid (CRA) in patients with recurrent malignant brain tumors. The objective of this study was to determine the clinical activity of CRA in patients with a histologically proven diagnosis of malignant brain tumor and documented progressive or recurrent disease after radiation and chemotherapy. Fifty patients with documented recurrent disease were treated with CRA as a single agent p.o. at a dose of 60–100 mg/m² per day. Three weeks of treatment were followed by 1 week of rest. Of the 43 patients who received more than 4 weeks of therapy, 3 (7%) achieved partial response, 7 (16%) achieved minor response, 13 (30%) remained stable, and 20 (47%) had disease progression. The median time from onset of treatment to disease progression for the whole group of 43 patients was 16 weeks (19 weeks for glioblastomas and 11 weeks for anaplastic glioma), whereas that for the 23 patients with partial response and minor response and who remained stable was 66 weeks, and that for the 20 patients with progressive disease was only 8 weeks. The median survival time for glioblastoma was 58 weeks, and 34 weeks for anaplastic astrocytoma. Toxicity was mainly dermatological, with dry skin and chelitis. These preliminary results suggest that 13-cis-retinoic acid is active against malignant gliomas and is very well tolerated.

INTRODUCTION
Malignant primary brain tumors account for 1.5% of all cancer in the United States. It is the most common solid tumor and the most common cause of cancer death in children. GBMs are the most common primary brain tumors in adults, and they carry a grave prognosis regarding patient survival. Radical surgery and radiation therapy have been valuable in managing these tumors (1), and the addition of chemotherapy has modestly increased the survival over radiation therapy alone (2). For patients with tumor recurrence or disease progression after initial treatment, nitrosourea or procarbazine remains the main treatment of choice (3). In several Phase II studies, other chemotherapeutic agents such as cisplatin, carboplatin, and aziridinylbenzoquinone have shown moderate effectiveness (4–7). In another study, monotherapy with efomithine (difuoromethylomithine) was effective against recurrent gliomas, particularly anaplastic astrocytoma (8).

Retinoids, the natural and synthetic derivatives of vitamin A, are clinically active in diverse premalignant and malignant conditions, including cutaneous T-cell lymphomas, leukoplakia, squamous cell carcinomas of the skin, and basal cell carcinomas (9). Retinoids, both CRA (isoretinoïn) and etretinate, have shown about a 60% response rate (10–20% CR) in cutaneous T-cell lymphoma (10) and a 40–50% response rate (10% CR) in advanced nonmelanoma skin cancer (11, 12). This type of systemic therapy has been used primarily in localized disease but has also proved effective in metastatic lesions and in patients with multifocal disease. Although modest activity was observed in a randomized Phase II trial in head and neck cancer (13), CRA does not appear to be active as a single agent in common advanced solid tumors, such as non-small cell lung, breast, and colon cancer (9). Recently, retinoids have also been used in the treatment of preleukemic and leukemic conditions. The rationale for the use of these agents has been their differentiation-inducing effects in vitro. Hematological improvement has been noted in myelodysplasia syndrome patients treated with CRA. Gold et al. (14) described hematological responses in 5 of 15 myelodysplasia syndrome patients. Responses were not seen until at least 3 weeks of therapy were completed. More recently, several investigators have documented dramatic improvement in patients with acute promyelocytic leukemia treated with isotretinoin and, even more so, with all-trans-retinoic acid (15–18).

The rationale for the use of retinoic acid in human gliomas comes from in vitro studies demonstrating differentiating and growth-inhibitory effects of retinoic acid on neuroblastoma and glioma cells. The in vitro response among the various glioma cell lines studied is heterogeneous, and the effective concentration among the more sensitive lines is approximately 1 × 10⁻⁶ M (19). Moreover, the growth-inhibitory effect in human glioma cells is related to a decrease in epidermal growth factor receptor-mediated phosphorylation activity.

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PATIENTS AND METHODS

This Phase II study was conducted at The University of Texas M. D. Anderson Cancer Center, and the protocol was approved by the institutional review board. All patients with histologically proven malignant gliomas, including GBM, anaplastic astrocytoma, anaplastic oligodendroglioma, mixed malignant gliomas, and other malignant gliomas were eligible for this protocol. Eligibility criteria included unequivocal evidence of tumor recurrence or disease progression by CT or MRI scans after failing prior radiation therapy and chemotherapy, measurable disease on a contrast CT/MRI scan of the brain, a KPS score ≥60, and a signed informed consent form that indicated each patient's awareness of the investigational nature of this study. Before treatment, each patient underwent a careful clinical evaluation that included complete history, neurological examination, and numerous laboratory studies (complete blood count, differential, platelet, electrolytes, Sequential Multiple Analysis 12-channel biochemical profile, cholesterol, triglyceride, urinalysis, and contrast-enhanced CT or MRI scan).

A total of 50 patients was entered into the study. CRA was given p.o. daily at a dose of 60–100 mg/m² per day for 3 weeks, followed by 1 week with no treatment. Two 4-week cycles constituted one course of treatment. Patients were considered evaluable for response after completing a minimum of 4 weeks of treatment.

All patients were monitored with complete blood and platelet counts every 2 weeks; Sequential Multiple Analysis 12-channel biochemical profile, electrolyte, cholesterol, triglyceride, amylase, and lipase every 8 weeks; and a complete neurological examination and CT/MRI scan every 8 weeks. R was defined as a definite decrease in the size of the tumor on CT/MRI scan while on stable or decreasing doses of corticosteroids. This includes CR (complete disappearance of the tumor), PR (a decrease of 50% or more in tumor size), and MR (a decrease of 25–50% in tumor size). S was defined as no change in tumor size while on stable or decreasing doses of corticosteroids. PD was defined as a definite increase of 25% or more in tumor size while on stable or decreasing doses of corticosteroids. TTP was measured from the first date of CRA treatment to when tumor progression was documented. Survival time was measured from the first date of CRA treatment to the time of death.

RESULTS

Fifty patients were entered into this study. Five patients returned to their home city without initiating therapy, and two patients discontinued treatment after 1 week because of rapid clinical deterioration. Thus, 43 patients received at least 4 weeks of therapy and were considered evaluable for toxicity and response. Of the 43 patients (Table 1), 15 had GBM; 15 had anaplastic astrocytoma; 4 had anaplastic oligodendroglioma; 2 had anaplastic mixed glioma; and 7 had other gliomas, which included 3 with infiltrative glioma and 4 with infiltrative oligodendroglioma. Thus, the 28 patients with anaplastic astrocytoma, anaplastic oligodendroglioma, infiltrative gliomas, and infiltrative oligodendroglioma were considered as a group as AG. All 43 patients had prior radiation therapy and one to four regimens of chemotherapy. There were 24 male and 19 female patients with a median age of 40 years (range, 18–67 years), and the median KPS score was 80 (range, 50–90).

Two patients received a starting dose of 60 mg/m² per day. The starting dose was escalated to 80 mg/m² in the next seven patients. The other 34 patients received a daily dose of 100 mg/m²; this included six patients who were started at 120 mg/m² per day, but this dose level produced significant skin toxicity, requiring dose reduction to 100 mg/m² in subsequent courses in all six patients.

As it is described in Table 2, 10 patients (23%) achieved R, and 13 patients (30%) remained stable, with a total response rate (R + S) of 53%. Of the 15 GBM patients, 2 achieved MR, none achieved PR or CR, and 6 achieved a stable condition. Of the 28 non-GBM patients, 3 achieved PR (1 anaplastic astrocytoma, 1

| Table 1 | Characteristics of all evaluable patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total number of patients | 43 | Sex | Male | 24 | Female | 19 |
| Age | | Median | 37 | Range | 18–67 |
| KPS score | | Median | 80 | Range | 50–90 |
| Pathology | | Glioblastoma | 15 | Anaplastic astrocytoma | 15 | Anaplastic oligodendroglioma | 4 | Anaplastic mixed glioma | 2 | Other gliomas | 7 |

| Table 2 | Number of responses by pathological classes |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Tumor type | PR | MR | S | PD |
| Glioblastoma | | 2 | 6 | 7 |
| Anaplastic astrocytoma | 1 | 2 | 3 | 9 |
| Anaplastic oligodendroglioma | 1 | 2 | 1 |
| Anaplastic mixed glioma | 1 | 1 |
| Others | 2 | 2 | 3 |
| Total | 3 (7) | 7 (16) | 13 (30) | 20 (47) |

a (%) , percentage.

| Table 3 | Summary of patient responses to CRA |
|-----------------|-----------------|-----------------|-----------------|
| No. of patients | MTP (weeks) | MST (weeks) | Progression-free survival (%) |
| GBM | 15 | 19 | 58 | 39 |
| AG | 28 | 11 | 34 | 35 |
| PR + MR | 9 | 66 | NR* | |
| S | 14 | 44 | 58 | |
| R + S | 23 | 48 | NR | |
| PD | 20 | 8 | 24 | |

* NR, not reached.
CRA in Recurrent Malignant Gliomas

![Probability vs Time to Progression in Weeks](image1)

**Fig. 1** Kaplan-Meier TTP plot for all patients as well as GBM and AG patients.

CRA in Recurrent Malignant Gliomas

![Probability vs Survival in Weeks](image2)

**Fig. 2** Kaplan-Meier survival plot for GBM and AG patients.

anaplastic oligodendroglioma, and 1 anaplastic mixed glioma), 5 achieved MR, and 7 remained stable.

The MTP among all 43 patients was 16 weeks as estimated by the Kaplan-Meier method (Table 3). Of the 15 patients with GBMs, the MTP was 19 weeks, which is slightly better, but not statistically significant, than the MTP of 11 weeks for the 28 patients with AGs (Fig. 1). The MTP for the 23 patients with R and S (R + S) was 48 weeks (Table 3), which is significantly better ($P < 0.001$) than that for the 20 patients with PD. If one only looked at the 14 patients with S, their MTP was 44 weeks, which is also significantly better ($P < 0.001$) than that for the patients with PD. There were no obvious differences between the responders and nonresponders in KPS or in the number of prior chemotherapy regimens received before CRA.

MST for the 43 patients was 52 weeks (Table 3). The MST for the 15 GBMs was 58 weeks, which was again better, but not statistically significant, than the MST of 34 weeks for the 28 AG patients (Fig. 2). Fewer than 50% of the nine patients with PR or MR had died; thus, the MST was not computed. More importantly, 39% of patients remained progression free at 6 months, and the GBM patients did slightly better than the AG patients (43% versus 35%; Table 3). Most patients showed no
change or a less than 50% decrease in the size of the tumor, and several patients showed only a decrease in the intensity of contrast enhancement, suggesting a change in the integrity of the vasculature in the tumors.

Toxicities for CRA therapy were in general mild to moderate and tolerable. The most common side effects involved the skin and mucus membranes. Most patients complained of dry skin, cracked lips, and occasional ulcers in oral mucosa. These occurred more severely at higher doses, e.g., 120 mg/m². Erythema of skin was common at the 100 mg/m² level. Dryness and itchiness of skin were relieved with cold cream or lotion. Cheilitis and conjunctivitis were the second most common complaints, occurring at the 100 mg/m² level. Mild nausea and vomiting were encountered in some patients. No severe headache or pseudotumor cerebri was seen. Grade 1 granulocytopenia and thrombocytopenia were observed. Elevation of triglycerides was seen in four patients after 2–6 months of therapy. Two of the four patients also developed an elevated cholesterol level. One patient developed marked elevation of serum triglycerides and primary acute pancreatitis and unfortunately succumbed to the pancreatitis.

DISCUSSION

It is generally accepted that chemotherapy plays an important role in prolonging the life of patients with anaplastic astrocytoma, but the addition of chemotherapy to radiation has not changed the survival of patients with GBMs (1). Bis-chloroethyl-nitrosourea and procarbazine remain the two most active drugs for the treatment of malignant gliomas as adjuvant to radiation or as salvage therapy at the time of tumor recurrence (4). In several Phase II studies, agents such as aziridinylbenzoquinone (5, 6) and carboplatin (7) have shown a R rate of 15–30%, and a S rate of 25–35%, and the MTP for the response and S patients (R + S) was around 25 weeks.

The results of this study suggest that CRA has definite activity in recurrent malignant glioma. The mechanism of this antitumor activity is not clearly known. The large number of patients achieving only MR and stabilization of disease suggests that CRA is working as a cytostatic rather than a cytolytic agent. This is also consistent with the in vitro data demonstrating the growth-inhibitory activity of CRA on glioma cells in culture corresponding with tyrosine kinase activity (19).

Up to now, the activity of a new chemotherapeutic agent is determined by its ability to induce CR or PR. However, such criteria may be more applicable to cytotoxic agents than to biological agents such as IFN or differentiating/growth inhibitory agents such as CRA. For this class of agents and others, such as antiangiogenesis agents, the TTP or the progression-free survival at 6 months may be a better end point to measure activity, as demonstrated in Table 3, because both end points take into account the contribution of those patients in the S group. Recently, we have reanalyzed the results of seven Phase II studies, performed previously at M. D. Anderson, of 209 patients with recurrent malignant gliomas. The MTP for the entire group was 9.6 weeks, and MTPs for GBM and AG patients were 10 and 18 weeks, respectively (20). The MTPs of 19 (GBM), 11 (AG), and 16 weeks (all patients) are better than that for the combined studies. The combined studies analysis also demonstrated a positive correlation between TTP and overall response rates of CR, PR, MR, and S, suggesting that TTP, as an end point, will include the S group in the consideration of the overall benefit to the patients. Indeed, in the current study, the 14 patients who remained in stable condition have a MTP of 44 weeks, which is statistically significantly better than the MTP of 8 weeks for the 20 patients with disease progression. The three patients with a PR (3) and six patients with a MR showed an even higher MTP of 66 weeks, again a figure significantly better than the PD group (Table 3). Moreover, the MST of 52 weeks for the entire group is very encouraging. It is even more remarkable for the 15 GBM patients to have a median survival of 58 weeks, which is longer than that reported in a recent study of high-dose tamoxifen in recurrent GBM patients (21). It is remarkable to see 39% of patients remain progression free at 6 months, which is much better than that shown in patients who received high-dose procarbazine, a widely used salvage regimen for patients with recurrent malignant gliomas (22). It is also of interest to see that GBM patients did as well as the AG patients. This could be an age effect, because both groups of patients are relatively young, with a median age of 38 and 41 years, respectively, for GBMs and AG.

Radiographically, several patients were observed to show a decrease in contrast enhancement without a decrease in the size of the tumor. A similar observation was described in a previous study with recombinant IFN-β (23). It is possible that CRA may suppress tumor vascular proliferation by inhibiting biosynthesis of angiogenic factor by the tumor cells. Laboratory investigation to this effect is currently ongoing.

A major advantage of CRA in this group of patients who had been treated previously with several cytotoxic agents is its mild toxicity profile. No grade 3 or 4 hematological toxicities are observed. The dermatological toxicities are mild to moderate and are managed easily with frequent application of skin lubricant. Because all patients were on steroids to reduce cerebral edema, it is possible that steroids help prevent more severe dermatological toxicity from CRA. Two patients developed elevated cholesterol (601 and 359 mg/dl) and triglyceride (2710 mg/dl) levels, as reported previously with CRA treatment (24). The patient with a triglyceride level of 2710 mg/dl developed acute pancreatitis and died, presumably from the pancreatitis.

In summary, this report presents encouraging preliminary results of CRA in 43 patients with recurrent malignant gliomas. More importantly, CRA appears to provide significant benefit with a mild degree of toxicity for this group of patients, who are pretreated heavily with multiple cytotoxic agents. A larger randomized study will be required to establish the true benefit of CRA in recurrent malignant gliomas. However, a combination regimen of CRA with other biological agents or cytotoxic agents should also be considered a higher priority.

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