Phase II Study of Trimetrexate in Recurrent Anaplastic Glioma

National Cancer Institute of Canada Clinical Trials Group Study

J. Gregory Cairncross, Elizabeth A. Eisenhauer, David R. Macdonald, Michel P. Rathbone, Malcolm J. Moore, Carol A. Sawka, Ronald E. MacCormick and Ian G. Kerr

ABSTRACT: The National Cancer Institute of Canada Clinical Trials Group conducted a phase II trial of trimetrexate given in a daily × 5 intravenous bolus schedule every 3 weeks in patients with measurable recurrent anaplastic glioma and limited prior treatment. There were no responses in 14 evaluable patients. We conclude that trimetrexate, given as described, is not an active agent in this disease.

RÉSUMÉ: Étude de phase II du trimetrexate dans le gliome anaplasique récurrent : étude du Groupe d'Essais Cliniques de l'Institut National du Cancer du Canada Le Groupe d'Essais Cliniques de l'Institut National du Cancer du Canada a mené un essai de phase II du trimetrexate administré en bolus intraveineux 5 fois par jour à toutes les 3 semaines chez des patients porteurs de gliomes anaplasiques récurrents qui étaient mesurables et dont le traitement antérieur avait été limité. Il n'y a pas eu de réponse chez les 14 patients évaluables. Nous concluons que le trimetrexate, donné tel que décrit ici, n'est pas un agent actif dans cette maladie.

Can. J. Neurol. Sci. 1990; 17:21-23

The prognosis for most patients with anaplastic glioma that recurs following surgical resection and radiotherapy is poor. Reoperation and interstitial radiation benefit selected patients.[1,2] Except for anaplastic oligodendroglioma,[3,4] treatment with systemic chemotherapy has proved to be of only modest benefit with low response rates and short response durations.[5-7] The search for effective antiglioma chemotherapeutic agents continues.

Trimetrexate glucuronate (NSC 352122; 2,4-diamino-5-methyl-6[(3,4,5-trimethoxyanilino) methyl] quinazoline) a low molecular weight (369.4), lipid-soluble, methotrexate analogue is an investigational antifolate currently undergoing evaluation as an anticancer drug. It is a potent dihydrofolate reductase inhibitor[8] and shows promising cytotoxic activity in animal systems. It exhibits antitumor effects in several methotrexate resistant murine solid tumors.[9] The explanation for this may be trimetrexate's ability to enter tumor cells via a different transport mechanism than methotrexate.[10]

Prompted by reports that methotrexate may have activity against anaplastic glioma,[11] the National Cancer Institute of Canada Clinical Trials Group conducted a phase II study of trimetrexate in patients with recurrent anaplastic glioma. We report the results of that trial.

Methods

The eligibility criteria for this study were as follows: biopsy-proven anaplastic glioma (i.e., glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic mixed glioma — repeat biopsy of recurrent tumor was not required); CT scan measurable recurrent tumor; no surgery within 6 weeks, or radiotherapy within 2 months; no prior chemotherapy for recurrent tumor (prior adjuvant chemotherapy was permitted but not within 2 months of study entry); ECOG performance status ≤3 with a life expectancy of at least 12 weeks; absolute peripheral granulocyte count ≥1.5 × 10^9/L; platelet count ≥150 × 10^9/L; bilirubin ≤20 μmol/L and normal hepatic enzymes; serum creatinine ≤130 μmol/L; stable (for at least 2 weeks) or decreasing steroid dose; no previous malignancy (except in situ carcinoma of the cervix or non-melanomatous skin cancer); and signed informed consent.

Trimetrexate was supplied by the Investigational Drug Branch, National Cancer Institute, Bethesda, Maryland and was given as an intravenous bolus (i.e., over 2-3 minutes) daily for five days every 3 weeks at a starting dose of 8 mg/m^2/day. The starting dose was reduced to 6 mg/m^2/day during the study. Doses in subsequent cycles were adjusted for hematologic and other toxicity using established guidelines. Patients were consid-

From the University of Western Ontario, London (J.G.C., D.R.M.); National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston (E.A.E.); McMaster University, Hamilton (M.P.R.); University of Toronto, Toronto (M.J.M., C.A.S., I.G.K.); Dalhousie University, Halifax (R.E.M.)

Received August 22, 1989. Accepted October 24, 1989

Reprint requests to: Dr. E.A. Eisenhauer, National Cancer Institute of Canada, Investigational New Drug Program, Queen's University, 82-84 Barrie St., Kingston, Ontario, Canada K7L 3N6

ered evaluable for response if they had received at least one course of trimetrexate and had a post-treatment CT scan and clinical assessment. Responding patients were to continue treatment until unmanageable toxicity or disease progression supervened. Stable patients would receive a maximum of six courses of trimetrexate.

Blood counts were measured on day 1 of each 3 week cycle and once midcycle to assess toxicity. History, physical examination and CT scans were obtained every 3 weeks to document response. The assessment of response was based on a combination of factors including the CT scan dimensions of the enhancing tumor, steroid requirements and the neurological examination. The baseline and response evaluation CT scans were performed without and immediately following intravenous contrast. Response was defined as follows: >50% decrease in tumor size (i.e., largest cross-sectional diameter × largest diameter perpendicular to it) with steroid dose, stable or reduced, and clinically, stable or improved. Treatment failure (i.e., tumor progression) was defined as follows: an increase in tumor size with steroid dose, stable or increased, and clinically, stable or worse. All other situations were considered stable disease. The duration of response was considered to be the interval from the beginning of chemotherapy for recurrence to CT scan-documented progression.

Results

Fifteen patients entered the study. One patient was declared ineligible because he had received prior chemotherapy for recurrent tumor. The pre-study characteristics of 14 patients treated and evaluable for response are summarized in Table 1.

There were no responses. We observed stable disease for 9.4 and 18 weeks in 2 patients and progressive disease within 8 weeks of starting trimetrexate in 12 patients. Hematologic and other toxicites were mild and easily managed. No patients were removed from this study due to toxicity. The neutrophil and platelet nadir counts are summarized by dose and cycle in Tables 2 and 3. The non-hematologic toxicities are summarized in Table 4.

Table 1: Patient Characteristics (N = 14)

Median Age (range)	60 (33-65)
Sex	
Male	10
Female	4
Performance Status (ECOG)	
1	5
2	3
3	6
Prior Therapy	
Radiotherapy	14
Adjuvant chemotherapy	8
Tumor Histology	
Glioblastoma	10
Anaplastic astrocytoma	4

Table 2: Trimetrexate Toxicity — Neutrophils

Treatment Dose	No. of Evaluable Cycles	Neutrophil Nadir × 10^9/L				
		<.5	.5-.9	1.0-1.4	1.5-1.9	≥2.0
8 mg/m²	6	0	0	0	1	5
6 mg/m²	11	0	0	0	0	11

Table 3: Trimetrexate Toxicity — Platelets

Treatment Dose	No. of Evaluable Cycles	Platelet Nadir × 10^9/L				
		<25	25-49	50-99	100-149	≥150
8 mg/m²	6	0	0	1	0	5
6 mg/m²	10	0	0	1	3	6

Table 4: Non-Hematologic Trimetrexate Toxicity* (N = 14)

Type of Toxicity	Grade+ 1	2	3	4	5	No. of Patients
Diarrhea	1	0	0	0	0	1
Fatigue	1	1	0	0	0	2
Hepatic	1	0	0	0	0	1
Mucositis	0	0	1	0	0	1
Nausea/vomiting	3	0	0	0	0	3
Bleeding	1	0	0	0	0	1
None						8

*Includes toxicities considered to be "possibly", "probably", or "definitely" related to the drug.

+Toxicity was graded according to National Cancer Institute-U.S. standard criteria.

Discussion

We observed no responses in 14 patients. This excludes a true response rate of ≥20% with 95% confidence. We conclude that trimetrexate given as an intravenous bolus for 5 days every 3 weeks at a starting dose of 6-8 mg/m²/day has no meaningful activity in anaplastic glioma.

The starting dose was reduced from 8 to 6 mg/m²/day because of toxicity observed in concurrent National Cancer Institute of Canada phase II trials of melanoma, soft tissue sarcoma and ovarian carcinoma.[12] In retrospect this reduction may not have been necessary. Patients with anaplastic glioma, unlike those with other cancers, are usually in good health and may be less vulnerable to certain drug toxicities. Patients with disseminated melanoma, sarcoma and ovarian cancer (frequently involving liver and bone marrow) were more susceptible to the toxic effects of trimetrexate. Although a negative study in terms of response our observation that patients with anaplastic glioma may tolerate higher doses of some anticancer drugs is noteworthy.

Acknowledgements

The authors thank the National Cancer Institute of Canada for its support, N. Wainman for data management and P. Gray for preparing the manuscript.

References

1. Young B, Oldfield EH, Markesbery WR, et al. Re-operation for glioblastoma. J Neurosurg 1981; 55: 917-921.
2. Gutin PH, Leibel SA, Wara WM, et al. Recurrent malignant gliomas: survival following interstitial brachytherapy with high-activity iodine-125 sources. J Neurosurg 1987; 67: 864-871.

3. Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. Ann Neurol 1988; 23: 360-364.
4. Macdonald DR, Cairncross JG. Chemotherapy as initial treatment for aggressive oligodendroglioma. Neurology 1989; 39: 261 (Suppl 1).
5. Edwards MS, Levin VA, Wilson CB. Brain tumor chemotherapy: an evaluation of agents in current use in phase II and phase III trials. Cancer Treat Rep 1980; 64: 1179-1205.
6. Schold SH, Cairncross JG, Bullard DE. Chemotherapy for primary brain tumors. *In*: Wilkins RH, Rengachary SS, eds. *Neurosurgery. New York: McGraw-Hill 1985; 1143-1153.*
7. Kornblith PL, Walker MD. Chemotherapy for malignant gliomas. J Neurosurg 1988; 68: 1-17.
8. Richter WE, McCormack JJ. Inhibition of mammalian dihydrofolate reductase by selected 2,4-diaminoquinazolines and related compounds. J Med Chem 1974; 17: 943-947.
9. Clinical Brochure. Trimetrexate glucuronate (TMTX) NSC 352122. July 1984. Prepared by: Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland.
10. Ohnoshi T, Ohnuma T, Takahashi I, et al. Establishment of methotrexate-resistant human acute lymphoblastic leukemia cells in culture and effects of folate antagonists. Cancer Res 1982; 42: 1655-1660.
11. Djerassi I, Kim JS, Reggev A. Response of astrocytoma to high dose methotrexate with citrovorum rescue. Cancer 1985; 55: 2741-2747.
12. Eisenhauer EA, Zee BC, Pater JL, et al. Trimetrexate: predictors of severe or life-threatening toxic effects. JNCI 1988; 80: 1318-1322.