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CLINICAL TRIAL REPORT

A phase II trial of continuous low-dose oral cyclophosphamide and celecoxib in patients with renal cell carcinoma

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Abstract
Purpose The lack of effective systemic therapies for patients with advanced renal cell carcinoma (RCC) has stimulated interest in evaluating novel treatment strategies for this disease.
Methods This was a two-institution, two-stage, phase II trial of continuous low-dose oral cyclophosphamide (50 mg daily) in combination with celecoxib (400 mg twice daily) in patients with progressive, locally advanced or metastatic RCC. The primary endpoint was disease control rate (DCR) defined as the number of patients with complete (CR) or partial response (PR) or prolonged (≥6 months) stable disease (SD). Secondary endpoints included time to progression and toxicity.
Results Between May 2001 and January 2003, 36 patients were enrolled onto the trial of which 32 were evaluable for response. One patient had a PR and three others had SD for longer than 6 months (DCR 12.5%, 95% CI 3.5–29.0%). The median progression free survival was 3.5 months (95% CI, 1.9–4.1 months) and the median overall survival was 14.5 months (95% CI, 8.4–20.8 months). One patient experienced grade five gastrointestinal bleeding. Otherwise, the treatment was well tolerated.
Conclusions Although generally well tolerated, continuous therapy with low-dose cyclophosphamide and celecoxib had limited activity in RCC.

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Introduction

Most forms of systemic therapy have yielded disappointing results in the management of patients with renal cell carcinoma (RCC). Standard types of chemotherapy have been particularly ineffective [1]; this is not surprising since kidney cells are responsible for excreting toxins from the body, and both they and tumours derived from them express markers of drug resistance [2]. Until recently, the main therapeutic options for patients with advanced disease were interferon and interleukin-2, but the overall response rates to single agent or combination treatment are less than 20% [3–5]. The lack of effective therapies for this disease has prompted the evaluation of novel treatment strategies.

Renal tumours have an extensive vasculature that appears to be stimulated by vascular endothelial growth factor (VEGF). Overexpression of VEGF has been demonstrated in RCC both at the tissue level as well as in serum [6–8]. Furthermore, the von Hippel Lindau gene which is often mutated both in familial as well sporadic cases of RCC has been found to be a negative regulator of VEGF expression [9–11]. Since RCCs are highly vascular, but contain tumour cells that

are intrinsically resistant to most drugs, it is logical to evaluate therapeutic approaches that target the blood supply. This might be achieved by targeting VEGF or its receptors, or using continuous low-dose chemotherapy in combination with agents that have anti-angiogenic properties.

Various chemotherapeutic agents have been shown to have antiangiogenic effects [12, 13]. The lack of significant long-term anti-vascular effects with standard doses of chemotherapy has been attributed to the rest period between doses, which allows the endothelial cells to undergo repopulation. Browder et al. [14] postulated that this recovery process could be compromised by the administration of more frequent, but lower doses of standard chemotherapeutic agents. They demonstrated a response to cyclophosphamide in a subline of Lewis lung carcinoma previously selected in vivo for acquired resistance to higher doses of cyclophosphamide by using continuous low-dose treatment. There have been a handful of studies of cyclophosphamide in renal cancer, but they have all used intravenous rather than oral cyclophosphamide, gave the drug at much higher doses, in intermittent fashion and often in combination with other cytotoxic agents [15–18]. Furthermore, while it has been appreciated for some time that cyclophosphamide has immunomodulatory effects including inhibition of regulatory T-cells [19], some data suggest that lower doses of the drug may be associated with more immunomodulatory effects than high doses of cyclophosphamide which likely work through cytotoxic mechanisms [20]. For the above reasons, it appears that administration of low-doses of cyclophosphamide even in tumours previously thought to be resistant to the drug may be much more effective through exploitation of these differential mechanisms of action.

To further evaluate the anti-angiogenesis hypothesis of low-dose (so called "metronomic") chemotherapy, Klement and colleagues [21] explored the use of low-dose vinblastine and the anti-VEGF antibody DC101 alone and in combination in SCID mice bearing human neuroblastoma cell lines. Vinblastine and DC101 treatment alone resulted in transient tumour regression and inhibition of angiogenesis; combination therapy resulted in complete and sustained regressions that have lasted for at least 6 months. A small clinical trial evaluated the combination of low-dose oral methotrexate (2.5 mg twice a day on days 1, 2 every week) and cyclophosphamide (50 mg per day continuously) in 64 women with metastatic breast cancer who have failed at least one standard chemotherapy regimen [22]. Of the 63 evaluable patients, two had a complete response (CR) and ten a partial response (PR), for an overall response rate of 19%. The treatment was associated with minimal toxicity despite some patients receiving the drug combination for up to 2 years.

Cyclooxygenases (COX) are a group of enzymes that convert arachidonic acid to prostaglandins and play a key role in inflammation. COX-1 is an enzyme that is constitutively expressed in humans whereas COX-2 has more limited expression [23]. COX-2 specific agents such as Celecoxib were developed with the goal of retaining their anti-inflammatory activity while minimizing side effects. COX-2 overexpression has been reported in many human tumours including renal carcinoma cell lines [24] and RCC tumour specimens [25–27]. The COX-2 specific inhibitor, celecoxib has shown anti-tumour activity in preclinical models of lung and colon cancer including synergistic activity when given in combination with chemotherapeutic agents such as 5-fluorouracil and cyclophosphamide [28–30]. In RCC specifically, several studies have reported associations between COX-2 expression and a number of clinicopathologic features such as tumour stage and markers of cell proliferation [27]. This suggests a role for [25, 26] COX-2 in RCC pathogenesis and supports COX-2 as a logical therapeutic target to test in this disease. With the above in mind, we undertook the present study to evaluate the effects of antiangiogenic therapy using low-dose continuous cyclophosphamide and the COX-2 specific inhibitor celecoxib in patients with RCC.

Methods

Patient eligibility

Patients with histologically documented, progressive, metastatic or locally advanced RCC not amenable to surgical resection were eligible for this study. Other eligibility criteria included: age $\geq$18, ECOG performance status of 0 or 1, measurable disease, life expectancy $\geq$3 months, and adequate organ function. Adequate hepatic function was defined as serum aspartate transaminase and total bilirubin levels $\leq$2 times the upper limit of normal (ULN), and serum alkaline phosphatase $\leq$3 times ULN. Adequate renal function was defined as serum creatinine $\leq$2 times ULN. Granulocyte count $\geq 1.5 \times 10^9$ per litre and platelet count $\geq 100 \times 10^9$ per litre were considered adequate hematologic function.

Exclusion criteria included: treatment with chemotherapy or immunotherapy within 4 weeks of receiving study drug; prior therapy with cyclophosphamide or other alkylating agents; contraindications to chronic

NSAID therapy such as hypersensitivity to cyclooxygenase inhibitors, active peptic ulcer disease, previous NSAID-related gastrointestinal bleeding or other bleeding disorders, and pregnancy or breast-feeding. Patients with hypercalcemia, brain metastases, history of other malignancies within 5 years of study entry, those with medical conditions that might be dependent on angiogenesis such as surgery within 4 weeks of receiving study drug or open venous or arterial ulcers were excluded. Patients who used NSAIDs or corticosteroids within 4 weeks of receiving study drug or who had dementia, psychosis, or other significant impairment of mental status that would prohibit the understanding and giving of informed consent or the participation in self-care or reporting of toxicity were also excluded. All patients gave written informed consent in accordance with institutional guidelines prior to study entry.

Study design and treatment

This was an open label, two-center, single arm, phase II study to evaluate the safety and efficacy of celecoxib given in combination with oral cyclophosphamide. Celecoxib was supplied by Pharmacia Corp. (Mississauga, ON, Canada). Patients took 400 mg of celecoxib by mouth twice daily and cyclophosphamide 50 mg once daily, also by mouth. Both drugs were given continuously starting with the first day of treatment. A treatment cycle was defined as 28 days. Patients were given a 28 day supply of study drugs and were asked to return the containers to check for compliance. For each patient, the treatment continued until disease progression or development of severe toxicity. The rationale for the selected dose of celecoxib arises from a study by Steinbach et al. [31] in patients with familial adenomatous polyposis. In this study patients were randomized to receive celecoxib 100 mg BID, celecoxib 400 mg BID or placebo for 6 months. The primary endpoint was adenoma regression. At the end of the study only treatment with the 400 mg BID dose was associated with a significant reduction from baseline in the number of colorectal polyps as compared with the placebo group. Both doses of celecoxib were well tolerated and there were no significant differences in the incidence of adverse effects between the celecoxib groups and the placebo group.

Pre-treatment and follow-up evaluation

Baseline assessment was completed within 28 days prior to receiving study drug; it included history, physical examination, bloodwork, and radiologic tests. During the first 8 weeks of treatment, laboratory examinations were repeated every 2 weeks then every 4 weeks thereafter if stable. Physical examination was repeated at 4 week intervals. Tumor assessment by radiological methods was performed every 8 weeks. If radiologic examination indicated response, bloodwork and radiologic tests were repeated in 4 weeks to confirm response then every 8 weeks until progression. Patients with progressive disease identified early in the study were encouraged to continue treatment for a maximum of 16 weeks. Patients who discontinued treatment were asked to return for assessment at 4 week intervals for a maximum of 6 months.

Assessment of response

The primary endpoint of the study was the disease control rate (DCR) defined as the rate of response and prolonged stable disease (SD) (defined as disease that has been stable for $\geq$6 months). Secondary endpoints included time to tumor progression and toxicity.

Assessment of tumour response was based on clinically or radiologically measurable disease. A maximum of ten lesions representative of all involved organs were identified as target lesions at baseline. These lesions were selected on the basis of their size (lesions with largest diameter) and their suitability for accurate repetitive measurements. The minimum size of target measurable lesions was 20 mm in at least one dimension. Other lesions were considered non-measurable. Response was based on the sum of the products of the largest diameter of the tumours and its perpendicular for all target lesions (bidimensional measurement) as defined by World Health Organization criteria. Response rates are reported for all patients who initiated treatment. Complete response was defined as the disappearance of all clinical and radiological evidence of tumour (both target and non-target lesions) maintained for at least 4 weeks. Partial response was defined as $\geq$50% reduction in the sum of the products of the sizes of all measurable lesions for at least 4 weeks with no progression in non-measurable lesions. Progressive disease (PD) was defined as $\geq$25% increase in the size of at least one lesion, evidence of progression in non-measurable disease, or the appearance of any new lesion. Stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Transient SD was not a criterion of response, but merely an indication to continue treatment in the absence of major toxicity. Time to tumour progression (TTP) was defined as time from entry in the study to time of objectively documented progression. In patients who continued on therapy in face of

early progression the first documentation of progression rather than time of discontinuation of treatment was used to assess TTP.

Statistical considerations

The study was designed as a two-stage, phase II trial [32]. We regarded the combination of these drugs to be inactive, if the DCR (defined as the rate of response and prolonged SD of ≥6 months) was at most 5%, and active if it was at least 20% (such that we would be interested in further studies of the combination). If no responses or prolonged SD were seen in the first 15 patients then the trial was to be terminated. Otherwise, accrual was to continue to a total of 32 patients. The sample size assumes a 5% significance level, 80% power, and a 10% rate of loss to follow-up.

Results

Patient and treatment characteristics

Between 9 May 2001 and 23 January 2003, 36 patients enrolled onto the study of which 32 were evaluable for response. Among the non-evaluable patients, three progressed too quickly to start treatment and one was taken off study for psychiatric reasons. Baseline characteristics of the 32 evaluable patients are presented in Table 1. The median age of the group was 62 years, and 22% were women. The majority of patients had an ECOG performance status of zero. Eight patients had received prior systemic therapy including one patient who had received interferon-α, interleukin-2 and chemotherapy. Approximately one third of patients had prior nephrectomy. Almost all of the patients had metastatic disease and most had clear cell histology.

Patients received a median of four cycles of treatment (range 1–22). The most common reason for study discontinuation was disease progression (18 patients, 56%). Other reasons for discontinuation included death (6 patients), toxicity (2 patients), hypercalcemia (1 patient), overall deterioration in clinical status (1 patient), surgery to stabilize a lytic lesion (1 patient), and study completion (1 patient). Two patients discontinued treatment at their own request without evidence of disease progression or toxicity.

Table 1 Baseline patient characteristics (n = 32)

Characteristic	No. of patients (%)
Age (years)	
Median (range)	62 (46–76)
Sex	
Male	25 (78)
Female	7 (22)
ECOG performance status	
0	17 (53)
1	14 (44)
Unknown	1 (3)
Prior nephrectomy	11 (34)
Prior systemic therapy	
Interferon	7 (22)
IL-2	1 (3)
Chemotherapy	4 (12)
Disease stage	
Locally advanced	2 (6)
Metastatic	30 (94)
Histologic subtype	
Clear cell	27 (84)
Papillary	2 (6)
Other	3 (9)
MSKCC risk category[a]	
Favorable (no risk factors)	7 (22)
Intermediate (1–2 risk factors)	21 (66)
Poor (≥3 risk factors)	4 (6)

MSKCC Memorial Sloan Kettering Cancer Center

[a] MSKCC risk was assessed using the following risk factors: low Karnofsky performance status (<80%), high lactate dehydrogenase (>1.5 times the upper limit of normal), low serum hemoglobin (<lower limit of normal), high corrected serum calcium (>10 mg/dl), and absence of prior nephrectomy [40]

Efficacy

One patient had a confirmed PR that lasted 22.5 months and three patients had prolonged SD (≥6 months), for a DCR of 12.5% (95% CI, 3.5–29.0%). Patient response in relation to histology and prior therapy is reported in Table 2. All of the responders were treatment naïve and had clear cell histology tumours. At the time of last follow-up, all 32 patients have progressed and at least 16 (50.0%) have died. The median progression free survival was 3.5 months (95% CI, 1.9–4.1 months) and the median overall survival was 14.5 months (95% CI, 8.4–20.8 months).

Toxicity

Grade 3 or greater toxicity felt to be potentially or definitely treatment-related is presented in Table 3. Overall, there were ten such adverse events during the study period. One patient experienced grade 4 anemia during cycle 4 of therapy and three patients developed grade 3 hypokalemia (serum potassium <3.2 mmol/l). The most serious toxicity was a gastrointestinal bleed that occurred during cycle five of therapy. The patient

Table 2 Histology, prior therapy and treatment outcome

Patient	Histology	Prior therapy	Response	Response duration (months)
1	Clear cell	None	PD	–
2	Chromophobe	None	SD	1.8
3	Not specified[a]	None	PD	–
4	Clear cell	None	PD	–
5	Clear cell	None	SD	1.8
6	Papillary	None	SD	5.6
7	Clear cell	None	PD	–
8	Clear cell	Interferon	SD	2.1
9	Papillary	None	SD	3.8
10	Clear cell	None	SD	11.0
11	Clear cell	None	SD	1.7
12	Clear cell	None	PD	–
13	Clear cell	None	SD	5.0
14	Clear cell	None	SD	7.5
15	Clear cell	None	PD	–
16	Clear cell	None	PR	22.5
17	Clear cell	None	SD	4.2
18	Clear cell	None	PD	–
19	Clear cell/ papillary	None	PD	–
20	Granular cell	None	PD	–
21	Clear cell	Chemotherapy	SD	2.8
22	Clear cell	None	PD	–
23	Clear cell	Interferon	PD	–
24	Clear cell	None	PD	–
25	Clear cell	None	PD	–
26	Clear cell	None	SD	2.2
27	Clear cell	None	SD	8.8
28	Clear cell	Interferon, IL-2, chemotherapy	PD	–
29	Clear cell	None	PD	–
30	Clear cell	Interferon	PD	–
31	Clear cell	None	SD	2.0
32	Clear cell	Interferon	SD	2.8

PD progressive disease, *SD* stable disease; *PR* partial response

[a] Diagnosis made from metastatic site, histologic subtype not specified

Table 3 Serious toxicity that was possibly or definitely treatment-related

Toxicity	No. of patients (%)		
	Grade 3	Grade 4	Grade 5
Hematologic			
Anemia	1 (3)	1 (3)	–
Transfusion	1 (3)	–	–
Gastrointestinal			
GI bleed	–	–	1 (3)
Other			
Hypokalemia	3 (10)	–	–
Elevated creatinine	2 (7)	–	–
Pain	1 (3)	–	–

had prior history of unexplained anemia that predated the study and the gastrointestinal bleeding occurred during an episode of acute gastroenteritis associated with severe nausea and vomiting. A gastroscopy that was performed to evaluate the bleeding showed a duodenal ulcer. The patient was supported with blood products; proton pump inhibitors and the study drugs were discontinued. The patient was discharged home, but presented with melena 2 weeks later. A repeat gastroscopy at that time revealed no upper gastrointestinal source for the bleeding and the previously seen ulcer had healed. However, neither colonoscopy nor angiography were able to visualize the source of bleeding and this bleeding episode was complicated by sepsis and disseminated intravascular coagulation as a result of which the patient died.

Discussion

The rationale underlying the current study was that the continuous administration of chemotherapy in combination with a drug that has anti-angiogenic properties would

target endothelial cells within the extensive vasculature of renal tumours. We found, however, that the combination of continuous oral cyclophosphamide and celecoxib, while fairly well tolerated, had only minimal activity and we would not recommend it for further testing in this disease. There have been recent concerns regarding the safety of COX-2 inhibitors in view of reports of increased risk of cardiovascular toxicity [33]. We did not observe cardiac events in our study, but it was small relative to the trials that have demonstrated increased cardiac risk, and compared to participants of those trials, our patients received the drug for a relatively short time period.

This study was conducted at a time when treatment options for advanced RCC were limited and our findings, while disappointing, are similar to those observed for many other systemic agents evaluated against this disease. A 1995 review [1] of over 80 phase II trials in RCC conducted between 1983 and 1993 testing various single and combination chemotherapy regimens reported an overall response rate of only 6%, many of the trials since this review have been similarly disappointing [34, 35]. The handful of studies that have specifically evaluated cyclophosphamide in this disease have also shown limited efficacy, but all of them have used the drug at much higher doses and in an intermittent schedule [15–18]. We felt that by administering the drug in a continuous fashion, we may exploit different mechanisms of action of the drug associated with low-dose chemotherapy and thus overcome resistance associated with more cytotoxic scheduling of chemotherapy utilized in previous trials in this disease. To our knowledge, only one previous study has evaluated the efficacy of COX-2 inhibitors in RCC [36]; it reported a response rate of 12% in 25 patients treated with interferon alpha in combination with celecoxib. Fortunately, recent studies of newer agents such as the small molecules sorafenib [BAY 43-9006] [37] and sunitinib [SU11248] [38], which inhibit signaling from growth factor receptors (including the VEGF receptor), and the anti-VEGF monoclonal antibody bevacizumab [39] have shown that there may be agents with more substantial activity against this disease. The results of phase III trials evaluating these agents in comparison with interferon-α are awaited with enthusiasm.

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