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CLINICAL TRIAL REPORT

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A phase II study of temozolomide in hormone-refractory prostate cancer

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Abstract *Introduction*: Hormone-refractory disseminated prostate cancer is a major oncological problem. Preclinical studies with temozolomide, an oral alkylating agent, in prostate cancer have shown encouraging results. In phase I studies the safety of temozolomide in non-prostate cancer patients has been demonstrated. Based on these results, a phase II study of temozolomide in patients with metastatic disease who had developed progressive symptomatic disease while on antiandrogen therapy, was initiated. *Methods*: A group of 18 patients started a 5-day temozolomide regimen, with a 28-day treatment cycle. Response parameters (prostate-specific antigen, bone scan, quality of life questionnaire) and toxicity (common toxicity criteria for international studies) were recorded at regular intervals. *Results*: Of the 18 patients, 16 were evaluable by completing two or three cycles. All patients developed progressive disease within two cycles, except one who had progressive disease at the end of cycle 3. Of the 16 evaluable patients, 11 developed new bone metastases (bone scan), 1 developed lung metastases, 4 had progressive disease as reflected by a 25% increase in serum PSA together with subjective progression, and 7 and 5 had progressive disease as reflected by decreased quality of life and increased pain score, respectively. Toxicity was limited to nausea and vomiting, which was effectively treated with antiemetic medication, and anemia and thrombocytopenia, which returned to normal values within 1 week. *Discussion*: Treatment with temozolomide was generally well tolerated, with occasionally moderate toxicity. As all patients developed progressive disease the results are rather discouraging. Temozolomide is ineffective for the treatment of patients with symptomatic progressive hormone-refractory prostate cancer.

Key words Chemotherapy · Prostate cancer · Safety · Efficacy · Temozolomide

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Introduction

The incidence of and mortality from prostate cancer has climbed in the last decades. Overall worldwide prevalence was estimated at 942,000 men in 1993 and is expected to reach nearly 1.6 million by the year 2007. This represents an annual growth of 3.8%. Of these men, approximately 10–16% will die of prostate cancer [1].

Methods for treating prostate cancer vary according to the stage of the disease and include 'watchful waiting', surgery, radiation, hormonal drug therapy or castration and chemotherapy. Surgery or radiotherapy are treatments of choice in locally confined disease. Current standard therapy for symptomatic advanced prostate cancer is hormone therapy. However, patients on hormone therapy will eventually relapse and at present the generally accepted median survival is 6 months [2].

The treatment of hormone-refractory prostate cancer remains palliative although various regimens have been evaluated in both single arm and randomized trials. All patients can be expected to die of their disease [3, 4]. Until now, chemotherapy has shown no impact on overall survival. Therefore, the search for new active therapies to palliate the disease, improve quality of life (QoL) or, ideally, prolong survival is required. Alkylating agents, such as cyclophosphamide, doxorubicin and epirubicin have shown activity in hormone-refrac-

tory prostate cancer, although objective responses remain low [2]. Chemotherapy with mitoxantrone and prednisone provides palliation for some patients with symptomatic hormone-refractory prostate cancer [5].

Temozolomide is an oral alkylating agent of the imidazotetrazine class [6]. It exhibits broad-spectrum antitumor activity both in vitro and against murine tumors, including activity against prostate cancer cell lines [7]. Promising data from phase II studies in high-grade glioma, advanced malignant melanoma and low-grade non-Hodgkin's lymphoma encouraged us to initiate a phase II study of temozolomide in hormone-refractory prostate cancer. The objectives of this study were to determine the safety, tolerability and efficacy of temozolomide, as assessed by the common toxicity criteria (CTC) for international studies, appropriate imaging and prostate-specific antigen (PSA) response, respectively.

Patients and methods

This study was performed according to the design of Gehan [8]. Included in the study were 18 patients meeting the inclusion and exclusion criteria noted in Table 1. A medical history, chest radiograph and ECG were taken, a physical examination carried out, and laboratory parameters, Karnofsky performance status (KPS), pain score (ranging from no pain to very severe pain, requiring continuous narcotic analgesia) and analgesic use determined. Date of initial diagnosis (which included stage and grade) and progression of the prostate cancer, as defined in the inclusion criteria, were documented. These data were noted in the clinical file and in the clinical research file.

Subsequently, the first of up to 12 cycles of temozolomide could be administered in an outpatient setting, consisting of a 5-day oral regimen of 150 mg/m^2 temozolomide at the beginning of a 28-day cycle. On day 22 of each cycle patients visited the outpatient clinic for assessment of changes in medication, scoring of adverse effects according to the CTC criteria, determination of KPS, pain score and analgesic use, administration of QoL questionnaire, and blood samples to be taken for hematologic parameters. Before initiating the next cycle, medical history, changes in medication, adverse events, KPS, pain score and analgesic use were recorded. Vital signs (blood pressure, pulse, weight) were also measured and laboratory values (hematology, biochemistry and urinalysis) assessed.

In the absence of myelotoxicity and only mild nonhematologic toxicity in the first cycle, the dose of temozolomide could be increased to 200 mg/m^2 per day. Dose reduction to 100 mg/m^2 was applied if patients experienced a grade 3 to 4 hematologic toxicity with recovery within 2 weeks or grade 3 nonhematologic toxicity, improving to at least grade 1 within 2 weeks. Drug administration was postponed if the hematologic parameters had not fully recovered from the previous course of treatment. Patients who required a treatment delay of more than 2 weeks were also taken off study. Patients requiring a dose reduction to less than 100 mg/m^2 were taken off study. Every 8 weeks, the PSA level was determined and evaluable lesions assessed radiologically. This was also done if progression was suspected. The study was ended after 12 treatment cycles, if tumor progression, unacceptable toxicity or patient death occurred, or if the patient requested withdrawal. All patients were followed for survival and were considered evaluable for response after completion of at least two study cycles.

Subjective responses were evaluated with a QoL questionnaire comparing the monthly value on a five-point scale (much better to much worse) with the score after the previous cycle and with a three-point baseline scale (good–fair–poor). Also, the KPS and the pain score with analgesic use were determined. Subjective response was defined as improvement of the KPS with by at least 20%, a reduction in pain score by at least two points and an increase in QoL to much better. Subjective progression was defined as a decrease in KPS by at least 20%, an increase in pain score by at least two points and a decrease in QoL to much worse.

Objective responses were defined as follows. Complete response (CR) was defined as complete disappearance of all measurable and evaluable disease, including PSA normalization, without appearance of new lesions, and partial response (PR) as a more than 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions, or a more than 25% improvement in the bone scan, as reflected by a decrease in intensity or number of lesions, or a significant drop in PSA ($>25\%$), compared with the baseline value, and the occurrence of no new lesions or subjective progression. Progression of disease (PD) was defined as a more than 25% increase in the sum of products of measurable disease, reappearance of any lesion or the appearance of new lesions or clear worsening of present lesions. PSA progression was defined as a more than 25% increase in the lowest value obtained during the study if combined with a deterioration in KPS of at least 20%, an increase in pain score by at least two points or a QoL deterioration to much worse. Stable disease was a disease status not qualifying for CR, PR or PD.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age >18 years	Prior chemotherapy (including estramustine phosphate)
Radiologically (CT, bone scan, MRI, radiograph) documented progression of metastatic prostate cancer or	Single dose radiotherapy in the last 4 weeks on painful bone lesions prior to entry into the study
Biochemical progression reflected by a PSA increase[a] together with an increase in pain score or a decrease in Karnofsky performance score	Prior radiotherapy to ≥30% of bone marrow
Patient has received one prior first-line hormone therapy regimen for metastatic disease[b]	More than one cycle of strontium chloride therapy
Karnofsky performance status $>60\%$	Any other active primary tumor, basal or squamous cell carcinoma of the skin or carcinoma in situ excluded
Life expectancy >3 months	Uncontrolled bacterial, viral or fungal infection
Neutrophils $\geq 1.5 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; Hb ≥10 g/dl (≥6.21 mmol/l)	Any condition which would prevent adequate follow-up during the study
Bilirubin and transaminases less than twice the upper limit of normal	
Creatinine not more than 1.5 times the upper limit of normal	
Written informed consent	

[a] Defined as PSA increase of $>25\%$ compared to the previous value

[b] LHRH agonist or orchiectomy with or without an antiandrogen; antiandrogens should have been stopped at least 4 weeks prior to commencing temozolomide

Results

After providing informed consent, 18 patients were included. Two patients went off study before starting the temozolomide regimen because of intractable bone pain requiring hospitalization and immediate radiotherapy on bone metastases.

Responses

Of the 16 evaluable patients, all developed progressive disease while on study, 2 in cycle 1, 13 in cycle 2 and 1 in cycle 3 (Table 2). This last patient, who may have had stable disease during the first two treatment cycles, unfortunately failed to undergo a bone scan and therefore was not evaluable for objective response. Regarding subjective response, he had stable disease during the first two cycles and developed PD (pain score and QoL) in the third cycle.

PD was reflected as the appearance of new bone metastases on the bone scan in 11 patients. One of these patients suffered a pathologic fracture of thoracic vertebra 1, requiring immediate hospitalization and radiotherapy. One patient had new lung metastases as documented by a chest radiograph. Four patients had PD as reflected by an increase in serum PSA of more than 25% combined with deterioration in QoL or KPS or an increase in pain score. Seven patients experienced subjective progression reflected by a decreased QoL, five patients showed an increased pain score of at least two points while on treatment, and one patient's subjective progression was reflected by a decrease in KPS (Table 2).

Table 2 Responses and toxicity (*OP* objective progression, *SP* subjective progression; *BS* bone scan new lesions, *PS* pain score deterioration by two points or more, *PSA* PSA increase of 25% or more, *QoL* QoL deterioration by two points or more, *X-thorax* chest radiography; *N* nausea, *V* vomiting, *A* anemia, *T* thrombocytopenia)

Patient	Response	Cycle	Toxicity	Symptoms
1	SP (PS + QoL)	3	3	N
2	SP (PS + QoL)	2	0	
3	OP (fracture, PS)	1	2	N
4	OP (BS, PSA)	2	2	A
5	OP (BS, PSA + QoL)	2	2	V
6	OP (BS, PSA)	2	3	T
7	OP (BS, PSA + PS + QoL)	2	3	V
8	OP (BS, PSA)	2	2	N, V
9	OP (BS)	2	2	V
10	OP (BS)	2	1	N
11	OP (BS, X-thorax)	2	1	N
12	OP (PSA + QoL)	2	2	T, A
13	SP (PS + QoL)	1	0	
14	OP (BS, PSA)	2	2	N, V
15	OP (BS, PSA + QoL)	2	2	N, V
16	OP (BS, PSA)	2	1	N, V

Toxicity

Toxicity was generally mild (Table 2). Gastrointestinal discomfort was the most common, with one patient suffering grade 3 nausea and one patient grade 3 vomiting that could be adequately suppressed by antiemetic medication. One patient suffered grade 3 thrombocytopenia that recovered within 1 week. In these patients dose reduction was required.

Discussion

Based on promising data from phase II studies with temozolomide in several malignancies, the present study was started in patients with symptomatic hormone-refractory metastatic prostate cancer. The goals of this study were to determine the efficacy, safety and tolerability of temozolomide.

No responses were observed and all patients had PD after up to three treatment cycles. Therefore, we must conclude that temozolomide is not effective in prostate cancer, at least in regimens as applied in the current study. However, better results may be obtained if patients start treatment in a less-advanced stage of disease. Patients with biochemically detected hormone relapse but clinically asymptomatic may benefit from treatment with temozolomide, possibly reflected by a prolongation of the period of asymptomatic hormone relapse. With regard to safety, no hematologic or nonhematologic toxicity necessitated patients being removed from the study. Temozolomide was well tolerated, with occasional moderate gastrointestinal discomfort requiring antiemetics.

In conclusion, administration of temozolomide to prostate cancer patients is safe, but not advisable considering its ineffectiveness in the treatment of patients with symptomatic hormone-refractory metastatic prostate cancer.

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