Cytokines and Cytotoxic Agents in Renal Cell Carcinoma: A Review

Michael Stahl, Hans-J. Wilke, Siegfried Seeber, and Hans-J. Schmoll

WITH increasing incidence, approximately 20,000 new cases of renal cell carcinoma (RCC) are diagnosed in the United States per year. Up to 80% of these patients will develop metastases, and prognosis of metastatic disease is poor. The clinical course of metastatic RCC is very heterogeneous. Long-lasting stable periods as well as rapid tumor growth are well known and rather unique for adult malignancies. Even spontaneous tumor regressions may occur. Based on cumulated data, the incidence of this phenomenon is less than 1%,[1] although it was reported in up to 7% of patients in selected series.[2] Spontaneous regression is believed to be immune mediated and a result of a host's antitumor response.[3,4] This was one of the rationales behind the fact that, besides conventional chemotherapy and hormonal approaches, an increasing number of studies with biologic response modifiers have been conducted in RCC during the last 10 years.

Comparable to other tumor entities, several prognostic factors have been determined; these have proved to be important predictors for response and survival of systemically treated patients with metastatic RCC. Prognostic favorable factors are good performance status, resection of primary tumor, long interval between nephrectomy and development of metastases, lung metastases only, and no bone involvement.[3,5-7] For example, Sarna et al[6] retrospectively analyzed their data from three consecutive interferon (IFN) trials. Thirty-seven percent of the 84 patients showed tumor response, whereas in patients with only lung metastases, the response rate was 53%. Overall median survival had been 49 weeks, but patients with a good performance status and only lung metastases had a median survival of 102 weeks. Patient selection has therefore taken into consideration when comparing treatment results.

From the Department of Internal Medicine (Cancer Research), Essen University Medical School, West German Cancer Center, Essen, Germany; and the Department Hematology/Oncology, Hannover University Medical School, Hannover, Germany.

Address reprint requests to Michael Stahl, MD, Innere Klinik und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Hufelandstr. 55, D-4300 Essen 1, Germany.

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HORMONAL THERAPY

Autochthonous kidney tumors can be induced in syrian hamsters by prolonged administration of diethylstilbestrol.[8] In this animal model, tumor growth can be influenced by progesterones, androgens, and anti-estrogens,[9] supporting the rationale for numerous phase II studies with hormonal agents, as did the detection of hormone receptors on RCCs.[10]

However, in clinical trials, hormonal treatment failed to show significant activity in RCC. Progesterones, 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[9]). This may be partly due to the fact that the role of hormone receptors in renal cancer had been overestimated. In more recent investigations, the number of receptor-positive tumors and their receptor contents were markedly lower than previously reported.[11]

An estrogen receptor-independent, cytotoxic effect of the anti-estrogen tamoxifen was described in vitro with doses above 1×10^{-6} mol/L.[12,13] These findings prompted two clinical trials with high-dose tamoxifen (100 to 150 mg/m^2/d) in patients with progressive RCC (documented prior to treatment). In a study of 34 patients, Stahl et al reported four patients with objective responses (12%) lasting a median of 20 months, and 17 patients with no change (50%).[14] These results were confirmed by a German multicenter trial[15] in which 12% of patients had objective responses, 63% of patients had no change, and there was a median overall survival of 15 months. Only one third of the patients had good prognostic factors.

CHEMOTHERAPY

In the past 15 years, more than 50 single-agent phase II trials of RCC using different cytotoxic drugs have been reported.[9,16] However, only vin-

Table 1. Recombinant Interferon-α in Metastatic Renal Cell Carcinoma

Study	IFN	Dose/Schedule (10^6 Units)	No. of Evaluable Patients	CR + PR (%)	Median Remission Duration (mo)	Median Survival (mo)
Quesada et al[26] * (1985)	2a	2/m² qd	15	0	—	—
	2a	20/m² qd	15	27	3	13
Quesada et al[26] (1985)	2a	20/m² qd	26	31	NA	NA
Umeda and Niijima[27] (1986)	2a	3-36/m² qd	108	14		
Umeda and Niijima[27] (1986)	2b	3-10/m² 3-5 d/wk	45	18	2.5	NA
Figlin et al[28] (1988)	2a	3-36/m² qd	19	26	9.5	18.5
Muss et al[29] * (1987)	2b	2-10/m² tiw	51	10		
	2b	30-50/m² d 1-5 every 3 wk	46	7	16	NA
Fossa et al[30] (1988)	2a	18 tiw	86	7	NA	9
Marshall et al[31] (1989)	2b	1 qd	16	25	NA	NA
Levens et al[32] (1989)	2a	10 qd	15	27	9	NA
Fossa et al[33] † (1990)	2a	18 tiw	23	23	9	11
Summarized			465	14% (95% CI, 11%-17.5%)		

Abbreviations: qd, daily; tiw, three times per week; NA, not available; 95% CI, 95% confidence interval.

* Randomized trial.

† Plus prednisone orally daily.

blastine and floxuridin (FUDR) have shown reproducible moderate activity. In 1977, Hrushesky and Murphy reported 33 responses in a series of 135 patients (25%) being treated with vinblastine in different trials.[17] In most of these trials, response criteria were not clearly defined or did not fulfill modern standard criteria for response estimation. Analyzing vinblastine studies being published since 1979, an overall remission rate of 16% (45 of 277 patients) was achieved, with few complete remissions (CRs), short-lasting remission duration (5 to 6 months), and a median survival time of approximately 8 months.[1,18]

Of interest are the results being achieved with the fluoropyrimidine FUDR, given by circadian-shaped 14-day infusion, as described by Hrushesky et al.[19] These investigators observed 11 objective remissions (four CRs and seven partial remissions [PRs]) in 56 patients (19.6%) with metastatic RCC. The remission duration was 11 months and overall survival was 14 months. All patients were previously nephrectomized and one third had a good performance status and/or only lung metastases. These data are in concordance with the results of Wilkinson et al[20] and Geoffrois et al,[21] who reported three PRs of 10 patients and four PRs of 25 patients, respectively. A completely negative result was published by Richards et al,[22] who used a 5-day continuous-infusion schedule of FUDR. No objective remission was observed in 29 evaluable patients, whose characteristics were comparable to those of the Hrushesky et al trial.

Combination chemotherapy, mostly based on vinca alkaloids, did not result in higher remission rates or longer survival times compared with vinblastine monotherapy, but frequently increased toxicity.[9]

IMMUNOTHERAPY

Interferon-α

Since the first report of IFN-α (human leukocyte derived) by Quesada et al in 1983,[23] numerous phase II and III studies using IFN-α derived from human leukocytes, lymphocytes, or recombinant interferon (rIFN) have been published. From these trials it can be concluded that neither the source of IFN-α nor the route of administration significantly influenced its efficacy.[24]

Because of the better availability of rIFNs, most trials of the last years were conducted with rIFN-α. Summarizing study results with rIFN, an overall remission rate of 14% (95% confidence interval, 11% to 17.5%), median remission durations of 2.5 to 16 months, and median survival times of 9 to 18.5 months were achieved in 465 patients (Table 1). Two thirds of these trials accrued less than 30 patients. This fact and patient selection may be an explanation for the partly marked differences of published treatment results.

Table 2. Recombinant Interferon-α and Vinblastine in Metastatic Renal Cell Carcinoma

Study	IFN (10^6 Units)/Vinblastine Dose (mg/kg)	No. of Evaluable Patients	CR + PR (%)	No Change (%)	Median Response Duration (mo)	Median Survival (mo)
Fossa et al[42] (1986)	2a 36 tiw + 0.1-0.15 qd for 2-3 wk	16	31	31	8	NA
Fossa[43] (1988)	2a 18 tiw + 0.1 qd for 3 wk	12	17	33	7.5	NA
Fossa et al[30] (1988)	2a 18 tiw + 0.1 qd for 3 wk	91	22	35	NA	9
Bergerat et al[44] (1988)	2a 10-20/m^2 tiw + 0.075-0.15 qd for 3 wk	20	40	25	8	NA
Bergerat et al[44] (1988)	2a 18/m^2 tiw + 0.1 qd for 3 wk	20	45	15	8	NA
Cetto et al[45] (1988)	2b 3/m^2 tiw + 0.1 qd for 3 wk	18	44	17	5	16
Schornagel et al[46] (1989)	2a 18 tiw + 0.1 qd for 3 wk	56	16	57	6	9
Sertoli et al[47] (1989)	2a 18 tiw + 0.1 qd for 3 wk	20	10	55	9+	NA
Schuster et al[48] (1990)	2a 18 tiw + 0.1 qd for 3 wk	34	18	47	10	NA
Palmeri et al[49] (1990)	2a 18 tiw + 0.1 qd for 3 wk	11	18	46	7	NA
Kriegmair et al[50] (1990)	NA NA	16	31	NA	NA	NA
Summarized		324	23.5%	38% (95% CI, 18.5%–28%)		

Abbreviations: tiw, three times per week; qd, daily; NA, not available; 95% CI, 95% confidence interval.

Two randomized trials have addressed the issue of whether the rIFN activity in RCC is dose dependent, as suggested by several investigators.[25] Quesada et al[26] randomized 30 patients between low-dose (2×10^6 U/m^2 intramuscularly) and high-dose (20×10^6 U/m^2 intramuscularly) rIFN-α A daily. In the low-dose arm, no objective remission was observed, compared with 27% in the high-dose arm. However, toxicity significantly increased with high-dose rIFN and survival times were the same in both arms (13 months).

Muss et al randomized two different doses and schedules of rIFN-α 2b[29] (2 to 10×10^6 U/m^2 three times per week *v* 30 to 50×10^6 U/m^2 days 1 to 5 every 3 weeks). Activity was equal in both arms, and patients with tumor progression in the low-dose arm did not benefit from cross-over to the high-dose schedule.

It cannot be concluded from these trials whether IFN dose influences treatment results. The patient numbers per treatment arm were too small to detect differences of significant power and to avoid the bias of patient selection (prognostic factors).

Other Interferons and Combinations of Interferons

Few phase I/II trials of RCC using IFN-β, or IFN-γ have been published, and they were without evidence of superior activity compared with studies using interferon-α.[34-36]

In vitro, IFN-α and IFN-γ show synergistic activity,[37] partly explained by the different cell surface receptor for both compounds, giving the basis for combining them in clinical trials. Two randomized studies that compared IFN-α and IFN-γ alone with IFN-α plus IFN-γ failed to show a clinical relevant synergism of the combination in advanced RCC.[38,39]

A more recent approach is the application of so called biologically active doses of IFN-γ.[40] Aulitzky et al treated 20 patients with very low doses of IFN-γ (10 to 500 μg once per week).[40] Two CRs lasting more than 20 months and four PRs lasting 6 to 24+ months were achieved (response rate, 30%). Because of the moderate side effects, a long median treatment period of 10 months was possible. Besides the selection of patients with good prognosis (only one patient had primary tumor and half of the patients had normal performance status and only lung metastases), this may be one reason for the good treatment results, which warrant further evaluation.

Interferons Combined With Cytotoxic Agents

In vitro studies with different cell lines showed synergism of interferons, mainly IFN-α, with a number of cytotoxic agents.[41] Because of their single-agent activity against RCC, most investigators combined vinblastine and IFN-α in clinical trials. The results of 11 phase II and III studies

are summarized in Table 2. With this combination, a remission rate of 23.5% (range, 10% to 45%; 95% confidence interval, 18.5% to 28%) and a tumor stabilization rate of approximately 30% were achieved in 324 evaluable patients. Median remission duration was 5 to 10 months. Median survival times were available from only three trials (9, 9, and 16 months, respectively). Compared with treatment results obtained using IFN-α alone (Table 1), the combination with vinblastine seems to induce slightly higher objective remission rates, but without any impact on remission duration or survival.

A direct comparison between IFN-α alone or in combination with vinblastine was done in two randomized studies with contradictory results. Fossa et al stated in a European multicenter trial that the combination of IFN and vinblastine resulted in higher response rates (22% *v* 7%) and longer median survival times (8.7 *v* 9.2 months) without increased toxicity.[30] Although the difference in response rates and the corresponding 95% confidence intervals (1.5 to 12.5% *v* 13.5 to 30.5%) are impressive, a survival advantage of 13 days is not clinically relevant. In a recently published randomized multicenter trial with IFN-α-n1 with or without vinblastine,[51] the combination failed to improve treatment results. It is of note that a small subset of 16 patients with lung metastases only had a response rate of 44% in this study. This again emphasizes the role of patient selection in the treatment of RCC.

Combinations of IFNs and other cytotoxic agents are currently under investigation. First results with rIFN-α 2a, 5-fluorouracil, and mitomycin C with or without embolization of primary tumor are promising, but preliminary.[52]

Polychemotherapy did not increase efficacy of IFN in metastatic RCC. Despite some promising results with combination chemotherapy (5-fluorouracil, doxorubicin, mitomycin, and cisplatin) following IFN in a phase II trial,[53] a randomized trial revealed only marginal efficacy of this chemotherapy alone or alternated with IFN-α.[54]

Recombinant Interleukin-2

Interleukin-2 (IL-2), a product of activated T lymphocytes, is able to induce regression of metastases in animal models.[55] Since 1985, clinical studies with high-dose intravenous IL-2 have demonstrated antitumor activity in patients presenting with metastatic RCC. Rosenberg et al reported one complete remission in 21 evaluable patients,[56] but IL-2 treatment was associated with severe side effects. In the recent past, a lot of trials have been conducted with IL-2 using different doses, schedules, and routes of administration to improve efficacy and to reduce toxicity (Table 3). It could be demonstrated that lower doses of IL-2 ($<3 \times 10^6$ U/m^2) are sufficient to produce immune enhancement comparable to that of high-dose IL-2[67] and that dose reduction can avoid the most severe side effects of IL-2, such as capillary leak syndrome and hypotension. Summarizing the results of 15 phase I/II, phase II, and phase III studies, recombinant IL-2 (rIL-2) achieved a remission rate of 18% (range, 0% to 33%; 95% confidence interval, 14% to 22%) and median remission durations of 5 to 19 months for CRs and 2 to 6.5 months for PRs. Median survival times available from three of these studies were 8.5, 11, and 11+ months, respectively.

Interleukin-2 Combined With Interferon-α

Interleukin-2 or IFN-α alone are only marginally active in RCC. Their different modes of action and their synergistic effects when used in experimental murine models[72] prompted the investigation of combinated IL-2/IFN-α therapy in advanced RCC. The differences in dose and application duration of IL-2 (bolus injection or continuous infusion), dose and route of administration of IFN (intravenous, intramuscularly, subcutaneous), as well as the different timing of the two cytokines make the comparison of published data difficult. Remission rates ranged from 0% to 50%, with infrequent but mostly long-lasting complete remissions (Table 4). The majority of the patients entered into these trials had a good performance status, prior nephrectomy, and low tumor burden. The influence of treatment with IL-2 and IFN-α on patient survival cannot be estimated because overall survival data are not available from the literature (Table 4). Comparable to the trials with IL-2 alone, the more recent trials reported obtaining substantially less toxicity by using continuous infusions of lower doses of IL-2 (2×10^6 U/m^2)[80] or by giving only a 2-day pulse with high doses followed by a low-dose maintenance subcutaneously.[79] This enabled patients to be treated in an outpatient fashion, and efficacy of the treatment seems to be comparable.

Table 3. Recombinant Interleukin-2 in Advanced Renal Cell Carcinoma

Study	Dose	No. of Patients	No. of CRs	CR + PR (%)	Median Response Duration (mo) (CR/PR)	Median Survival (mo)
Whitehead et al[57] (1987)	LD/HD SQ	14	0	0	—/—	NA
Rosenberg et al[58] (1988)	HD-BI	38	4	18.5	6/NA	NA
Sosman et al[59] (1988)	LD-BI/CI	17	0	18	—/2	NA
Paciucci et al[60] (1988)	HD-CI	5	0	20	—/NA	NA
Perez et al[61] (1989)	HD-CI	12	0	8	—/NA	NA
Klasa and Silver[62] (1989)	HD-BI*	13	0	8	—/NA	NA
Stoter et al[63] (1989)	HD-CI	18	1	18	5/6.5	NA
Aso et al[64] (1989)	LD-CI qd	60	3	15	5+	NA
Negrier et al[65] (1989)	HD-CI	32	2	19	6+	8.5
Bukowski et al[66] (1990)	HD-BI tiw	41	1	12	19/3.5	11
Atzpodient et al[67] (1990)	LD SQ tiw	5	0	20	—/5	11+
Galligioni et al[68] (1990)	HD-CI	18	3	33	4+/4+	NA
Bajorin et al[69] (1990)	LD-CI	24	1	12	16+/NA	NA
Poo et al[70] (1991)	HD-BI	15	0	27	—/NA	NA
Atkins et al[71] (1991)	HD-BI	30	1	27	7+/4+	NA
Summarized		342	16	18 (95% CI, 14%-22%)		

Abbreviations: LD, low dose (<3 × 10^6/m^2); HD, high dose; BI, bolus injection; CI, continuous infusion; qd, every day; tiw, three times per week; SQ, subcutaneous; NA, not available; 95% CI, 95% confidence interval.

* Splenic artery perfusion.

However, there is still no clear evidence of superiority of the combination compared with IL-2 alone. Preliminary results of a randomized phase II trial conducted by the NCI Extramural IL-2 Working Group[71] showed a lower response rate in the IL-2/IFN-α arm compared with IL-2 alone (three of 28 patients [11%] *v* eight of 30 patients [27%]).

Adoptive Immunotherapy

In 1987, the treatment with lymphokine-activated killer (LAK) cells and high-dose IL-2 promised to become a breakthrough in the management of metastatic RCC. Rosenberg et al achieved 12 objective and seven minor responses in 36 patients (53%) with RCC.[59] This so-called adoptive immunotherapy used IL-2 and the patients' autologous lymphocytes, which were stimulated by IL-2 ex vivo and were then reinfused. Adoptive immunotherapy was complicated by severe and partially life-threatening side effects, which make it necessary to treat many of the patients within intensive care units. The modification of this approach by using continuous-infusion IL-2[87] decreased toxicity, but selection of patients with normal performance status and without comorbidities was still necessary. Despite this careful patient selection, further phase II trials with IL-2 and LAK cells could not confirm the good results obtained by Rosenberg et al (Table 5). In two larger studies, one a study from the National Cancer Institute[98] and the other a European multicenter study,[65] remission rates of only 9% and 21% were achieved, respectively. Preliminary data of a randomized trial with 45 evaluable patients[69] showed no increase in efficacy by administration of LAK cells to IL-2 (objective response rate, 9.5% *v* 11% with IL-2 alone). Survival of responding patients often exceeded 15 months, but overall survival data have not been reported.

Treatment with tumor-infiltrating lymphocytes (TILs) is a second form of adoptive immunotherapy. For this approach, TILs were isolated from resected renal tumors or biopsy samples of tumors, then expanded in vitro with IL-2; they were then reinfused over several days. Despite their specific cytolytic activities against autologous tumor cells in vitro,[100] clinical results with TIL in metastatic RCC were not superior to any other immunotherapy.[101,102]

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