Cancer Chemother Pharmacol (1994) 34: 179–180

Cancer Chemotherapy and Pharmacology

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Clinical trial report

A phase II evaluation of fazarabine in high-grade gliomas: a Southwest Oncology Group study

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Received: 10 September 1993/Accepted: 6 December 1993

Introduction

Patients with high-grade gliomas, glioblastoma multiforme, and anaplastic astrocytomas have a median survival of approximately 1 year following resection and radiation therapy [6]. The addition of chemotherapy makes only a modest contribution to prolonging survival [1], and little progress has been made in the chemotherapy of these tumors since the introduction of the nitrosoureas [4].

Fazarabine (Ara-AC, 1-B-D-arabinofuranosyl-5-azacytosine) is an analog of both cytosine arabinoside (Ara-C) and 5-azacytidine (5-AC). Like Ara-C, fazarabine inhibits DNA synthesis and DNA methylation, albeit with little inhibition of RNA synthesis [2, 5]. Since activity of this agent against experimental tumor models, including TE-671 medulloblastoma, has been documented and because fazarabine crosses the blood-brain barrier, achieving cerebrospinal fluid concentrations equal to 13%–18% of serum levels [3], a phase II trial of this agent as treatment for high-grade gliomas was undertaken.

Patients and methods

A total of 27 patients with a biopsy-confirmed diagnosis of glioblastoma multiforme (n = 13) or anaplastic astrocytoma (n = 14) that had failed radiotherapy and progressed following any prior resection as documented radiographically were enrolled in the present study between July 1990 and May 1991. All had a Southwest Oncology Group (SWOG) performance status of 2 or better. The median age was 45 years (range, 28–70 years). In all, 52% of the patients were men and all but one patient were white. All but seven had had prior surgery. In all, 22 patients had received a single regimen of chemotherapy prior to enrollment, but all treatment-related toxicities had resolved. All patients had measurable disease and adequate hematologic, renal, and hepatic function. All patients were aware of the investigational nature of the drug and gave written informed consent in accordance with institutional and SWOG guidelines.

Fazarabine at 30 mg/m^2 in lactated Ringer's solution was infused intravenously over 45 min daily for 5 consecutive days, and treatment was repeated every 28 days. Fazarabine dose escalation to 45 mg/m^2 was allowed, depending on hematologic parameters. Complete responses required the total resolution of radiographic enhancement, mass effect, and edema. A 50% or greater reduction in the product of the length of the perpendicular diameters of the enhanced lesion with or without a reduction in cerebral edema and the absence of new tumor foci comprised a partial response. Both partial and complete responses were to be confirmed 4 weeks following the initial documentation of response. Treatments were continued either until progression of the tumor was noted by computerized tomography or magnetic resonance imaging or until toxicities became intolerable.

Results

All of the 27 enrolled patients were eligible. All patients are currently off treatment due to either progression/relapse (n = 12), patient request (n = 4), death (n = 2) or deterioration without radiographic progression (n = 9). In all, 18 patients received at least 2 cycles of chemotherapy (mean, 4 cycles; median, 3 cycles). Dose escalation was possible in eight patients, whereas treatment-related delays occurred twice. Standard SWOG toxicity grading was used, and over half of the patients (n = 15) had at least one episode of grade 3 or worse toxicity. Granulocytopenia was the most common grade 3 or greater toxicity, with incidence rate being 26% and one patient developing an infection. There were also five cases of grade 3–4 leukopenia. Malaise or thromboembolic syndromes occurred thrice and nausea, twice at grade 3 or worse intensity. Other grade 3 or greater toxicities encountered once were diarrhea, headache, lymphopenia, emesis, and hyperglycemia.

There was no confirmed complete or partial response to fazarabine. The exact 95% confidence interval for a con-

This investigation was supported in part by the following PHS Cooperative Agreement grants awarded by the National Cancer Institute, DHHS: CA-38926, CA-42777, CA-04919, CA-04920, CA-28862, CA-45807, CA-4 CA-52772, CA-58658, CA-58686, CA-46113, CA-20319, CA-52654, and CA-32102.

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firmed response is 0–13%. The median time to treatment failure was 2 months, with the median survival being 5 months.

Discussion

This study confirms that myelosuppression is the dose-limiting toxicity of fazarabine, with leukopenia (granulocytopenia/lymphopenia) being more severe than thrombocytopenia. Severe or worse nausea, emesis, thromboembolism, fatigue, headache, infection, and diarrhea also occasionally occur. Unfortunately, it appears that when delivered in a multiday, short-infusion regimen, fazarabine must join the list of chemotherapeutic agents that fail to have any activity in high-grade gliomas.

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