Clinical Study

A II-trans-retinoic acid: a phase II radiation therapy oncology group study (RTOG 91-13) in patients with recurrent malignant astrocytoma

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Summary

The Radiation Therapy Oncology Group enrolled 30 patients with recurrent malignant astrocytomas onto a phase II study (RTOG 91-13). Patients were treated with all-trans-retinoic acid at a starting dose of 120 mg/m² per day orally continuously until disease progression. Fourteen patients had glioblastoma, 14 had anaplastic astrocytoma, and 2 had other histologies; 53% were under 50 years of age. A II patients had failed radiation therapy and/or at least one chemotherapy regimen. A II patients had a K arnofsky performance status score of at least 70, but only 37% had a K PS of 90-100. Forty percent had a neurologic function status of grade 1 (able to work). A minimum of 4 weeks of all-trans-retinoic acid defined adequate treatment. Twenty-five patients received adequate therapy.

Most common toxicities were dry skin, cheilitis, anemia, and headache; 3 patients had grade 3 headache requiring suspension of all-trans-retinoic acid. No grade 3 hematologic toxicity was observed. Of 25 adequately treated patients, 3 showed objective regression of tumor on magnetic resonance imaging and computed tomography scans, 3 patients remained stable, and 19 patients had disease progression. The median time to tumor progression was 3.8 months and the median survival time was 5.7 months.

This study suggests that this dose of single agent all-trans-retinoic acid has modest clinical activity against recurrent malignant gliomas with tolerable side effects. A response rate of 12% and a stabilization rate of 12% are lower than expected. Future studies with higher dosage or in combination with biological response modifiers or chemotherapy may be warranted.

Introduction

Glioblastoma multiforme and anaplastic astrocytoma account for more than 60% of all primary brain tumors in adults and carry a grave prognosis. Radical surgery, corticosteroids, and radiotherapy may prolong survival of patients with these tumors [1]. The addition of BCNU (carmustine) has modestly increased survival over that obtained with radiotherapy alone with median survival times of 45 vs 35 weeks and 18 month survival rates of 25% vs 5%, respectively [2]. Several chemotherapeutic agents such as diaziquone, cisplatin, and carboplatin have shown activity in phase 2 trials, but response rates are less than 20% and are usually of short duration. Fine et al. [3] carried out a meta-analysis on 17 randomized chemotherapeutic trials and demonstrated a modest benefit for adjuvant chemotherapy in addition to radiation treatment. However, since treatment is rarely curative and recurrences are common, newer more effective therapy, including new chemotherapeutic and biological agents are needed.
Retinoids, the natural and synthetic derivatives of vitamin A, are clinically active in diverse preneoplastic and malignant conditions [4]. The maximum tolerated dose (MTD) for all-trans-retinoic acid (t-RA) in advanced solid malignancies with a daily dose of 45 to 200 mg/m² has provided the basis for the dose used in this phase II study. Although the data are limited, the dose-limiting toxicity of t-RA is nonhematologic. In a study by Huang et al. [11] treatment with t-RA (45 to 100 mg/m² per day) resulted in generally mild toxicity that consisted of dryness of the lips and skin (100%), headache (25%), nausea or vomiting (20.8%), moderate bone or joint pain (12.5%), and mild exfoliation (8.3%). These side effects were well tolerated or alleviated by a reduction in t-RA dosage. The rationale for the use of retinoic acid in human gliomas was derived from in vitro studies that demonstrated the differentiating and growth-inhibitory effects of retinoic acid in neuroblastoma and glioma cells. The in vitro response demonstrated in various cell lines studies was heterogenous, and the effective concentration among the sensitive lines was approximately $1 \times 10^{-6}$ M [15]. Moreover, the growth inhibitory effect in human glioma cells was related to a decrease in epidermal growth factor (EGF) receptor-mediated phosphorylation activity.

**Patients and methods**

**Patient eligibility**

Patients were at least 18 years of age with a life expectancy greater than eight weeks. All patients had histologically proven malignant astrocytoma (anaplastic astrocytoma and glioblastoma multiforme) as well as evidence of tumor recurrence or progression by computed tomography (CT) or magnetic resonance imaging (MRI) after prior surgery, radiation therapy and/or chemotherapy. Patients must have discontinued prior radiation at least four weeks before registration and discontinued nitrosoureas at least eight weeks prior to therapy. Patients had to have a Karnofsky performance status score of ≥ 70%. Other eligibility requirements included: complete blood counts, platelets, electrolytes, serum chemistries and liver function tests, prothrombin time, and partial thromboplastin times, lipid profiles (triglycerides, cholesterol, low- and high-density lipoprotein) Vitamin A level, and contrast-enhanced CT or MRI within two weeks of registration. Adequate bone marrow functions (absolute granulocyte count > 1500 and platelet count > 100,000), adequate liver functions (serum glutamic-oxaloacetic transaminase or serum glutamic pyruvic transaminase, and alkaline phosphatase < 2 times normal and bilirubin < 1.5 mg%), and adequate renal function (blood urea nitrogen or creatinine < 1.5 times normal) prior to starting therapy were required. Pregnant patients and those with active infections were excluded. This study was performed under the Food and Drug Administration Investigation New Drug Application #122758 and was approved by the IRB (Institutional Review Board) at each institution where patients were entered on the study. The study was fully discussed with each patient, and written informed consent was obtained before enrollment. A complete medical history and physical and neurologic examination was performed on each patient prior to enrollment.

**Study design and methods**

All patients were given t-RA at a starting dose of 120 mg/m² daily by mouth. Calculation of body surface area was based on actual weight. Since t-RA is supplied in a 10-mg gelatin capsule, the calculated dose was rounded to the closest 10 mg. Eight weeks of treatment were considered one course, and treatment was continued without interruption in the absence of tumor progression unacceptable toxicity. The t-RA was provided for this study by the Division of Cancer Treatment, National Cancer Institute, National Institute of Health.

t-RA was dose escalated by increments of 20 mg/m² per day with adjustments after each course of treatment every eight weeks. The treatment was continued without dose adjustment for an eight-week treatment period as long as there were no grade ≥ 3 toxicities. When toxicities of at least grade 3 were seen, treatment was withheld and the patients were monitored until toxicities improved...