

# Current status of cytokine therapy in management of patients with metastatic renal cell carcinoma

Anil K. Kapoor, MD, FRCSC;\* Sébastien J. Hotte, MD, FRCPC†

## Abstract

Cytokine therapy with interferon- $\alpha$  and interleukin-2 has arguably been the standard treatment for patients with metastatic renal cell carcinoma for more than 20 years. In this paper, the current evidence for the use of cytokine therapy in this patient population is discussed, including the significant toxicity associated with these agents. A low overall response rate and a marginal survival advantage are observed with interferon- $\alpha$  and interleukin-2; however, these therapies have significant toxicity and impair quality of life. Unlike the current tyrosine-kinase inhibitors, complete tumour responses may be seen with interleukin-2, but again this therapy has significant morbidity and mortality. Newer anti-angiogenesis agents may be combined with current standard cytokine therapy for patients with metastatic renal cell carcinoma.

Before the modern era of anti-angiogenesis in advanced renal cell cancer (RCC) with tyrosine-kinase inhibition, cytokine therapy with interferon and interleukin was used as first-line therapy. RCC is reported to be highly resistant to chemotherapy; no single agent demonstrates significant activity for this disease.<sup>1</sup> Although vinblastine has minor activity as a single agent, there are no reports of prolonged survival.<sup>2</sup> Hormonal therapy with medroxyprogesterone produces infrequent responses (less than 10%), but again, no reports of prolonged survival exist.<sup>3</sup> With observations of rare spontaneous regression after nephrectomy, prolonged stable disease in certain patients and late relapses after nephrectomy, host immune mechanisms are thought to be implicated in regulating tumour growth and form the basis for combating this disease with immunotherapy.<sup>4</sup> As a result, more than 80 studies have examined the role of immunotherapy in metastatic RCC, dating back to the 1980s.<sup>5</sup>

## Interferons

Interferons, which are members of a group of regulatory cellular glycoproteins called cytokines, have antiviral activity and also modulate immune response and cell proliferation.<sup>6</sup> There are 3 subtypes of interferons:  $\alpha$ ,  $\beta$ , and  $\gamma$ . Interferon- $\alpha$  and interferon- $\beta$ , type I interferons, are encoded on chromosome 9.<sup>6</sup> Interferon- $\alpha$  upregulates the expression of HLA class I and tumour-associated antigens on tumour cells, theoretically making tumour cells more immunogenic.<sup>6</sup> Interferon- $\gamma$ , a type II interferon, is encoded on chromosome 12.<sup>6</sup> This interferon, called immune interferon, is produced by T cells.<sup>6</sup>

Studies examining the efficacy of immunotherapy have used a variety of end points such as response rate (RR), complete response (CR) or partial response (PR); rate of progression; and progression-free and median survival. However, these studies used different definitions of these end points and none was blinded.<sup>5</sup> Further, RR has been reported to be an unreliable surrogate of survival.<sup>5</sup>

A meta-analysis<sup>7</sup> of 1042 patients found that the overall proportion of responses (CR and PR) to interferon- $\alpha$  was 12%. CRs were quite rare. Favourable characteristics of responders included patients with prior nephrectomy and patients with lung metastases. In this particular patient population, the proportion of objective responses was as high as 44%.<sup>7</sup> The average time from the start of treatment to an objective response was about 3–4 months. Metastases of the central nervous system tended not to respond to interferon, and soft-tissue disease tended to respond more readily than bony metastases. Results of a review of more than 1500 patients<sup>8</sup> suggest that the disease RR is between 12% and 15% for patients receiving interferon- $\alpha$ . CRs occurred in 2%–5% patients, usually in those with pulmonary metastases. The recently published Cochrane collaboration review<sup>5</sup> estimated a gain of 3.8 months and a 1-year risk of mortality reduction by 44% for patients randomized to interferon- $\alpha$ 2a, compared with patients randomized to control arms. Toxicity with interferon- $\alpha$  includes fever, malaise, flu-like symptoms and night sweats, and is markedly less than that with interleukin-2 (IL-2).<sup>9</sup>

Interferon has also been evaluated with vinblastine and medroxyprogesterone for patients with metastatic RCC. In general, the results have been mixed for trials examining interferon and vinblastine, whereas medroxy-

progesterone has not been shown to augment the effect of interferon.<sup>10,11</sup>

Only 1 study has shown increased patient survival when vinblastine is combined with interferon. The randomized controlled trial of 160 patients done by Pyrhonen and others<sup>12</sup> compared a combination of interferon- $\alpha$ 2a and vinblastine with vinblastine alone, and showed that patients treated with interferon (18 million units 3 times/wk) and vinblastine (0.1 mg/kg q3weeks) had a RR of 16%, compared with 2.5% for vinblastine (0.1 mg/kg q3weeks) alone. Median survival was also significantly different between the 2 groups (15.8 mo v. 8.8 mo). Fossa and others<sup>13</sup> randomized 178 patients to receive interferon- $\alpha$ 2a or interferon- $\alpha$ 2a with vinblastine with the exact same dosages as those used in the study by Pyrhonen and others.<sup>12</sup> Like that study, Fossa and others<sup>13</sup> found vinblastine increased RR (from 11% to 24%), but unlike that study, they found no difference in survival rate between the 2 groups. Differences in the calculation of survival may explain the difference in conclusions: Pyrhonen and others<sup>12</sup> calculated survival in months, whereas Fossa and others<sup>13</sup> compared the percentage of surviving patients.

Kriegmair and others<sup>14</sup> found a higher RR for patients receiving interferon and vinblastine than that for patients receiving only medroxyprogesterone, but found no difference in survival. There were several important limitations of this study: patients who received medroxyprogesterone rather than interferon in the control arm, a lower dose of interferon (8 million units 3 times weekly) and the small sample size ( $n = 89$  patients). The study was likely too underpowered to be able to detect a difference in survival rates.

A key Medical Research Council study<sup>15</sup> compared interferon- $\alpha$  (10 million units, subcutaneously 3 times weekly for 12 weeks) with medroxyprogesterone (300 mg/d for 12 weeks). This study enrolled 335 patients with metastatic RCC and was stopped early because of differences in the 1-year survival rates. Patients treated with interferon- $\alpha$  had a 13.5% RR and those treated with medroxyprogesterone, 7%. The 1-year survival rate was 43% for the interferon- $\alpha$  arm and 31% for the medroxyprogesterone arm (median survival rate 8.5 mo v. 6.0 mo). Quality of life, which was assessed in this study at 4 weeks, 12 weeks and 6 months, was significantly worse in the interfer-

on group. Lack of appetite, fatigue, nausea, shivering, dry mouth and heartburn were reported. Most of these symptoms were not different at 12 weeks and no differences remained at month 6. This landmark study concluded that patients with metastatic RCC treated with interferon- $\alpha$  had significantly improved survival over those treated with medroxyprogesterone.

Across studies, the average dose range of interferon- $\alpha$  administered subcutaneously was between 5 million units and 20 million units per day, usually 3–5 times per week.<sup>8,9,12,15–17</sup> Higher doses were associated with significantly higher toxicity.<sup>18</sup> The average period of time to any objective response was 3–4 months.<sup>7,9,12,15–17</sup> Two studies (Pyrhonen and others<sup>12</sup> and Medical Research Council<sup>15</sup>) suggested a survival benefit with interferon- $\alpha$ ; however, response was low, and long-term survival was rare and not without significant toxicity.

In a randomized, double-blind, placebo-controlled phase 4 trial,<sup>19</sup> the Canadian Urologic Oncology Group studied interferon- $\gamma$  given to 180 patients with metastatic RCC. Interferon- $\gamma$  (60  $\mu$ g/m<sup>2</sup> body surface area subcutaneously, once every 7 days) was compared with a placebo. All patients required control of their primary tumour with either nephrectomy or angioinfarction. The placebo group had an RR of 6%, compared with 4% for patients receiving interferon- $\gamma$ . As a result of this trial, interferon- $\gamma$  is not used for the treatment of advanced RCC.

## Interleukin-2

Recombinant human IL-2, a T cell growth-factor protein, affects tumour growth by activating lymphoid cells in vivo, but does not affect tumour proliferation directly.<sup>20</sup> IL-2 affects the proliferation and maturation of effector cells, enhancing natural killer T cell function, generating lymphokine-activated killer (LAK) cells, and stimulating T cell and B cell growth, resulting in a reduction in tumour growth.

IL-2 can be administered by 3 routes: in a high-dose IL-2 bolus, by continuous intravenous infusion or by subcutaneous injection. The CRs observed in patients receiving IL-2 are usually in those patients receiving high-dose IL-2.<sup>18</sup> In addition, patients with a performance status of 1 or more, a primary tumour in place, or liver or bone metastases have been shown to be less likely to respond.<sup>21</sup>

An initial study<sup>22</sup> by the National Cancer Institute (NCI) used short intravenous infusions of high-dose IL-2 in combination with LAK autologous lymphocytes, and showed objective responses in 30% of patients. Subsequently, it was shown that LAK cells added no therapeutic benefit and could no longer be used in treatment.<sup>23</sup> The results of a later NCI randomized trial<sup>16</sup> ( $n = 200$  patients) comparing high-dose IL-2 (720 000 IU/kg every 8 h for 15 doses) with a lower-dose bolus (72 000 IU/kg every 8 h for 15 doses) showed a 19% RR in the high-dose IL-2 treatment arm, compared with 10% in the low-dose IL-2 treatment arm. No difference in median survival between the 2 groups was found.

In 1992, the Federal Drug Administration approved the use of single-agent IL-2, based on 7 phase 2 studies of 255 patients between 1986 and 1992.<sup>17</sup> The treatment schedule consisted of 600 000 IU/kg of IL-2, administered intravenously every 8 hours for 14 doses over 5 days, which was repeated after a 9-day rest period. CRs were observed for 4% patients and PRs for 8% patients,<sup>17</sup> with an overall RR of 15%. Median survival for the 255 patients was 16.3 months. The majority of responders were patients with soft-tissue disease (mainly lung and lymph-node disease). In this study, however, patients with a good performance status (Eastern Cooperative Oncology Group performance status [ECOG] 0 or 1) were selected, so caution must be used when these findings are extrapolated to all patients. Further, treatment-related toxicity was significant: 4% (9 patients) had a CR, and an equal proportion (4%, 11 patients) died because of the treatment. When this study was updated in 1997,<sup>24</sup> the authors reported a 15% RR (37 patients): 17 (7%) patients with a CR and 20 (8%) with a PR. The increased RR was partly due to the inclusion of patients who had surgical resection of their residual disease after their PR to high-dose IL-2.

Results of a review<sup>25</sup> of clinical results for more than 1700 patients suggest that objective responses (CR and PR) in patients receiving high-dose IL-2 are 15%–16%. The most important prognosticator for metastatic patients is performance status (ECOG 0 or 1).<sup>17</sup> In addition, nonnephrectomized patients or those with bone or liver metastases are less likely to respond to IL-2.<sup>17</sup>

Treatment-related morbidity and mortality has declined because of restricted patient selection. Patients with a good performance status are like-

ly to better tolerate treatment. Screening patients with exercise tests or thallium scans and pulmonary function tests has been used to exclude patients with cardiopulmonary disease.<sup>18</sup> However, as Negrier<sup>26</sup> points out, these results cannot necessarily be extended to all patients. Furthermore, Kammula and others<sup>27</sup> reported no treatment-related mortality in a review of 809 patients treated with high-dose IL-2, and another group<sup>28</sup> could find no difference in quality of life between patients given high-dose IL-2 and those given low-dose IL-2. Nonetheless, the toxicity associated with high-dose IL-2 must be considered in patients with a poor performance status.

The significant toxicity of IL-2 is related to endothelial injury that increases vascular permeability.<sup>29</sup> This increased vascular permeability leads to extravasation of intravascular fluid in the interstitial space, causing overall organ edema. The toxicity profile includes cardiovascular, pulmonary, renal, neurologic and metabolic effects, many of which can be severe and may be life-threatening.<sup>17</sup> The more common side effects of IL-2 include hypotension (96%); acute myocardial infarction (2%); arrhythmias (14%); respiratory (30%); renal toxicity with oliguria (81%); neurologic, including agitation and confusion (82%); nausea and vomiting (81%); and diarrhea (81%).<sup>23</sup> Hypotension often requires vasopressor support with dopamine or phenylephrine. A capillary leak in the lung often mimics an adult respiratory distress syndrome-like picture. Often intensive care monitoring is required when these patients receive high-dose IL-2.

Low-dose subcutaneous IL-2 has significantly less toxicity and may have comparable RR.<sup>23</sup> Buter and others<sup>30</sup> examined 46 patients treated with subcutaneous IL-2 in a phase 2 trial. IL-2 was administered at 18 million units daily for 5 days; the dose was then reduced to 9 million units every other day, alternating with 18 million units for 4 weeks. Two patients (4%) had a CR, and 7 patients (15%) had a PR, for an overall RR of 20%. Those (10 patients) without cytoreductive nephrectomy did not respond to low-dose IL-2. Toxicities were mild to moderate and included fever, chills, nausea, vomiting, diarrhea and mild hypotension.

Results of systematic reviews conducted by the Cochrane group<sup>5</sup> and by the Cancer Care Ontario Program in Evidence-based Care<sup>31</sup> demonstrated no survival advantage of regimens containing low-dose IL-2 over those not based on IL-2. In a phase

3 study of low-dose IL-2 conducted by the NCI,<sup>32</sup> patients were randomized to 1 of 2 IL-2 treatment arms, either high-dose (720 000 IU/kg) or low-dose (72 000 IU/kg). Of the 60 patients in the low-dose arm, 4 CRs and 5 PRs were observed (15% overall RR); of the 65 patients in the high-dose arm, 2 CRs and 11 PRs were observed (20% overall RR). No difference in overall survival and no difference in response duration were observed. Results of the study were updated in 1997<sup>33</sup> with a 52-month follow-up period: a 10% RR in the low-dose arm (5 CRs, 6 PRs) and a 19% RR in the high-dose arm (9 CRs, 13 PRs) were found. Although the overall RR was significantly higher in the high-dose arm, no difference in overall survival was observed.

The same group recently reported the results of their randomized study<sup>18</sup> of high-dose and low-dose IL-2. This 3-arm study compared high-dose (720 000 U/kg) intravenous IL-2, low-dose (72 000 U/kg) intravenous IL-2 and low-dose (125 000 U/kg) daily subcutaneous IL-2. The RR in the intravenous high-dose arm (21%) was higher than that in the intravenous low-dose IL-2 (13%) and subcutaneous IL-2 (10%) arms. No overall difference in survival was found.

The systematic review conducted by Hotte and others<sup>31</sup> identified 6 randomized studies<sup>34–38</sup> that compared regimens containing low-dose IL-2 and regimens devoid of IL-2. RRs were higher in patients receiving regimens containing IL-2, but mortality at 1 year was not different. The authors concluded that there was no difference in treatment efficacy between low-dose IL-2 regimens and those devoid of IL-2, and that toxicity in regimens containing IL-2 increased. This finding is in keeping with the results of a recent Cochrane collaboration review<sup>5</sup> that concluded no difference in RR or survival.

### Interferon and IL-2 combination regimens

Preclinical observations that interferon- $\alpha$  and IL-2 may have synergistic antitumour activity led to a number of clinical studies examining this premise. Results of a review<sup>39</sup> of more than 1400 patients receiving interferon- $\alpha$  and IL-2 indicated an overall RR of 20% for the combination, and found that 3%–5% of patients had CRs.

Atkins and others,<sup>39</sup> in their randomized phase 2 trial of high-dose IL-2 with and without interferon- $\alpha$ , found no difference in response in either

group. However, toxicity was higher with the addition of interferon- $\alpha$ .

Quan and others<sup>40</sup> examined the addition of famotidine to IL-2 for treatment of 15 patients with metastatic RCC. Famotidine may augment LAK activity against kidney cancer cells. IL-2 was given for 72 hours along with famotidine (20 mg, intravenously, twice per day, in 3-week cycles). One CR and 1 PR were seen. The overall RR was 47% (median duration of response 9 mo; median survival of all patients 20 mo). The authors of this small study suggested that famotidine in combination with IL-2 improves RRs for patients with metastatic RCC; however, no definitive conclusion is possible because of the lack of a control group.

A randomized 3-arm study by Negrier and the French Immunotherapy Intergroup<sup>9</sup> studied 425 patients treated with either continuous intravenous infusion of recombinant IL-2 (18 million units per square metre of body surface area [MIU/m<sup>2</sup>]) alone or human IL-2 (18 MIU/m<sup>2</sup> per day) and interferon- $\alpha$  (6 MIU 3 times weekly), or human interferon- $\alpha$  (18 MIU 3 times weekly) alone. The results at week 10 showed that the combination arm had a higher RR (18.6%) than the interferon- $\alpha$ -alone arm (7.5%) or the IL-2-alone arm (6.5%). The toxicity of the combination arm was significant; therapy-related mortality was high. Although the RR was higher in the combination arm, overall survival among the 3 arms was not different (combination arm, 12 mo; interferon- $\alpha$  arm, 13 mo; IL-2 arm, 17 mo).

This same French Immunotherapy Group recently reported on their PERCY Quattro randomized trial<sup>41</sup> for patients with metastatic RCC of intermediate prognosis. This trial compared medroxyprogesterone acetate (MPA arm), interferon (9 MIU 3 times/wk) (IFN arm), subcutaneous IL-2 (18 MIU 5 d/wk for 2 cycles of 4 weeks) (IL-2 arm), and combined subcutaneous IL-2 (18 MIU 5 d/wk for 2 cycles of 4 weeks) and interferon (6 MIU 3 times/wk) (IFN/IL-2 arm) for patients with an intermediate prognosis. A minimum of 114 patients were required for each arm; a total of 492 patients were enrolled. Comparison of the interferon and noninterferon arms showed no overall survival advantage (15.4 mo v. 15.1 mo). Comparison of the IL-2 and the non-IL-2 arms showed no survival advantage (15.7 mo v. 14.9 mo;  $p = 0.52$ ). No survival advantage was found among all arms (MPA,

14.9 mo; IFN, 15.2 mo; IL-2, 15.3 mo; IFN/IL-2, 16.8 mo). The RR at 6 months was 1.6% for the MPA arm, 8.7% for the IFN arm, 4.2% for the IL-2 arm and 7.1% for the IFN/IL-2 arm. Based on these data, the French Immunotherapy Intergroup concluded that they could no longer recommend the use of cytokines for the treatment of patients with an intermediate prognosis for metastatic RCC.

In a randomized phase 3 trial, McDermott and others<sup>21</sup> compared a combination of IL-2 (5 MIU/m<sup>2</sup>, subcutaneously every 8 hours for 3 doses on day 1, then daily 5 d/wk for 4 weeks) and interferon- $\alpha$  (5 MIU/m<sup>2</sup>, subcutaneously, 3 times per week for 4 weeks) every 6 weeks with high-dose IL-2 (600000 U/kg per dose, intravenously, every 8 hours on days 1 through 5 and days 15 through 19) every 12 weeks. Unlike other reports, patients were stratified within treatment, based on ECOG status (0 or 1), liver or bone metastases, and prior nephrectomy. The study recruited 192 patients. RR was 23% for the high-dose IL-2 group and 9.9% for the subcutaneous IL-2 and interferon group. Overall median survival was not significantly different, 17.5 months and 13 months, respectively ( $p = 0.24$ ). However, in patients without nephrectomy and with liver or bone metastases, high-dose IL-2 did result in a longer median survival rate (14.7% v. 8.0% and 12.4% and 8.2%, respectively). This study concluded that a combination of subcutaneous IL-2 and interferon was inferior to high-dose IL-2 therapy when all patients were compared.

To date, no sufficiently powered phase 3 study has demonstrated a survival benefit for combination therapy over a single agent alone for the treatment of patients with metastatic RCC.

### Cytokine and new agent combination regimens

Recent studies with tyrosine-kinase inhibitors and other new agents often use interferon- $\alpha$  for the comparative treatment arm, arguably the current standard of care. These studies are discussed elsewhere in this supplement. Studies comparing combination therapy with these new agents, including sunitinib, sorafenib and bevacizumab with interferon- $\alpha$  therapy, are ongoing. Recent results from a 3-arm randomized trial<sup>42</sup> comparing interferon- $\alpha$ , intravenous temsirolimus, and combination temsirolimus and interferon- $\alpha$  suggest no additional

benefit with interferon. Single-agent temsirolimus ( $n = 209$ ), compared with interferon- $\alpha$  ( $n = 207$ ), has been shown to significantly increase the overall survival (10.9 mo v. 7.3 mo;  $p = 0.0069$ ) of patients with metastatic RCC and poor risk factors. Overall survival by treatment arm was 7.3 months (interferon), 10.9 months (temsirolimus) and 8.4 months (temsirolimus + interferon). Median progression-free survival was 1.9 months, 3.7 months and 3.7 months, respectively. Objective response (CR + PR) was 7%, 9% and 11%, respectively. Compared with interferon, single-agent temsirolimus (25 mg, intravenously, weekly) used as a first-line therapy significantly increased the overall survival of poor-risk patients with advanced RCC and has an acceptable safety profile. Interferon offered no advantage in combination therapy, and the toxicity found in results for this arm was largely attributable to interferon- $\alpha$ .

### Conclusions

Metastatic RCC remains a disease highly resistant to conventional systemic therapy. Cytokine therapy has been the mainstay of treatment in this patient population for many years. However, only small numbers of patients (about 15%–20%) respond to cytokine therapy. CRs, although rare, are more often seen with high-dose IL-2 than with interferon- $\alpha$ , but high-dose IL-2 is associated with significant toxicity and should be offered with caution.

New treatments that specifically target angiogenesis have profoundly affected the way we treat advanced RCC and have rapidly become the standard of care. The role of cytokine therapy, especially interferon and non-high-dose IL-2, is likely to be relegated to the treatment patients who have progressed through these treatments and have exhausted their therapeutic options. High-dose IL-2 may occasionally be considered for curative attempts, but because of toxicity must be used with caution. Combination studies with anti-angiogenesis inhibitors are ongoing and may show more promise than existing cytokine therapies.

From the \*Department of Surgery (Urology), McMaster University, and the †Department of Oncology, Juravinski Cancer Centre, Hamilton, Ont.

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**Correspondence:** Dr. Anil Kapoor, McMaster Institute of Urology, St. Joseph's Health Care, 50 Charlton Ave. E., Hamilton ON L8N 4A6; kapoor4@mcmaster.ca