Phase II Study of Trimetrexate in Recurrent Anaplastic Glioma

National Cancer Institute of Canada Clinical Trials Group Study

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ABSTRACT: The National Cancer Institute of Canada Clinical Trials Group conducted a phase II trial of trimetrexate given in a daily \( \times 5 \) 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.

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 \( \times 10^9/L \); platelet count >150 \( \times 10^9/L \); bilirubin <20 \( \mu \)mol/L and normal hepatic enzymes; serum creatinine <130 \( \mu \)mol/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-
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 x 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 toxicities 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.

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.

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