

Phase II Trial of 5-Fluorouracil and Leucovorin in Combination With Interferon-alpha and Interleukin-2 for Advanced Renal Cell Cancer

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Abstract: Recent clinical trials have demonstrated activity of chemoimmunotherapy with interleukin-2 (IL-2), interferon- α , and 5-fluorouracil (5-FU) in advanced renal cell cancer. A phase II study was performed to evaluate the effect of adding the potentiating agent leucovorin to this combination regimen. Treatment courses consisted of IL-2 5 MIU/m² subcutaneously days 1, 3, and 5 of weeks 1 to 4, interferon- α 3 MIU/m² subcutaneously on days 1, 3, and 5 of weeks 1 to 4, and leucovorin 50 mg/m² IV followed by 5-FU 450 mg/m² IV infusion weekly weeks 1 to 4. Patients were given no treatment on weeks 5 and 6 of the 6-week treatment cycle. Of the 20 patients enrolled in the study, 16 were evaluable for toxicity and 15 were evaluable for tumor response. The most severe toxicities included three reports of grade IV diarrhea; overall, nine incidents of grade III or IV toxicity were reported. No objective antitumor responses were observed, and the median time to progression was 2.8 months. We conclude that this combination chemoimmunotherapy regimen has substantial toxicity but no significant antitumor activity in patients with advanced stage renal cell carcinoma.

Key Words: renal cell carcinoma, chemoimmunotherapy, 5-fluorouracil, leucovorin

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Renal cell carcinoma has minimal sensitivity to traditional chemotherapeutics. However, this tumor can respond to modulation of the immune system via the administration of recombinant cytokines including interleukin 2 (rIL-2) or

interferon- α (IFN- α 2B). Multiple studies have demonstrated that a modest percentage (12–20%) of good performance status patients can experience partial or complete responses of metastatic renal cell carcinoma with either agent.^{1,2} A small fraction will experience long-term survival. rIL-2 demonstrates its highest therapeutic potential when administered as a high-dose bolus infusion, although the therapeutic index is compromised by toxicity.^{3,4} Lower dose regimens of rIL-2 are better tolerated, but this appears to come at the expense of reduced efficacy.⁵ Multiple regimens of IFN- α have been investigated, all of which demonstrate response rates similar to those seen with lower doses of rIL-2.^{1,6,7}

rIL-2 and IFN- α have been shown to produce synergy in preclinical testing.^{8,9} Several doses and schedules have been investigated and demonstrate levels of toxicity similar to the single-drug regimens in early phase clinical studies. Furthermore, prospective studies of rIL-2 and IFN- α 2B in combination have demonstrated response rates similar to those observed for high-dose single-agent rIL-2.^{10–12}

The antimetabolite 5-fluorouracil (5-FU) has modest antitumor activity in human renal cell cancer as a single agent. Preclinical studies demonstrated enhanced efficacy of 5-FU in treatment of gastrointestinal malignancies when used in combination with IFN- α .^{13,14} This modulatory effect was further substantiated in studies using a mouse model of renal cell carcinoma. In the RENCA mouse model system, IFN- α was shown to reduce thymidine kinase activity and subsequently enhance 5-FU cytotoxicity.¹⁵ 5-FU in combination with IFN- α and/or rIL-2 has been studied in several phase II renal cell cancer trials with mixed results. The first of these studies reported a response rate of 48.6% with response duration of 7+ months.¹⁶ Although subsequent studies demonstrated response rates ranging from 1.8% to 38%,^{17–24} a more recent study from Atzpodien et al. in a controlled randomized clinical trial demonstrated a 39.1% overall objective response rate using concomitant dosing of rIL-2, IFN- α 2A, and weekly infusional 5-FU.²⁵

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Leucovorin (folinic acid) has long been used to enhance the cytotoxicity of 5-FU in the treatment of gastrointestinal malignancies. Biochemically, this occurs via an interaction between leucovorin and thymidylate synthetase that enhances the inhibition of this enzyme by 5-FU. This results in increased activity of the drug in causing S-phase-specific cell killing. Potentially, treatment of renal cell cancers with immunologic therapy and leucovorin-modulated 5-FU should result in enhanced cell killing, greater response rates, and ideally, delayed time to progression.

PATIENTS AND METHODS

Patient Selection

Patients at the Hospital of the University of Pennsylvania and community affiliates of the Penn Cancer Clinical Trials Group were registered and eligible for treatment in this study. Eligible patients had metastatic, locally recurrent, or unresectable measurable renal cell carcinoma. Patients with brain or leptomeningeal metastasis were excluded. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. No prior malignancies were permitted, with the exception of basal cell or noninvasive squamous cell cancer of the skin or in situ squamous cell carcinoma of the cervix. No prior chemotherapy was permitted for this study, and no radiation was permitted within 4 weeks prior to study entry. Patients receiving glucocorticoids were excluded. Patients had adequate hematologic (leukocyte $\geq 4,000/\text{mm}^3$, hemoglobin ≥ 10 g/dl, platelet count $\geq 120,000/\text{mm}^3$), hepatic (bilirubin ≤ 1.5 mg/dl), and renal (creatinine ≤ 2.0 mg/dl) function. All participants in the study were greater than 18 years of age. The study was approved by institutional review boards of each treatment location, and all patients signed informed consent.

Treatment Plan

A treatment cycle consisted of leucovorin, 50 mg/m² by IV bolus followed by 5-FU, 450 mg/m² IV infusion over 30 minutes one day per week for weeks 1 to 4, rIL-2, 5 MIU/m² delivered subcutaneously on days 1, 3, and 5 of weeks 1 to 4, and IFN α 2B, 3 MU/m² delivered subcutaneously on days 1, 3, and 5 of weeks 1 to 4. No treatment was administered during weeks 5 and 6.

Dose Modification and Toxicity Monitoring

Patients received a clinical examination weekly on the day of treatment and toxicity data were recorded. Additionally, a weekly complete blood count and measurement of serum chemistry was performed. Doses were adjusted according to routine guidelines. 5-FU was withheld if patients developed grade III or higher stomatitis/mucositis, diarrhea, infection, leukopenia, thrombocytopenia, or neuropathy.

Treatment was resumed without dose adjustment when the toxicity had resolved.

Response Assessment

Response was measured by clinical evaluation and radiographic imaging of previously documented disease. Patients underwent repeat imaging of the chest, abdomen, and pelvis after two cycles of therapy. Patients with responding or stable disease were continued on therapy until disease progression.

Statistical Considerations

The primary objective of this phase II trial was to determine the response rate of 5-FU, leucovorin, rIL-2, and IFN- α in patients with metastatic or unresectable renal cell carcinoma. This study was originally planned with a two-stage design. At the completion of the first stage of the study, patient accrual was terminated due to the observed lack of antitumor activity. Secondary objectives included assessment of toxicity of this regimen and time to disease progression.

RESULTS

Patient Accrual

Of the 20 patients initially enrolled in the study, 3 patients were lost to follow-up and 1 ineligible patient was withdrawn prior to treatment. Sixteen patients enrolled in the study were evaluable for toxicity. Fifteen of the original 20 patients were evaluated for treatment response as treatment was discontinued for 1 patient after one cycle of treatment due to recurrent immune thrombocytopenic purpura (ITP).

Patient Characteristics

The median age of the patients enrolled in this study was 63, and all had an ECOG performance status of 0 or 1. Nine of the patients had undergone primary nephrectomy. Lung was the most common site of metastatic disease.

Treatment Course

The median number of treatment cycles per patient was two. Ten patients (62%) completed more than 1 cycle of treatment, and 5 patients (31%) completed more than 2 cycles. The number of cycles completed ranged from 0 to 4. One patient did not complete the first cycle due to recurrent ITP and was withdrawn from the study. Four patients developed disease progression prior to the completion of the first cycle.

Toxicity

The most common toxicity reported was gastrointestinal complaints including nausea, vomiting, constipation, diarrhea, mucositis, and dehydration. The most severe toxic events included three patients with grade IV diarrhea. All of these patients were hospitalized for management of this complication. Other severe toxicities (grades III and IV)

included mucositis, myalgia, neuromotor weakness, and respiratory complaints. A patient with grade IV thrombocytopenia also developed recurrence of previously diagnosed ITP following one cycle of treatment. It should be noted that this patient had a normal platelet count at the time of enrollment in the study. There were no treatment-related deaths.

Response to Treatment

No objective antitumor responses were observed in this study. Patients were evaluated for response after two cycles. Six patients presented with disease progression prior to receiving two cycles of therapy. Five of the remaining 10 patients had stable disease after 2 cycles, but all patients ultimately developed objective evidence of disease progression. The mean time to progression was only 2.8 months.

DISCUSSION

This phase II study sought to build on the previously reported activity of chemoimmunotherapy in metastatic or unresectable renal cell carcinoma. Several previous studies have observed a response rate of 12% to 20% with treatment with either IFN- α or IL-2. In two studies, Atzpodien et al.^{16,26} demonstrated enhancement of the response rate with combination immunologic therapy and 5-FU. The regimen we present builds on advances in biochemical modulation of 5-FU by leucovorin. Despite the theoretical advances this regimen brings to treatments with previously demonstrated activity in renal cell carcinoma, the regimen reported here demonstrated no activity in our patient population. Recently, other similar regimens using biologic response modifiers in combination with 5-FU have been evaluated in advanced renal cell carcinoma and did not demonstrate significant increase in activity.^{21–24,27}

There are several possible reasons why this regimen did not demonstrate activity. Although the characteristics of our patients correlate with those of similar studies, we noted a mean time to progression of only 2.8 months, perhaps evidence of more advanced nature of our patients' disease. Additionally, five patients failed to complete even two cycles of therapy. These patients, representing one third of the group of evaluable patients, may not have received sufficient therapy to determine benefit.

The combination of immunotherapy and chemotherapy in this study did not offer any advantage over previous regimens. Furthermore, the lack of activity supports a growing number of studies that have failed to demonstrate activity of IL-2, IFN- α , and 5-FU in advanced renal cell carcinoma. Our experience parallels that of other groups, which have observed that the addition of chemotherapy agents to immunomodulatory therapy adds toxicity without adding treatment efficacy. Treatment with single-agent immunotherapy remains the standard of care for treatment of advanced renal cell cancer.

The treatment of advanced renal cell carcinoma remains a difficult problem. Further investigations in the cellular mechanisms that underlie the pathogenesis of renal cell carcinoma may provide important explanations for this tumor's poor response to traditional chemotherapeutics. This combination chemoimmunotherapy regimen resulted in substantial toxicity in our patient group without any objective antitumor responses. We conclude that this chemoimmunotherapy regimen lacks significant activity and carries a risk of severe toxicity in patients with advanced stages of renal cell carcinoma.

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