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CLINICAL TRIAL REPORT

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A phase II trial of oral temozolomide in patients with metastatic renal cell cancer

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Abstract *Purpose:* To determine the activity of temozolomide, an oral imidazotetrazine alkylating agent that has exhibited broad antitumor activity in preclinical studies, in renal cell cancer (RCC) patients. *Methods:* Metastatic RCC patients were treated with temozolomide, 200 mg/m^2 per day orally, and traditional radiologic response endpoints were assessed. O^6-Alkylguanine-DNA alkyltransferase (AGT) activity was measured in four pretreatment biopsies. *Results:* Among 12 patients, there were no responses. High AGT activity was observed in all four biopsies analyzed. *Conclusions:* Temozolomide is not active against RCC and this clinical observation may be due to high levels of AGT in this tumor.

Keywords Phase II trial · Renal cell cancer · DNA repair · O^6-Alkylguanine-DNA alkyltransferase

Introduction

At the time of diagnosis, approximately 30% of patients with renal cell cancer have unresectable or metastatic disease. About half of the patients who have surgical resection of a renal cell cancer with curative intent will develop recurrent disease [14]. For unresectable or metastatic disease, immunotherapy with interferon-alpha and/or interleukin-2 achieves only a 10–20% objective response rate. There is no standard therapy for patients who fail or are ineligible for such immunotherapy.

Temozolamide is an imidazotetrazinone alkylating agent with 100% bioavailability [1]. It is currently commonly used in gliomas [2, 6] and is being studied in various other neoplasms including melanoma [9] and mycosis fungoides [4]. Its main toxicities are hematologic and are dose-limiting [7]. Preclinical data suggest that levels of the alkylation repair protein O^6-alkylguanine-DNA alkyltransferase (AGT) in tumor tissues correlate inversely with sensitivity to temozolomide [4, 8]. Since activity has been noted with this drug in human tumor colony-forming assays performed with primary renal cell cancer tumors [12], a phase II study in this patient population was initiated. We also attempted to measure tumor AGT levels as a potential predictor of response. We did not observe any responses in 12 patients treated, and AGT levels in biopsies from 4 patients suggest that high tumor AGT levels may be partially responsible for the lack of activity.

Patients and methods

The ethical and regulatory considerations necessary to comply with the Food and Drug Administration and National Cancer Institute regulations for the conduct and monitoring of clinical investigations were observed, and all patients provided written informed consent. Patients had histologically confirmed, unresectable or metastatic renal cell carcinoma with a WHO performance status of 2 or better. Organ function requirements included: absolute neutrophil count at least 1500/mm^3; platelets at least 100,000/mm^3 without a transfusion in the last 7 days; hemoglobin at least 10 g/dl; bilirubin less than 1.5 mg/dl; SGOT less than three times the upper limit of normal; and creatinine less than 2.0 mg/dl. Exclusion criteria included history of another cancer within the last 5 years, prior therapy for renal cell cancer with another alkylating agent, pregnancy or lactation, and inability to take oral medications.

Temozolomide was administered orally, in a fasting state, once a day for five consecutive days at a starting dose of 200 mg/m^2 per day with cycles repeated every 28 days. Patients previously treated

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with chemotherapy (but not immunotherapy) began at a dose of 150 mg/m^2 per day. Protocol-specified dose reductions to 150 and 100 mg/m^2 per day were made for myelosuppression and grade 3 or 4 nonhematologic toxicity. A standard 50% decrease in the sum of bidimensional tumor measurements was required for an objective response.

Determination of AGT activity was performed as previously described [3, 5]. Briefly, O^6-[^{3}H]Methylguanine removal from a [^{3}H]methylated DNA substrate (5.9 Ci/mmol) was assessed by reverse-phase high-performance liquid chromatography following incubation of the substrate with a protein extract from biopsied tissue at 37°C for 30 min. This assay has been used to correlate AGT activity with temozolomide sensitivity in previous studies [4].

The principal objective of this study was to assess the frequency and extent of antitumor activity of temozolomide in a population of patients with metastatic renal cell cancer. Patients were accrued using a Simon optimal phase II design [13]. The regimen would be rejected if the estimated true response rate was less than 5% and would be accepted as active if the estimated true response rate was greater than 20%. Using an alpha error of 0.10 and a beta error of 0.10, the first stage accrued 12 patients. Since no responses were observed accrual to the second stage was not initiated.

Results

From December 1998 to October 1999, 12 patients were accrued. Table 1 lists the patient characteristics. The median age was 59 years. All patients had a performance status of 0 or 1. Two-thirds had undergone a prior nephrectomy.

There were no objective responses. Two patients experienced stable disease for 14 weeks and one patient had disease stabilization for 24 weeks, at which point the patient withdrew from the study in order to receive an allogeneic stem cell transplant and remains alive 35 months after beginning temozolomide. The Kaplan-Meier estimated median survival time was 29 weeks, with a range of 2 months to 35 months or more and with 43% of patients alive at the end of 1 year.

Hematologic and nonhematologic toxicities are shown in Table 2. There were no grade 4 toxicities. Three patients experienced significant anemia, and one patient had significant thrombocytopenia, with a nadir platelet count of 54,000/mm^3 that recovered within 1 week. Six patients (50%) experienced significant nausea and/or vomiting. In two of these patients, including the patient who experienced grade 3 toxicity, these symptoms were self-limited to the day after receiving the first dose of temozolomide in each cycle. In all other patients, the nausea and vomiting were well controlled with oral prochlorperazine. No patients withdrew from the study due to medication-related toxicity. Two patients were withdrawn from the study after only one cycle of treatment due to clinical disease progression. Out of 31 cycles of chemotherapy, only two (6.5%) were delayed for toxicity, both as a result of thrombocytopenia. One cycle was delayed for personal reasons.

AGT activity levels were measured in pretherapy biopsies taken from five patients. Biopsies were not obtained in seven patients due to lack of an appropriate lesion for a research biopsy or patient refusal. The biopsy sample in one patient was inadequate for analysis. All of the four remaining biopsies had levels of >400 fmol/mg and therefore would be expected to be highly resistant to temozolomide [11]. Two of these patients experienced such rapid clinical progression of disease that only one cycle of chemotherapy was administered. The other two patients progressed after 8 and 15 weeks.

Table 1. Patient characteristics ($n=12$)

Age (years)	
Median	59
Range	48–77
Sex	
Male	7
Female	5
Number of metastatic sites	
1	1
2	1
3+	10
Prior nephrectomy	
Yes	8
No	4
Performance status	
0	6
1	6

Table 2. Adverse events in study patients ($n=12$)

Toxicity	Grade 2 (no. of patients)	Grade 3 (no. of patients)
Hematologic		
Anemia	3	1
Thrombocytopenia	1	0
Leukopenia	0	0
Neutropenia	0	0
Nonhematologic		
Fatigue	6	1
Nausea	5	1
Vomiting	3	1
Anorexia	3	0
Diarrhea	0	0
Mucositis	0	0
Fever	0	0

Discussion

Renal cell carcinoma continues to be a difficult disease to treat due to the failure of multiple chemotherapeutic agents to control advanced or metastatic disease. Given some promising preclinical data, this phase II study of temozolomide was performed. No objective responses out of 12 treated patients were observed and thus the statistical null hypothesis of a true response rate of $<5\%$ could not be rejected. This observation is consistent with lack of activity with multiple other alkylating agents, and specifically nitrosoureas [10, 14, 15] in this disease. AGT activity was significantly elevated in all four patients in whom it was measured, providing a plausible explanation for the observed clinical resistance. It should be noted, however, that only a limited number

of biopsies were examined for AGT activity and other putative resistance factors were not examined. Thus the exact mechanism for renal cell carcinoma resistance to temozolomide remains unclear.

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