Brief report

Phase II study of continuous infusion recombinant gamma interferon in renal carcinoma

A Southwest Oncology Group Study

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Introduction

A previous phase I study of 24-hour intravenous infusion for five days using gamma interferon (r-GIFN) noted one partial response in renal cell carcinoma [1]. Dose-limiting toxicities were similar to those seen with other interferon preparations but at lower doses of r-GIFN where serum levels could not be detected. This phase II trial was designed to study the response and toxicity of continuous infusion r-GIFN.

Materials

Twenty-seven patients with metastatic renal cell carcinoma were entered on this Southwest Oncology Group (SWOG) study. Eligibility criteria included performance status 0–2, measurable disease, no prior chemotherapy, WBC ≥ 3500/µl, platelet count ≥ 100,000/µl, serum bilirubin ≤ 2.0 mg/dl, creatinine ≤ 1.5 mg/dl, and informed consent. Three patients were deemed ineligible because of protocol violations. The median age of the 24 remaining patients was 59 (36–76). Eighteen were male and 11 were performance status 2. Seven had undergone previous nephrectomy and one a renal artery embolization. Six had three or more metastatic disease sites.

Treatment consisted of r-GIFN supplied by the Schering Corp. given as a 24-hour infusion for five days at a dose of $0.25 \times 10^6$ IU/m²/day (0.1 mg/m²/day) in 1000 cc 5% dextrose in water. All patients were premedicated with acetaminophen. This regimen was repeated every four weeks or until disease progression. The infusion was stopped upon the occurrence of Grade 2 or worse central nervous system, pulmonary, gastrointestinal, renal, or hepatic toxicities or Grade 3 or worse fever, flu-like symptoms, nausea and vomiting, weight loss, hypotension, or myelosuppression. Objective tumor responses and toxicity were classified using SWOG criteria.

Results

Of 24 evaluable patients, 20 completed at least two cycles of therapy, range 1–7. No objective responses were noted, 95% confidence interval 0–14.3%. Ten patients had stable disease lasting 4–22 weeks, median 8.4 weeks. Median survival was 4.4 months. Twenty patients have died, three prior to a second cycle of interferon.

Toxicity was similar to that reported for alpha-interferon. Flu-like symptoms of fever, chills, and malaise were universal. Grade 3 or 4 toxicity included fever > 40°C in six patients, leukopenia (WBC < 2000/µl) in three, and weight loss > 10% in two. Other severe side effects occurring in one patient each included hypotension, nausea and vomiting, anemia (Hgb < 8.0 gm/dl), and elevated liver en-
### Table 1. Summary of r-GIFN trials in metastatic renal cell cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>r-GIFN Source</th>
<th>Schedule</th>
<th>No. Patients</th>
<th>CR</th>
<th>PR</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garnick et al.³</td>
<td>Biogen</td>
<td>.01-30 mg/m² Cl × 7d q 3wk, .01-30 mg/m² IV × 7d q 3wk</td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Rinehart et al.⁴</td>
<td>Biogen</td>
<td>.0001-0.75 mg/m² IV over 4² 2 ×/wk</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Quesada et al.⁵</td>
<td>Genentech</td>
<td>.01-0.05 mg/m² Cl qd, .25-1.0 mg/m² IM qd</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Koise et al.⁶</td>
<td>Shionogi</td>
<td>8-12 × 10⁶U/m² IM or IV qd × 28, 40 × 10⁶U/m² IV days 1-5, 15-19, 29 31, 33, 43, 45, 47</td>
<td>32²</td>
<td>0</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 mg/m² Cl × 5 d q 4 wk</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>Schering</td>
<td></td>
<td>171</td>
<td>2</td>
<td>12²</td>
<td>71</td>
</tr>
</tbody>
</table>

² includes 10% stage I-III patients
² overall CR + PR = 8.2%

zymes. Only one patient with persistent fevers required removal from study.

### Discussion

*In vitro* studies suggest that activation of immune effector cells is enhanced upon prolonged incubation in the presence of r-GIFN [2]. However, no responses were observed in this trial of 5-day continuous infusion at a daily r-GIFN dose of 0.1 mg/m². Using a similar schedule, Garnick *et al.* observed one response at 3 mg/m², a dose which produced unacceptable toxicity [3]. It remains unclear whether continuous low dose infusion of r-GIFN lacks direct anti-tumor activity or is unable to enhance immunologic parameters.

Response rates from 5 to 20% have been reported using different sources of r-GIFN, Table 1. The overall response rate for r-GIFN in renal cell carcinoma of 8.2% is less than 16.4% reported for alpha-interferon in a recent review [4]. We conclude that continuous infusion r-GIFN produces significant toxicity but no responses in metastatic renal cell cancer.

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### References