Daily Subcutaneous Ultra-Low-Dose Interleukin 2 with Daily Low-Dose Interferon-α in Patients with Advanced Renal Cell Carcinoma

Joseph I. Clark, Ellen R. Gaynor, Brenda Martone, Susan C. Budds, Rajini Manjunath, Robert C. Flanigan, W. Bedford Waters, and Jeffrey A. Sosman


ABSTRACT

A limited institution Phase II pilot study was performed using a very low-dose combination of daily s.c. interleukin (IL)-2 with IFN-α-2b in patients with advanced renal cancer in an attempt to duplicate or increase the response documented with higher dose schedules without the attendant toxicity profile. We selected a dose of IL-2 with documented immunological activity and combined it with clinically active low-dose IFN. Between August 1994 and September 1996, 19 patients with metastatic renal cell carcinoma, who had been judged incapable of tolerating high-dose i.v. IL-2, were treated with IL-2 (1 million units/m²/day) and IFN (1 million units/day), administered s.c. daily. All treatments were administered on an outpatient basis. Virtually all patients had bulky tumor burden with multiple sites of involvement, including five patients with bone metastases. No major objective responses were observed; however, one patient experienced a minor response lasting 13 months, with an associated improvement in performance status. Median survival was 6 months, and 1-year survival was 16%. Toxicity was generally mild and consisted almost entirely of constitutional symptoms. No serious grade 3 or 4 toxicity was observed, although two patients withdrew from treatment due to treatment-related fatigue. On therapy, mild eosinophilia but no lymphocytosis was noted; in fact, peripheral lymphocyte counts decreased, only to rebound after treatment was discontinued. No toxic deaths occurred. Despite the reasonable tolerability of this daily low-dose s.c. regimen, we conclude that this regimen is an ineffective treatment in metastatic renal cell carcinoma patients who are incapable of tolerating high-dose i.v. IL-2.

INTRODUCTION

Approximately 30,000 cases of RCC are diagnosed in the United States annually (1). Patients with metastatic RCC have a poor prognosis, with a median survival of <1 year and a 5-year mortality rate approaching 100% (2). High-dose bolus IL-2 is the only Food and Drug Administration-approved agent for the treatment of advanced RCC. This approval was based on data presented on 255 patients who were treated on seven clinical trials at 21 institutions (3). The overall objective response rate was reported as 14%: 12 patients (5%) achieved a complete response, and 24 patients (9%) achieved a partial response. The overall median duration of response was nearly 24 months; the median duration was 18.8 months for partial responders, and the median duration of response was not reached for complete responders. This therapy is limited due to its toxicity (4): with this therapy, a vascular leak syndrome is frequently seen, leading to hypotension requiring pressor support, oliguria, respiratory distress, cardiac arrhythmias, and mental status changes. Morbidity and cost may be substantial; therefore, this therapy is restricted to patients with excellent performance status and organ function.

In an attempt to maintain clinical efficacy yet avoid significant toxicity, a number of trials have evaluated the use of IL-2 administered by alternative schedules or doses (5-12). Continuous infusion or s.c. regimens have induced response rates of 15–25%, with a small number of these responses appearing durable (5). These single-agent approaches are tolerable but toxic, exhibiting a high incidence of constitutional symptoms such as fatigue, fever, anorexia, and decline in performance status. Yet the extreme toxicity of a vascular leak syndrome is rarely observed. Very low doses of IL-2, up to 1 million units/m² of body surface area, have been investigated (13, 14). At this low dose, serum concentrations of IL-2 appear to saturate only the high-affinity receptors present on the CD56 bright subset of NK cells and activated T cells (15). Such high-affinity receptors are absent from resting T cells and the majority of NK cells. The CD56 bright NK cells are preferentially expanded, inducing target cell cytotoxicity, without significant cytokine production in vitro. Expansion of CD56 bright NK cells in the peripheral blood occurs in patients with solid
tumors and hematological malignancies treated with this low-dose regimen by continuous infusion or with 1 million IU/m² daily by s.c. injection, without significant toxicity (13, 14, 16).

IFN-α has demonstrable single-agent activity in the treatment of metastatic RCC, with observed response rates of 15–20% (17–23). Clinical activity with an improved toxicity profile has been observed using very low doses of IFN (23). A 15% overall response rate and 12-month median survival was observed in 40 evaluable patients treated with IFN 1 million units s.c. daily (23). Therapy was well tolerated, and patients experienced fewer constitutional symptoms than has been observed with other higher-dose IFN regimens.

Although the response rates for IL-2 and IFN alone are generally <20%, synergy between the agents has been demonstrated in a variety of models (24–28). Uncertainty remains as to the mechanism of this synergy, but it may be mediated by IFN-induced up-regulation of major histocompatibility antigens, leading to enhanced recognition of tumor cells by IL-2-activated lymphocytes (28). A number of clinical trials reporting response rates of 15–35% have been performed using this combination in the treatment of advanced RCC to take advantage of this principle (29–33). Toxicity is manageable in the outpatient setting, but the degree of constitutional symptoms can be problematic.

In an effort to maintain clinical efficacy yet decrease systemic symptomatology, we conducted a limited institution pilot Phase II clinical trial incorporating a daily s.c. schedule of very low-dose IL-2 known to be immunologically active (14) in combination with low-dose IFN shown to have clinical activity in the treatment of patients with advanced/unresectable RCC (23). It was felt that such a low-dose daily regimen might offer a more rational, immunologically based approach that may retain or enhance the antitumor activity observed with other IL-2 plus IFN-α regimens, but with less toxicity.

**PATIENTS AND METHODS**

Inclusion criteria for this study were: histologically confirmed RCC that was advanced/unresectable or metastatic, including treated, asymptomatic brain metastases; age of ≥18 years; Southwest Oncology Group performance status of 0, 1, or 2; measurable or evaluable disease; life expectancy of at least 12 weeks; and ability to provide written informed consent. Patients may have received up to one prior regimen of each of the following: chemotherapy, immunotherapy (including other IFNs or ILs), or hormonal therapy for metastatic disease. Patients were excluded if they had received prior IFN or IL-2 for metastatic RCC or if they had received either IFN or IL-2 for adjuvant disease within 6 months prior to the start of the study. Eligibility criteria included: adequate organ function, defined as a granulocyte count of ≥1,500/mℓ, a platelet count of ≥100,000/mℓ, hemoglobin level of ≥8.0 g/dℓ, serum creatinine of <2.0 mg/dℓ, and creatinine clearance of >50 ml/min; aspartate aminotransferase/alanine aminotransferase levels of <4 times the upper limit of normal.

**Table 1** Overall patient characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Median age, yr (range)</th>
<th>PS,a</th>
<th>Sex, M:F</th>
<th>Median no. of disease sites (range)</th>
<th>No. of patients with prior nephrectomy</th>
<th>No. of patients with prior therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>64 (45–78)</td>
<td>0–1:2</td>
<td>14:5</td>
<td>3 (1–5)</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

*a PS, performance status.

**Table 2** Toxocities of low-dose IL-2/IFN

<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>No. of patients exhibiting toxicity of:</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/chills</td>
<td></td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sweats</td>
<td></td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>1</td>
<td></td>
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**Table 3** Lymphocyte counts

<table>
<thead>
<tr>
<th>Week of treatment</th>
<th>Mean lymphocyte count (cells/μl)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>1,141</td>
<td>1,374–1,908</td>
</tr>
<tr>
<td>1</td>
<td>1,195</td>
<td>870–1,520</td>
</tr>
<tr>
<td>2</td>
<td>1,285</td>
<td>894–1,676</td>
</tr>
<tr>
<td>3</td>
<td>1,310</td>
<td>958–1,662</td>
</tr>
<tr>
<td>4</td>
<td>1,321</td>
<td>1,016–1,626</td>
</tr>
<tr>
<td>5</td>
<td>1,268</td>
<td>827–1,709</td>
</tr>
<tr>
<td>6</td>
<td>1,137</td>
<td>796–1,478</td>
</tr>
<tr>
<td>7</td>
<td>925</td>
<td>530–1,320</td>
</tr>
<tr>
<td>8</td>
<td>979</td>
<td>522–1,436</td>
</tr>
<tr>
<td>9</td>
<td>979</td>
<td>99–1,859</td>
</tr>
<tr>
<td>10</td>
<td>841</td>
<td>62–1,620</td>
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<tr>
<td>11</td>
<td>839</td>
<td>37–1,641</td>
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<tr>
<td>Posttreatment</td>
<td>1,343</td>
<td>1,000–1,686</td>
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</table>

**Table 4** Eosinophil counts

<table>
<thead>
<tr>
<th>Week of treatment</th>
<th>Mean eosinophil count (cells/μl)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>111</td>
<td>47–175</td>
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<tr>
<td>1</td>
<td>926</td>
<td>227–1,625</td>
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<tr>
<td>2</td>
<td>962</td>
<td>585–1,339</td>
</tr>
<tr>
<td>3</td>
<td>776</td>
<td>360–1,192</td>
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<tr>
<td>4</td>
<td>914</td>
<td>523–1,305</td>
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<td>5</td>
<td>668</td>
<td>340–996</td>
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<tr>
<td>6</td>
<td>736</td>
<td>495–977</td>
</tr>
<tr>
<td>7</td>
<td>670</td>
<td>349–991</td>
</tr>
<tr>
<td>8</td>
<td>1,111</td>
<td>336–1,886</td>
</tr>
<tr>
<td>9</td>
<td>433</td>
<td>8–858</td>
</tr>
<tr>
<td>10</td>
<td>303</td>
<td>196–410</td>
</tr>
<tr>
<td>11</td>
<td>279</td>
<td>269–827</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>698</td>
<td>451–945</td>
</tr>
</tbody>
</table>

*a CI, confidence interval.
upper limit of normal; and bilirubin levels of <2.0 mg/dl.
Patients with symptomatic active pulmonary or cardiac disease
and those with a concurrent invasive malignancy were excluded.

The s.c. doses selected for the trial were 1 million units/
\( m^2/\text{day} \) IL-2 and 1 million units/day IFN. All treatment
was administered on an outpatient basis. Patients were advised
to have their daily treatment administered in the late afternoon or
early evening. Premedication 0.5 h prior to treatment with
acetaminophen at 650 mg p.o. was recommended, with doses
repeated at 4–6-h intervals as needed for fever or chills. Anti-
emetics and antidiarrheal medication were permitted as needed.
Neither corticosteroids nor anticoagulants were permitted dur-
ding study treatment. Patients were seen every 2 weeks while on
therapy. Partial responders and patients with stable disease
could continue treatment after their initial assessment at 12
weeks. Patients who demonstrated progressive disease or unac-
tetable toxicity during the study were withdrawn.

Response and Toxicity Assessment. Each patient un-
derwent a complete history and physical examination, assessment
of performance status, a chest radiograph, and routine
laboratory evaluation (complete blood cell count, differential,
platelets, and chemistry profile) before therapy began and at
completion, termination, or withdrawal from study. Tumor eval-
uation included computed tomographic scans of the head, chest,
abdomen, or pelvis and bone scan, as indicated. These evalua-
tions were performed once after 12 weeks of treatment, followed
by three times at 8-week intervals, and then at 12-week intervals
thereafter. Standard response criteria were used (34). Duration
of response was measured from the initial date of treatment to
the most recent evaluation or to documentation of progression.
Patient survival was calculated from the date of study entry.

RESULTS
From August 1994 to September 1996, 19 patients with
metastatic RCC who had been largely judged to be incapable of
tolerating high-dose i.v. IL-2 were entered into the study, after
informed consent was obtained. All patients were enrolled at the
Edward Hines, Jr., Veterans Affairs Hospital (3 patients) and at
the Loyola University Medical Center (16 patients). No patients
were declared ineligible. Individual patient characteristics are
listed in Table 1. The median age was 64 years (range, 45–78
years). There were 14 men and 5 women. Forty-seven % of
patients (9 of 19) had undergone a prior nephrectomy for cura-
tive intent at the time of their original diagnosis. The median
number of metastatic sites at onset of the therapy was three, and
five patients had documented bony metastases; however, virtual-
ly all patients had bulky tumor burden. No patients had re-
ceived prior systemic therapy for RCC. The median perform-
ance status at time of enrollment was 1.

![Average weekly circulating lymphocyte counts, depicted for patients treated with ultra-low-dose IFN and IL-2. A relative lymphopenia was observed during treatment, whereas a mild lymphocytosis occurred after discontinuation of therapy.](clincancerres.aacrjournals.org)
Toxicity. The toxicity of this daily s.c. outpatient regimen was mild (Table 2) and consisted almost entirely of systemic symptoms. No substantial grade 3 or 4 toxicity was observed, although two patients withdrew from therapy due to treatment related toxicity (fatigue). No significant hematological toxicity occurred. Virtually all patients experienced some degree of fever or chills and fatigue. Approximately one-quarter of those treated (five patients) experienced grade 3 fatigue, and three patients complained of grade 3 sweats. Other grade 3 toxicities were rare and consisted of pain, nausea, anorexia, hypotension, and hyperglycemia in one patient each. The remainder of the toxicities observed were grade 1 or 2. All toxicities resolved shortly after treatment was discontinued. No hospitalizations due to toxicity were required, and there were no treatment-related deaths.

Response. All patients were evaluable for response. One patient experienced a minor response lasting 13 months, with an associated improvement in overall performance status. This patient had undergone a nephrectomy ~14 years prior to her diagnosis of metastatic disease involving retroperitoneal and pelvic sites. She experienced grade 2 fatigue with her therapy that required a 50% dose reduction of the IL-2. Her fatigue subsequently resolved, and her symptoms of abdominal fullness and early satiety abated, improving her performance status to a level of 0. She received treatment for a total of 15 months. Her overall survival was 30 months.

The remaining eighteen patients experienced disease progression after a mean of 2.9 months of treatment. The median survival in all patients enrolled was 6 months, with a range of 1–30 months. Three patients achieved an overall survival of >1 year, their survivals lasting 18, 29, and 30 months. Thus, the 1-year survival was 16%. No patients went on to receive further systemic chemotherapy or immunotherapy, including high-dose IL-2. A few patients received palliative radiation therapy to symptomatic metastatic sites or the progestational agent megestrol acetate; however, no objective responses were observed. All patients eventually died of their disease.

Immune Analysis. Serial blood counts were drawn throughout the treatment course in each patient, although no immunophenotypic analyses of circulating mononuclear cells were performed. A nonstatistically significant trend in eosinophilia and lymphopenia was observed during therapy, followed by normalization of eosinophil counts and a mild rebound lymphocytosis once treatment was discontinued (Tables 3 and 4; Figs. 1 and 2). No unique correlation was observed between these counts and the patient with a minor response nor in the other patients whose survivals were >1 year.

DISCUSSION
IL-2 and IFN combinations in the treatment of advanced RCC have provided well-documented, clinically meaningful
responses (Table 5; Refs. 29, 31, and 35–39). Despite variations in dose, schedule, and patient selection, overall response rates and 95% confidence intervals are quite comparable among previous studies. Reported median survivals are also remarkably similar, ranging from 13 to 20.9 months, whether treatment administration was required on an inpatient (29) or outpatient (31, 35, 37, 38) basis. Thus, as yet, no clearly optimal dose and schedule of IL-2 combined with IFN have been defined for the treatment of RCC.

Toxicity of IL-2 and IFN combinations administered in the outpatient setting, although less severe and more manageable than high-dose inpatient schedules, remains problematic, with respect to effects on quality of life due to fatigue, anorexia, and decline in performance status. In an attempt to retain or enhance the antitumor activity observed with other IL-2/IFN regimens while reducing toxicity, we combined an immunologically active (14) very low-dose of s.c. IL-2 with a clinically active (23) low dose of daily s.c. IFN for the treatment of patients with advanced RCC. It was felt that such an approach might be more accessible to a greater majority of patients and, thus, have the potential to impact more favorably on the quality of life of a large number of patients suffering from this disease.

This daily s.c. ultra-low-dose combination of IL-2 and IFN was, as anticipated, quite well tolerated. Virtually all toxicities could be regarded as mild and consisted almost entirely of constitutional symptoms. Two patients did withdraw from treatment due to treatment-related fatigue; however, no severe grade 3 or 4 toxicity was observed. There was no significant hematological toxicity, and there were no treatment-related deaths. All toxicities resolved shortly after treatment was discontinued.

Despite the acceptable toxicity profile associated with this daily s.c. regimen, no major objective responses were observed in the 19 patients treated. One patient did experience a minor response lasting 13 months, with improvement in her baseline performance status, while receiving therapy. For this patient and one other who experienced stable disease for 13 months, an impressive survival was observed, lasting ~2.5 years from the time of study enrollment. However, for the remainder of the patients, disease progression occurred after a mean of 2.5 months of treatment. Median survival was 6 months for all patients enrolled, with a 1-year survival of only 16%. No correlation could be made between circulating lymphocyte or eosinophil counts and duration of survival. We, therefore, conclude that this regimen is ineffective treatment for patients with metastatic RCC who are incapable of tolerating high-dose i.v. IL-2.

When compared with other trials (see Table 5), the reason for such poor results using this ultra-low-dose schedule of combination immunotherapy may be twofold. Patient selection very likely was a key factor. That is, enrollment onto this trial was designed for patients who were largely felt to be incapable of tolerating high-dose i.v. IL-2 for various reasons, such as patient age or vital organ function. In a review of 610 patients with recurrent or metastatic RCC enrolled onto a number of

<table>
<thead>
<tr>
<th>Investigator (Ref.)</th>
<th>IL-2 dose</th>
<th>IFN-α dose</th>
<th>No. of patients</th>
<th>Overall response rate, % (95% CI)</th>
<th>Toxicity grade 3/4</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutcher et al. (35)</td>
<td>5 MU/m² s.c. q. 8 h × 3 then q.d. 5 days/week × 4 weeks</td>
<td>5 MU/m² tiw × 4 weeks</td>
<td>47</td>
<td>2/6</td>
<td>17</td>
<td>Fatigue, cl, CNS, constitutional symptoms, skin, decreased BP, edema, SOB</td>
</tr>
<tr>
<td>Négrier et al. (36)</td>
<td>Continuous 18 MU/m²/day i.v. days 1–5 and 12–15</td>
<td>6 MU t.i.w. days 1–17</td>
<td>140</td>
<td>26</td>
<td>18.6</td>
<td>NR</td>
</tr>
<tr>
<td>Vogelzang et al. (37)</td>
<td>9 MU s.c. day 1 and 4/week × 4 weeks</td>
<td>6 MU s.c. day 1 and 4/week × 4 weeks</td>
<td>42</td>
<td>2/3</td>
<td>12 (2–22)</td>
<td>Two hospitalizations; skin</td>
</tr>
<tr>
<td>Figlin et al. (31)</td>
<td>Continuous 6 MU/m²/day i.v. day 1–4/week × 4 weeks</td>
<td>6 MU s.c. day 1 and 4/week × 4 weeks</td>
<td>30</td>
<td>2/7</td>
<td>30 (16–45)</td>
<td>Fatigue, renal, infectious</td>
</tr>
<tr>
<td>Atkins et al. (29)</td>
<td>0.8 mg/m² i.v. q. 8 h days 1–5 and 15–19</td>
<td>3 MU/m² i.v. q 8 h day 1–5 and 15–19</td>
<td>28</td>
<td>0/3</td>
<td>11 (2–28)</td>
<td>Decreased WBC, cardiac</td>
</tr>
<tr>
<td>Lipton et al. (38)</td>
<td>Continuous 1–4 MU/m²/day i.v. 4–5 days/week × 4 weeks</td>
<td>3–12 MU/m²/day IM 2–5 days/week × 4 weeks</td>
<td>39</td>
<td>6/7</td>
<td>33 (20–49)</td>
<td>Fatigue, decreased PLT</td>
</tr>
<tr>
<td>Atzpodien et al. (39)</td>
<td>20 MU/m² s.c. t.i.w. week 1 and 4, 5 MU/m² t.i.w. weeks 2, 3, 5, 6</td>
<td>6 MU/m² s.c. q.w.k. weeks 1 and 4, t.i.w. weeks 2, 3, 5, 6</td>
<td>152</td>
<td>9/29</td>
<td>25 (19–32)</td>
<td>CNS, fever/chills, GI, SOB</td>
</tr>
<tr>
<td>Clark et al. (this study)</td>
<td>1 MU/m²/day s.c.</td>
<td>1 MU/day s.c.</td>
<td>19</td>
<td>0/0</td>
<td>0</td>
<td>Fatigue, sweats</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; CI, confidence interval; MU, million units; q., every; q.d., every day; t.i.w., three times per week; BP, blood pressure; PLT, platelet count; IM, intramuscular; q.w.k., weekly; GI, gastrointestinal; CNS, central nervous system; SOB, shortness of breath; NR, not reported.
studies conducted by the Eastern Cooperative Oncology Group, Elson et al. (40) identified five prognostic subgroups that are predictive of survival, based on five prognostic factors: performance status, time from diagnosis, number of metastatic sites, prior therapy, and weight loss. The vast majority of patients enrolled into the study reported here would fall into the second and third risk groups. Elson et al. (40) reported that patients with two and three of the identified risk factors had median survivals of 7.7 and 5.3 months, respectively (40), which are nearly identical to the median survival of 6 months reported here.

A second explanation for the lack of benefit with this regimen is that the biological activity induced by this combination may, in fact, be inadequate to produce clinical efficacy, i.e., perhaps a threshold of activity is required to obtain the full antitumor effect. Secondary cytokine release by activated NK cells, including tumor necrosis factor-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor, may be required leading to recruitment of monocytes, macrophages, and other antigen-presenting cells. Further release of proinflammatory cytokines would then ensue, allowing for enhanced cytotoxicity of the target tumor cells. Such a cascade would not be induced with the ultra-low-dose therapy applied here, i.e., in vitro and in vivo studies reveal preferential expansion of CD56 bright NK and activated T effector cells due to saturation of high-affinity IL-2R by low-dose IL-2 without significant cytokine production (13, 14).

The question arises as to whether this low-dose therapy provides any meaningful immune activation despite its lack of clinical benefit. Eosinophilia, to a mild degree, was observed in the majority of patients treated. This is a well-described phenomenon in patients treated with IL-2 based therapy of uncertain significance. Mild lymphopenia during treatment was also commonly observed as was a mild rebound lymphocytosis once treatment was discontinued in a majority of patients. IFN may have impaired the expansion of lymphocytes, thus potentially negating the immunostimulatory effect of ultra-low-dose IL-2 on high-affinity IL-2R. Qualitative evaluation of circulating mononuclear cells by flow cytometry was not performed, nor were measures of expression of soluble or membrane-bound high-affinity IL-2 receptors.

The optimal dose and schedule for the combination of IL-2 and IFN in the treatment of advanced RCC remain unclear. Attempts at better defining these parameters are currently ongoing. Phase III trials are required to fully assess the role of IFN in combination with IL-2, define the dose-response curve of IL-2/IFN combinations, and assess the durability of responses to such combinations.

REFERENCES


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