Gemcitabine and Oxaliplatin in the Treatment of Patients with Immunotherapy-Resistant Advanced Renal Cell Carcinoma

Final Results of a Single-Institution Phase II Study

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BACKGROUND. Currently, there is no standard treatment for patients with advanced renal cell carcinoma (RCC) who do not experience a response to first-line immunotherapy. In the current Phase II study, the authors explored the antitumor activity of a combination of gemcitabine and oxaliplatin (L-OHP) in this setting.

METHODS. Forty-two patients with RCC who had progressive disease following immunotherapy received gemcitabine (1000 mg/m^2 intravenously on Days 1 and 8 every 21 days) and L-OHP (90 mg/m^2 intravenously on Day 1 every 21 days) for a minimum of 2 cycles before responses were evaluated. Responses to treatment and toxicity were recorded according to the Response Evaluation Criteria in Solid Tumors and the National Cancer Institute Common Toxicity Criteria, respectively.

RESULTS. No complete responses were recorded; however, 6 patients experienced a partial response (14.28%; 95% confidence interval, 5.43–28.5%), 11 patients (26.19%) had temporary stable disease as a best response, and the remaining 25 patients (59.52%) experienced progression despite receiving treatment. The median time to disease progression was 2.5 months (mean, 3.86 months; range, 1.5–11.0 months), whereas the median overall survival was 9.5 months (mean, 10.46 months; range, 4.0–22.5 months). With regard to toxicity, treatment generally was well tolerated, with only one episode of Grade 4 toxicity and expected episodes of Grade 3 toxicity, including myelosuppression and neuropathy.

CONCLUSIONS. The current results suggest that the combination of gemcitabine and L-OHP possesses a certain level of activity and an acceptable toxicity profile in patients with immunotherapy-resistant advanced RCC. ***Cancer* 2004;100:2132–8.**

KEYWORDS: chemotherapy, renal cell carcinoma, gemcitabine, oxaliplatin.

Renal cell carcinoma (RCC) is the seventh leading cause of malignancy-related death. It is estimated that there will be approximately 31,900 patients with newly diagnosed RCC and approximately 11,900 deaths due to RCC this year in the United States alone.[1] At the time of diagnosis, approximately 30% of patients who are diagnosed with RCC have unresectable and, thus, incurable disease;[2] furthermore, approximately 50% of patients with RCC who undergo curative resection will develop recurrent and/or metastatic disease. Overall, patients with advanced RCC have a very poor prognosis, with a median survival of approximately 10 months.[3]

Due to frequent overexpression of the *MDR* gene product, P-glycoprotein,[4] RCC typically is a chemoresistant tumor. Consequently, immunotherapy is used as a first-line treatment option.[5]

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Although it has been demonstrated that different interleukin-2 (IL-2)-based immunotherapy schedules often are active, leading to objective responses or long-term disease stabilization in ≈ 20% of patients,[5–8] at present, there is no standard treatment for patients with immunotherapy-resistant disease.

Traditional cytotoxic chemotherapeutic regimens fail to affect the natural history of RCC and thus typically yield poor results. In fact, a comprehensive review on these regimens by Yagoda et al. in 1995 revealed an overall response rate of 6% among 4093 patients with advanced RCC who received adequate treatment, with only a slight improvement (to 14.6%) in a subgroup of patients who were treated with an antimetabolite (floxuridine or 5-fluorouracil [5-FU]).[9] Despite the discovery of a number of new cytotoxic agents in the last 10 years, the unsatisfactory state of RCC treatment was no different by the year 2000, when Ruiz et al. reviewed single and multiagent Phase II and III trials that were performed between 1993 and 1998, enrolling more than 2300 patients.[10]

More recently, it has been shown that gemcitabine-containing combinations also exert some antitumor activity in patients with immunotherapy-resistant advanced RCC.[11–20] Herein, we report the results of a single-institution Phase II study in which we evaluated the antitumor activity and toxicity of a combination of gemcitabine with the platinum derivative oxaliplatin (L-OHP).

MATERIALS AND METHODS

Study Design and Statistical Considerations

The objective of the current single-institution Phase II study was to assess the antitumor activity and toxicity of the combination of gemcitabine and L-OHP in a population of patients with immunotherapy-resistant advanced RCC. We used a three-stage Phase II design that was adopted previously in the same setting by other investigators.[14]

The study regimen was to be rejected if the estimated response rate was $< 5\%$ and accepted as active if the estimated response rate was $> 20\%$. Using an α error of 0.05 (representing the probability of accepting the regimen as active even with a response rate $< 5\%$) and a β error of 0.10 (representing the probability of rejecting the regimen as active even with a response rate $> 20\%$), the first stage was designed to accrue 14 patients. If none of those patients experienced a response, then the regimen would be considered inactive, and the study would be closed. If at least 1 of the first 14 patients responded, then an additional 16 patients (for a cumulative total of 30 patients) would be accrued. If ≤ 2 of those 30 patients responded, then the regimen would be rejected as inactive, and the study would be closed to limit the number of patients exposed to an inactive and possibly toxic treatment. In contrast, if ≥ 3 of the 30 patients had responses, then accrual would continue until the final enrollment of a total of 42 patients; in this stage of the trial, the regimen would be rejected as inactive if ≤ 4 patients responded.

Using this design, under the null hypothesis, the likelihood of closing the trial after the first stage was 0.49, whereas the likelihood of closing the trial after the second stage was 0.83. Although survival is not an endpoint in Phase II studies, survival rates were calculated and plotted according to the Kaplan–Meier method.

Patients

Eligibility criteria included histologically proven RCC, metastatic disease that progressed after a first-line immunotherapy treatment, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, age ≥ 18 years and < 70 years, life expectancy ≥ 12 weeks, and written informed consent obtained according to institutional requirements. Patients also were required to have adequate organ function, which was defined by the following: white blood cell count $\geq 3000/\mu L$, platelet count $\geq 100{,}000/\mu L$, hemoglobin levels ≥ 9.5 g/dL, bilirubin levels < 1.5 mg/dL, alanine and aspartate aminotransferase levels < 3 times the upper limit of normal, and creatinine levels < 2.0 mg/dL.

Exclusion criteria included nonmeasurable disease; previous treatment with any kind of chemotherapy; the presence of central nervous system metastases; significant comorbidity, including uncontrolled diabetes; a history of severe coronary artery disease or myocardial infarction within the last 6 months; psychiatric conditions that had the potential to interfere with the treatment schedule or compromise the patient's ability to consent to treatment; and a history of metastatic disease within the previous 5 years (except for localized, nonmelanomatous skin carcinoma or cervical carcinoma in situ). Pregnant or lactating women also were excluded from enrollment into the study. Finally, palliative radiotherapy (only for patients with symptomatic bone metastases) and the administration of intravenous bisphosphonates were allowed.

Treatment

Treatment involved the administration of gemcitabine at a dose of 1000 mg/m^2 intravenously on Days 1 and 8 every 21 days and L-OHP at a dose of 90 mg/m^2 intravenously on Day 1 every 21 days. Treatment was

administered for a minimum of two cycles before response evaluation. In patients who received more than two cycles, disease reevaluation was performed after every two cycles.

Computed tomography scans represented the only allowed assessments of disease status both at baseline and at each reevaluation. Treatment was administered mainly, but not exclusively, on an outpatient basis.

Response and Toxicity Criteria

Response to treatment, which was calculated from the start of the current study, was assessed according to the Response Evaluation Criteria in Solid Tumors,[21] which are based on the evaluation of both target and nontarget lesions. Target lesions are defined as all measurable lesions per organ, representative of all involved organs, whereas nontarget lesions include all measurable lesions that are not included as target lesions as well as all nonmeasurable lesions.

Briefly, a complete response (CR) was defined as the complete disappearance of all known target and nontarget lesions. A partial response (PR) was defined either as the complete disappearance of all target lesions with nontarget lesions exhibiting the characteristics of an incomplete response/stable disease (SD) or as a decrease of $\geq$ 30% in the sum of the longest dimensions of all target lesions (relative to the baseline sum of the longest dimensions) without progression of nontarget lesions.

Progressive disease (PD) was defined as either an increase of $\geq$ 20% in the sum of the longest dimensions of target and/or nontarget lesions or the appearance of any new lesion(s). SD was defined as disease that did not meet the criteria for CR, PR, or PD. In assigning a CR or a PR, changes in tumor measurements were confirmed by repeating tumor assessment no less than 4 weeks after the criteria for response first were met. Chemotherapy-related toxic effects were recorded after each treatment cycle and at the end of treatment and were graded according to the National Cancer Institute Common Toxicity Criteria (Version 3.0).[22]

RESULTS

Patient Demographics

Forty-two patients were enrolled in the 3 phases of the current study and were treated from April 2000 to January 2003. Thirty-one patients were men (73.80%), and 11 were women (26.19%). Median patient age was 62.5 years (average, 61.5 years; range, 45–70 years).

The ECOG performance status was 0 in 8 patients (19.04%), 1 in 28 patients (66.66%), and 2 in the remaining 6 patients (14.28%). With regard to the sites of disease at the time of enrollment, the majority of patients (28 of 42; 66.66%) presented with $\geq$ 2 metastatic sites; overall, lung metastases represented the most common type of metastatic disease and were evident in 31 patients (73.80%).

All patients had been treated previously with one of the following immunotherapy regimens: very low doses of subcutaneous IL-2 plus interferon-α (n = 29; 69.04%), high doses of subcutaneous IL-2 plus interferon-α (n = 11; 26.19%), or interferon-α alone (n = 2; 4.76%). Furthermore, 28 patients (66.66%) also underwent nephrectomy. Patient characteristics are summarized in Table 1.

Response to Treatment

All enrolled patients were evaluable for response. No CRs were recorded; however, 6 patients obtained a PR (objective response rate, 14.28%; 95% confidence interval, 5.43–28.5%). In four patients, responses were recorded at the first disease evaluation, which was performed at the conclusion of the first two treatment cycles; in the remaining two patients, responses were evaluated after completion of the fourth treatment cycle. Eleven patients (26.19%) had only temporary SD as their best response, whereas the remaining 25 patients (59.52%) experienced disease progression despite receiving treatment.

The clinical characteristics of the six patients who experienced responses are reported in Table 2. Figure 1 shows representative computed tomography scans from a patient who had complete disappearance of lung metastases, although this patient still presented with abdominal lymph node metastases as well as a renal primary tumor at the time of reevaluation.

The median time to progression (TTP) was 2.5 months (mean, 3.86 months; range, 1.5–11 months), and the median overall survival was 9.5 months (mean, 10.46 months; range, 4–23 months). TTP and overall survival curves are shown in Figure 2. As expected, survival was significantly longer for patients who experienced responses (median, 20.25 months; mean, 20.08 months; range, 18–23 months) compared with patients who did not (median, 8 months; mean, 8.86 months; range, 4–19.5 months).

Toxicity

A median of 2 cycles of treatment per patient (mean, 3.3 cycles; range, 1–10 cycles) were administered; treatment generally was well tolerated, and only 1 episode of Grade 4 toxicity was observed. This Grade 4 toxicity, which was noted in a 65-year-old male patient, was a pulmonary embolism that developed

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median	62.5
Range	45–70
Gender	
Male	31 (73.80)
Female	11 (26.19)
ECOG performance status	
0	8 (19.04)
1	28 (66.66)
2	6 (14.28)
Histology	
Clear cell carcinoma	30 (71.42)
Papillary carcinoma	10 (23.80)
Undifferentiated carcinoma	1 (2.38)
Sarcomatoid carcinoma	1 (2.38)
Nuclear grading (Fuhrman criteria)	
Grade 1	8 (19.04)
Grade 2	12 (28.57)
Grade 3	18 (42.85)
Grade 4	4 (9.52)
No. of disease sites	
1	14 (33.33)
2	20 (47.61)
≥ 3	8 (19.04)
Disease site	
Lung	31 (73.80)
Lymph nodes	21 (50.00)
Kidney	14 (33.33)
Liver	7 (16.66)
Bone	5 (11.90)
Skin	1 (2.38)
Prior treatment	
Nephrectomy	28 (66.66)
Immunotherapy	42 (100.00)
Previous best response to immunotherapy	
Complete response	0 (0.00)
Partial response	8 (19.04)
Stable disease	11 (26.19)
Progressive disease	23 (54.76)
Duration of previous immunotherapy (mos)	
Median	5
Range	1–18

ECOG: Eastern Cooperative Oncology Group.

shortly after the completion of the patient's second and final chemotherapy cycle; no clear evidence of deep venous thrombosis was observed. Grade 3 toxicities included myelosuppression and neuropathy; other, less severe (i.e., Grade 2) side effects included nonneutropenic fever, nausea/emesis, mucositis, diarrhea, anorexia, asthenia/fatigue, elevated blood urea nitrogen levels, and transiently increased creatinine levels.

Adverse events noted in the current study are summarized in Table 3. Neither treatment withdrawals nor dose reductions were necessary. One patient had a 1-week delay in the administration of his fourth (and last) cycle due to persistent Grade 3 neutropenia, which resolved without the use of hematopoietic growth factors.

TABLE 2
Characteristics of the Six Patients Who Achieved Responses to Treatment

Gender	Age (yrs)	Metastatic site(s)	Site(s) of response	Response duration (mos)
Male	66	Lung, kidney, abdominal LNs	Lung	8.0
Female	45	Lung	Lung	8.0
Male	67	Kidney, lung	Lung	4.5
Male	55	Abdominal LNs	Abdominal LNs	4.5
Male	55	Abdominal LNs, liver	Abdominal LNs, liver	3.5
Male	51	Kidney, abdominal LNs, lung	Abdominal LNs, lung	9.0

LNs: lymph nodes.

DISCUSSION

The development of active, second-line treatment protocols is the key to improving the overall survival of patients affected with RCC. Their survival remains unsatisfactory at best; in fact, at present, no standard treatment options are available when patients do not experience a response or when they develop progressive disease after first-line immunotherapy.[23] For these reasons, there is a great need for new approaches.

Among more recent chemotherapeutic agents, gemcitabine appears to be the most promising drug available, in part because it is not a known substrate for P-glycoprotein,[24] which is responsible for the well known chemoresistance of RCC.[25] Recently, the combination of gemcitabine and 5-FU proved to be active against RCC,[14] but no further improvements were recorded when either cisplatin,[19] interferon, or IL-2[18] was added; furthermore, a Phase II study of gemcitabine, 5-FU, and oral thalidomide resulted in an unacceptably high incidence of thromboembolic complications.[20]

In the current Phase II study, we tested the combination of gemcitabine with L-OHP in a population of chemotherapy-naïve patients with RCC who experienced disease progression after first-line immunotherapy. The regimen was well tolerated, with few unexpected toxicities: myelosuppression and neuropathy were the most common side effects recorded. In terms of antitumor efficacy, 6 patients (14.28%) had objective responses, suggesting that the regimen possesses a certain level of activity.

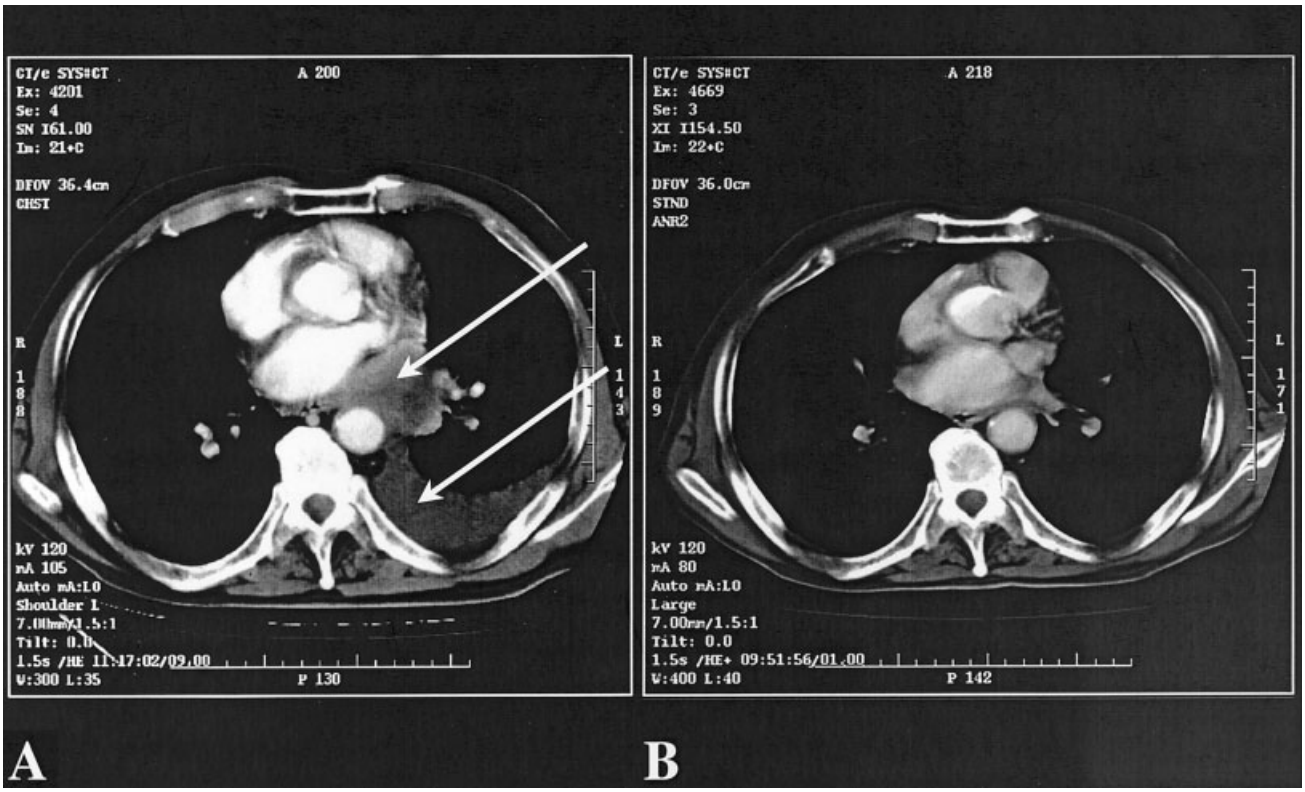

FIGURE 1. (A) Pretreatment and (B) posttreatment chest computed tomography scans from a male patient age 66 years with lung metastases from renal cell carcinoma; arrows indicate pulmonary metastatic disease sites and pleural effusion. Treatment yielded a complete response in the lung, with extrapulmonary disease persisting. According to the Response Evaluation Criteria in Solid Tumors, this patient had achieved a global partial response.

The results of the current study are more favorable than the results that have been reported for gemcitabine alone (i.e., a 6% overall response rate in a small National Cancer Institute of Canada Phase II study[11] and an 8.1% response rate in a numerically adequate Dutch Phase II study[12]). However, our findings are in agreement with results reported by a group at the University of Chicago; in 2 distinct Phase II studies, those investigators tested the antitumor activity of gemcitabine combined with continuous-infusion 5-FU alone or with continuous-infusion 5-FU plus immunotherapy (IL-2 and interferon-α) and found overall response rates of 17% and 14.6%, respectively.[14,18]

At least two other gemcitabine-based Phase II studies have reported higher response rates (31% in a single-agent feasibility study[15] and 28% for the combination of gemcitabine, IL-2, and interferon-α.[17]) than the one noted in the current study. However, the small number of patients enrolled in those studies (16 and 18, respectively) may be indicative of a relevant bias.

Gemcitabine appeared to be the key drug in the current study regimen, as was evidenced by the poor

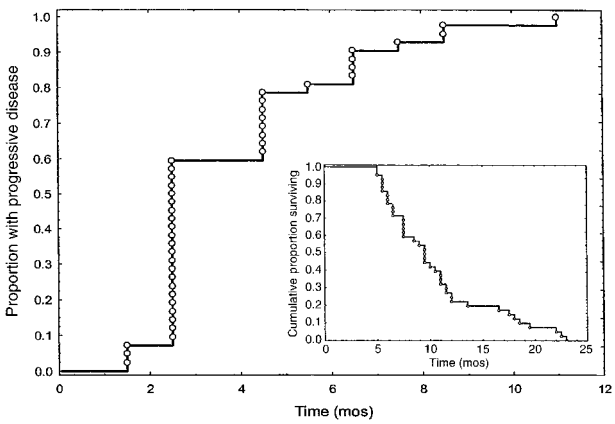

FIGURE 2. Progression-free survival and overall survival (*inset*) curves for the entire patient population treated in the current Phase II study.

results obtained previously with L-OHP in patients with RCC. In fact, no objective responses were observed in either a small pilot study of the FOLFOX-4 (5-FU, leucovorin, and L-OHP) regimen[26] or a larger (n = 59) Phase II study of the same regimen.[27]

In conclusion, our results suggest a certain level of activity, with an acceptable toxicity profile, for the

TABLE 3
Chemotherapy-Related Adverse Events[a]

	No. of patients with toxicity (%)		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic			
Anemia	17 (40.47)	5 (11.90)	0 (0.0)
Neutropenia	9 (21.42)	13 (30.95)	0 (0.0)
Thrombocytopenia	8 (19.04)	7 (16.66)	0 (0.0)
Nonhematologic			
Nausea/emesis	7 (16.66)	0 (0.0)	0 (0.0)
Asthenia/fatigue	11 (26.19)	0 (0.0)	0 (0.0)
Nonneutropenic fever	15 (35.71)	0 (0.0)	0 (0.0)
Mucositis	10 (23.80)	0 (0.0)	0 (0.0)
Neuropathy, sensory	5 (11.90)	10 (23.80)	0 (0.0)
Diarrhea	2 (4.76)	0 (0.0)	0 (0.0)
Anorexia	3 (7.14)	0 (0.0)	0 (0.0)
Vascular[b]	0 (0.0)	0 (0.0)	1 (2.38)
Elevated blood urea nitrogen levels	3 (7.14)	0 (0.0)	0 (0.0)
Elevated creatinine levels	1 (2.38)	0 (0.0)	0 (0.0)

[a] Side effects were recorded at the conclusion of each treatment cycle.
[b] Pulmonary embolism.

combination of gemcitabine and L-OHP in patients with immunotherapy-resistant advanced RCC; however, as reported by many other investigators, these results remain unsatisfactory in terms of both objective response and survival. Consequently, our regimen should not be considered to be standard treatment for patients with immunotherapy-refractory RCC, and newer therapeutic strategies should be pursued within adequately large Phase I and II studies of new agents.

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