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REVIEW

A. J. Schrader · Z. Varga · A. Hegele · S. Pfoertner
P. Olbert · R. Hofmann

Second-line strategies for metastatic renal cell carcinoma: classics and novel approaches

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Abstract *Objectives*: Renal cell carcinoma is an aggressive malignancy with a high propensity for both early and metachronous regional and distant metastasis. While surgical resection is the mainstay of therapy for patients with localized disease, the prognosis for patients with distant metastasis is poor with a 5-year survival rate of less than 10%. Response rates to first-line immunotherapy or immunochemotherapy range from 10–35%; responses achieved are predominantly partial remissions of short duration. Until today, there is no standard therapeutic procedure for the growing number of patients who relapse following first-line therapy and desire further active treatment. *Materials and Methods*: This article reviews classic and recent publications about second- and third-line approaches, their potential efficacy and toxicity. *Results*: Several novel approaches have raised well-founded hope. Especially the application of monoclonal antibodies targeting VEGF signalling as well as different receptor tyrosine kinase inhibitors have the potential to change the face of second-line treatment of patients with metastatic RCC. Both groups of agents are focused in current phase III trials, either as mono- and/or combination therapy. *Conclusions*: Until today, second-line treatment of patients with metastatic RCC progressing under therapy with biological response modifiers remains an unresolved issue. The results of ongoing clinical trials evaluating novel targeted approaches can be expected with suspense.

A. J. Schrader (✉) · Z. Varga · A. Hegele · P. Olbert
R. Hofmann
Department of Urology, Philipps-University Medical School,
Baldingerstrasse, 35043 Marburg, Germany
E-mail: ajschrader@gmx.de
Tel.: +49-6421-2863013
Fax: +49-6421-2865590

A. J. Schrader · S. Pfoertner
Department of Cell Biology and Immunology, German Research
Centre for Biotechnology, Mascheroder Weg 1,
38124 Braunschweig, Germany

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Introduction

Renal cell carcinoma (RCC) is a common urologic tumour 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 (Kirkali et al. 2001; Pantuck et al. 2001). 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 complete resection of the primary tumour by radical nephrectomy, relapse occurs in 20–30% of patients (Whelan 2003). Those who present with metastasis have a 5-year survival of less than 10%; the overall 5-year survival rate is 60% (Kirkali and Oebek 2003).

RCC is insensitive to traditional cytotoxic agents as well as radiotherapy (Amato 2000). Until today, 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 (Law et al. 1995; Minasian et al. 1993; Motzer and Russo 2000; Whelan 2003; Yang et al. 2003b). 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 (Amato 2000; Atzpodien et al. 2004; Heidenreich et al. 2003; Motzer and Russo 2000). However, responses are predominantly partial remissions of short duration (Motzer and Russo 2000; Whelan 2003). Until today, there is no standard treatment for patients who fail immunotherapy resulting in a multitude of experimental second- and third-line therapeutic regimens published during the last decade. This review scrutinizes these publications and focuses on established and the

most promising novel approaches. Moreover, it is intended to support the urologist or oncologist in finding an adequate therapeutic regimen for the growing number of patients with progressive metastatic RCC refractory to first-line immuno(chemo)therapy who desire further active treatment.

Chemotherapy

In metastatic RCC, most conventional antineoplastic drugs have yielded no or little efficacy. One reason might be the overexpression of multidrug resistance (MDR) genes/P-glycoprotein 170 which act as an efflux pump, reducing intracellular concentration of drugs. A number of excellent reviews provide a full discussion of this inherent resistance of metastatic RCC to chemotherapy and emphasize the need for new development in overcoming drug resistance (Amato 2000; Motzer and Russo 2000; Yagoda et al. 1995). In the following, we will focus only on the most interesting, promising and recent approaches.

Fluorouracil (5-FU) is a standard pyrimidine analogue chemotherapeutic agent that depletes intracellular deoxynucleotide triphosphates, including deoxythymidine triphosphate, via inhibition of thymidylate synthetase (Schilsky 1992). As a single agent, it has modest activity in metastatic RCC, producing almost exclusively partial responses in 5–10% of patients (Hartmann and Bokemeyer 1999; Yagoda et al. 1995). As other refractory tumours such as pancreas, gastric and colorectal appeared to respond to a continuous infusion therapy with 5-FU; Kish et al. (1994) treated 61 patients with 300 mg 5-FU/m^2/day for 7 days. The underlying concept was that in low growth fraction tumours, the continuous infusion, as opposed to bolus therapy, might increase the attack rate of cancer cells during sensitive phases of the tumour growth cycle. However, only three patients (6%) achieved objective tumour remissions; disease stabilization was observed in 25 out of 53 evaluable patients (47%). The median survival did not exceed 12 months (Table 1).

On the basis of the synergistic effects of 5-FU and oxaliplatin in the treatment of colorectal carcinoma (Bleiberg and de Gramont 1998) and a promising case report (Chauffert et al. 1998), Chaouche et al. (2000) initiated a second-line pilot study for patients with metastatic RCC combining these agents. Fourteen progressive patients, who had previously been treated with IL-2 alone or in combination with IFN-α, received six courses of oxaliplatin (85 mg/m^2/day; day 1), 5-FU (1g/m^2/day; days 1 + 2), and folinic acid (200 mg/m^2/day; days 1 + 2). No grade ≥3 toxicities were reported. However, disease stabilization was observed only in two patients (14%).

Rini et al. (2000) achieved partial remissions in 5 out of 34 patients (15%) with metastatic RCC refractory to previous treatment with biologic response modifiers using the combination of 5-FU (150 mg/m^2/day; continuous infusion on days 1–21) with weekly gemcitabine (600 mg/m^2/day; days 1, 8, 15) in a 28-day cycle. The response duration ranged from 7 to 14 months (median, 10 months). The authors reckon that this combination regimen has at least modest activity in patients with metastatic RCC.

Wenzel et al. (2003) used capecitabine, an orally administered fluoropyrimidine carbamate that is activated by a three-step enzymatic conversion to 5-FU, to treat several patient cohorts with metastatic RCC refractory to immunotherapy in second- and third-line settings. In a subgroup of 24 patients who received second-line capecitabine monotherapy at 2500 mg/m^2 daily divided into two doses for 14 days, followed by a 7-day rest, the authors observed a clinical benefit in 22 patients (92%). The median time to treatment failure was 6.5 months, the overall survival 3–50+ months (median, 11.5 months). Capecitabine monotherapy was well tolerated and all patients completed the therapy on an outpatient basis. In further studies the addition of biological response modifiers (IL-2, IFN-α) did not improve response rates or survival. It was concluded that capecitabine monotherapy is a promising candidate for prospective phase III trials. However, these encouraging results could not be reproduced by Pagliaro et al. (2003), who used the same regimen.

Stadler et al. (2004) initiated a phase II multicentre study to assess the activity of capecitabine (830 mg/m^2; twice daily; days 1–21; q28) in combination with gemcitabine (1 g/m^2; days 1, 8, 15; q28). In these dosages they observed partial responses in 8 out of 55 evaluable patients for a response rate of 15%. Median duration of response was 7.1 months, median time to progression was 5.1 months. However, side effects were reported to have been considerable. Main grade 3/4 toxicities included neutropenia (40%), anaemia (15%), and nausea (11%).

Waters et al. (2003) conducted a similar phase II trial. Sixteen patients with heavily pretreated metastatic RCC received capecitabine at 1,300 mg/m^2 twice daily for 14 days every 3 weeks plus gemcitabine at 1,200 mg/m^2 on days 1 and 8. In 14 evaluable patients, an objective response rate of 21% was achieved. Disease stabilization was observed in five patients (36%). However, grade 3/4 toxicity included diarrhoea (13%), hand–foot syndrome (19%), rash (13%), neutropenia (56%), thrombocytopenia (19%), and infection (19%). In addition, two patients (13%) had thromboembolic events during therapy. Comparable results were reported by Tannir et al. (2005).

Even though the results of the discussed studies are heterogeneous, 5-FU and its pro-drug capecitabine appear to be effective in a significant fraction of patients suffering from metastatic RCC. However, toxicity is considerable and dose dependent. To evaluate its future significance, further studies are needed to assess its efficacy in homogeneous patient cohorts with defined pretreatment risk profiles (Motzer et al. 2004a).

Table 1 Results of second-line regimens in the treatment of advanced renal cell carcinoma

Regimen	Number of patients[a]	Objective remissions[b] (%)	Stable disease (%)	Median overall survival (months)[c]	References
Chemotherapy					
Vinblastine	14	7	29	NA	Lopez Hanninen et al. (1993)
5-FU[d]	53	6	47	12	Kish et al. (1994)
5-FU, oxaliplatin, folinic acid	14	0	14	NA	Chaouche et al. (2000)
5-FU, gemcitabine	34	15	NA	NA	Rini et al. 2000
Capecitabine	24	NA	91.7[e]	11.5	Wenzel et al. (2003)
Capecitabine[d]	14	0	21	NA	Pagliaro et al. (2003)
Capecitabine, gemcitabine[d]	55	15	NA	NA	Stadler et al. (2004)
Capecitabine, gemcitabine	14	21	36	NA	Waters et al. (2003)
Capecitabine, gemcitabine	75	9	NA	14+	Tannir et al. 2005
Temozolomide	45	18	42	11.9[f]	Heidenreich et al. (2005)
Carboxyamidotriazole	52	2	25	11	Friedland et al. (2002)
Irinotecan, cisplatin, mitomycin C	31	3	55	9.2	Shamash et al. (2003)
Ixabepilone[d]	39	10	13	NA	Zhuang et al. (2004)
Chemoimmunotherapy					
IFN-α, vinblastine	20	15	65	NA	Lopez Hanninen et al. (1993)
IFN-α, vinblastine	13	15	38	NA	Paolorossi et al. (1995)
Vinorelbine, IFN-α	37	8	46	15	Schmidinger et al. (2000)
IL-2, IFN-α, 5-FU	35	6	40	14	Ravaud et al. (2003)
Immunotherapy					
IL-2	13	31	54	7+	Lissoni et al. (1992)
IL-2	65	5	6	NA	Escudier et al. (1999)
IFN-α	48	2	19	NA	Escudier et al. (1999)
IFN-α, 13-*cis* RA	21	24	43	NA	Buer et al. (1997)
13-*cis* RA	25	0	32	11.4	Berg et al. (1997)
Thalidomide-based therapy					
Thalidomide	25	0	12	NA	Famoyin et al. (2004)
Thalidomide, IL-2	12	0	33	12+	Schrader et al. (2005)
Thalidomide, capecitabine, IFN-α	14	0	38	NA	Minor and Amato (2004)
Monoclonal antibodies					
Bevacizumab	39	10	54	16	Yang et al. (2003a)
G250	20	0	30	15+	Bleumer et al. (2004)
Receptor kinase inhibitors					
SU011248	63	40	33	16	Motzer et al. (2005)
BAY 43-9006[g]	63	38	28	NA	Ratain et al. (2004)
AG-013736	52	40	29	NA	Rini et al. (2005)
PTK787 (PTK/ZK)[d]	37	3	62	NA	George et al. (2003)
CCI-779[d]	111	7	43	15	Atkins et al. (2004)
Miscellaneous					
Dolastatin-10	30	10	10	NA	Pitot et al. (2002)
Motexafin gadolinium	22	0	36	NA	Jac et al. (2005)
NST, DLI	19	53	NA	11.5	Childs et al. (2000)

IFN interferon, *RA* retinoic acid, *5-FU* 5- fluorouracil, *NST* nonmyeloablative stem cell transplantation, *DLI* donor lymphocyte infusion, *NA* not available

[a] Assessable for response

[b] Complete or partial remission

[c] From the start of second-line treatment

[d] First- and second-line

[e] Partial remission plus stable disease

[f] Mean

[g] Response defined as 25% tumour reduction, stable disease as tumour burden within 25% of baseline

Only recently, Heidenreich et al. (2005) reported about first results of their phase II trial employing temozolomide in cytokine-refractory metastatic RCC. Temozolomide is an imidazotetrazinone alkylating agent with full bioavailability which is established in the treatment of several solid neoplasms such as gliomas and melanoma (Brandes et al. 2000; Friedman et al. 2000; Middleton et al. 2000). They treated 45 patients who had previously failed immunochemotherapy according to the Hannover protocol (s.c. IL-2, IFN-α, and i.v. 5-FU), with six cycles of oral temozolomide at 200 mg/m^2 (days 1–5; q28). After a mean follow-up of 25 months, 8 patients (18%) demonstrated a partial response, 19 patients (42%) exhibited disease stabilization. The mean time to progression in responding patients was 7.2 months, and mean survival was 11.9 months. Side effects were moderate with grade 2 nausea, fatigue, and headache in no more than 25% of patients. The authors conclude that temozolomide might be a valuable therapeutic alternative in immunorefractory metastatic RCC with tolerable side effects. Similar results were reported by Sunkara et al. (2004), who combined temozolomide

with IFN-α in a first-line setting. However, using the same regimen, Park et al. (2002) observed disease stabilization in 3/12 patients (25%), only, with a median response duration of 3.5 months. They suspected that the limited efficacy of temozolomide in metastatic RCC was due to high levels of alkylguanine–DNA alkyltransferase (AGT) expressed in the tumour.

Irinotecan is a topoisomerase-1 inhibitor that has shown activity in renal xenografts (Miki et al. 1998). In other tumour types, synergy has been demonstrated with either cisplatin (Boku et al. 1999) or mitomycin C (Gil-Delgado et al. 2001). Therefore Shamash et al. (2003) employed a novel combination chemotherapy of cisplatin (40 mg/m^2/day; days 1 + 15), irinotecan (100 mg/m^2/day; days 1 + 15), and mitomycin C (6 mg/m^2/day; day 1) in a 28-day cycle. Thirty-three heavily pretreated patients with immuno(chemo)therapy refractory RCC were treated in this trial; 31 were evaluable for response. One patient (3%) had a partial response, eight (26%) had minor responses and nine (29%) had stable disease. The median progression-free interval was 4.8 months, median overall survival 9.2 months. Quality-of-life assessment did not change significantly during therapy. The most common grade 3 toxicities were malaise and neutropenia, which occurred in 17 and 19% of cycles. As a degree of non-cross-resistance to cytokine therapy was seen, the authors conclude that this triple chemotherapy might be particularly considered in patients with renal cancer following failure of cytokine-based treatment.

In conclusion, only few chemotherapeutic regimens have shown significant activity in metastatic RCC. Moreover, results published by different groups vary considerably. Therefore the future role of certain cytotoxic drugs might be their use in combination with biotherapy or targeted therapy (see below).

Chemoimmunotherapy

Fossa et al. (1992) published a randomized phase III trial comparing the efficacy of IFN-α with or without vinblastine in patients with metastatic RCC as first-line therapy. The combination of both agents resulted in a doubling of the response rate (24 vs 11%), however, with no impact on overall survival. On the basis of these results, Lopez Hanninen et al. (1993) conducted a pilot study for pretreated patients addressing the same topic. Fourteen patients were treated with vinblastine (6 mg/m^2, weeks 2, 5, 8), only, 20 patients received combination therapy including IFN-α at 6 million IU/m^2 thrice weekly. Objective remissions were seen in 7 and 15%, stable disease in 29 and 65% of patients, respectively, favouring the combination treatment. Either regimen was well tolerated with moderate systemic toxicity. Similar results were reported by Paolorossi et al. (1995), who administered vinblastine in combination with a lower dosage of IFN-α (3×10^6 IU, thrice weekly). They achieved partial responses and disease stabilization in 15 and 38%, respectively.

Schmidinger et al. (2000) designed a second-line protocol for 37 patients failing or relapsing after first-line treatment with subcutaneous IFN-γ and IL-2. They combined vinorelbine (30 mg/m^2; 22q) with IFN-α (4.8×10^6 IU; thrice weekly) and achieved partial responses in three (8%) and disease stabilization in 17 patients (46%) for an overall response rate of 54%. Median time to disease progression and median overall survival were 9 and 15 months, respectively. No major toxicities occurred; the most common side effects were anaemia and neutropenia in 30% of all patients.

At least in western Europe, one of the most popular first-line regimens for metastatic RCC comprises the combined application of IL-2, IFN-α and 5-FU (Atzpodien et al. 2004). It is based on (pre)clinical data suggesting synergistic effects between IL-2 and 5-FU on one hand and IFN-α and 5-FU on the other, added to the well-known synergism of the association of IL-2 and IFN-α (Cameron et al. 1988). The interaction between IFN-α and 5-FU has been most intensively studied. IFN-α induces thymidine phosphorylase, enhancing the conversion of 5-FU to the active 5-fluorodeoxyuridine monophosphate (Morita and Tokue 1999; Wadler et al. 1990). Moreover, IFN-α inhibits the intracellular uptake of thymidine (Pfeffer and Tamm 1984) and thymidilate synthase (Elias and Sandoval 1989). Thus Ravaud et al. (2003) evaluated s.c. IL-2, s.c IFN-α, and i.v. 5-FU also as second-line treatment in patients with metastatic RCC. Thirty-five patients were entered into the trial, all suffering from progressive metastatic disease following immunotherapy with IFN-α and/or IL-2. Two patients (6%) achieved objective responses for 6 and 56+ months, and 14 patients (40%) had stable disease for a median time of 4 months (range, 2–16 months). The median survival of all patients was 14 months. Seventeen patients (49%) experienced grade 3 toxicity (e.g. fever, decrease on performance status, nausea, hypotension, mucositis, anaemia, and neutropenia). The only predictive factor for progression to the second-line treatment was the efficacy of the primary immunotherapy. Parameters favourably affecting survival were a good general performance status at initiation of second-line treatment, the delay from primary tumour to metastasis and the response to second-line therapy. Hence the authors recommend the second-line application of this combination regimen for selected patients who show an objective response at evaluation of first-line immunotherapy, who have a good general status, and a delay from the primary tumour to metastasis longer than 12 months.

Immunotherapy

Lissoni et al. (1992) performed a pilot study to evaluate the efficacy of subcutaneous immunotherapy with IL-2 alone as a second-line treatment in advanced RCC patients who failed to first-line therapy with IFN-α plus vinblastine. Thirteen evaluable patients received IL-2 at

9×10^6 IU/m^2 twice daily for 2 days, followed by 1.8×10^6 IU/m^2 twice daily for 5 days per week for 6 weeks. Partial remission and disease stabilization were seen in 4 (31%) and 7 (54%) patients, respectively, according to an overall response of 85%. The median time to disease progression for all responding patients (partial remission and stable disease) was 7+ months. The authors drew the conclusion that IL-2 monotherapy is an effective and well-tolerated treatment in advanced RCC patients progressing under IFN-α based therapy.

Unfortunately, later studies could not confirm these encouraging results. To determine whether either IL-2 or IFN-α might be efficient after failure of the other, Escudier et al. (1999) analysed a series of 113 patients treated with either agent as second-line treatment. Forty-eight patients, who had progressed under IL-2 received IFN-α, and 65 patients were treated with IL-2 after failure of IFN-α. IL-2 was administered as a continuous intravenous infusion for 5 days 18×10^6 IU/m^2/day, and IFN-α was given subcutaneously three times weekly at 18×10^6 IU. In both groups, toxicity during second-line treatment was similar to that observed during first-line treatment. One (2%) and nine (19%) out of 48 patients receiving second-line IFN-α achieved a partial remission and stable disease, respectively. Regarding second-line IL-2, 3 (5%) out of 65 patients developed a partial remission, 4 (6%) patients achieved disease stabilization. There was only one long-term response (18 months); no difference in survival was observed between either group (18 and 19 months from the beginning of first-line treatment in the IFN-α and IL-2 group, respectively). The authors concluded that only few patients with good prognostic factors responded to this cross-over treatment.

In 1997, Atzpodien and co-workers treated 21 patients with metastatic RCC resistant to prior IFN-α-based regimens, with a combination of 13-*cis* RA and IFN-α. They observed one complete (5%) and four (19%) partial remissions with a median duration of 8+ months. An additional 9 patients (43%) achieved disease stabilization with a median duration of 8 months. According to the authors, these results suggested that 13-*cis* RA might reverse IFN-α resistance in a significant fraction of patients with metastatic RCC. Unfortunately, other groups could not reproduce these promising results gained with RA-based regimens (Berg et al. 1997; Schrader et al. 2004).

Thalidomide-based therapy

Thalidomide is an immunomodulatory agent that blocks angiogenesis (D'Amato et al. 1994), inhibits cytokines (TNFα, bFGF, VEGF) (Adlard 2000; D'Amato et al. 1994), and modifies cell adhesion molecule expression (Amato 2003). On the basis of this activity, thalidomide has recently been applied in the treatment of various malignancies including metastatic RCC. Objective response rates in first-line settings ranged from 0 to 22% (median, 5.2 months); disease stabilization was achieved in 13–64% of patients (Amato 2003; Hernberg et al. 2003; Rini and Small 2005). Nevertheless several authors reported considerable thalidomide related, dose-dependent toxicity, especially somnolence, constipation, lethargy, venous thromboembolism, and neurotoxicity, increasing with prolonged therapy (Adlard 2000; Amato 2003; Desai et al. 2002; Escudier et al. 2002; Nathan et al. 2002).

A first study of s.c. IL-2 in combination with thalidomide (400 mg/day) was presented by Amato et al. (2003). In this phase II study with 37 patients who had received no prior systemic therapy, 15 patients (41%) responded and 11 patients (30%) achieved stable disease. The treatment was well tolerated with no reported grade ≥3 adverse events, time on treatment ranged from 3 to 15 months. Similar promising results were reported by Morgan et al. (2005), who added GM-CSF to Amato's regimen. Kedar et al. (2004) were the first to use an IL-2/thalidomide combination for patients who were refractory to first-line systemic treatment. They retreated four patients with advanced metastatic RCC, who had experienced disease progression on IL-2 with the same IL-2-based regimen combined with oral thalidomide (300 mg/day). Two patients (50%) achieved partial responses and prolonged disease stabilization (22+ and 18+ months).

On the basis of these encouraging results, we hypothesized that the addition of thalidomide to IL-2 might result in improved response rates also in a significant fraction of patients with progressive disease refractory to prior immuno(chemo)therapy. Twelve patients with metastatic RCC were treated with a combined IL-2/thalidomide regimen (Schrader et al. 2005). Oral thalidomide was started at 200 mg/day and escalated after 2 days to 400 mg/day at week 0. IL-2 at 7 MIU/m^2 was given by subcutaneous injection, starting at week 1, days 1–5, weeks 1–4, with rest from IL-2 at weeks 5 and 6. All patients had advanced disease and poor performance status, associated with disease progression following primary local and systemic therapy and several salvage regimens. However, all patients desired further active treatment hoping to achieve disease stabilization and to maintain acceptable quality-of-life throughout the remaining period. No objective response was observed, but disease stabilization was achieved in four patients (33%) for 9 to 14+ months. Three patients (25%) still remain progression-free, however all patients discontinued treatment due to substantial toxicity (lethargy, constipation, and flu-like symptoms). During the course of therapy (3–44 weeks, median, 20 weeks), eight patients (67%) required IL-2 dose reduction. The median survival from the start of thalidomide-based treatment for all patients was 12+ months. Thus the results of our pilot clinical study were in accordance with those of recent single agent thalidomide trials in patients with poor prognosis RCC (Famoyin et al. 2004). In contrast, we could not reproduce the encouraging results by Kedar et al. (2004), suggesting that the combined

application of IL-2 and thalidomide could considerably improve response rates in heavily pretreated patients.

Minor and Amato (2004) studied the activity of usual dosages for thalidomide (400 mg/day) and capecitabine (600 mg/m^2/bid; days 1–14; q21) combined with a low daily dosage of IFN-α (1×10^6 IU/day; s.c.) in 16 patients with previously treated symptomatic RCC patients. No objective responses were seen in 14 evaluable patients. Six patients (38%) were stable at 6 months. In contrast to our study combining thalidomide and IL-2, only few dosage reductions were needed with this regimen. However, neither combination produced objective responses employed in a second-line setting.

Monoclonal antibodies

Antiangiogenic strategies for the treatment of cancer have generated widespread enthusiasm based on promising in vitro and preclinical studies. The concepts that growing tumours require the manufacture of new blood vessels and that very little of the rest of the normal adult body has such a requirement have led to the belief that there is valuable therapeutic potential in this area (Fig. 1). The von Hippel–Lindau tumour suppressor gene is mutated both in hereditary RCC and in most cases of sporadic clear-cell RCC. One consequence of these mutations is the overproduction of vascular endothelial growth factor (VEGF) through a mechanism involving hypoxia-inducible factor alpha (Iliopoulos et al. 1996; Maxwell et al. 1999; Mukhopadhyay et al. 1997; Rini and Small 2005). On the basis of these findings, Yang et al. (2003a) published a highly interesting randomized double-blind placebo-controlled phase II study evaluating bevacizumab, a neutralizing antibody against VEGF, in 116 patients with metastatic RCC. All patients had received prior systemic treatment, mainly IL-2. They compared placebo ($n=40$) with bevacizumab at doses of 3 mg ($n=37$) and 10 mg ($n=39$) per kilogram of body weight, given every 2 weeks. Toxic effects were mild, with reversible hypertension and asymptomatic proteinuria predominating. Median time to progression in the group receiving 10 mg of bevacizumab per kilogram was 4.8 months and thus significantly longer than that in the placebo group (median, 2.5 months; $P<0.001$, log rank). The difference between the time to progression of disease in the group receiving 3 mg of the antibody per kilogram (median, 3.0 months) and that in the placebo group was of borderline significance. Only four patients had partial responses, all had received high-dose bevacizumab. There was no significant difference in overall survival between each group; however, cross-over treatment in case of disease progression was permitted in this study.

A different target gene was chosen by Maisey et al. (2004). As TNF-α has also been found to be overexpressed in a significant proportion of RCC, they performed a phase II study of infliximab, a chimeric human/mouse monoclonal antibody against TNF-α, in 15 heavily pre-treated patients with progressive metastatic RCC. Three objective responses (20%) were observed; again toxicity was relatively mild.

WX-G250 is a monoclonal antibody which recognizes the carbonic anhydrase IX (CA-IX MN/G250) antigen, a transmembrane glycoprotein that is expressed in >90% of RCC of the clear cell type (Bleumer et al. 2004). Twenty patients with progressive RCC and prior immunotherapy were treated with 50 mg WX-G250 once a week for at least 12 weeks. None of the patients experienced any drug-related grade ≥3 toxicity. Six patients (30%) had stable disease and received extended treatment. The median survival after the start of the treatment was 15+ months (Bleumer et al. 2004). As the treatment has been very well tolerated with hardly any side effects and as WX-G250 seems to be able to modulate metastatic RCC to a certain extent, just recently an adjuvant randomized phase III study has been started to evaluate the efficacy of this antibody in high-risk patients after nephrectomy.

Recent data indicate that the combination of monoclonal antibodies with different specific receptor blockers might be even more effective. Hainsworth et al. (2004) presented results of their phase II trial combining bevacizumab (10 mg/kg, i.v., q2 weeks) with erlotinib (150 mg p.o., daily), an epidermal growth factor (EGF) receptor antagonist, in 57 patients with metastatic RCC. Objective response rates and disease stabilization were 25 and 62%, respectively. Median progression-free survival was 11 months; 78% of all patients were alive at 12 months (Spigel et al. 2005). Even though patients included in this trial were predominantly in good clinical condition and only 40% of patients had received prior systemic treatment, these results were particularly promising and prompted the same group to initiate a new phase II study. Here, a third drug, imatinib (a PDGF receptor antagonist) was added to their successful regimen; first results are expected shortly and may raise hope for future first- and second-line use (Hainsworth et al. 2005).

Taken together, the application of monoclonal antibodies, especially those targeting VEGF signalling, seems to be a promising approach with low toxicity.

Receptor kinase inhibitors

On the basis of the rationale that targeting key molecules or combinations of molecules in signal transduction pathways can achieve clinical responses in various cancer entities, SU011248 was developed as an oral multitargeted receptor tyrosine kinase (RTK) inhibitor. It is a small molecule that potently inhibits platelet-derived growth factor receptors (PDGFR) α and β, VEGF receptor 1 and 2, KIT, and FLT3 (fms-related tyrosine kinase/Flk2/Stk-2), and therefore has both direct antitumour and antiangiogenic properties (Abrams et al. 2003; O'Farrell et al. 2003). Motzer and co-workers initiated a phase II trial designed to evaluate the efficacy

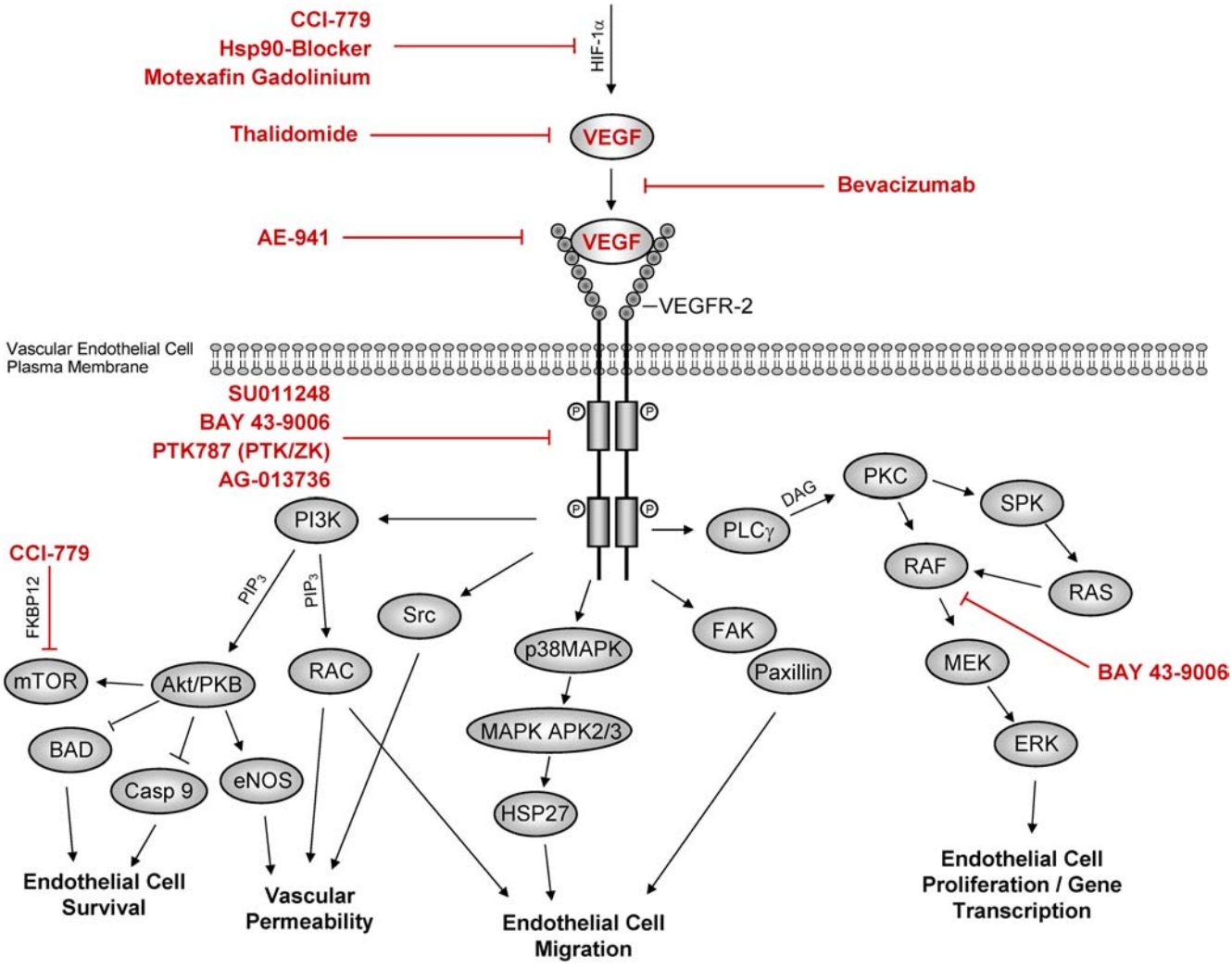

Fig. 1 Specific targeting of VEGF receptor signalling. Binding of VEGF to its receptor leads to dimerization and autophosphorylation of the intracellular receptor tyrosine kinases. Subsequently, several downstream protein pathways are activated, leading to biologic effects on endothelial cells [only the major proteins in each pathway are depicted (Cross et al. 2003; Rini and Small 2005)]. Motexafin gadolinium inhibits thioredoxin reductase which is implicated in activation of hypoxia-inducible factor-1α. Hsp90 blockers inhibit the proper folding of HIF-1α protein. Bevacizumab binds VEGF protein, preventing its interaction with the receptor. Thalidomide is supposed to reduce transcription of VEGF. AE-941 may compete with VEGF for binding with VEGFR-2. SU011248, AG-013736, PTK787, and BAY 43-9006 inhibit phosphorylation of the VEGF receptor. BAY 43-9006 additionally inhibits Raf-kinase enzyme. CCI-779 inhibits mTOR and therefore cell cycle progression, cell proliferation, survival and mobility, and—in addition—HIF-1α protein translation. Abbreviations: *Akt*/*PKB* protein kinase B, *DAG* 1,2-diacylglycerol, *eNOS* endothelial nitric oxide synthase, *Erk* extracellular receptor kinase, *FAK* focal adhesion kinase, *FKBP12* FK-binding protein 12, *HIF* hypoxia-inducible factor, *HSP* heat-shock protein, *MAPKAP 2*/*3* MAPK-activating protein kinase-2 and 3, *MEK* mitogen and extracellular kinase, *mTOR* mammalian target of rapamycin, *p38MAPK* p38 mitogen-activated protein kinase, *PKC* protein kinase C, *PLC* phospholipase C, *SPK* sphingosine kinase, *PI3K* phosphoinositide 3-kinase, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor

and toxicity of SU011248 in the treatment of metastatic RCC refractory to prior systemic cytokine-based therapy. Sixty-three patients were treated with repeat cycles of SU011248 orally at 50 mg daily for 4 weeks followed by a two-week rest period (Motzer et al. 2004b, 2005). Eventually, 25 (40%) and 21 (33%) patients achieved partial responses and stable disease, respectively, for an overall response of >70%. Of the 25 patients who achieved objective remissions, the median duration of response was 10+ months (range, 2–19+ months). The median time to progression and median survival were 8.3 and 16 months, respectively (Motzer et al. 2005). The toxicity profile was acceptable with mostly grade 1/2 events including fatigue/asthenia (78%), nausea (56%), diarrhoea (51%), and stomatitis (44%) (Motzer et al. 2004b). Grade 3/4 toxicities included lymphopenia (30%), elevated lipase (21%), and amylase (8%) without clinical signs of pancreatitis. The authors concluded that SU011248 exhibits promising antitumour activity; a randomized phase III trial versus IFN-α monotherapy in

untreated metastatic RCC patients is currently being conducted (Rini and Small 2005).

BAY 43-9006 is an orally bioavailable bi-aryl Raf-kinase inhibitor, with demonstrated inhibition of Ras-dependent human tumour xenograft models (Lyons et al. 2001). It has also shown direct inhibition of VEGFR-2/3 and PDGFR signalling (Rini and Small 2005). A phase II study with BAY 43-9006 (400 mg bid) has recently been reported in 65 patients with refractory metastatic RCC (Ahmad and Eisen 2004; Ratain et al. 2004). Of 63 assessable patients who had reached the initial 12-week assessment, 25 patients (38%) achieved a response, which was defined in this trial as 25% tumour reduction in bidimensional measurements. Another 18 patients (28%) achieved stable disease (defined as tumour burden within 25% of baseline). Toxic effects were manageable and included hypertension, oedema, diarrhoea, hand and foot syndrome, and rash. A phase III trial is under way; preliminary results indicate that BAY 43-9006 significantly prolongs progression-free survival compared with placebo in patients with previously treated advanced RCC (Escudier et al. 2005).

PTK787 is an oral selective tyrosine kinase inhibitor blocking VEGFR-1/2/3 and PDGFR-β signalling. A phase I/II trial of PTK787 in metastatic RCC has recently been reported. Clinical activity observed in 37 evaluable patients included a partial response in one patient (3%) and minor responses in six patients (16%) with a median time to progression of 5.5 months. A further 17 patients (46%) achieved stable disease. The most common adverse events observed were nausea (59%), fatigue (41%), vomiting (35%), and dizziness (29%) (George et al. 2003).

Only recently, Rini et al. (2005) reported about early results with AG-013736, which is another oral small molecule with potent inhibitory effects against the VEGF receptors 1 and 2 and PDGF-ß receptor. Fifty-two patients with failure of one prior cytokine-based therapy were treated with repeat 4-week cycles at 5 mg twice daily. In this phase II trial 21 patients (40%) achieved a partial response, 15 patients (29%) remained on study with stable disease. Drug-related grade 2 hypertension was observed in 17 patients (33%), and one patient was discontinued for worsening hypertension. Other grade 1/2 events included fatigue (29%), nausea (29%), diarrhoea (27%), hoarseness (19%), anorexia (17%), and weight loss (15%).

CCI-779 is a derivative of rapamycin, a macrolide antibiotic. Its mechanism of action is to inhibit the kinase mammalian target of rapamycin (mTOR), thereby suppressing growth and proliferation in tumour cells (Huang and Houghton 2003; Morgensztern and McLeod 2005). By targeting mTOR (a serine/threonine kinase), CCI-779 indirectly downregulates mRNA expression of HIF-1α as well as several proteins required for progression through the cell cycle, finally causing G_1 arrest (Amato 2005; Atkins et al. 2004; Lam et al. 2005). In a recent phase II study, 111 patients with advanced RCC were randomly assigned to receive weekly infusions of one of three doses of CCI-779 (25, 75, or 250 mg). The vast majority had been pretreated with (chemo)immunotherapy. CCI-779 produced an objective response rate of 7% (one complete response and seven partial responses) and minor responses in 26% of these advanced RCC patients. Median time to tumour progression was 5.8 months and median survival was 15 months. Neither toxicity nor efficacy was significantly influenced by CCI-779 dose level. The most frequently occurring CCI-779-related adverse events of all grades were maculopapular rash (76%), mucositis (70%), asthenia (50%), and nausea (43%). The most frequently occurring grade 3 or 4 adverse events were hyperglycemia (17%), hypophosphatemia (13%), anaemia (9%), and hypertriglyceridemia (6%) (Atkins et al. 2004). The investigators concluded that in patients with advanced RCC, CCI-779 showed distinct antitumour activity and encouraging survival. A phase III trial has been initiated that compares the combination of CCI-779 and IFN with each agent alone as first-line therapy in poor-risk patients with metastatic RCC.

In summary, along with VEGF-targeted monoclonal antibodies the new receptor kinase inhibitors are the most promising recently, if ever, evaluated agents in the treatment of metastatic RCC. Further studies are needed; however, they appear to have the potential to revolutionize both first- and second-line treatment of advanced RCC (Table 1).

Miscellaneous innovative approaches

AE-941 (Neovastat) is composed of water-soluble molecules extracted from cartilage and was developed based on the observation that shark cartilage may contain biologically active inhibitors of angiogenesis. At the molecular level, AE-941 appears to exhibit multiple different mechanisms of action. It selectively inhibits matrix metalloproteinases (MMP-2, -9, and -12), and stimulates tissue plasminogen activator enzymatic activities. It also selectively competes for the binding of VEGF to its receptor (VEGFR-2) and finally induces apoptotic activities in endothelial cells (Bukowski 2003; Rini and Small 2005). A first phase II trial evaluating the efficacy and toxicity of AE-941 in 22 patients with metastatic RCC has shown promising dose-dependent results with objective responses of up to 14% (Batist et al. 2002). A prospective, randomized, double-blind, placebo-controlled phase III trial to determine the exact efficacy of AE-941 as second-line monotherapy in metastatic RCC patients has been initiated (Escudier et al. 2003). Final results are still pending.

Another target was chosen by Pitot et al. (2002) who performed a phase II trial to evaluate the response rate and systemic toxicities of dolastatin-10 in patients with advanced RCC who failed to respond to prior immunotherapy. Dolastatin-10 is a potent antimitotic peptide first isolated in 1987 from the marine mollusk, *Dolabella auricularia*. It acts via an inhibition of microtubule

assembly (Bai et al. 1990) and induction of apoptosis, possibly through phosphorylation of the bcl-2 protein (Kalemkerian et al. 1999). On a molar basis, dolastatin-10 is one of the most potent antineoplastic agents in vitro, with inhibitory concentrations in the nanomolar and subnanomolar range. However, earlier studies in colorectal cancer failed to achieve major objective responses (Saad et al. 2002). In Pitot's trial, 30 patients received dolastatin-10 as an intravenous bolus at the recommended phase II dose of 400 mg/m^2 once every 3 weeks. The most common grade 3/4 toxicities included neutropenia (47%), leukopenia (17%), anaemia (10%), dyspnea (6%), pleural effusion (6%), fatigue (7%), and constipation (7%). Neurologic toxicity was mild and did not appear cumulative. Three patients (10%) achieved a partial response for 6, 10.3, and 16.5+ months, respectively, and three patients (10%) maintained a stable response for >24 weeks. However, the median time to progression was only 2.2 months. The authors recommend a further evaluation of dolastatin-10 in combination with immunotherapy.

Motexafin gadolinium inhibits thioredoxin reductase. Thioredoxin is implicated in activation of hypoxia-inducible factor-1 alpha, which is overexpressed in >85% of RCC (Rini and Small 2005). Therefore, Jac et al. (2005) initiated a phase II trial evaluating the efficacy of motexafin gadolinium in patients with progressive metastatic RCC. Twenty-two patients were enrolled; only eight and two patients were stable for at least 3 and 6 months, respectively. However, treatment was well tolerated and stabilization of disease was observed in patients with progressive disease. Future studies will have to clarify the value of this approach in the treatment of RCC.

Allogeneic stem-cell transplantation

Nonmyeloablative allogeneic stem cell transplantation (NST) and donor lymphocyte infusions are currently under clinical investigation as an innovative therapeutic option for patients with metastatic RCC. The underlying concept, adopted from patients with haematologic malignancies, aims at a reduction of conditioning toxicity and exploits the graft versus malignancy effect of donor T lymphocytes after transplantation.

The first clinical data on the treatment of metastatic RCC were published by Childs et al. (2000). In this study, 19 cytokine refractory patients underwent NST from an HLA compatible-related donor. Eight patients (42%) additionally received donor lymphocyte infusions for conversion of mixed chimerism to complete donor T cell chimerism or in case of rapid tumour progression. Objective remissions were observed in 10/19 patients (53%; three complete and seven partial remissions). After a median follow-up of 13.2 months, nine patients (47%) were still alive. Two patients (11%) had died due to transplant-related complications, eight patients (42%) from progressive disease. These results prompted several groups to establish NST regimens for progressive RCC. However, results of recent studies were less enthusiastic (Blaise et al. 2004; Massenkeil et al. 2004; Rini et al. 2002; Tykodi et al. 2004; Ueno et al. 2003).

Altogether, clinical data from more than 100 patients treated worldwide have been published so far and have been reviewed by Roigas and Massenkeil (2005). The data provide evidence that NST is feasible with a decreasing rate of engraftment failure. Objective remissions in these heterogeneous studies were observed in 23% (range, 0–57%) of the patients with complete remission of 5% (range, 0–16%). Remissions after NST developed only after complete engraftment of donor lymphoid cells. Objective responses were almost always accompanied by graft versus host disease (GvHD) after withdrawal of immunosuppression and/or donor lymphocyte infusion. GvHD and infections were the main contributors to a substantial transplant-related morbidity and mortality, the major drawbacks of allogeneic stem cell transplantation. Moreover, only a minority of eligible patients finally underwent NST because of the limited availability of donors, advanced age, co-morbidity, and rapid tumour progression. Therefore, if this approach is going to be continued, clinical studies will be necessary to further investigate and improve the selection of patients with metastatic RCC for NST and to reduce post-transplant complications.

Conclusions

Second-line treatment of patients with metastatic RCC progressing under therapy with biological response modifiers remains an unresolved issue. However, especially in recent years numerous innovative approaches have been published, partly with promising results. Nevertheless, even evaluating the efficacy and/or toxicity of the same drug or combination regimen, the results published by different groups vary considerably. Reasons for that phenomenon may include small patient groups, comparison of patient cohorts with unlike prognosis, different restaging intervals and modalities, inconsistent definitions of response, as well as lack of an external/central reviewing of images and thus response and progression. For future trials that evaluate toxicity and efficacy of certain drugs or regimes, it is of utmost importance that specific prognostic factors are considered during patient stratification and subgroup configuration (Motzer et al. 2004a). The initiation of controlled prospective randomized phase III studies is desperately needed to definitely exclude accidental or systemic errors evaluating novel therapeutic approaches and to gain significant reproducible results. However, several novel approaches have raised well-founded hope. Especially the application of monoclonal antibodies targeting VEGF signalling as well as different receptor tyrosine kinase inhibitors has the potential to change the face of first- and second-line treatment of patients with metastatic RCC. Both groups of agents will be focused

in ongoing phase III trials, either as mono- and/or combination therapy. Further results can be expected with suspense.

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