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INTERLEUKIN-2 AND INTERFERON IN RENAL CELL CARCINOMA

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Renal cell cancer (RCC) represents an unusual solid tumor for which no treatment other than surgical therapy has been effective. This tumor demonstrates a remarkably heterogeneous behaviour and rare reports of spontaneous regressions suggest an unusual sensitivity to host immunologic control. In recent years the rapid development in molecular genetics, growth factors and cytokine – lymphocyte interactions have increased the interest and possibilities for immunotherapy of RCC. Interleukin-2 (IL-2) or Interferon alpha (IFNα) alone are only marginally active in RCC. Their different modes of action and their synergistic effects when used in experimental murine models prompted the investigation of combined IL-2/INFα therapy in advanced RCC. The advantage of a combination of IL-2 and IFNα treatment as compared to LAK cell treatment seems to be that IL-2 and IFNα can be given at lower dosages without compromising the results in an outpatient setting. This article reviews the use of IL-2 and IFNα in combination for treatment of RCC and discusses the current problems and future challenges in this field.

Key Words: **Renal cell cancer, Interferon, Interleukin-2, Prognostic factors.**

INTRODUCTION

1,220 cases of renal cell carcinoma were registered in Sweden in 1988, *i.e.* 3% of all cancer cases in Sweden. RCC affects males twice as often as females. The aetiological factors are not known. However, there seems to be an inherited genetic defect predisposing to renal cancer in studies of a few familiar occurrences.[1] Recent evidence indicates that deletions and translocation involving the short arm of chromosome 3 are important for the oncogenesis and tumor progression of RCC.[2] 85% of kidney cancers are adenocarcinomas arising from the proximal tubules which may be subdivided into clear cell and granular cell carcinoma.

Patients who have distant metastases from RCC have a poor prognosis, with a median survival of 10 months.[3] The clinical course of metastatic RCC is heterogeneous. Long-lasting stable periods as well as rapid tumor growth and even spontaneous tumor regression may occur. Approximately 25% of patients with RCC have established distant metastases and an additional 25% regional lymph node mestatases at the time of diagnosis.[3] Surgical treatments are generally ineffective in curing metastatic disease. In addition, at least 50% of patients initially diagnosed with local disease, develop metastatic disease. Consequently there is an urgent need for an effective treatment of this malignancy.

There are three possible forms of systemic treatment of renal cell carcinoma:

1) Chemotherapy.
2) Hormonal treatment.
3) Immunotherapy.

Responses to chemotherapy have proved to be extremely low. Vinblastin showed the highest activity in single agent treatment. The objective response rate rarely exceeded 16%. Attempts to improve these results by combination chemotherapy have been unsuccessful.[4]

Progesterons, androgens, or anti-estrogens, alone or in combination, induced less than 10% objective remissions in more than 700 treated patients (cumulative data from phase II/III trials).[4] Bono[5] found that in more recent trials hormonal therapy led to objective remissions (partial responses) in < 5%. Therefore, it must be concluded that hormonal therapy is also of no value in the treatment of metastasized RCC.

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IMMUNOTHERAPY

Interferons

Since the first report of IFNα (human leukocyte derived) by Quesada *et al.* in 1983[6] numerous phase II and phase III studies using IFNα derived from human leukocytes or recombinant interferon (rIFN) have been published. From these trials it can be concluded that neither the source of IFNα nor the route of administration significantly influenced its efficacy.[7–8]

Summarizing the results with rIFN, an overall remission rate of 14%, a median remission duration time of 2.5–6 months, and median survival times of 9–18.5 months were achieved in 465 patients.[9] In patients with metastases to the lungs only, and with a good performance status, response rates of 40% can be achieved with IFNα.[10] On the other hand, IFNα shows only little activity on metastases in bone, brain and liver.[10] In some studies, prior nephrectomy seemed to favourably influence the response rate, but this could not be confirmed by other authors. Few phase I/II trials of RCC using IFNβ or IFNγ have been published. No evidence of superior activity compared to studies using interferon-α was seen.[11–13]

In vitro, IFNα and IFNγ show synergistic activity,[14] partly explained by the different cells surface receptors for both compounds, giving the basis for combining them in clinical trials. Two randomized studies that compared IFNα and IFNγ alone with IFNα plus IFNγ failed to show a clinical relevant synergism of the combination in advanced RCC.[15–16]

INTERLEUKIN 2

IL-2 was originally termed T cell growth factor and was first described in 1976 by Morgan *et al.*.[16] In 1983 Rosenberg[17] at the National Cancer Institute (NCI) first applied this substance as anti-tumor drug in man, since *in vitro* studies and studies in animal models had shown a strong anti-tumor activity of IL-2.[18] Since that time, IL-2 has been widely tested in human malignancies alone or in combination therapy. The rates of objective remission (CR+PR) in single agent therapy of RCC rarely exceed 20% and are in the same range as in IFNα mono therapy.

The contribution of lymphokine activated killer (LAK) cells to the therapeutic efficacy has still not been clarified. There seems to be no increase in the total number of responding patients although it has been claimed that there may be a higher percentage of complete responses when rIL-2 is combined with LAK cells.[19]

COMBINATION THERAPY WITH IL-2 AND IFNα

To achieve an improved therapeutic index there has been some interest in combining interferon with IL-2. The rationale for the combined use of these agents was the following: The combination of IL-2 and IFNα *in vitro* and in animal experiments had greater antitumor effects than did either agent alone.[20]

IFNα has both immunomodulatory and antiproliferative activities and acts through another surface receptor than IL-2.[21]

IFNα may augment the immunogenicity of tumor cells by enhancing their expression of HLA class I antigens and tumor associated antigens making them more susceptible to IL-2 sensitized T-lymphocytes.[22]

The investigations at the NCI which demonstrated the same activity of a combination therapy of IL-2 and IFNα as for IL-2 and LAK cells in patients with renal cell cancer led to extensive investigation of this form of therapy (Table 1). Today there are many reports[23–25] on the use of rIL-2 and rIFNα in combination. These phase I trials used different administration schedules of rIL-2 (continuos infusion versus bolus) and different doses of each cytokine.

IL-2 in combination with IFNα also leads to response rates which are in the range of 20% in unselected patients (Table 1). Patient selection (good performance status and low tumor load) seems to be responsible for more favourable results as reported by some investigators. The side effects of IL-2 are dose dependent and highest after bolus injection. In the continuos infusion schedule used by West *et al.*,[26] IL-2 side effects were reduced, but still substantial. Lower dosages of IL-2 and IFNα as described by Atzpodien *et al.*[25] can reduce the side effects and simplify administration.

The advantage of a combination therapy of IL-2 and IFNα treatment as compared to LAK cell treatment seems to be that IL-2 and IFNα can be administered in an out-patient setting in lower dosages without compromising the results.[27–29]

CURRENT PROBLEMS AND FUTURE CHALLENGES WITH CYTOKINE THERAPY

All conventional cytotoxic drugs are tested at the maximum tolerated dose. When IL-2 was first investigated this was the approach used, despite the demonstration from IFNα that this was not the best way to get maximum benefit using cytokines.[30,31] The only trial to provide extensive dose-response escalation using IL-2 and IFNα showed a bell-shaped dose response with lower responses at high compared with intermediate doses.[32,33] In view of this it may be that the optimum dosing schedule has yet to be defined. This will require a means for determining the

Table 1. IL-2 and IFN-γ in the treatment of renal cell cancer.

Authors	Year	Dose × $10^6/m^2$ schedule		Patients evaluable	CR n	PR n	CR + %
		IL-2	IFM- .U				
Rosenberg *et al.*[46]	1989	1–4.5 U i.v. × 8 h. 5 days	3–6 × 8 h. 5 days	35	4	7	31
Talpaz *et al.*[47]	1989	1–3 IU × 4 days	2–10 (3 to 5 week intervals)	32	not available		22
Markowitz *et al.*[48]	1989	2–3 IU × 4 days	2–10 (3 to 4 week intervals)	14	–	3	21
Mittelman *et al.*[49]	1989	0.5–7 U × 4 days/week	6–12	19	–	4	21
Altzpodien *et al.*[25]	1990	9 IU 2 × daily × 2 days 1.8 IU × 2 × daily × 5 days weekly	5 3 × weekly for 6 weeks	14	2	3	36
Bartsch *et al.*[50]	1990	18 IU day 8–12	10 day 1–5	19	–	3	19
Figlin *et al.*[28]	1990	2 IU day 1-4 weekly (for 4 weeks. 6 week intervals)	6 day 1. 4 weekly	22	–	7	32
Lindemann *et al.*[29]	1990	3 IU day 1-4	6 day: 1, 4 (2 week intervals)	24	1	–	4
Lipton *et al.*[51]	1990	1–2 IU 5 days/week	3–12 day 1, 3, 5/week (3 to 5 week intervals)	12	3	3	50
Mittelman *et al.*[52]	1990	3U	5 (4 days/week)	7	1	2	42
Morant *et al.*[53]	1990	3 U	6 days 1, 3, 5, 8, 10, 12 (4 week intervals)	6	–	2	33
Pichert *et al.*[54]	1990	3 U x 4 days	6 (2 week intervals)	6	–	–	–
Ilson *et al.*[55]	1992	3 U x 4 days/week x 3 weeks	5 x 4 days/week x3 weeks	28	1	3	12
Total					206	12(6%)	37(18%)

optimal immunomodulatory dose which today is still missing.

A major issue for the clinician for the future will be to define the biological characteristics of responding patients, allowing one to decide either their eligibility or their exclusion from the therapeutic protocol after the first course of therapy, or even prior to therapy. This would also help to design more relevant protocols for nonresponding patients.

In vitro, it has been shown that IL-2-activated lymphocytes kill LAK-susceptible cells, in a non MHC-restricted manner, after contact between target and effector cells.[34] However, the exact mechanism of the *in vivo* antitumoral effect of IL-2 in humans remains unclear. Although cytolytic activity of LAK cells has been found in some reports to correlate with the *in vivo* antitumoral effect,[26,35] several recent studies failed to demonstrate any correlation between the lytic capacity of peripheral blood lymphocytes and the clinical response *in vivo*.[36,37] Moreover, observations that human LAK cells apparently do not move to sites of metastatic tumors suggests the possible involvement of soluble factors in the antitumoral effect of IL-2 *in vivo*.[37,38] Blay *et al.* found that the clinical response to IL-2 + LAK therapy in patients with metastatic renal

Table 2. Suggested tools for response prediction in renal cell cancer.

Parameter	Author
Rebound lymphocytosis	West 1987
Rebound lymphocytosis	Banerjee 1991
Thyroid dysfunction and anti-microsomal antibodies	Atkins 1990
Serum TNF concentrations	Blay 1990
Serum IL-2 concentration	Wersäll 1991

cell carcinoma is correlated to a higher TNF concentration in serum 48 h after the end of IL-2 infusion.[39]

West reported that patients responding to adoptive cellular therapy with IL-2 + LAK cells can be identified by a rebound lymphocytosis in response to IL-2. Banerjee *et al.* reported recently similar findings although several other authors failed to show this phenomenon.[36,37,40]

Atkins showed a significant correlation between development of thyroid dysfunction and response. Also, patients with antimicrosomal antibodies (AMA) against thyroid tissue before treatment responded in a higher degree than did patients without AMA. In our study we found higher serum IL-2 levels during therapy in responding RCC after treatment with low doses of cyclophosphamide, IL-2 and IFNα.[40] These suggested 'prediction factors' have been found retrospectively in small materials and remains to be verified.

IL-2 immunotherapy itself, in addition to the activation of antitumor immune reactions, has been proven to induce concomitantly immunosuppressive events such as a decreased delayed type hypersensitivity response.[41] The mechanisms responsible for these immunosuppressive events have still to be better characterised, but they would include an increased production of transforming growth factor-β (TGF-β), which inhibits the IL-2 induced antitumor immune response,[42] as well as soluble IL-2 receptors (SIL-2R),[43,44] which could reduce IL-2 availability by binding IL-2 and competing for it with IL-2 cell surface receptors.[45]

Finally, there is major heterogeneity in tumors of identical histologic types in different patients and even within one tumor in one patient. One of the most studied and critical variables is the defective expression of class I and class II histocompatibility antigens in tumors. This might explain why, for individual patients, partial responses are more frequent than complete responses.

Probably there are not only one but several immunological pathways leading to clinical response; their characterisation will require a parallel analysis of the mononuclear cell population in the blood and in the tumor, together with the characterisation of malignant cells. In the future this might also imply an adaptation of the therapy to each patient, in accordance with his own tumor characteristics.

REFERENCES

1. Holleb A I, Fink D J, Murphy G P: *American cancer society textbook of clinical oncology*. Atlanta, Am Cancer Soc, Inc. (1991).
2. Kovacs G, Frisch S: Clonal chromosome abnormalities in tumor cells from patients with sporadic renal cell carcinoma. *Cancer Res* **49,** 651 (1989).
3. Vugrin D: *Seminars in Nephrology* vol. 7, pp.152–162. (1987).
4. Harris D T: Hormonal therapy and chemotherapy of renal-cell carcinoma. *Semin Oncol* **10,** 422 (1983).
5. Bono A V: Steroid hormones and hormonal treatment in renal cell carcinoma, in DeKernion, Pavone-Macaluso: *Tumors of the kidney,* vol. 13, pp.205–227. Baltimore, Williams and Wilkins (1986).
6. Quesada J R, Swanson D A, Tindale A, *et al.*: Renal cell carcinoma: Antitumor effects of leucocyte interferon. *Cancer Res* **43**, 940 (1983).
7. Krown S E: Therapeutic options in renal-cell carcinoma. *Semin Oncol* **12,** 13 (1985).
8. Stahl M, Wilke J, Seeber S, Schmoll H-J: Cytokines and cytotoxic agents in renal cell carcinoma a review. *Semin Oncol* **19**(2), (suppl. 4), 70–79 (1992).
9. Quesada J R: Role of interferons in the therapy of metastatic renal cell carcinoma. *Urology* **34,** 80 (1989).
10. Garnick M B, Reich S D, Maxwell B, *et al.*: Phase I/II study of recombinant interferon gamma in advanced renal cell carcinoma. *J Urol* **139,** 251 (1988).
11. Quesada J R, Kurzrock R, Sherwin A, *et al.*: Phase II studies of recombinant human interferon gamma in metastatic renal cell carcinoma. *J Biol Response Mod* **6,** 20 (1987).
12. Rinehart J J, Young D, Laforge J, *et al.*: Phase I/II trial of interferon-beta-serine in patients with renal cell carcinoma: Immunological and biological effects. *Cancer Res* **47**, 2481 (1987).
13. Czarniecki C W, Fennie C W, Powers D B, *et al.*: Synergistic antiviral and antiproliferative activities of E coli derived human alpha, beta, and gamma interferons. *J Virol* **49**, 490 (1984).
14. De Mulder P H, Debruyne F M J, von Oosterom A, *et al.*: EORTC randomized phase II study of recombinant interferon alpha and recombinant interferon alpha and gamma in advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* **10**, 166 abstr. (1991).
15. Foon K, Doroshow J, Bonnem E, *et al.*: A prospective randomized trial of alpha 2B-interferon/gamma-interferon or the combination in advanced metastatic renal cell carcinoma. *J Biol Response Mod* **7**, 540 (1988).
16. Morgan D A, Ruscetti F W, Gallo R C: Selective *in vitro* growth of T-lymphocytes from normal bone marrows. *Science* **193,** 1007 (1976).
17. Rosenberg S A: The development of new immunotherapies for the treatment of cancer using interleukin-2. A review. *Ann Surg* **208,** 121 (1988).
18. Krigel R L, Padavic-Shaller R A, Rudolph A R, Konrad M, Bradley E C, Comis R L: Renal cell carcinoma: treatment

with recombinant interleukin-2 plus beta-interferon. *J Clin Oncol* **8**, 460 (1990).

19. Rosenberg S A: Clinical immunotherapy studies in the surgery branch of the US national cancer institute: brief review. *Cancer Treat Rev* **16,** 115 (1989).
20. Cameron R B, McIntosh J R, Rosenberg S A: Synergistic antitumor effects of combination immunotherapy with recombinant interleukin-2 and recombinant hybrid alpha-interferon in the treatment of established murine hepatic metastases. *Cancer Res* **48**, 5810 (1988).
21. Nanus D M, Pfeffer L N, Bander N H, *et al.*: Antiproliferative and antitumor effect of alpha-interferon in renal cell carcinoma: Correlation to the expression of a kidney associated differentiation glycoprotein. *Cancer Res* **50,** 4190 (1990).
22. Lindahl P, Leary P, Gresser I: Enhancement of the expression of histocompatibility antigens of mouse lymphoid cells by interferon *in vitro*. *Eur J Immunol* **4,** 779 (1974).
23. Figlin R A, Citron M, Whitehead R, *et al.*: Low dose continuous infusion recombinant human interleukin-2 and Roferon-A: An active outpatient regimen for metastatic renal cell carcinoma. *Proc ASCO* **9,** 142 (1990).
24. Hirsh M, Lipton A, Harvery H, *et al.*: Phase I study of interleukin-2 and interferon alfa-2a as outpatient therapy for patients with advanced malignancy. *J Clin Oncol* **8,** 1657 (1990) .
25. Atzpoiden J, Korfer A, Franks C R, *et al.*: Therapy with recombinant interleukin-2 and interferon-alpha-2b in advanced human malignancies. *Lancet* **335,** 1509 (1990).
26. West W H, Tauer K W, Yannelli J R, Marshall G D, Orr D W, Thurman G B, Oldham R K: Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. *New Engl J Med* **316,** 893 (1987).
27. Atzpoiden J, Kirchner H: Cancer, cytokines, and cytotoxic cells: Interleukin-2 in the immunotherapy of human neoplasms. *Klin Wschr* **68,** 1 (1990).
28. Figlin R, Citron M, Whitehead R, Dekernion J, Desner M, Smith A, Jones G, Levitt D: Low dose continuous infusion recombinant human interleukin-2 (RHIL-2) and roferon-a: an active outpatient regimen for metastatic renal cell carcinoma (RCCA). *Proc Am Soc Clin Oncol* **9,** 142 (1990).
29. Lindemann A, Monson J R T, Stahel R A, Calabresi F, Ludwig C, Osterwalder B, Decoster G, Mertelsmann R: Low intensity combination treatment with r-interleukin-2 (RH-IL-2) and r-interferon alfa-2a (RH-IFN-ALFA-2a) in renal cell carcinoma: a multicenter phase II trial. *Proc Am Soc Clin Oncol* **9,** 150 (1990).
30. Rohatiner A Z, Prior P F, Burton AC, *et al.*: Central nervous system toxicity of interferon. *Br J Cancer* **47,** 417 (1979).
31. Balkwill F R: *Understanding and exploiting the cytokine network: Cytokines in Cancer Therapy*, pp. 207–235. Oxford, Oxford University Press (1989).
32. Rosenberg S A, Lotze M T, Yang J C, *et al.*: Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. *J Clin Oncol* **12,** 1863 (1989).
33. Oliver R T D: New views on rejection mechanisms and their relevance to interleukin-2 as a treatment for renal cell cancer. *Eur J Cancer* **27**(9), 1168–1172 (1991).
34. Grimm E A, Muzumder A, Zhang M Z, Rosenberg S A: Lymphokine activated killer cells phenomenon: lysis of natural killer-resistant fresh solid tumor cells by interleukin 2 activated autologous human peripheral blood lymphocytes. *J Exp Med* **155,** 1823 (1982).
35. Mule J J, Yang J, Shu S, Rosenberg S A: The antitumor efficacy of lymphokine-activated killer cells and recombinant interleukin 2 *in vivo*: direct correlation between reduction of established metastases and cytolytic activity of lymphokine-activated killer cells. *J Immunol* **136,** 3899 (1986).
36. Favrot M C, Combaret V, Negrier S, Philip I, Thiesse P, Freydel C, Bijmann J T, Franks C R, Mercatello A, Philip T: Functional and immunophenotypic modifications induced by IL2 did not predict response to therapy in patients with renal cell carcinoma. *J Biol Response Modif,* in press (1990).
37. Kradin R L, Kurnick J T, Lazarus D S, Preffer F I, Dubinett S M, Pinto C E, Gifford J, Davidson E, Grave B, Callaham R J, Strauss H W: Tumor infiltrating lymphocytes and IL2 in the treatment of advanced cancer. *Lancet* **1,** 577 (1989).
38. Lotze M T, Line B R, Mathiesen D J: The *in vivo* distribution of autologous human and murine lymphoid cells grown in T cell growth factor: implication for the adoptive immunotherapy of tumors. *J Immunol* **125,** 1487 (1990).
39. Blay J-Y, Favrot M C, Negrier S, Combaret V, Chouaib S, Mercatello A, Kaemmerlen P, Franks C R, Philip T: Correlation between clinical response to interleukin 2 therapy and sustained production of tumor necrosis factor. *Cancer Res* **50,** 2371 (1990).
40. Wersäll J P, Masucci G, Hjelm A-L, Ragnhammar P, Fagerberg J, Frödin J-E, Merk K, Lindemalm C, Eriksson K, Landin B, Mellstedt H: Low dose cyclophosphamide, alpha-interferon and continuous infusion of interleukin-2 in advanced renal cell carcinoma. *Biother* (submitted for publication).
41. Wiebke E A, Rosenberg S A, Lotze M T: Acute immunologic effects in interleukin-2 therapy in cancer patients: decreased delayed type hypersensitivity response and decreased proliferative response to soluble antigens. *J Clin Oncol* **6,** 1440 (1988).
42. Kasid A, Bell G I, Director E P: Effects of transforming growth factor-β on human lymphokine-activated killer cell precursors: autocrine inhibition of cellular proliferation and differentiation to immune killer cells. *J Immunol* **141,** 690 (1988).
43. Lotze M T, Custer M C, Sharrow S O, Rubin L A, Nelson D L, Rosenberg S A: *In vivo* administration of purified interleukin-2 to patients with cancer: development of interleukin-2 receptors following interleukin-2 administration. *Cancer Res* **47**, 2188 (1987).
44. Urba W J, Steis R G, Longo D L, *et al.*: Immunomodulatory properties and toxicity of interleukin 2 in patients with cancer. *Cancer Res* **50,** 185 (1990).
45. Rubin L A, Jay G, Nelson D L: The released interleukin-2 receptor binds interleukin-2 efficiently. *J Immunol* **137,** 3841 (1986).
46. Rosenberg S A, Lotze M T, Yang J C, Linehan W M, Seipp C, Calabro S, Karp S E, Sherry R M, Steinberg S, White D E: Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. *J Clin Oncol* **7,** 1863 (1989).
47. Talpaz M, Lee K, Markowitz A, Kavanaugh M, Gutterman J U: *Interferon alfa-2a and interleukin-2 in renal cell*

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