

Adjuvant treatment with interleukin-2- and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: Results of a prospectively randomised Trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN)

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We conducted a prospectively randomised clinical trial to investigate the role of adjuvant outpatient immunochemotherapy administered postoperatively in high-risk patients with renal cell carcinoma. In total, 203 renal carcinoma patients' status post radical tumour nephrectomy were stratified into three risk groups: patients with tumour extending into renal vein/vena cava or invading beyond Gerota's fascia (pT3b/c pN0 or pT4pN0), patients with locoregional lymph node infiltration (pN+), and patients after complete resection of tumour relapse or solitary metastasis (R0). Patients were randomised to undergo either (A) 8 weeks of outpatient subcutaneous interleukin-2 (sc-rIL-2), subcutaneous interferon-alpha2a (sc-rIFN- α 2a), and intravenous 5-fluorouracil (iv-5-FU) according to the standard Atzpodien regimen (Atzpodien *et al*, 2004) or (B) observation. Two-, 5-, and 8-year survival rates were 81, 58, and 58% in the treatment arm, and 91, 76, and 66% in the observation arm (log rank $P=0.0278$), with a median follow-up of 4.3 years. Two-, 5-, and 8-year relapse-free survival rates were calculated at 54, 42, and 39% in the treatment arm, and at 62, 49, and 49% in the observation arm (log rank $P=0.2398$). Stage-adapted subanalyses revealed no survival advantages of treatment over observation, as well. Our results established that there was no relapse-free survival benefit and the overall survival was inferior with an adjuvant 8-week-outpatient sc-rIL-2/sc-rIFN- α 2a/iv-5-FU-based immunochemotherapy compared to observation in high-risk renal cell carcinoma patients following radical tumour nephrectomy.

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During the last decades, renal cell cancer has been increasing in incidence in North America and Europe, with approximately one-third having metastatic disease at the time of diagnosis. Patients with locally advanced renal cell carcinoma are at high risk of recurrence, since relapse rates range from 50 to 85% depending on tumour (T) stage and nodal (N) status, and reach close to 100% in recurrent disease patients who

have undergone R0 resection (Fleischmann *et al*, 1997; Messing *et al*, 2003).

Until now, no adjuvant treatment including radiation, chemotherapy, or immunotherapy of locally advanced renal cell carcinoma has shown satisfactory results (Clark *et al*, 2003).

Promising results in the therapy of stage IV metastatic renal cell carcinoma were reported using interleukin-2 (rIL-2) given intravenously or subcutaneously as outpatient therapy alone or in combination with interferon- α (rINF- α) yielding objective response rates between 19 and 31% (Slejfer *et al*, 1992; Rosenberg *et al*, 1994; Atzpodien *et al*, 1995). Hereby, cytokine outpatient therapy regimens (Atzpodien *et al*, 1995) showed highly reduced systemic toxicities as compared to i.v. bolus

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infusions. The combination of subcutaneous cytokines with the chemotherapeutic i.v. 5-fluorouracil (5-FU) further enhanced antineoplastic activity achieving objective response rates between 18 and 39% (Lopez-Hänninen *et al*, 1996; Dutcher *et al*, 2000; Atzpodien *et al*, 2001, 2004). Based on its efficacy in metastatic renal cell carcinoma, we hypothesized that outpatient sc-rIL-2/sc-rIFN- α 2a/iv-5-FU-based immunochemotherapy according to the standard Atzpodien regimen (Atzpodien *et al*, 2004) might extend progression-free and/or overall survival of high-risk renal cell carcinoma patients in the postsurgical adjuvant setting.

We, therefore, performed a prospective randomized clinical study to compare the efficacy of sc-rIL-2/sc-rIFN- α 2a/iv-5-FU vs observation as an adjuvant approach in high-risk renal carcinoma patients.

PATIENTS AND METHODS

Patients

Between October 1993 and February 2002, 203 high-risk patients with resected renal cell carcinoma were stratified into three risk groups: (1) patients with tumour extending into renal vein/vena cava or invading beyond Gerota's fascia (pT3b/c pN0 or pT4pN0; $n=77$), (2) patients with locoregional lymph node infiltration (pN+, $n=36$), and (3) patients after complete resection of tumour relapse or solitary metastasis (pR0; $n=90$); spontaneous 5-year systemic survival rates were 84, 70, and 71% in pT3b/c pN0 or pT4pN0 patients, pN+ patients, and R0 patients, respectively. Systemic pretreatment included, chemotherapy ($n=1$), immunotherapy ($n=10$), and naturopathic therapy ($n=1$) (Table 1).

Criteria for entry into the study were: histologically confirmed renal cell carcinoma (pT3b/c pN0 or pT4pN0; pN+; R0), age between 18 and 80 years; white blood cell count $\geq 3500 \mu\text{l}^{-1}$; platelet count $\geq 100.000 \mu\text{l}^{-1}$; hematocrit $\geq 30\%$; serum bilirubin ≤ 1.25 , and creatinine ≤ 1.5 of the upper normal limit; Karnofsky performance status $\geq 80\%$; no evidence of congestive heart failure, no severe coronary artery disease, no cardiac arrhythmias, no clinically symptomatic CNS disease or seizure disorders, no human immunodeficiency virus infection, no evidence of chronic active hepatitis, no concomitant corticosteroid therapy. In all patients treated, no chemotherapy or immunomodulatory treatment had been performed during the previous 4 weeks. Also, pregnant and lactating women were excluded.

This study was approved by the institutional review board of the Medizinische Hochschule Hannover. Upon written receipt of patient pre-study evaluation, randomisation was performed; 135 patients were assigned to arm A, and 68 patients were assigned to arm B.

Regimens

Patients randomised to adjuvant therapy (arm A) received one 8-week treatment cycle of sc rIFN- α 2a (Roferon[®], Hoffmann-La Roche; Grenzach-Wyhlen, Germany) ($5 \times 10^6 \text{ IU m}^{-2}$, day 1, weeks 1 + 4; days 1, 3, 5, weeks 2 + 3; $10 \times 10^6 \text{ IU m}^{-2}$, days 1, 3, 5, weeks 5–8), sc rIL-2 (Proleukin[®], Chiron, Emeryville, CA, USA) ($10 \times 10^6 \text{ IU m}^{-2}$, twice daily days 3–5, weeks 1 + 4; $5 \times 10^6 \text{ IU m}^{-2}$, days 1, 3, 5, weeks 2 + 3) and iv 5-FU (1000 mg m^{-2} , day 1, weeks 5–8). Patients at an age of 60 years and older received a 20% dose reduction of sc IL-2 to avoid toxic complications. Concomitant medication was given as needed to control adverse effects of immunochemotherapy. Patients randomised to undergo observation (arm B/control) received no adjuvant therapy. In the event of relapse, all patients were offered individual care outside the present study.

Table 1 Patients characteristics and pretreatment

Characteristics	Treatment		
	Arm A ^a (n)	Arm B ^a (n)	All patients (n)
Entered	135	68	203
Age (years)			
Median	59	60	59
Range	31–77	38–77	31–77
Sex			
Male	97	54	151
Female	38	14	52
Radical nephrectomy	135	68	203
Stratum			
pT3b/c pN0 or T4pN0	50	27	77
pN+	28	8	36
R0	57	33	90
Local	9	4	13
Lymph nodes	5	5	10
Organ metastases	37	22	59
Site unknown	6	2	8
Histological subtype			
Clear cell	84	41	125
Granular	3	2	5
Sarkomatoid	2	1	3
Papillary	1	1	2
Mixed	22	8	30
Unknown	23	15	38
Systemic pretreatment			
Chemotherapy	0	1	1
Immunotherapy ^b	4	6	10
Naturopathic therapy	1	0	1
Unknown	6	0	6

^aArm A (8 weeks of sc-rIL-2/sc-rIFN- α /iv 5-FU); Arm B (observation). ^bIncluding IL-2/IFN- α 2, IL-2/Vaccine, and Vaccine. sc-rIL-2 = subcutaneous interleukin-2; sc-rIFN- α 2 = subcutaneous interferon-alpha2a, and iv-5-FU = intravenous 5-fluorouracil.

Assessment of survival

Survival was measured from start of therapy to date of death or to the last known date to be alive. In case of progression upon first re-evaluation after 8 weeks, relapse-free survival was calculated at 0 months. All patients had to be followed up for survival for at least 2 years as cutoff.

Statistical analysis

The statistical end points in our analysis were (1) relapse-free survival (primary end point) and, (2) overall survival of patients. The probability of relapse-free survival and overall survival was plotted over time according to the method of Kaplan and Meier (1958).

The potential 2-year relapse-free survival rates were hypothesised to show a 20% advantage of Arm A over Arm B (90 vs 70%). Using an α of 0.05 (one-sided), a sample size of 59 patients plus 20% potential drop outs per arm was needed to have 80% power to statistically establish the assumed difference in relapse-free survivals. The present 2:1 (treatment vs observation) randomisation was capable of meeting these statistical end points.

Statistical significance was assessed using the log rank test. For statistical analysis, the SPSS software for Windows (SPSS, Inc., Chicago, IL, USA) was applied.

RESULTS

In total, 203 stratified renal carcinoma patients were prospectively randomised to undergo either an 8-week treatment with sc rIL-2, sc rIFN- α 2a, and iv 5-FU (arm A, $n = 135$ patients) or to undergo observation (arm B, $n = 68$ patients).

Overall survival

After a median follow-up of 4.3 years (range, 0.2–9.7 years), 82 patients (61%) in arm A (sc-rIL-2/sc-rIFN- α 2a/iv-5-FU) and 51 patients (75%) in arm B (observation) continued to be alive. No therapy-induced toxic deaths occurred. Two-, 5-, and 8-year survival probabilities were 81, 58, and 58% on the treatment arm, and 91, 76, and 66% on the observation arm (Figure 1). Overall survival was significantly decreased (log rank $P = 0.0278$) after treatment with immunochemotherapy (range, 0.2–8.4 years), when compared with the control (range, 0.3–9.7 years) (Figure 1).

Stage-related (pT3b/c pN0 or pT4pN0, pN+, and R0) analysis revealed no survival advantages of treatment over observation in patient subgroups.

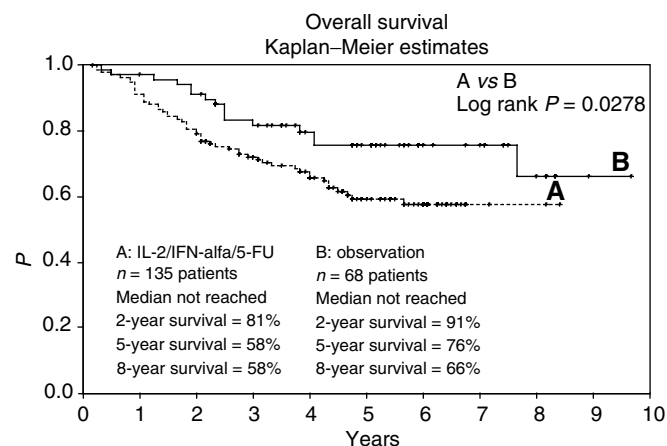


Figure 1 Overall survival for all 203 patients receiving (A) sc interleukin-2, sc interferon- α , and iv 5-fluorouracil, or (B) observation. Plots were generated by the Kaplan–Meier method.

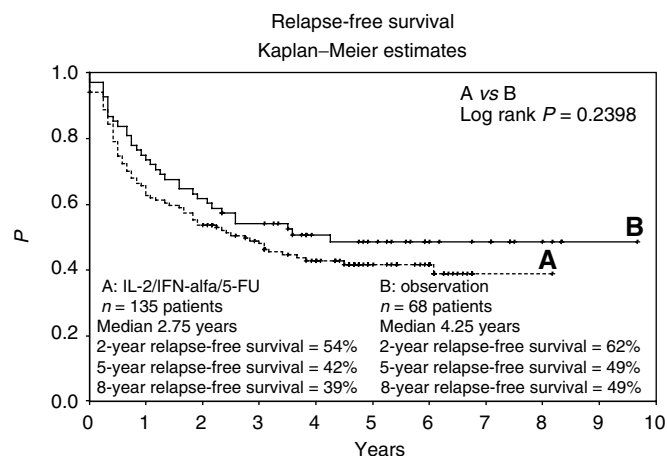


Figure 2 Relapse-free survival for all 203 patients receiving (A) sc interleukin-2, sc interferon- α , and iv 5-fluorouracil, or (B) observation. Plots were generated by the Kaplan–Meier method.

Relapse-free survival

A total of 77 patients (57%) in arm A (sc-rIL-2/sc-rIFN- α 2a/iv-5-FU) and 34 patients (50%) in arm B (observation) exhibited tumour progression at last follow-up. Two-, 5-, and 8-year relapse-free survival probabilities were calculated at 54, 42, and 39% on the treatment arm, with a median relapse-free survival of 2.75 years (range, 0–8.2 years), and at 62, 49, and 49% on the observation arm, with a median relapse-free survival of 4.25 years (range, 0–9.7 years) (log rank $P = 0.2398$) (Figure 2). Thus, the statistical hypotheses could not be established.

Within the three stratification groups (pT3b/c pN0 or pT4pN0, pN+, and R0), median relapse-free survival did not differ significantly between arm A (sc-rIL-2/sc-rIFN- α 2a/iv-5-FU) and arm B (observation).

DISCUSSION

In this prospectively randomised trial, we reported the results of 203 tumour-free renal cell carcinoma patients after surgery of locally advanced or distant metastatic disease who underwent an adjuvant treatment with sc-rIL-2/sc-rIFN- α 2a/iv-5-FU (arm A) or underwent observation (arm B).

We demonstrated that high-risk renal cell carcinoma patients did not benefit from an eight-week postoperative adjuvant immunochemotherapy, both with respect to relapse-free survival and with respect to overall survival. Thus, the primary relapse-free survival end point of the current trial was not reached.

The lack of sc-rIL-2/sc-rIFN- α 2a/iv-5-FU-related survival benefit in the adjuvant renal carcinoma therapy was disappointing, particularly when compared to the established efficacy in metastatic renal cell carcinoma patients (Lopez-Hänninen *et al*, 1996; Elias *et al*, 1999; Atzpodien *et al*, 2001, 2004).

However, recent studies employing α -IFN-based therapy in the adjuvant setting for renal cell carcinoma patients also did not result in significant improvement regarding relapse-free survival and overall survival (Pizzocaro *et al*, 2001; Messing *et al*, 2003).

In studies of Pizzocaro *et al* (2001), an adjuvant treatment with IFN- α 2b demonstrated a decrease in relapse rates in 26 patients with extensive nodal disease (pN2/pN3), but an increase in recurrence rates in node negative renal carcinoma patients.

Using tumour vaccination protocols with no interleukin-2 or α -interferon, Repmann *et al* (2003) and Jocham *et al* (2004) were the first investigators reporting positive adjuvant treatment results in locally advanced renal cell carcinoma.

Overall, the present prospectively randomised clinical trial reported here established that adjuvant 8-week outpatient sc rIL-2/sc rIFN- α 2a/iv 5-FU-based immunochemotherapy was inferior to observation when administered to high-risk patients with resected renal cell carcinoma. It should be noted, though, that patients did not benefit from therapy, but indeed may have been harmed. This could be with toxicity, however, in the current trial toxicity was not systematically studied; this should also be subject of future trials.

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