Med Oncol (2009) 26:S13–S17
DOI 10.1007/s12032-008-9152-1

ORIGINAL PAPER

The application of high-dose interleukin-2 for metastatic renal cell carcinoma

David F. McDermott

Received: 1 December 2008 / Accepted: 10 December 2008 / Published online: 16 January 2009

Abstract Renal cell carcinoma (RCC) evokes an immune response, which has occasionally resulted in spontaneous and dramatic remissions [1–3]. In an attempt to reproduce or accentuate this response, various immunotherapeutic strategies have been studied. The most consistent anti-tumor activity has been reported with interferon alfa (IFN-α) and interleukin 2 (IL-2). In recent years, randomized trials have suggested that high-dose intravenous bolus IL-2 is superior in terms of response rate and possibly response quality to regimens that involve either low-dose IL-2 and IFN-α, intermediate- or low-dose IL-2 alone, or low-dose IFN-α alone. As this list of effective therapies for RCC grows, improvements in patient selection will be necessary to ensure that the only therapy capable of producing durable remissions will remain available to the patients who should receive it [4–7].

Keywords Immunotherapy · Renal cancer · Interleukin-2 · Carbonic anhydrase IX

D. F. McDermott (✉)
Biologic Therapy Program, Beth Israel Deaconess Medical Center, 375 Longwood Avenue, MS-428, Boston, MA 02215, USA
e-mail: dmcdermo@bidmc.harvard.edu

D. F. McDermott
Harvard Medical School, Boston, MA, USA

D. F. McDermott
Clinical Research Sub-Committee, Dana-Farber/Harvard Cancer Center Renal Cancer Program, Boston, MA, USA

High-dose IL-2 therapy

In 1992, high-dose bolus IL-2 was approved by the FDA for the treatment of patients with metastatic renal cell cancer based on data presented on 255 patients entered onto 7 phase II clinical trials [8]. In these studies, 600,000–720,000 IU/kg of recombinant human IL-2 was administered by 15-min infusion every 8 h × 14 doses, thereby constituting a cycle of therapy. Patients received a course of therapy, consisting of 2 cycles separated by 5–9 days of rest (maximum of 28 doses), and courses were repeated every 8–12 weeks in stable or responding patients. Although 35% of patients received 720,000 IU/kg of IL-2 per dose and the remainder received 600,000 IU/kg per dose, the median cumulative amount of IL-2 administered was the same in both groups, since patients receiving 720,000 IU/kg per dose tolerated fewer IL-2 doses. Ninety-six percent of these patients had an ECOG performance status of 0 or 1, 85% had undergone a nephrectomy prior to starting IL-2 therapy, none had received prior immunotherapy, and the median time from diagnosis to treatment was 8.5 months.

Objective responses were seen in 37 of the 255 patients (RR 15%). There were 17 (7%) complete responses (CRs) and 20 (8%) partial responses (PRs). Fourteen of the responding patients (38%) began therapy with tumor burdens greater than 50 cm^2 on pretreatment scans, and 60% of PRs had greater than 90% regression of all measurable disease. The median duration of response was 54 months for all responders, 20 months for PRs, and has not yet been reached for CRs. The median survival was 16 months for all 255 patients.

Follow-up data on these patients has now been accumulated through June 2002 with a median follow-up of over 10 years [9, 10]. Although some late relapses are still

being observed, the response duration curve appears to have leveled off after the 30 month time point and 60% of CRs remain in remission. In addition, 4 PRs who underwent surgical resection of residual disease while still in response remain alive and disease-free at a minimum of 65+ months. Therefore, many CRs remaining free from progression for more than 30 months and those PRs resected to NED after a response to high-dose IL-2 are unlikely to progress and may be cured. IL-2 remains the only FDA-approved systemic therapy that can produce durable remissions of metastatic RCC that can last years following completion of therapy.

Randomized trials with IL-2 ± IFN

Given that high-dose bolus IL-2 was approved by the FDA for its ability to produce durable tumor responses, before accepting lower dose regimens as equivalent it was imperative to establish that the quality of the tumor responses with these lower dose regimens was not inferior. Four large-scale randomized trials have now been completed that provide clinicians with useful insights into the relative merits of these various regimens (Table 1).

The French Immunotherapy Group conducted a large-scale, phase 3 randomized trial that compared intermediate-dose IL-2 administered by continuous intravenous (IV) infusion plus subcutaneous IFN-α with either IL-2 or IFN-α administered alone [11]. Four hundred and twenty-five patients were enrolled. The three treatment groups were well balanced for age and sex, as well as known predictors of response and survival. The response rate and 1-year event-free survival were significantly greater for the combined IL-2 and IFN-α arm than for either of the single-agent arms, although there was no significant difference in overall survival among the three groups. Of note, responses were seen in only 6.5% and 7.5% of patients receiving IL-2 or IFN-α alone, respectively, with only 2.9% and 6.1% of these patients still responding at the week 25 evaluations. Although more anti-tumor activity was seen with the combination arm, this was largely due to the rather limited activity of the single-agent regimens. How an intermediate-dose combination of IL-2 and IFN-α would compare with high-dose IL-2 alone remained to be established.

The National Cancer Institute Surgery Branch investigators performed a randomized trial comparing standard high-dose IV bolus IL-2 and a low-dose IV bolus IL-2 regimen developed by Yang et al. [12]. After randomizing 117 patients, a third arm was added that involved subcutaneous IL-2 administered according to the regimen described by Sleijfer et al. [13]. Results were analyzed and reported according to groups that were concurrently randomized. Among the 306 patients concurrently assigned to either high- or low-dose IV IL-2, the response rate was significantly higher with high-dose therapy (21% vs 13%), with a trend toward more durable responses. Duration of response was superior in patients who received the high-dose IV IL-2 compared with those who received the low-dose IV IL-2. There were no differences in overall survival. Although toxic effects were also significantly greater in the high-dose group (particularly hypotension), there were no deaths attributable to IL-2 in either arm, and patient assessments of quality of life were found to be roughly equivalent. Among the patients concurrently assigned to either subcutaneous IL-2 or high-dose IV IL-2, a higher response rate was seen with high-dose IV IL-2 (21% vs 10%), but the difference

Table 1 Select randomized trials of cytokine therapy in metastatic RCC

Trial	Treatment regimens	*N*	Response rate (%)	Durable complete response (%)	Overall survival (months)	Overall survival difference
FIG[13]	CIV IL-2	138	6.5	1	12	NS
	LD SC IFN-α	147	7.5	2	13	
	CIV IL-2 + IFN-α	140	18.6	5	17	
	MPA	123	2.5	1	14.9	
FIG[17]	LD SC IFN-α	122	4.4	3	15.2	NS
	LD SC IL-2	125	4.1	0	15.3	
	SC IL-2 + IFN	122	10.9	0	16.8	
NCI SB[14]	HD IV IL-2	156	21	8	NR	NS
	LD IV IL-2	150	13	3	NR	
	HD IV IL-2	95	23	7	17.5	
CWG[16]	LD SC IL-2/IFN-α	91	10	NR	13	NS
	HD IV IL-2	95	23	NR	17.5	

HD high dose, *LD* low dose, *IV* intravenous, *SC* Subcutaneous, *CIV* continuous IV infusion, *NS* not statistically significant, *MPA* medroxyprogesterone acetate, *NCI SB* National Cancer Institute Surgery Branch, *CWG* Cytokine Working Group, *FIG* French Immunotherapy Group, *RR* response rate, *CR* complete response

was of borderline statistical significance. Once again there were no differences in overall survival.

In an effort to determine the value of outpatient subcutaneous IL-2 and IFN-α relative to high-dose IV IL-2, the Cytokine Working Group (CWG) performed a phase 3 trial in which patients were randomized to receive either outpatient IL-2 and IFN-α every 6 weeks or standard high-dose inpatient IL-2 every 12 weeks [14]. One hundred and ninety-three patients were enrolled, and 192 were evaluable for toxicity and tumor response.

The response rate for high-dose IL-2 was 23% (22/96) vs 10% (9/96) for IL-2 and IFN-α ($P = .018$). Eight patients achieved a complete response while taking high-dose IL-2 versus only 3 taking low-dose IL-2 and IFN-α. The median response durations were 24 months for high-dose IL-2 and 15 months for IL-2 and IFN-α ($P = .18$). Median overall survivals were 17.5 and 13 months ($P = .12$), favoring high-dose IL-2. Ten patients (nine major responders) who received high-dose IL-2 were progression free at 3 years versus 3 patients (2 major responders) who received IL-2 and IFN-α ($P = .08$). Of note, responses to high-dose IL-2 were seen with equal frequency across the stratification criteria, whereas low-dose IL-2 and IFN-α appeared to produce fewer responses in patients with liver and/or bone metastases and in those who had not undergone prior nephrectomy to remove the primary tumor. For patients with bone or liver metastases ($P = .001$) or primary in place ($P = .04$), survival was superior with high-dose IL-2 compared with IL-2 and IFN-α, whereas no significant survival differences between the two treatments were noted for patients who had undergone prior nephrectomy or who were without bone or liver metastases.

In a subsequent phase 3 trial, the French Immunotherapy Group studied the impact of low-dose cytokine therapy on survival in patients with intermediate likelihood of response to IL-2 and IFN-α as defined in prior studies with these cytokines [15]. Untreated patients with Karnofsky performance status of 80 or greater and more than one site of metastatic disease were randomized to receive medroxyprogesterone (control group), subcutaneous IFN-α, subcutaneous IL-2, or the combination of IFN-α and IL-2. Four hundred and ninety-two patients were randomized, and the treatment groups were well balanced for predictors of response and survival. Although significant toxicity was more common in the IL-2 and IFN-α arm, median overall survival did not differ between the arms. The investigators concluded that subcutaneous IFN-α and IL-2 should no longer be recommended in patients with metastatic renal cell carcinoma and intermediate prognosis.

Taken together, these studies suggest that high-dose IV bolus IL-2 is superior in terms of response rate and possibly response quality to regimens that involve either low-dose IL-2 and IFN-α, intermediate- or low-dose IL-2 alone, or low-dose IFN-α alone. Consequently, although low-dose cytokine therapy has a limited role in metastatic renal cell carcinoma, we must conclude that high-dose IV IL-2 should remain the preferred therapy for appropriately selected patients with access to such therapy. However, given the toxicity and limited efficacy of high-dose IV IL-2 therapy, additional efforts should be directed at better defining the patient population for whom this therapy is appropriate.

Clinical predictors of benefit from cytokine-based therapy

Many groups have attempted to determine reliable predictors of response and survival for patients with metastatic renal cell carcinoma who were receiving immunotherapy. Factors that have been variably associated with response to IL-2 include performance status [8], number of organs with metastases (one versus two or more) [16], absence of bone metastases [17], prior nephrectomy [18, 19], degree of treatment-related thrombocytopenia, absence of prior interferon therapy [20], thyroid dysfunction [21], lymphocyte count [22], rebound lymphocytosis [23], erythropoietin production [24], and post-treatment elevations of blood TNF-α and IL-1 levels.

Negrier et al. identified independent predictors of rapid disease progression, defined as progression within 10 weeks of initiation of therapy [25]. These included greater than one metastatic site, disease-free interval of less than 1 year, and presence of liver metastases or mediastinal nodes as well as type of immunotherapy used. Patients with liver metastases, more than one site of disease, and disease-free interval of less than 1 year had a lower response rate and a median survival of only 6 months, even while receiving combination IL-2 and IFN-α therapy. Figlin et al. identified prior nephrectomy and time from nephrectomy to relapse as important predictors of survival in patients receiving IL-2-based therapy [18]. In their series, patients who received systemic immunotherapy for metastatic disease more than 6 months after nephrectomy had the best median survival and had a 3-year survival rate of 46%. A recent multivariate analysis by the same group of investigators that was confined to patients who received IL-2 after nephrectomy revealed survival to be inversely associated with lymph node involvement, constitutional symptoms, sarcomatoid histology, metastases involving sites other than bone or lung or multiple sites, and a TSH level >2.0 mIU/l [19]. They proposed a scoring algorithm based on these features in which survival at 1-year was predicted to vary from 1 to 92%.

Recent data from the CWG phase III trial, mentioned above, suggested that disease site factors such as primary in place or hepatic or bone metastases may be more predictive of a poor response to low-dose IL-2 and IFN-α regimens

than to high-dose IL-2 [14]. Furthermore, this study suggested the greatest benefit from high-dose IL-2, relative to lower dose regimens might be seen in patients with primaries in place and/or liver and bone metastases. This data calls into question some of the prior studies and suggests that additional predictors of response and survival in patients receiving cytokine-based immunotherapy are necessary.

Current investigation in patient selection

The CWG has launched the high-dose IL-2 "Select" Trial to determine, in a prospective fashion, if the predictive model proposed by Atkins et al. (described in a separate article) can identify a group of patients who are significantly more likely to respond to high-dose IL-2-based therapy ("good" risk) than a historical, unselected patient population [26, 27]. New factors (including baseline immune function, immunohistochemical markers, and gene expression patterns) that might be associated with response to high-dose IL-2 therapy will also be explored in an attempt to more narrowly limit the application of IL-2 to those patients most likely to benefit [28, 29]. As the list of effective therapies for metastatic RCC grows, improvements in patient selection will be necessary to ensure that patients who might attain a durable remission with IL-2 will not miss this opportunity.

IL-2 therapy following VEGF pathway directed therapy

The emergence of molecularly targeted therapies has offered hope for improved clinical outcome for patients with RCC. VEGF pathway directed therapy has been recommended for frontline use with other treatments reserved for time of disease progression. However, a retrospective analysis suggests that the toxicity of IL-2 therapy may be higher in patients who have received prior VEGF-targeted therapy, particularly sunitinib, and anti-tumor activity may be diminished [30]. Twenty-three consecutive points who received salvage IL-2 therapy were analyzed. Fifteen patients had received prior tyrosine kinase inhibitors (TKI) (sorafenib or sunitinib), while 8 patients had received bevacizumab alone. Six of twenty-three patients did not receive week 2 of cycle 1 of treatment. All six of these patients had received prior TKI. The incidence of severe cardiac toxicities, including one sudden cardiac death, in patients receiving prior TKI was 40%, significantly higher than what is expected from historical experience. Only 1 of 23 patients proceeded to receive a second cycle of IL-2. No patients achieved a partial or complete response to therapy. This retrospective analysis highlights unexpected and severe cardiac toxicities in patients receiving IL-2 after VEGF-targeted TKI therapy. While the mechanism for the observed increased incidence of cardiovascular complications remains speculative, the assumption that IL-2 can be given safely following VEGF pathway targeted therapy may not be valid. Further examination of the safety of this sequential approach is necessary and more cautious patient selection appears warranted.

Conclusions

RCC has long been considered an immunologically influenced malignancy and thus served as a platform for the clinical testing of anti-cancer immunotherapy. The non-specific cytokines, IL-2 and IFNα, have undergone the most testing and produced only modest benefits for unselected patients. High-dose IL-2 remains the only approach to produce durable responses in patients with metastatic RCC and can thus be considered in appropriately selected patients. Additional molecular and pathologic selection opportunities exist for cytokines, but considerable validation work is needed before these selection features can be used clinically. Cytokine therapy optimally should be given in the context of a clinical trial investigating combination therapy and/or patient selection to maximize the benefit of this approach.

In recent years, the list of effective therapies (e.g., angiogenesis inhibition, signal transduction inhibition, and immunotherapy) for metastatic RCC has grown substantially. The advent of targeted therapy in RCC does not eliminate the potential utility of IL-2 in RCC, but rather requires a rational refinement of this therapy through patient selection that will hopefully increase the cure rate for patients with this disease.

Acknowledgments This work was supported in part by the DF/HCC Renal Cancer SPORE: P50 CA101942-01.

References

1. Gleave ME, Ehilali M, Fradet Y, et al. Canadian Urologic Oncology Group: interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. N Engl J Med. 1998;338:1265–71. doi:10.1056/NEJM199804303381804.
2. Oliver RT, Nethersell AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. Br J Urol. 1989;63:128–31. doi:10.1111/j.1464-410X.1989.tb05147.x.
3. Vogelzang NJ, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case with 5-year followup. J Urol. 1992;148:1247–8.
4. Escudier B, Eisen T, Stadler W, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34. doi:10.1056/NEJMoa060655.

5. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–24. doi:10.1056/NEJMoa065044.
6. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. N Engl J Med. 2007;356(22):2271–81. doi:10.1056/NEJMoa066838.
7. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind Phase III trial. Lancet. 2007; 370(9605):2103–11. doi:10.1016/S0140-6736(07)61904-7.
8. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol. 1995;13:688–96.
9. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant Interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am. 2000;6:S55–7.
10. Rosenberg SA, Yang JC, White DE, Steinberg SM, et al. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2 Identification of the antigens mediating response. Ann Surg. 1998;228:307–19. doi:10.1097/00000658-199809000-00004.
11. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma: Groupe Francais d'Immunotherapie. N Engl J Med. 1998;338:1272–8. doi:10.1056/NEJM199804303381805.
12. Yang JC, Sherry RM, Stienberg SM, et al. A three-arm randomized comparison of high and low dose intravenous and subcutaneous interleukin-2 in the treatment of metastatic renal cancer. J Clin Oncol. 2003;21:3127–32. doi:10.1200/JCO.2003.02.122.
13. Sleijfer DT, Janssen RA, Buter J, et al. Phase II study of subcutaneous interleukin-2 in unselected patients with advanced renal cell cancer on an outpatient basis. J Clin Oncol. 1992;10: 1119–23.
14. McDermott DF, Regan MM, Clark JI, et al. A randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol. 2005;23(1):133–41. doi:10.1200/JCO.2005.03.206.
15. Negrier S, Perol D, Ravaud C, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results from a randomized controlled trial. Cancer. 2007;110(11):2468–77. doi:10.1002/cncr.23056.
16. Besana C, Borri A, Bucci E, et al. Treatment of advanced renal cell cancer with sequential intravenous recombinant interleukin-2 and subcutaneous α-interferon. Eur J Cancer. 1994;9:1292–8. doi:10.1016/0959-8049(94)90176-7.
17. Rosenberg SA, Lotze MT, Yang JC, et al. Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. J Clin Oncol. 1989;7:1863–74.
18. Figlin R, Gitlitz B, Franklin J, et al. Interleukin-2-based immunotherapy for the treatment of metastatic renal cell carcinoma: an analysis of 203 consecutively treated patients. Cancer J Sci Am. 1997;3:S92–7.
19. Leibovich BC, Han KR, Bui MH, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer. 2003;98(12):2566–75. doi:10.1002/cncr.11851.
20. Royal RE, Steinberg SM, Krouse RS, et al. Correlates of response to IL-2 therapy in patients treated for metastatic renal cancer and melanoma. Cancer J Sci Am. 1996;2:91–8.
21. Atkins MB, Mier JW, Parkinson DR, et al. Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. N Engl J Med. 1988;318:1557–63.
22. Fumagalli LA, Vinke J, Hoff W, et al. Lymphocyte counts independently predict overall survival in advanced cancer patients: a biomarker for IL-2 immunotherapy. J. Immunother. 2003;26:394–402. doi:10.1097/00002371-200309000-00002.
23. West WH, Tauer KW, Yanelli JR, et al. Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. N Engl J Med. 1987;316:898–905.
24. Janik JE, Sznol M, Urba WJ, et al. Erythropoietin production. A potential marker for interleukin-2/interferon-responsive tumors. Cancer. 1993;72:2656–9. doi:10.1002/1097-0142(19931101)72:9<2656::AID-CNCR2820720922>3.0.CO;2-A.
25. Negrier S, et al. Treatment of patients with metastatic renal carcinoma with a combination of subcutaneous interleukin-2 and interferon alfa with or without fluorouracil. J Clin Oncol. 2000; 18:4009–15.
26. Bui MHT, Seligson D, Han K, et al. Carbonic anhydrase IX is an independent predictor of survival in advanced renal cell carcinoma: implications for prognosis and therapy. Clin Cancer Res. 2003;9:802–11.
27. Atkins M, Regan M, McDermott D, et al. Carbonic anhydrase IX expression predicts outcome of interleukin-2 therapy for renal cancer. Clin Cancer Res. 2005;11(10):3714–21. doi:10.1158/1078-0432.CCR-04-2019.
28. Pantuck AJ, Fang Z, Liu X, et al. Gene expression and tissue microarray analysis of interleukin-2 complete responders in patients with metastatic renal cell carcinoma. Proc Am Soc Clin Oncol. 2005;4:535.
29. Jaeger E, Waldman R, Roydasgupta T, et al. Array-based comparative genomic hybridization identifies chromosomal imbalances between interleukin-2 complete and non-responders. J Clin Oncol. 2008;26 (May 20 suppl; abstr 5043).
30. Schwarzberg T, Regan MM, Liu V, et al. Retrospective analysis of interleukin-2 therapy in patients with metastatic renal cell carcinoma who had received prior antiangiogenic therapy. J Clin Oncol. 2008 (May 20 suppl; abstr 5044).