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REVIEW

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Use of interleukin-2 in advanced renal carcinoma: meta-analysis and review of the literature

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Abstract *Objective*: Interleukin-2 (IL-2) is a glycoprotein that influences the immunoendocrine network by several actions. This cytokine is commonly used in the patients with renal carcinoma, both as neo-adjuvant treatment prior to surgery and as adjuvant therapy. The aims of our study were to evaluate the IL-2 efficacy on postoperative survival rate in patients with metastatic renal carcinoma, to compare the efficacy of treatment with IL-2 alone with the results achieved by conventional systemic chemotherapy or association protocols IL-2-based and to examine the toxic effects of the IL-2-based therapeutic regimens in renal cell carcinoma (RCC).
Design: We enrolled 7 randomised trials concerning the IL-2-based treatments of RCC and performed meta-analytic processing by the Mantel-Haenszel-Peto method in order to achieve odds ratios and 95% confidence intervals of the examined treatments. We also considered 11 non-randomised trials, evaluating them in terms of survival rate through the endpoints available. In all trials taken into account, we finally examined the toxic effects as WHO grade, specifying study by study the main site involved.
Results and conclusions: Complete or partial response rates have been obtained in 6% to 30% of treated patients in all the trials considered. Our study revealed the need for careful screening as well as a continuous adjustment of doses when an immunotherapeutic protocol is employed in order to treat a metastatic renal carcinoma. Treatment with IL-2 alone achieves better results than systemic chemotherapy, even if the two types of treatment showed an almost overlapping medium- to long-term mortality rate. IL-2 plus lymphokine-activated killer cells accomplish only a partial response. The protocol with IL-2 plus IFN alpha displayed an interesting efficacy associated with a low toxicity even if the cumulative toxic effect of the two drugs should be carefully monitored. To date, the association of tumour-infiltrating lymphocytes, IL-2 and IFN alpha provided the best results in terms of survival and toxicity.

Keywords IL-2 treatment · IFN alpha · Renal carcinoma

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Introduction

Interleukin-2 (IL-2), a glycoprotein discovered in 1976, is mainly produced by T helper (CD4+) lymphocytes after stimulation with various substances of different mitogenic and antigenic nature (viral particles, heterologous cells, etc.) [1]. This cytokine exerts numerous effects on the immunoendocrine network. These effects include the stimulation of alpha interferon (IFN) production by macrophages and the differentiation of lymphokine-activated killer (LAK) cells. The latter is one of the key factors in cell-mediated immunologic response to various antigens [2].

The early studies on IL-2, alone or associated with other drugs, revealed its capacity to induce, enhance and hold a strong cytotoxic activity against various histotypes of tumoral cells. These studies led to the setting up of immunotherapeutic and immunochemotherapeutic experimental protocols [3, 4].

The aims of our study were: (1) to assess the effectiveness of IL-2 treatment on postoperative survival rate as well as on pathological response in patients with metastatic renal carcinoma, (2) to compare the results of the treatment with IL-2 alone with those achieved using conventional systemic chemotherapy associated or not to IL-2 and (3) to evaluate the most frequent toxic effects of the various IL-2-based treatments.

Materials and methods

We selected 42 studies concerning the IL-2-based treatments of renal carcinoma. In order to find the papers suitable to our aim we used a "Medline" data bank and performed specific research in the Libraries of the Departments of Oncology of our City.

Inclusion and exclusion criteria

We took into account only complete studies concerning IL-2 treatment of advanced renal carcinoma containing one or more treatment arms, trials with a follow-up period of almost 30 months, abstracts containing the fundamental data useful for meta-analysis and trials with data on toxic effects only. On the other hand we ruled out from our study clinical trials characterised by a noteworthy heterogeneity with reference to enrolled patients' age, clinical features at start, tumour staging, presence of co-morbidity, studies containing radiotherapy protocols and studies based only on preliminary conclusions or without a follow-up period longer than 30 months. We know that heterogeneity of the parameters previously cited is part of the clinical reality, but these differences could significantly bias the data obtained. Each study was examined independently, in order to avoid the Authors influencing one another in the final choice. Furthermore, our selection did not take into account the Authors' judgement about effectiveness of various treatments. After these processes, we selected 18 studies only, of which 7 [5, 6, 7, 8, 9, 10, 11] have been found suitable to be meta-analysed. Five studies compared the efficacy of IL-2-based protocols versus systemic not specified chemotherapy (IL-2 versus systemic chemotherapy), combined treatment with IL-2 plus IFN alpha (IL-2 alone versus IL-2 plus IFN alpha), IL-2 plus LAK cells (IL-2 alone versus IL-2 at same doses plus LAK cells) and IFN gamma. The remaining two studies focused on the effectiveness of the cytokine by a more complex design. Figlin et al. [10] used four different treatments in their study series [IL-2 alone, IL-2 plus IFN alpha, IL-2 plus IFN alpha plus tumour-infiltrating lymphocytes (TIL) and IL-2 plus IFN alpha plus 5-fluorouracil (5FU)], while Lopez Hanninen et al. [11] used three (IL-2 alone, IL-2 plus IFN alpha and IL-2 plus IFN alpha plus 5FU).

Analyzed data

We extracted the following data: global survival, expressed in months from the start of the treatment and, where possible, evaluated at various end-points, and drug and dose-related side effects observed during the treatment.

Statistical analysis

We applied a "survival meta-analysis" model to the extrapolated data, employing the Mantel-Haenszel-Peto method [12] in order to evaluate the survival odds ratios and 95% confidence intervals of the various treatments assessed.

Results

Survival

Survival curves shown in Fig. 1 highlight the lower survival rate achieved in patients treated with systemic chemotherapy compared to those treated with IL-2 alone, IL-2 plus IFN alpha, IL-2 plus LAK cells, IL-2 plus TIL and IL-2 plus IFN alpha plus 5FU (Table 1). The difference between the five protocols assessed has been noteworthy after the first 6 and 12 months of treatment. Survival rates reported during systemic chemotherapy after 6 and 12 months of treatment were 60% and 30% of patients, respectively. The survival

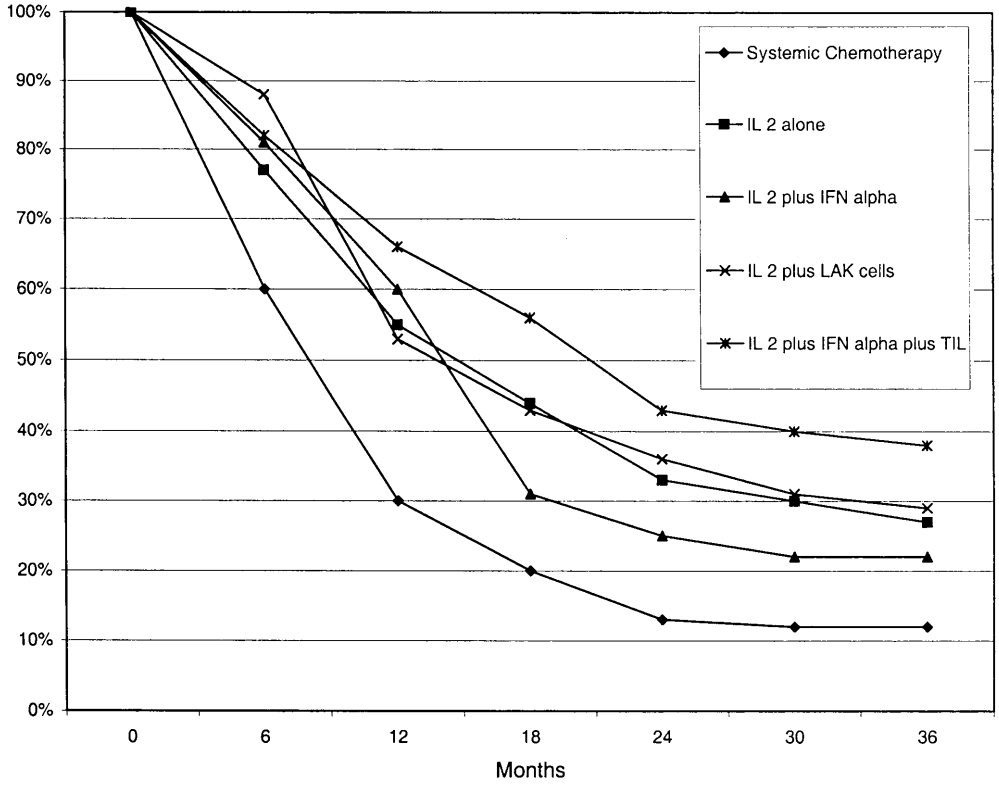

Fig. 1 Survival curves: a comparison between different therapeutic protocols of meta-analysed studies. *IL-2* Interleukin-2, *IFN* interferon, *LAK* lymphokine-activated killer cells, *TIL* tumour-infiltrating lymphocytes

Table 1 Data from meta-analysed studies. (*IL-2* Interleukin-2, *IFN* interferon, *TIL* tumour-infiltrating lymphocytes, *5FU* 5-fluorouracyl, *LAK* lymphokine-activated killer cells, *O.P.* overall patients, *C.A.* control arm, *M.S.* median survival, *O.R.* odds ratio, *CR* complete response, *PR* partial response, *PD* progression of disease, *SD* sustained disease)

Author	Drugs employed	Doses (drug)	O.P.	Treatment arm (*n*)	C.A.	Duration of treatment	Response		M.S. (months)
Lummen et al. [9]	IFN-gamma vs IL-2 and alpha 2B IFN	200 mg s.c. (IFNg); 4.8 MIU s.c. (IL-2); 6 MIU s.c. (IFN-a2b)	60	30	30	6 weeks	Group I: Group II:	SD 37% PD 63% CR 10% PR 13% PD 77%	13
Colavita et al. [8]	rIL-2 vs rIL-2 + IFN-a2a	4.5 MIU s.c. (rIL-2); 3 MIU s.c. (IFN-a2a)	94	47	47	6 weeks	Group I: Group II:	CR 10.5% PR 13.2% SD 23.6% CR 11% PR 3.7% SD 26%	30
Figlin et al. [10]	1. IL-2 vs IL-2 + IFN alpha 2. IL-2 + IFN alpha vs TIL + IL-2 + IFN alpha 3. IL-2 + IFN alpha + 5FU vs IL-2 + IFN alpha + TIL	Multiple dosages	203	1. 64 vs 52 2. 52 vs 56 3. 31 vs 56	/	Multiple duration of treatment	CR 6% PR 18%	SD 20% PD 56%	18
Lopez Hanninen et al. [11]	1. rIL-2 vs rIL-2 + IFN alpha 2. rIL-2 + IFN alpha2a vs rIL-2 + IFN alpha2a + 5FU	1. Up to 9 MIU/m^2 vs 20 MIU/m^2 + 6 MIU/m^2 2. Up to 9 MIU/m^2 vs 20 MIU/m^2 + 6 MIU/m^2 + 750 mg/m^2	215	1) 16 vs 79 2) 79 vs 120	/	6–8 weeks	CR 9%	PR 24%	20.2
Jones et al. [6]	IL-2 vs chemotherapy (not specified)	18 MIU/m^2 i.v.	717	327	390	2–3 weeks	Group I: Group II:	CR 1% PR 4% PR 2% CR 0.1%	8
Atkins et al. [5]	IL-2 alone vs IL-2 + IFN alpha2b	1. 600,000 UI/kg (IL-2 alone) i.v. 2. 0.8 mg/m^2 + 3 MIU/m^2 i.v. (IL-2 + IFN alpha2b)	99	71	28	3 weeks	Group I: Group II:	CR 4% PR 8% PR 3%	15.5
Murray Law et al. [7]	IL-2 alone vs IL-2 + LAK	3 MIU/m^2 i.v.. (IL-2)	71	36	35	4 weeks	Group I: Group II:	CR 3% PR 2% SD 53% PD 33% CR 3% PR 6% SD 56% PD 31%	13

data about the treatment with IL-2 plus 5FU plus IFN alpha are not available throughout the examined endpoints, and so they are not reported in Fig. 1 [11].

Effectiveness of various IL-2-based protocols

Application of the Mantel-Haenszel-Peto method confirmed the better response obtained with IL-2 alone treatment when compared to those achieved by systemic chemotherapy, even if this advantage disappeared at the 18-month endpoint, where the death trend was the same in the two arms (Fig. 1).

Throughout all considered endpoints, systemic chemotherapy using 5-fluorouracil showed a worse outcome than other treatments (IL-2 plus IFN alpha and IL-2 plus LAK cells). Table 2 shows the odds ratios obtained from another study [7] where the IL-2 doses were 18,000,000 IU/m^2 per day versus not specified systemic chemotherapy. Comparison between the IL-2 alone, IL-2 plus IFN alpha and IL-2 plus IFN alpha plus TIL treatments showed that the latter achieved the best results throughout all endpoints considered and this pharmacological association provided the best survival at the 36-month endpoint with respect to all treatments assessed (Fig. 1). In the group treated with association, those showing complete response (CR) were 11%, partial response (PR) were 3.7% and the stationary disease (SD) was 26%. In the other group CR, PR and SD were 10.5%, 13% and 23.6%, respectively (Table 1). At the end of the study, 50% of patients treated with association were living versus 40% in the other group. Median survival was 30 months with an odds ratio in favour of IL-2 alone treatment. Comparison between IL-2 alone arm and IL-2 plus LAK cells arm showed that association protocol achieved a better survival at the 6, 18 and 24 month endpoints. Increased mortality rate was observed in IL-2 plus LAK cells arm at the 12 and 36 month endpoints, with respect to IL-2 alone arm. We reported odds ratios in the Murray Law et al.'s [7] study. The IL-2 plus LAK cells association achieved better results in the short and middle term (Fig. 1), even if the IL-2 plus IFN alpha arm showed a most regular trend of mortality rates and better survival rates at the final endpoint considered. Comparison between the IFN alpha plus IL-2 efficacy and IFN gamma was the subject of a pilot study of Lummen et al. [9]. Even if a significant difference was not present in 60 patients, IL-2 provided the better results, as 7 remissions and 23 progressions in association-treated group versus 11 stationary disease and 19 progressions in the other group were found. After a median follow-up of 13 months, 5 patients were living in the association-treated group and 3 in the other. On the other hand, the latter showed a single survival for a patient better than that present in the first group. Survival was studied by Lopez Hanninen et al. [11] along a 48-month follow-up period and calculated on the basis of the death risk at the time of enrolment (on the basis of the clinical conditions at the start evaluated by ECOG or Karnofsky scores). Median survival was 39 months. In the group at intermediate death risk treated with 5FU, 65% of patients were living at the 2-year endpoint, being 27% and 0% in the patients treated with IFN and IL-2 alone, respectively. This trend was reflected in the patients at low death risk with a better survival percentage (78%, 52% and 18.8%, respectively). The survival odds ratio, in this trial, resulted in favour of 5FU plus IL-2 plus IFN alpha association. Figlin et al. [10] enlarged the previous cited experience and added a fourth protocol based on the use of IL-2, IFN alpha and TIL. They also considered, for the survival evaluation, the time of nephrectomy. Survival was better the earlier the nephrectomy, and TIL plus IL-2 plus IFN alpha resulted in the best treatment of the four examined.

Side effects

Evaluation of side effects linked to the doses in the treatments employing IL-2 provided the following results: in all trials enrolled, low doses (total dose 100,000–3,000,000 IU/day for a 30-month period) or high doses (total dose 600,000 IU/kg/day for a 30-month period) of IL-2 administration have been planned. Assessment of the studies showed that the

Table 2 Data from meta-analysed studies. (*TIL* Tumour-infiltrating lymphocytes, *LAK* lymphokine-activated killer cells, *IFN* interferon, *95% CI* 95% confidence interval)

Authors	Treatments	95% CI	Survival odds ratio (best treatment)
Colavita et al. [8]	IL-2 vs IL-2 + IFN alpha	0.8/3.12	2.1 (IL-2 + IFN alpha 2alpha)
Figlin et al. 10]	IL-2 vs IL-2 + IFN alpha	0.84/3.82	2.31 (IL-2 + IFN alpha 2alpha)
Lopez Hanninen et al. [11]	IL-2 vs IL-2 + IFN alpha	0.74/2.21	1.18 (IL-2 + IFN 2alpha)
Jones et al. [6]	IL-2 vs chemotherapy (n.s.)	0.72/1.9	0.88 (IL-2)
Atkins et al. [5]	IL-2 vs IL-2 + IFN alpha	0.49/2.70	0.98 (IL-2)
Murray Law et al. [7]	IL-2 vs IL-2 + LAK	0.48/9.48	2.33 (IL-2 + LAK)
Lopez Hanninen et al. [11]	IL-2 + IFN alpha vs IL-2 + IFN alpha + 5FU	0.62/2.6	1.84 (IL-2 + IFN alpha)
Figlin et al. [10]	IL-2 + IFN alpha vs IL-2 + IFN alpha + TIL	0.32/1.80	2.24 (IL-2 + IFN alpha + TIL)
Mean		0.67/3.87	1.63 (IL-2)

IL-2-related toxicity was rapidly reversible and no cumulative toxicity was observed after complete administration of the planned therapeutic protocol. All authors have not identified serious toxicity factors influencing the outcome of treated patients, even if the patients with cardiovascular or metabolic diseases were excluded from the studies. The data obtained from our analysis suggest that an increased incidence of haematological diseases was observed after administration of high doses of IL-2, even if an increased rate of infective diseases has not been shown. High rates of hypotension and arrhythmias occurred in IL-2-treated patients, and these side effects were potentially lethal (Table 3). Low doses of IL-2 provoked side effects too, and the most serious of these were renal failure, gastrointestinal toxicity and infective diseases. In none of the examined studies was toxicity so severe as to provoke dropouts. Some trials focused only on the evaluation of toxicity of IL-2 administered by different ways. A study by McFarlane et al. [13], although data on patients' survival and pathological response are not provided, shows in an extensive study series that haematological toxicity is tolerable as well as reversible and that the cytoreduction may act in a synergic way with IL-2, increasing the tumoral regression rate in metastatic renal cell carcinoma (RCC). Goedegebuure et al. [14] repeated this experience, but added TIL in their protocol. Even if it is a pilot study carried out on 26 patients, it confirms the moderate IL-2 toxicity. White et al. [15] took into account cardiopulmonary toxicity of high doses of the cytokine administered by various ways in RCC and melanoma patients. Toxicity was not severe enough to determine dropouts.

Table 3 Data from meta-analysed studies

Authors	Side effects	Toxicity
Lummen et al. [9]	90% Fever 80% Cardiac failure Pulmonary failure Neurological disorders Weight loss 16.6% Flu-like symptoms	III–IV WHO
Colavita et al. [8]	92% Fever 36% Fatigue 17% Nausea, vomiting	I–II WHO
Figlin et al. [10]	Not available	Not available
Lopez Hanninen et al. [11]	93% Fever 88% Mild anorexia 78% Thus 72% Malaise 57% Chills	I–II–III WHO
Jones et al. [6]	90% Fever 90% Hypotension 60% Kidney failure 66% Liver failure	Not available
Atkins et al. [5]	87% Fever 69% Hypotension 36% Oliguria 25% Nausea, vomiting	III–IV WHO
Murray Law et al. [7]	90% Fever 15% Liver failure 18% Infections 15% Pulmonary failure	I–IV WHO

Discussion

The management of renal carcinoma is often based on a nephrectomy associated with wide resection of regional lymph nodes and perirenal adipose tissue [16] To date, no chemotherapeutic treatment achieves good results [17]. Vinblastine achieves response in only 10% of patients, and is not able to control metastatic progression, nor achieve the same results obtained using the main radiotherapeutic protocols [18]. Therapy with hormones (testosterone) did not confirm the encouraging early results observed, because only part of the renal tumour presents specific receptors, this part then being responsive to the treatment. In addition, the side effects of hormone treatment must not be disregarded. Adoption of immunochemotherapeutic protocols using IL-2 seems to furnish interesting results, even if overall 5-year survival is achieved in only 20–25% of treated patients [19]. Attempts to establish protocols using associations including IL-2 increased the incidence of objective response, the percentage of patients with no progression of the disease and the overall survival rate.

The studies examined revealed that IL-2 treatment can provide better results than those over the short and long term obtained by systemic chemotherapy. Survival probabilities expected using IL-2 alone and systemic chemotherapy are comparable in the middle-term endpoint (between 12 and 20 months) [7]. The gap existing between these two types of treatment is particularly significant in the first 12 months of therapy when the therapeutic index of chemotherapy is much lower than that observed using IL-2 alone. In fact, the advantages of the tumoricide therapy are outweighted by its toxic effects which cause numerous deaths during the initial stages of treatment [20, 21, 22, 23, 24, 25]. The progressive worsening of the patients' performance status makes them more susceptible to the toxic effects of the chemotherapeutic treatment, while treatment with IL-2 alone showed lower death rates [7]. The efficacy was better in the IL-2 alone arm, especially regarding minor toxic effects. However, comparison between IL-2 alone and combined immunotherapeutic protocols (IL-2 plus IFN alpha and/or IL-2 plus LAK cells) revealed a significant gap in terms of time-related efficacy of IL-2 alone. Short-term survival was highest in the IL-2 plus LAK cells arm which also presented the highest survival odds, even if the efficacy of this protocol was not constant and was substantially lower in medium- and long-term endpoints than that observed using IL-2 alone or associated with IFN alpha. It seems very important to ascertain if this fact depends on a loss of efficacy linked to tumour-induced immunodepression. In fact, this phenomenon determines a reduced responsiveness to the therapy in some phase of the disease.

However, these two variables do not fully explain the partial failure of IL-2 plus LAK cells treatment which may be influenced by other factors as well as the side effects induced by the drugs used. Our analysis reveals an elevated probability of severe side effects (renal insufficiency, gastrointestinal toxicity, infections) that are particularly evident using relatively low IL-2 doses, such as those used by Murray-Law et al. [7]. The analysis of the two studies not enrolled in the statistical analysis [4, 13] confirms this data.

On the other hand, elevated IL-2 doses are accompanied by severe cardiac and haematological toxicity, having possible cumulative effects when IL-2 is associated to other cytokines, including IFN alpha. This association is able to achieve 23% survival at 36 months from start of treatment but is accompanied by a much higher mortality rate during the middle term (18–24 months) than that observed in the IL-2 alone arm. In Colavita et al. [8] as well as in Lummen et al. [9] trials, even if the findings seem in favour of IL-2 plus IFN alpha association (that determined complete remissions), the Authors did not find a statistically significant difference with other groups where they observed only SD or progressions. Figlin et al. [10] and Lopez Hanninen et al. [11] found that IL-2 plus IFN alpha, TIL and/or 5FU gave the best survival and toxicity results in the two trials, respectively. These results are not significantly better than those obtained by other authors, although they are most promising.

Conclusions

Our study reveals that associations between IL-2 and other drugs or cells are surely more efficacious than chemotherapy or IFN administration alone in the treatment of metastatic renal carcinoma, without a significant increase of side effects. Standard IL-2 protocols (high or low doses) must take into account the patients' initial clinical conditions, their performance status during treatment and possible changes in the doses. Treatment with IL-2 alone achieves better results than systemic chemotherapy, 5FU- or cyclophosphamide-based, even if there is not a striking difference between these two types of treatment in terms of mortality rate. IL-2 plus LAK cells provided only partial response and the variable efficacy and efficacy/toxicity ratio call for protocol adjustment during treatment. IL-2 plus IFN alpha-based treatment showed an interesting efficacy as well as a tolerable toxicity, even if the cumulative toxic effect of the two drugs should be carefully monitored.

Protocols enriched involving 5FU and/or TIL associated to IFN alpha and IL-2 seem to provide a slightly better clinical response rate but did not achieve a significant amelioration of survival rates with respect to IL-2 plus IFN alpha alone. Furthermore, IL-2 alone or in association is generally tolerated and is not a cause of dropouts. Only intravenous administration is not advisable, because on the one hand it is not related to an improvement of survival and response rates in RCC patients and on the other hand it is related to an increase in side effects.

References

1. Morgan DA, Ruscitti FW, Gallo RC (1976) Selective in vitro growth of lymphocytes from ormonal bone marrows. Science 193:1700–1800
2. Grimm EA, Mazumder A, Zhang HZ, et al (1982) The lymphokine activated killer cell phenomenon: lysis of NK resistant fresh solid tumor cells by rIL-2 activated autologous human peripheral blood lymphocytes. J Exp Med 155:1823–1841
3. Malaguarnera M, Scollo P, Ruggeri R, et al (1995) Efficacy of interleukin-2 associate with carboplatinum in the treatment of non operable ovarian carcinoma. Lancet 346:1627
4. Rosemberg SA, Lotze MT, Muul LMA, et al (1987) Progressive report on the treatment of 157 patients with advanced cancer using lymphokine activated killer cells and IL-2 or high-dose IL-2 alone. N Engl J Med 316:889–897
5. Atkins MB, Sparano J, Fisher RI, et al (1993) Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon alpha-2b in advanced renal cell carcinoma. J Clin Oncol 11:661–670
6. Jones M, Phillip T, Palmer P, et al (1993) The impact of interleukin-2 on survival in renal cancer: a multivariate analysis. Cancer Biother 8:275–287
7. Murray Law T, Motzer Robert J, Mazumdar M, et al (1995) Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. Cancer 76:824–832
8. Colavita M, Locatelli MCB, Valle A (1998) Interleuchina 2(rIL-2)+- interferone a2a (rIFN-a2a) sottocute a basso dosaggio nel trattamento delle metastasi da carcinoma renale in pazienti con 0–1 fattori prognostici sfavoreli. Book of abstract. Atti del Congresso nazionale della società italiana di urologia oncologica. Ischia 4–7 Ottobre Abst. n. 71
9. Lummen G, Goepel M, Mollhoff S, et al (1996) Phase II study of interferon-gamma versus interleukin-2 and interferon-a2b in metastatic renal cell carcinoma. J Urol 155:455–458
10. Figlin R, Gitlitz B, Franklin J, et al (1997) Interleukin-2 based immunotherapy for the treatment of metastatic renal cell carcinoma: an analysis of 203 consecutively treated patients. Cancer J 3:93–97
11. Lopez Hanninen E, Kirchner H, Atzpodien J (1996) Interleukin-2 based home therapy of metastatic renal cell carcinoma: risk and benefits in 215 consecutive single institution patients. J Urol 155:19–25
12. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC (1987) Meta-analysis of randomized controlled trials. N Engl J Med 316:450–455
13. MacFarlane MP, Yang JC, Guleria AS, et al (1995) The hematologic toxicity of interleukin-2 in patients with metastatic melanoma and renal cell carcinoma. Cancer 75:1030–1037
14. Goedegebuure PS, Douville LM, Richmond GC, et al (1995) Adoptive immunotherapy with tumor-infiltrating lymphocytes and interleukin-2 in patients with metastatic malignant melanoma and renal cell carcinoma: a pilot study. J Clin Oncol 13:1939–1949
15. White RL, Schwartzentruber DJ, Guleria A, et al (1994) Cardiopulmonary toxicity of treatment with high dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal cell carcinoma. Cancer 74:3212–3222
16. Belldegrun A, Pierce W, Kaboo R, et al (1993) Interferon-alpha primed tumor-infiltrating lymphocytes combined with interleukin-2 and interferon-alpha as therapy for metastatic renal cell carcinoma. J Urol 150:1384–1390

17. Novick AC (1995) Current surgical approaches, nephron-sparing surgery and the role of surgery in the integrated immunologic approach to renal cell carcinoma. Semin Oncol 22:29–33
18. Provet J, Tessler A, Brown J, et al (1991) Partial nephrectomy for renal cell carcinoma: indications, result and implication. J Urol 145:472–476
19. Klocker J, Pont J, Shumer J, et al (1991) Carboplatin, methotrexate and vinblastin (carbo-MV) for advanced urothelial cancer. A phase II trial. Am J Clin Oncol 14:328–330
20. Abrams JS, Raynor AA, Wiernik P, et al (1990) High dose recombinant interleukin-2 alone: a regimen with limited activity in the treatment of advanced renal cell carcinoma. J Natl Cancer Inst 82:1202–1206
21. Rosenberg SA, Lotze MD, Muul LM, et al (1985) Observations on the systemic administration of autologous LAK cells and recombinant IL2 to patients with metastatic cancer. N Engl J Med 313:1485–1486
22. Weiss GR, Margolin KA, Aronson FR, et al (1992) A randomized phase II trial of continuous infusion interleukin-2 or bolus injection interleukin-2 plus lymphokine activated killer cells for advanced renal cell carcinoma. J Clin Oncol 10:275–281
23. Huland E, Heinzer H (2000) Survival in renal cell carcinoma: a randomized evaluation of tamoxifen vs interleukin-2, alpha-interferon (leucocyte) and tamoxifen. Br J Cancer 82:246–247
24. Wolchok JD, Motzer RJ (2000) Management of renal cell carcinoma. Oncology (Huntingt) 14:29–34
25. Atzpodien J,Buer J, Sel S, et al (1999) Chemoimmunotherapy in the systemic treatment of advanced renal carcinoma. Urologe A 38:474–478