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Phase II Trial of Capecitabine and Weekly Docetaxel in Metastatic Renal Cell Carcinoma

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Abstract

Objectives—To evaluate the toxicity and efficacy of capecitabine and weekly docetaxel in a phase II clinical trial.

Methods—Eligibility included metastatic renal cancer with a maximum of 2 prior regimens, performance status of 0-2, and adequate renal, hepatic, and bone marrow function. Docetaxel was adminis-tered intravenously at a dose of 36 mg/m^2 weekly on days 1, 8, and 15 of a 28- day cycle and capecitabine was administered orally at a dose of 1800 mg/m^2 from days 5-18. Toxicity was assessed on days 1, 8, and 15 of each cycle, and response was evaluated every 2 cycles.

Results—Twenty-five patients, 19 white and 6 African American, were enrolled on this phase II trial. The median age was 60 years (range: 39-75 years). Eighteen patients had clear cell histology, 7 had papillary, sarcomatoid, or chromophobe histology. Thirteen had liver/bone metastases and 13 had ≥2 of the Memorial Sloan-Kettering Cancer Center prognostic risk factors. Twelve patients received prior immunotherapy. A total of 93 cycles were administered; median of 3 cycles and range from 0-10 cycles. The therapy was well tolerated. No treatment-related mortality was observed and 2 treatment-related hospitalizations for nausea, diarrhea, and dehydration occurred. Ten patients had stable disease. The median time to progression was 1.7 months and median survival was 11.1 months.

Conclusions—The combination of capecitabine and docetaxel was well tolerated in metastatic renal cancer. Clinical activity was predominantly noted in non-clear cell histology in which chemotherapy would be worthy of future investigation.

Metastatic renal cell carcinoma (RCC) was considered to be refractory to most systemic therapies. Immunotherapy played a dominant role in the treatment of advanced RCC because of minimal efficacy of cytotoxic chemotherapy. High-dose interleu-kin-2 produces about 15% response rate with only 7%-10% durable remissions.[1,2] Therapy with interleukin-2 is associated with significant side effects, making it less than ideal for the majority of patients. Sunitinib and sorafenib[3,4] are the targeted agents that have now demonstrated efficacy and are better tolerated than high-dose interleukin-2, in metastatic RCC.

The 5-fluorouracil (5-FU)-based biochemotherapy combinations have shown promising response rates in advanced RCC.[5,6] Capecitabine is an oral fluoropyrimidine, which is selectively converted to 5-FU by the enzyme thymidine phosphorylase (TP) within tumor

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tissue, hence increasing antitumor activity with relatively less side effects.[7] Clinically, capecitabine demonstrated efficacy in RCC, in combination with interleukin-2, interferon, and 13-cis-retinoic acid with an objective response rate and complete remission rate, respectively, of 34% and 7% in a phase II trial.[8] The conversion of capecitabine to 5-FU is controlled by an enzyme, TP, and the metabolism is dependent on the levels of dihydropyrimidine dehydrogenase (DPD). Quantitative analysis of TP levels and TP/DPD ratio as measured by enzyme-linked immunosorbent assay (ELISA), in 65 patients with RCC, were significantly higher in RCC than in adjacent non-cancerous kidney tissue.[9] This study also revealed TP and DPD expression were prognostic predictors of survival. Increased sensitivity to capecitabine was demonstrated in kidney cancer cells that were transfected with TP in a mouse model.[10] The efficacy and the therapeutic index of capecitabine could potentially be enhanced by increasing the activity of TP within tumors, which in turn would lead to greater intratumor formation of 5-FU through an increase in the TP/DPD ratio within tumors, suggesting the possibility of enhanced activity of this combination. Taxanes have shown an increase in TP levels, hence enhancing capecitabine efficacy.[11] This principle has been proven clinically, by improved efficacy and survival seen with the combination of docetaxel and capecitabine compared with docetaxel alone in a phase III randomized trial conducted in anthracycline-resistant metastatic breast cancer.[12] The combination of weekly docetaxel and capecitabine was well tolerated in a phase I trial.[13] Given the preclinical background for the combination and the promising clinical efficacy of capecitabine in RCC, we conducted a phase II trial of the combination in metastatic RCC.

Patients and Methods

Eligibility criteria for participation included age >18 years, locally advanced unresectable, recurrent, or metastatic RCC, and unidimensionally measurable disease with prior radiation therapy or immunotherapy completed 28 days before enrollment. A Zubrod performance status of 0-2 and no prior exposure to chemotherapy were required. Patients were required to have normal renal, liver, and marrow function. All patients signed an informed consent that was reviewed and approved by the Institutional Review Board.

Treatment Plan

All patients received docetaxel 36 mg/m^2 on days 1, 8, and 15 as a 30- to 60-minute infusion and capecitabine 1250 mg/m^2 orally divided into 2 equal doses on days 5-18. Cycles were repeated every 28 days. Dosage adjustments were made for severe hematologic and nonhematologic toxicities. A maximum of 2 docetaxel dose level reductions were allowed per patient: first to 30 mg/m^2, then to 26 mg/m^2, and a maximum of 2 capecitabine reductions were allowed per patient: first to 1000 mg/m^2 daily, then to 800 mg/m^2 daily. Treatment was discontinued if there was evidence of disease progression, unacceptable toxicity, >4 weeks delay in treatment, withdrawal from the study at any time for any reason, or for early study closure based on an unexpected high rate of toxicity or disease progression. All patients were followed until death.

Correlative Studies Methodology for Serum DPD Levels

Pretreatment blood samples for serum DPD were drawn on day 1 of cycle 1 and sent to the correlative laboratory located at Asterand, Inc, Detroit, MI. The mononuclear cells were separated on Ficoll, and slides were prepared using a Hettich Universal 16 cytospin centrifuge (GMI, Ramsey, MN). They were air-dried and kept at −20°C until stained.[14]

Two established breast cancer cell lines (MDA-MB-231 and ZR-75-1) and 1 bladder cancer cell line (T-24), in which the activity of DPD is well characterized, were chosen as controls.

These cell lines represented the extreme low (T-24 and MDA-MB-231) and the extreme high (ZR-75-1) TP/DPD ratios as determined by enzyme activity measurements. The cells were harvested from cultures, washed, and suspended in phosphate-buffered saline (PBS) solution at 10^5 cells per milliliter. One milliliter of this cell suspension was deposited on salinated slides by using a cytocentrifuge. Slides were processed, prepared, air-dried and kept at −20°C until stained.[14]

The stains that were used included a primary antibody, followed by a secondary antibody and propidium iodide (PI). For primary labeling of the DPD enzyme, rat anti-human DPD monoclonal antibody (Roche, Basel, Switzerland) was used. Appropriate species-matched antibody was used as an isotype control. The secondary antibody was a goat anti-rat immunoglobulin G (IgG) (Invitrogen catalogue A11006, Invitrogen Corp, Carlsbad, CA), labeled with Alexa Fluor 488.

After blocking nonspecific binding sites with Superblock (ScyTek, Logan, UT), slides were incubated at room temperature for 90 minutes with optimized concentration of primary antibody (1:500 dilution of a stock concentration was 1 mg/mL for anti-DPD). The slides were washed 3 times with PBS solution, followed by 30 minutes of incubation with the secondary antibodies also at room temperature. To stain nuclear DNA, the slides were washed 3 times with PBS solution and incubated for 10 minutes at room temperature with 0.002 fxg/mL of PI and 0.34 μg/mL RNase A in PBS solution.

The stained slides were analyzed using a Laser Scanning Computer II (CompuCyte Corp, Cambridge, MA).

Evaluation

Patients underwent computed tomography scans of the chest, abdomen, and pelvis at baseline and every 2 cycles thereafter. Investigators performed their evaluation on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[15] The response was coded as stable disease if neither sufficient decrease to call it partial or complete response, nor sufficient increase to call it progression, occurred. Toxicity was monitored on days of docetaxel therapy, and was categorized according to the National Cancer Institute's Common Toxicity Criteria (version 2.0). Serious adverse events were reported and monitored per the Wayne State University Institutional Review Board guidelines. Patients were considered evaluable for response if they received a minimum of 2 cycles of therapy.

Statistical Methods

This single-institution phase II trial was planned with a Simon 2-stage design.[16] The particular design chosen has near-optimal statistical properties, and resulted from the Simon algorithm modifications of Hintze.[17] The primary endpoint was complete or partial response (CR+PR). We wished to distinguish these regions of the true, unknown response rate: at most 0.05 vs at least 0.20. The 2-stage design called for a maximum of 29 response-evaluable (r-e) patients, 19 in stage I and 10 in stage II. The design had a type I error of 0.138 and power of 0.901. At least 2 (objective, confirmed) responders among the first 19 r-e patients were needed to justify beginning stage II of the study design. After accruing 25 patients, there were 19 r-e patients, and all 19 were nonresponders. Hence, the trial was stopped as per its statistical design. With no confirmed responders, it was concluded that the sample response rate among the r-e patients (0/19 = 0%) better supported the null hypothesis that the true, unknown response rate was at most .05.

Exact, minimum-width 90% confidence intervals (CI) for response and toxicity rates were calculated using the Casella method[18] as implemented in StatXact software (Cytel Software Corp, Cambridge, MA).[19] Time to progression (TTP) was measured from treatment start

date to the date of documented progressive disease. Overall survival (OS) was measured from treatment start date to the date of death from any cause. Standard Kaplan-Meier estimates of the censored TTP and OS distributions were computed. Because of the small sample sizes, survival statistics (eg, median) were estimated more conservatively using linear interpolation[20] among successive event times on the Kaplan-Meier curves.

Results

Between October 2002 and November 2004, 25 patients, 13 men and 12 women, were enrolled on this phase II trial. Zubrod scores were ≥1 in 80% of patients. The median age was 60 years (range: 50-80 years). Nineteen patients were white and 6 were African American. Thirteen patients had liver and/or bone metastases and 1 patient had brain metastases. Nine patients had ≥3 of the poor risk MSKCC prognostic criteria. Twelve patients had ≥3 metastatic sites and 10 patients had 2 metastatic sites. Prior therapies included nephrectomy in 84%, and immunotherapy in 48% (Table 1).

A total of 93 cycles of treatment were administered, with a median of 3 cycles and a range from 0-10 cycles. The therapy was well tolerated with grade 3 adverse events noted in 10 (40% grade 3 toxicity rate; 90% CI 0.25-0.58) of the 25 patients. One patient had a grade 4 toxicity, which was anemia. There was no treatment-related mortality. Two treatment-related hospitalizations occurred caused by diarrhea and dehydration.

No objective responses were noted among the 19 r-e patients. Ten patients had stable disease. The median time to progression for all 25 patients was 1.7 months (Table 2). One patient is still progression-free at 39.8 months after study entry. The median survival for all 25 patients was 11.1 months (90% CI 2.2-14.8 months). One-year and 2-year survival rates were 50% (with 90% CI 0.33-0.66) and 16% (with 90% CI 0.04-0.28), respectively.

DPD Levels

DPD levels were checked pretherapy on 13 of the 25 patients. The median immunoflourescence of isotype noted was 169% (range 54%-448%). The 2 cases of grade 3 diarrheas and hospitalization, as well as 1 patient with grade 3 anemia, had DPD levels less than the median. As expected, lower DPD levels appeared to predict for increased risk of toxicity. The median TTP was calculated for patients with DPD greater than median (> 169%), and lower than median (< 169%). There was very little difference in the observed TTP between the high and low DPD groups with median TTP of 1.5 months and 1.7 months, respectively (Table 3).

Comment

This phase II trial evaluated the efficacy and toxicity of the combination of capecitabine and docetaxel in metastatic RCC. Chemotherapy has been considered to be ineffective in RCC, especially in clear cell cancer.[21] Now a number of targeted therapies such as sunitinib, sorafenib bevacizumab, and temsirolimus[3,4,22,23] have demonstrated activity in clear cell carcinoma of the kidney. However, in non-clear cell histologies, it is still uncertain if any of these therapies have a role. In sarcomatoid RCC, the chemotherapy combination of doxorubicin and gemcitabine is considered effective.[24] Gemcitabine and capecitabine have also been previously evaluated in phase II trials with promising results.[25,26] In our trial, it is noteworthy that most of the patients achieving prolonged stable disease had non-clear cell histology. Of 3 patients with sarcomatoid RCC, 2 had stable disease and 1 patient with chromophilic, and 1 patient with chromophobic RCC had prolonged disease stabilization receiving 8 and 10 cycles, respectively.

With the advent of targeted agents, such as sunitinib, sorafenib, and bevacizumab, the mechanism of action of the intervention has gained critical importance. The pathogenesis of RCC cell proliferation, driven by the von Hippel-Lindau (VHL) gene mutation, resulting in increased expression of vascular endothelial growth factor, is unique to the clear cell histology of kidney cancer.[27] For non-clear cell histologies, the same rationale has not been proven to justify the use of the same targeted therapies. Previous experience indicates that interleukin, which is effective in clear cell RCC, is, however, ineffective against the non-clear cell kidney cancer histologies.[28] It is increasingly recognized now that, although these tumors originate in the kidney, they differ significantly in their pathogenesis. The treatment of non-clear cell histologies of kidney cancer would have to be separately developed. Recently, a mek-1 inhibitor XL-880 is being evaluated in c-met driven papillary RCCs. The preliminary results of this oral well-tolerated agent are extremely encouraging.[29] Also it needs to be explored whether the m-TOR pathway plays a role in tumor cell proliferation within each distinct RCC histology. The phase III trial of temsirolimus (m-TOR inhibitor) vs interferon included patients with non-clear cell histologies, and analysis of this subset demonstrated a favorable survival outcome with temsirolimus, compared with interferon therapy. Until more information is available regarding the use of targeted antiangiogenic therapies in papillary, chromophobe, or sarcomatoid RCCs, chemotherapy remains the backbone of treatment. The data from the above phase II trial present another tolerable therapeutic option to consider in the treatment of non-clear cell histologies of renal cancer.

Conclusions

In conclusion, capecitabine and docetaxel demonstrated good tolerability in metastatic renal cancer. The encouraging activity demonstrated in non clear cell histologies of kidney cancer makes the combination worthy of further investigation in this setting.

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Table 1

Patient characteristics (n = 25)

Characteristic	n (%)
Median age	60 y (range 50-80 y)
Gender	
Male	13 (52)
Female	12 (48)
Zubrod performance status	
0	5 (20)
1	11 (44)
2	9 (36)
Nephrectomy status	
Yes	21 (84)
No	4 (16)
Sites of metastases	
Liver and/or bone metastases	13 (52)
Brain	1 (4)
Lung only	1 (4)
Histology	
Clear cell	18 (72)
Papillary	3 (12)
Chromophobe	1 (4)
Sarcomatoid cell	3 (12)
Race	
White	19 (76)
African American	6 (24)
MSKCC prognostic criteria (number of risk factors)	
0	4 (16)
1	8 (32)
2	4 (16)
≥3	9 (36)
Prior therapy	
Immunotherapy	12 (48)
No immunotherapy	13 (52)
Number of metastatic organ sites involved	
1	3 (12)
2	10 (40)
≥3	12 (48)

MSKCC = Memorial Sloan-Kettering Cancer Center.

Table 2

Response and survival (n = 25)

Endpoint	n (%)	90% CI
Complete response	0 (0%)	0.00-0.11
Stable disease	10 (40%)	0.25-0.58
Progression	7 (28%)	0.16-0.46
Nonevaluable	6 (24%)	0.11-0.42
Time to progression	Median 1.7 mon	1.6-3.5 mon
Overall surivival	Median 11.1 mon	2.2-14.8 mon

CI = confidence interval.

Table 3

Time to progression and overall survival by blood DPD enzyme level

Median blood DPD level (%)	Endpoint	n	Events	Point estimate	90% CI
≤169	Median TTP	7	7	1.7 mon	1.6-5.2 mon
	3-mon rate			23%	0%-51%
	6-mon rate			0%	0%-22%
>169	Median TTP	6	6	1.5 mon	0.4-8.0 mon
	3-mon rate			37%	4%-71%
	6-mon rate			26%	0%-57%
≤169	Median OS	7	7	7.1 mon	5.7-16.3 mon
	3-mon rate			35%	4%-66%
	6-mon rate			6%	0%-28%
>169	Median OS	6	5	14.9 mon	0.0-29.6 mon
	3-mon rate			54%	20%-87%
	6-mon rate			29%	0%-60%

TTP = time to progression; OS = overall survival; DPD = dihydropyrimidine dehydrogenase; CI = confidence interval.