Application of retinoids in the treatment of renal cell carcinoma—a futile effort?

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The therapeutic benefit of adding retinoids such as all-*trans* retinoic acid (RA), 9-*cis*-RA or 13-*cis*-RA to established single-agent or combination immuno/chemotherapy regimens for the treatment of metastatic renal cell carcinoma (RCC) has been extensively investigated during the last decade. However, at present results are contradictory and their application controversial. Moreover, recent studies indicated a significantly higher incidence of toxic side-effects in patients treated with retinoids in addition to established bio/chemotherapy. This Commentary summarizes preclinical and clinical trials investigating efficacy and toxicity of retinoids in the treatment of RCC. *Anti-Cancer Drugs* 15:819–824 © 2004 Lippincott Williams & Wilkins.

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Introduction

Renal cell carcinoma (RCC) is a common urologic tumor and accounts for about 3% of all human malignancies. The incidence has increased steadily in recent decades. In 2000, 30 000 new cases were diagnosed in the USA and more than 20 000 in the European Union [1,2]. Annual mortality-to-incidence ratio with RCC is significantly higher compared to other urological malignancies. It is estimated that approximately 25–30% of all patients with RCC have metastases at presentation and even following a completely resected renal cell tumor by radical nephrectomy, relapse occurs in 20–30% of patients [3]. Those who present with metastases have a 5-year survival that is less than 10%; the overall 5-year survival rate is 60% [4].

Classical RCC is insensitive to cytotoxic agents as well as radiotherapy and no agent should be considered standard in the treatment of metastatic disease [5]. At present, the most effective agents used are recombinant cytokines, with single-agent interferon (IFN) or interleukin-2 (IL-2) showing objective response rates in the 10–20% range [3,6–9]. Combination therapies of IFN-α and IL-2 with or without chemotherapy show response rates up to 20–35%, and most responses occur in patients with pulmonary or soft tissue metastases [5,9–11]. However, achieved responses are predominantly partial and response durations are short with only a few long-term survivors [3,9].

Retinoids have perhaps been the most actively studied family of natural agents in the field of cancer. Even though great advances have recently been made, including the characterization of their biological structures and nuclear receptors, the exact mechanism of their action in cells of different origin remains elusive [12,13]. Retinoids in general exert potent growth and differentiation effects on normal, neoplastic and embryonic tissues. Numerous studies have shown that they induce differentiation and/or inhibition of tumor growth in a variety of *in vitro* model systems. Moreover, they induce humoral and cellular immune responses stimulating lymphocyte growth, promoting differentiation of monocytes and macrophages, and supporting their functions [12,13].

Retinoids have successfully been used in the treatment of hematologic malignancies such as acute promyelocytic leukemia (APL) and myelodysplasia [14,15]. They have proven effective in the treatment of patients with laryngeal papillomatosis as well as oral leukoplakia, and prevented the development of second primary malignancies in patients with head and neck cancer in a significant proportion of patients [16,17]. Concerning other solid malignancies such as breast, lung and cervical cancer, chemopreventive strategies with retinoids in early pre-malignant lesions also appear to be promising. However, the role of retinoids in the treatment of advanced disease is still unclear and contradictory results of early clinical studies merit further investigation [13].

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Finally, in contrast to malignant melanoma [18], basal cell carcinoma [19] and hormone refractory prostate cancer [20], specific retinoids have proven to be effective in the treatment of squamous cell carcinoma [21], AIDS-related Kaposi's sarcoma [22] and cutaneous T cell lymphoma [23].

While newer retinoid-derived agents have displayed better toxicity profiles, the traditionally studied compounds such as all-*trans* retinoic acid (ATRA), 9-*cis*-RA and 13-*cis*-RA have demonstrated significant toxicity that impairs the quality of life of the patients and precludes from long-term treatment. Common side-effects are dry skin, mucosal dryness, dermatitis, pruritus, ocular dryness, diminished dark adaptation, lacrimation and conjunctivitis. Less frequent manifestations may include neurological and gastrointestinal symptoms such as dyspepsia, nausea, abdominal pain and diarrhea [13,24,25].

In view of their antiproliferative and synergistic effects in combination with immunotherapeutic agents as well as their partly successful application in the treatment of various other malignancies, retinoids have been employed in the treatment of RCC. They have been tested as single agents or in addition to different 'established' regimens. In the following, we will summarize and analyze a number of studies performed during the last decade, and focus on effects and side-effects of retinoid derivatives.

Preclinical studies

As there was ample evidence that RA exerted anti-tumor activity by inhibition of proliferation in a series of different malignancies *in vitro* and *in vivo*, in 1995 Motzer *et al.* [26] studied the effects of 1 μM 13-*cis*-RA with or without IFN-α (1000 U/ml) on the proliferation of RCC cell lines. Nine of 12 cell lines were either resistant to RA or exhibited only minimal growth inhibition (20% or less). Growth of two cell lines was moderately inhibited (SK-RC-49 and SK-RC-02); one cell line (SK-RC-06) exhibited a 90% inhibition in response to RA. In three of five cell lines (CAKI, SK-RC-06 and SK-RC-49), which were sensitive to IFN alone, the addition of RA to IFN resulted in an increased growth inhibition, suggesting that RA can augment the antiproliferative effect of IFN on RCC cells. The expression of the nuclear RA receptors (RARs) was assessed, and demonstrated that RARα and RARγ were expressed in all RCC cell lines. In contrast, only the RA-sensitive SK-RC-06 cells expressed RARβ, which was further upregulated after RA treatment. The authors concluded that RA antiproliferative effects in RCC were mediated through RARβ. This result was confirmed later by the same group who concluded that the antiproliferative effects of RA in RCC were potentially mediated through the subtype $RAR\beta_1$ [27]. *In vivo*, they found that the majority of patients who responded to RA-based treatment displayed an increased RARβ expression after RA exposure [28].

Nanus *et al.* [29] stimulated four RCC cell lines with 1 μM 13-*cis*-RA or/and 1000 U/ml IFN-α. Using 13-*cis*-RA, only, growth of one cell line (SK-RC-06) was inhibited above 80%, whereas there was no inhibition of SK-RC-39 and only limited (25% or less) inhibition of SK-RC-45 and SK-RC-49 cells. The combination of both RA and IFN-α resulted in a significant increase in growth inhibition of all cell lines compared with RA or IFN-α alone. Buer *et al.* [30] demonstrated that in six of eight IFN-α-resistant RCC cultures the addition of 100 μg/ml 13-*cis*-RA significantly induced apoptotic cell death. However, RA exerted minimal or no effect on proliferation, i.e. growth inhibition.

Gerharz *et al.* [31] treated seven RCC cell lines with 0.1 and 1.0 μM ATRA. Exposure to RA resulted in significant, but modest, growth inhibition in only two of seven cell lines (clearCa-4 and chromphi-1, derived from a clear cell and a chromophilic carcinoma, respectively) with a maximum reduction of cell viability up to 83% of the control. However, the antiproliferative effect of RA was enhanced in combination with tumor necrosis factor-α. Using Northern blot analysis, RARα was detected in all cell lines; in contrast, no cell line expressed RARβ. Unlike Hoffman *et al.* [27], the authors concluded that there was no correlation between RAR status and RA response in RCC cell lines.

In summary, preclinical studies demonstrated that RA can induce direct anti-proliferative effects on human renal cell carcinomas *in vitro*. These effects, however, seem to be rather heterogeneous and of marked magnitude in few cell lines, only. The exact role of the expression of specific nuclear receptors remains controversial.

Clinical trials

The role of retinoids in the treatment of patients with renal cell carcinoma has been widely investigated during the last decade. The first promising clinical studies were published in 1995 by Atzpodien [32] and Motzer [26].

Atzpodien *et al.* conducted a phase I/II clinical trial to evaluate the sequential outpatient combination of s.c. IL-2, s.c. IFN-α, 5-fluorouracil (5-FU) and vinblastine (i.v.) in conjunction with oral 13-*cis*-RA (given continuously at 35 mg/m^2) [32]. Among 24 patients with progressive metastatic disease (seven of whom despite prior biochemotherapy), there were four complete remissions (lung and lymph nodes) and six partial remissions, for an overall objective response rate of 42%. An additional 13 patients achieved disease stabilization (54%; at a median of 2 months). Major RA-associated side-effects were not observed.

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Motzer *et al.* [26] presented a phase II trial of s.c. IFN-α in combination with 13-*cis*-RA (1 mg/kg/day, p.o.) including 44 patients with advanced RCC, who had not received IFN-α or RA before. Thirteen of 43 (30%) assessable patients achieved a major response (three complete and 10 partial); 16 of 43 patients had stable disease (37%) for at least 3 months. In the remaining 14 patients (33%), the disease progressed. Responding sites included lung and nodal metastases as well as bone disease and renal primary tumors. The median progression-free interval was 10+ months (range 8–19+ months), the median survival duration was 15.5 months. Toxicity was considerable; 18 patients (41%) had one or more dose reductions. Frequent side-effects, which were attributed to RA, included dry skin and mucous membranes, conjunctiva and hyperlipemia. Therapy was discontinued in nine patients (22%) for severe toxicity.

In 1997, Buer *et al.* [30] reported induction of apoptosis and objective tumor regression in response to 13-*cis*-RA in advanced RCC patients refractory to IFN-α, suggesting that RA may reverse IFN-α resistance in RCC. A total of 21 patients, pretreated with various IFN-α-based regimens, received s.c. IFN-α and p.o. 13-*cis*-RA (35 mg/m^2/day). There was one complete remission (pulmonary, hepatic) and four partial remissions (pulmonary, pleural), with an overall objective response rate of 24%. Median response duration was 8+ months. Moreover, nine patients (43%) achieved disease stabilization with a median duration of 8 months. Severe toxicity was not observed; however, the majority of patients complained about mucocutaneous dryness and moderate malaise.

Based on these promising results gained with combination biotherapy including RA, Stadler *et al.* [33] performed a multicenter phase II trial evaluating oral 13-*cis*-RA (1 mg/kg daily) added to an outpatient regimen of s.c. IL-2 and IFN-α in previously untreated patients with metastatic RCC. Eight of 47 assessable patients (17%) responded; four additional patients (8.5%) experienced a minor response in lung or soft tissue metastases. The median duration of response, including minor responses, was 42 weeks and median survival was 17 months. Significant cumulative toxicities were observed in 18 patients (38%); there was one therapy-related death. It was concluded that this combination therapy was at least modestly effective with an encouraging prolonged median survival, even though the overall response rate was similar to other studies of IL-2-based immunotherapy in RCC.

Theses clinical experiences raised substantial enthusiasm and were followed by multiple studies (summarized in Table 1). However, most trials failed to confirm and reproduce these early positive results. In 1997, a group around Berg and Motzer were the first to perform a phase II study to assess the antitumor effect of single-agent 13-*cis*-RA (1 mg/kg/day, p.o.; $n = 25$) as second-line treatment in patients with advanced RCC [34]. There was no major response achieved; only eight patients (32%) had stable disease for more than three months. The median overall survival was 11.4 months. At the dose administered, 13-*cis*-RA was declared inactive as a single agent in progressive RCC.

Wong *et al.* [35] observed 15% partial responses and 25% cases of stable disease treating 20 metastatic RCC patients with IFN-α (3–9 MU, s.c., daily) in combination with 13-*cis*-RA (1 mg/kg/day, p.o.). The median duration of response was 44 weeks (range 32–59 weeks). As overall response rates were low and toxicity considerable (35%), the authors did not recommend this combination as

Table 1 Results of RA-based regimens in the treatment of advanced RCC

Regimen	No. patients[e]	Response rate (CR+PR) (%)	Median response duration (months)	Median overall survival (months)	References
IL-2, IFN-α, 5-FU, vinblastine, 13-*cis*-RA	24	42 (17+25)	NA	NA	[32][c]
IFN-α, 13-*cis*-RA	43	30 (7+23)	10+	15.5	[26][c]
IFN-α, 13-*cis*-RA	21	24 (5+19)	8+	NA	[30][b]
13-*cis*-RA	25	0	–	11.4	[34][b]
IL-2, IFN-α, 13-*cis*-RA	47	17 (2+15)	13.4	17	[33][a]
IFN-α, ATRA	31	3 (0+3)	8	NA	[36][c]
IFN-α, 13-*cis*-RA	11	18 (0+18)	NA	NA	[43][b]
IFN-α, 13-*cis*-RA	25	20 (4+16)	5	23	[44][a]
IFN-α, 13-*cis*-RA	129	12 (4+8)	33	15	[42][a,d]
IFN-α, 9-*cis*-RA	26	4 (0+4)	36+	NA	[45][c]
IFN-α, 13-*cis*-RA, paclitaxel	20	5 (0+5)	7+	9.5	[40][c]
IFN-α, 13-*cis*-RA	20	15 (0+15)	10.2	9	[35][a]
IFN-α, 13-*cis*-RA	30	3 (0+3)	20	10	[37][a]
IFN-α, ATRA-IV	12	17 (0+17)	12.6+	NA	[41][c]
IL-2, IFN-α, 5-FU, 13-*cis*-RA	146	26 (8+18)	NA	27	[10][c,d]

[a]First-line therapy.
[b]Second-line therapy.
[c]Heterogeneous population, first- and second-line therapy.
[d]Randomized multicenter trial.
[e]Assessable for response. CR=complete response, PR=partial response, NA=not available.

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standard treatment of advanced RCC, even though 13-*cis*-RA seemed to lengthen the response to IFN-α.

Escudier *et al.* used a combined IFN-α/ATRA (p.o., 45 mg/kg/day, biweekly) regimen to treat 31 poor prognosis patients with advanced RCC [36]. Among all patients, there was only one partial remission (3%; 8 months); eight patients (26%) achieved stable disease. The partial remission was observed in a patient with lung metastases who had suffered disease progression during IL-2 pretreatment. Similar results were gained by Jaremtchuk *et al.* [37], even though they employed a phase II trial with previously untreated patients.

Based on early (pre)clinical findings indicating that combined IFN/RA application can increase the efficacy of paclitaxel in general as well as sensitivity to paclitaxel in bcl-2 and mutant p53 expressing RCC cell lines in particular [38,39], Vaishampayan *et al.* [40] conducted a phase II clinical trial on the combination of IFN-α, 13-*cis*-RA and weekly paclitaxel in 20 patients with advanced RCC. Only one objective partial response was observed in a patient with no prior treatment except for radical nephrectomy, who presented with lung metastases only.

Finally, Goldberg *et al.* performed a phase I/II trial combining liposome-encapsulated ATRA (ATRA-IV) plus IFN-α [41]. At 15 mg/m^2 ATRA-IV (TIW) and IFN-α (s.c. 5 MU, TIW), the authors reported partial remissions in two patients (17%) with acceptable toxicity and recommend this regimen for further investigation in patients with advanced RCC.

In the face of these heterogeneous and controversial data, there was a desperate need for randomized phase III studies. In 2000, again Motzer *et al.* [42] were the first to publish a phase III trial that was conducted to determine whether combination therapy with 13-*cis*-RA plus IFN-α was superior to IFN-α alone in patients with advanced RCC. 284 patients were randomized in this first line multicenter trial. IFN-α was given daily s.c., starting at a dose of 3 MU and escalated to 9 MU. Patients randomized to combination therapy received oral 13-*cis*-RA at 1 mg/kg/day plus IFN-α; 62% of the patients had two or more sites of metastases and half of the patients had undergone previous nephrectomy. There was no difference in the incidence of grade 2–4 toxicities between both arms. The overall response rate for patients treated with both agents (129 assessable patients) was 12% (five complete and 11 partial responses) and 6.8% (one complete and eight partial responses) for the group given IFN-α alone (132 assessable patients). Unfortunately, these results did not reach statistical significance ($p = 0.14$). Median duration of response in the group treated with the combination was 33 (range 9–50) versus 22 months (range 5–38 months) for the single-agent group ($p = 0.03$). 19% of patients treated with IFN-α plus 13-*cis*-RA were progression-free at 24 months, compared with 10% of patients treated with IFN-α alone ($p = 0.05$). Median survival time for all patients was 15 months, with no difference in survival between the two treatment arms. The authors concluded that the response proportion and survival did not improve significantly with the addition of 13-*cis*-RA to IFN-α therapy in patients with advanced RCC. However, RA significantly lengthened response to IFN-α therapy in patients with IFN-α sensitive tumors.

Just recently, Atzpodien *et al.* [10] published a prospectively randomized clinical phase III trial comparing the efficacy of three outpatient regimens comprising different combinations of IFN-α, IL-2, 5-FU or vinblastine and 13-*cis*-RA (p.o. 20 mg, 3 times daily). Forty-one arm A [s.c. IFN-α/s.c. IL-2/i.v. 5-FU ($n = 132$)] patients (31%) achieved objective responses compared with 38 arm B [arm A combined with 13-*cis*-RA ($n = 146$)] patients (26%). In arm C [s.c. IFN-α/i.v. vinblastine ($n = 63$)], the overall objective response rate was 20%. There were no statistically significant differences in objective response rates comparing all three arms. Arm B (regimen of arm A plus 13-*cis*-RA), but not arm A, showed a significantly improved progression-free survival compared with arm C (median 7 versus 5 months, $p = 0.03$). However, arm A and arm B median progression-free survival did not differ significantly, which could have been ascribed to the inclusion of 13-*cis*-RA (6 versus 7 months). Both arm A and arm B led to significantly improved overall survival compared with arm C (median overall survival; 25, 27 and 16 months, respectively). Nevertheless, arm A and B overall survival did not differ significantly ($p = 0.97$). All three IFN-α-based therapies were moderately or well tolerated; no toxic death occurred. Malaise, chills, nausea, diarrhea, arrhythmias and hypotension were most prominent in the group receiving 13-*cis*-RA even though no statistical significance was reached. In conclusion, this study indicated the advantage of a combined IFN/IL-2-based regimen compared to IFN/vinblastine; however, it also demonstrated that addition of 13-*cis*-RA to the former regime did not yield considerable benefit.

Conclusions

Retinoids have proven ineffective as single agents in patients with RCC. Even though preclinical data had been moderately promising, at present the addition of retinoids to established therapeutic regimens has failed to significantly improve response or survival in lager randomized controlled clinical trials. The most frequently used combination of IFN and RA has a low overall response rate and substantial toxicity, and cannot be recommended as a standard treatment for advanced RCC, despite several studies supporting the evidence that the addition of RA may lengthen the responses to IFN-α.

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However, as effective treatment for the majority of patients with advanced RCC is lacking, further investigations regarding the exact characterization of RA action are warranted as retinoids have proven to effectively influence proliferation and differentiation in RCC and other malignancies. A detailed description of the molecular processes modulated by these agents will serve to better define their role in the prevention and treatment of human cancer including RCC and to tailor specific targeted therapies in combination with other compounds.

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