Modern Therapeutic Approaches in Metastatic Renal Cell Carcinoma

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1. Introduction

Renal cell carcinoma (RCC) is the most deadly urological malignancy with only 62% of all patients surviving 5 years in all stages. Approximately 20–30% present initially with metastatic disease as well as 20–40% of patients who will develop systemic spread after surgery. New insights in angiogenesis lead to the development of new drugs directed against receptors and downstream signaling molecules of angiogenic regulation mechanisms. The results of clinical trials with these drugs will lead to a change of paradigm in the systemic treatment of RCC patients. Specially Sutent, Sorafenib and Temsirolimus proved efficacy in metastatic disease and should be added substantially to the therapeutic armamentarium when surgery of the primary or metastases is impossible.

Despite advances in biological and immune-based therapies, response rates for patients with metastatic RCC remain at about 15% to 25% [4–10].

2. Renal cell carcinoma and the hypoxia-inducible pathway

The hypoxia-inducible pathway plays an essential role in angiogenesis, epithelial proliferation, tumor invasion and metastasis, as well as apoptosis of common cancers. It is also responsible for their resistance to radiation and chemotherapy [11,12]. Hypoxia inducible factor (HIF) consists of mainly two molecular parts: α-subunits (HIF-1α, HIF-2α, HIF-3α) and HIF-1β. HIF-1β is constitutively

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expressed and plays no important role in tumorigenesis, whereas HIF-1α is controlled at the biosynthesis level as well as the posttranslational level depending on the oxygenation status of the cell and accumulates under hypoxic conditions [13]. Under normoxic conditions, HIF is expressed at low levels and undergoes hydroxylation at the alpha subunit. Von-Hippel–Lindau (VHL) gene regulates HIF expression. In the absence of VHL mutations, the VHL protein (pVHL) forms a multiprotein complex (VEC) at the α domain with elongin B, elongin C, Cullin 2, and Rbx1. Following the hydroxylation of HIF, the β domain of the VHL complex binds to HIFα and the unit is targeted for ubiquitylation and proteolysis by the 26S proteasome. Under hypoxic conditions, HIF does not undergo hydroxylation and initiates the transcription of hypoxia-inducible genes, which promote cell growth and survival in hypoxic conditions. The same mechanism is initiated by VHL gene mutation regardless of the oxygenation status resulting in the expression of mRNA encoding hypoxia-inducible genes such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-α (TGF-α), erythropoietin (EPO), glucose transporter 1 (GLUT-1), and carbonic anhydrase IX (CAIX) [12,14–22].

3. Growth factor receptor signaling pathways

Upon ligand binding growth factor receptors undergo autophosphorylation under utilisation of GTP. This stimulates specific intracellular tyrosine kinase activity and intracellular signal transduction pathways. Signaling pathways involved in positive cell growth include those mediated by phosphoinositide 3-kinase (PI3K)/AKT and ras/raf/MEK/ERK (ERK = extracellular signal-regulated kinase; MEK = mitogen-extracellular kinase) [30]. PI3K/AKT pathway can be repressed by inhibitors of mTOR and is regulated by the PTEN tumor suppressor gene, which is often down-regulated in RCC and acts as an activator of HIF [31,32]. Tumor cells have the capacity to over-express VEGFR that stimulates three major receptors located on vascular endothelial cells: VEGF-1, VEGF-2, and VEGF-3. Expression of these growth factors in RCC correlates with the possibility of tumor metastases, pathological stage of renal cancer and survival [28,29,33].

4. Antibody treatment

G250 (WX-G250, Wilex, Munich, Germany) is a chimeric monoclonal antibody of the subclass IgGl, that recognizes an antigen preferentially expressed on cell membranes of clear cell RCC (>90%) and not expressed in normal proximal tubular epithelium. In the majority of cases, staining of G250 in renal cancer tissue, as well as in metastases is possible [34]. In 16 patients treated with radiolabeled 131I-WX-mG250 significant accumulation in cancer tissue was

### Table 1 – Growth factors and their function

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Receptor</th>
<th>Function</th>
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<tbody>
<tr>
<td>VEGF</td>
<td>VEGFR-1, -2, -3</td>
<td>Proangiogenic, stimulation of endothelial cell division, migration, inhibition of apoptosis</td>
</tr>
<tr>
<td>EGF</td>
<td>EGFR</td>
<td>Stimulates VEGF expression</td>
</tr>
<tr>
<td>TGF-α</td>
<td>EGFR</td>
<td>Stimulates VEGF expression, survival, proliferation, differentiation, migration, and adhesion</td>
</tr>
<tr>
<td>PDGF</td>
<td>PDGFR</td>
<td>Structural support for endothelial cells, needed in later stages of blood vessel formation</td>
</tr>
<tr>
<td>CAIX</td>
<td></td>
<td>Regulates cell proliferation in hypoxic conditions</td>
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detectable [35]. Recently a study on 36 metastatic patients was conducted with unconjugated G250 to assess safety and efficacy. 10 patients had stable disease, one complete response and one significant regression was observed during the follow-up of the treatment. The median survival after treatment start was 15 months [36]. Phase II trials optimizing treatment schedules with both the conjugated and the unconjugated WX-G250 in combination with cytokines are finished. A multicenter study combined WX-G250 with low dose IL-2 could lead to an improved clinical outcome in patients with progressive RCC in 35 patients. A durable clinical benefit was achieved in 8 of 35 patients (23%), including 3 with a partial response and 5 with stabilization at 24 weeks or greater. Mean survival was 22 months. Survival was at least similar to that of currently used cytokine regimens but with a favourable toxicity profile [37]. A phase III clinical trial in the adjuvant situation in high risk patients after primary surgical therapy without metastasis is recruiting (ARISER study).

5. Tumor vaccine therapy

Three different kinds of cell-based vaccines for RCC are currently under investigation: isolated tumor cell suspensions, gene modified tumor cells and dendritic cells (DCs) expressing RCC-associated antigens. With autologous tumor cells in an adjuvant setting, an improved 5-year survival rate was achieved. At 5-year and 70-month follow-up, the hazard ratios for tumor progression were 1.58 (95% CI 1.05–2.37) and 1.59 (1.07–2.36), respectively, in favor of the vaccine group (p = 0.0204, log-rank test). 5-year and 70-month progression-free survival rates were 77.4% and 72%, respectively, in the vaccine group and 67.8% and 59.3%, respectively, in the control group. The vaccine was well tolerated, with only 12 adverse events associated with the treatment. Unfortunately this autologous treatment was not approved by the authorities so far, due to a missing central radiologic review [38].

6. Targeting VEGF

Single-agent use of drugs targeting VEGF has demonstrated efficacy in treating metastatic RCC. Bevacizumab (Avastin®, Roche) is a recombinant, humanized monoclonal antibody that binds to VEGF, depleting plasma stores of soluble VEGF and depriving VEGF receptors of its ligand. PTK787 (Schering) is a selective inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3 tyrosine kinases, whereas Sunitinib (Suent®, Pfizer) is a potent ATP competitive inhibitor of multi receptor tyrosine kinases (RTK): the platelet-derived growth factor receptors (PDGFR-α and -β), vascular endothelial growth factor receptors (VEGFR-1, -2 and -3), stem cell factor receptor (KIT), receptor for macrophage colony-stimulating factor (CSF-1R), Fms-like tyrosine kinase-3 receptor (FLT-3) and the RTK encoded by the ret proto-oncogene (RET). The VEGF trap contains portions of the extracellular domains of the human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G. A comparable mechanism of blocking the angiogenetic pathway is used by AG-013736 (Pfizer) [43]. Sorafenib (Nexavar®, Bayer) is also a multi-targeted tyrosin kinase inhibitor directed against VEGFR-2, VEGFR-3 and PDGFR-β receptor tyrosine kinases and has substantial activity against p38- Raf-1- and b-raf-kinases, and against Flt-3, c-KIT and RET as well. Sunitinib and Sorafenib both have the ability to block PDGFR and therefore prohibit vessel stabilization, which seems to be substantial in larger tumors [44] (Figs. 1 and 2).

![Fig. 1 – Relevant angiogenetic pathways.](image-url)
Clinical results with multi-targeted VEGFR and downstream signaling inhibitors

7.1. Sunitinib Malatatt and AG-013736

The oral VEGFR and PDGFR multi tyrosine kinase inhibitors (TKI) AG-013736 (Pfizer) and Sutent® (Sunitinib, Pfizer) have both demonstrated anti-tumor activity in patients who have failed prior systemic therapy of metastatic RCC and were proven to of progressive disease prior to TKI therapy [45–48]. Response evaluation was performed using RECIST criteria every 8–12 weeks. Being treated with AG-013736 an overall of 46% patients experienced a partial response (PR) and another 40% had stable disease (SD). 38% of the patients with SD had concurrent tumor shrinkage without a 30% reduction of the sum of the longest tumor diameters. Median time to progression was not reached after 18 months of treatment, but was expected somewhere around 22–24 months [47].

Sunitinib (Sutent®) was tested in two phase II trials in second line indication. In the first trial not all patients had tumor-nephrectomy but all failed initial systemic therapy. In the second trial only patients after kidney tumor surgery were included. Sunitinib was administered at 50 mg/die for 4 weeks followed by a 2 weeks washout phase. Tumor evaluation was performed according to the RECIST criteria by the investigator without central radiological review. In the first trial with n = 63 patients an extraordinary response rate of 40% (25/63) PR was achieved. Another 28% (18/63) had SD. No complete remission (CR) was recorded. 25% (16/63) patients had progressive disease (PD) and 4 patients were not evaluable for follow-up. In a pivotal trial including 106 patients these results were confirmed using the same study design. 38% (40/106) had PR. 1 patient even had complete response (CR). 25% (23/106) had SD and 33% (31/106) were progressive. 7 patients were not evaluable, rendering this trial slightly underpowered. PFS was longer in responding patients than in those with SD ≥ 3 months or PD/SD <3 months (14.8 versus 7.9 versus 2.1 months). As of May 2005, 10% of patients in trial 1 (n = 63) and 52% of patients in trial 2 (n = 106) remained on treatment; this difference likely reflects that trial 1 was initiated sooner than trial 2. With such a high response rate and substantial benefit for the patients, Sunitinib was approved by the Federal Food and Drug Administration (FDA) for use in advanced RCC in second line indication, although survival data with these uncontrolled trials are missing.

First line treatment with Sunitinib in mRCC was tested against interferon-alpha (IFN-α) monotherapy in a large phase III study. Untreated patients with clear-cell mRCC were randomized 1:1 to receive Sunitinib. They were treated with 6-week cycles: 50 mg orally once daily for 4 weeks, followed by a 2 weeks washout phase. The patients in the control arm received IFN-α at a dose of 9 MU given subcutaneously three times weekly for six weeks. The primary endpoint was progression-free survival (PFS). Based on a planned sample size of 690 patients, the trial was designed to have 90% power to detect a 35% improvement in median PFS from 20 weeks to 27 weeks (4.6 months to 6.2 months; 2-sided unstratified log-rank test; significance level 0.05). From August 2004 to October 2005, 750 patients were randomized: 375 to Sunitinib, 375 to IFN-α. Baseline characteristics were well balanced and typical for a mRCC population. Median PFS assessed by third-party independent review was 47.3 weeks (95% CI 40.9, not yet reached) for Sunitinib vs. 24.9 weeks (95% CI 21.9, 37.1) for IFN-α [hazard ratio 0.394 (95% CI 0.297, 0.521) (p < 0.000001)]. The objective response rate by third-party independent review was 35.7% (95% CI 30.9, 40.8) for Sunitinib vs. 8.8% (95% CI 6.1, 12.1) for IFN-α (p < 0.000001). 632 pts (85%) are alive, with 49 deaths on Sunitinib arm and 65 deaths on IFN-α arm. 8% withdrew from the study due to adverse event on Sunitinib arm vs. 13% on IFN-α arm. So far the follow-up period is to 15 months. Therefore median survival was not yet reached [49].

### 7.1.1. Side effects

Side effects of AG-01376 were mainly manageable grades 1–2 in severity. Grade 3–4 side effects were mostly hypertension (15%) and diarrhea or fatigue (8%). Nevertheless 12% of patients receiving AG-013736 withdrew because of treatment-related adverse events, and 35% and 22% of patients...
receiving Sunitinib in trial 1 and 2, respectively, received dose reductions predominantly because of fatigue, stomatitis, or increased amylase/lipase levels. Major side effects of Sunitinib were grade 2–3 left ventricular ejection fraction decline (11% and 5% of patients) and hypertension (5% and 14%). Also, grade 2–4 neutropenia, anemia, thrombocytopenia, and hyperlipasemia occurred in 18–45% of patients. With classic chemotherapy these side effects are common known and mostly easy to handle, but with chronic treatment side effects as of grade 2 and higher will usually lead to dose reduction or even withdrawal of the drug.

7.2. Sorafenib

Sorafenib (Nexavar®, Bayer Healthcare, Onyx Pharmaceuticals) was originally identified through inhibitory effects on the serine/threonine kinase Raf-1, further activity against B-Raf and additional receptor tyrosine kinases, including VEGFR-2, PDGFR, FLT-3, and c-KIT2. A broad-spectrum, antitumor activity in a number of tumor xenograft models, including renal adenocarcinoma was seen preclinical. Thus, continuous oral Sorafenib 400 mg twice daily, has been investigated as a monotherapy and in combination with interferon-α2b (IFN-α2b) in phase II/III trials in patients with RCC who have failed one prior systemic therapy or received one prior biologic response modifier regimen [50,51].

Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) evaluated the efficacy of single-agent Sorafenib versus placebo in the largest phase III trial performed to date in patients with clear-cell RCC [51]. Patients were stratified according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria (low or intermediate) [52] and randomized to Sorafenib (n = 451) or placebo (n = 452). 76% of the patients receiving Sorafenib had reductions in tumor volume from baseline versus 25% of the patients on placebo. Still it is not understood why placebo patients showed response in tumor size. As systemic therapy had to be stopped 4 weeks prior to TARGETs study entry, but had to be given within 8 months preceding the study, it is speculated that the initial therapies, especially immunotherapies, influence this phenomenon. In someway early data analysis might also have had an impact on these data. Nonetheless the patients had significantly prolonged PFS of 24 weeks versus 12 weeks with placebo. The Sorafenib-induced benefit on PFS was observed in all subsets of patients evaluated regardless of age, MSKCC score, prior cytokine treatment, location, count and size of metastases, time since diagnosis, or country. [51,53,54] This overcomes the negative predictive influence of these factors on overall survival. According to these data, Sorafenib was approved by the FDA as second line therapy for mRCC or in advanced RCC without treatment alternatives.

In contrast tumor responses according to the response evaluation criteria in solid tumors (RECIST) – or WHO-defined response rates – were low: only 8% of the patients had partial response. But 74% of the patients had stable disease. However, unlike the AG-013736 and Sunitinib trials, responses were assessed every 6 weeks as opposed to every 8–12 weeks.

Notably, the addition of IFNα to Sorafenib markedly improved response rates in a phase II trial, resulting in response rates superior to those observed with single-agent Sorafenib or IFNα: 37% of the patients had PR and another 47% had SD [55].

7.2.1. Side effects

Continuing application of oral Sorafenib 400 mg bid caused a variety of side effects. The most common treatment related adverse events were rash/desquamation, hand–foot skin reaction (HFS) different from the HFS seen with 5-FU, fatigue, and diarrhea. But also stomatitis, erectile dysfunction, alopecia, and a change of the hair structure towards grey and curly were observed. Clinically and dose limiting were diarrhea and HFS. The proportion of patients discontinuing treatment was similar between Sorafenib- and placebo-treated patients (10% and 8% of patients) while dose interruptions occurred in 20% and 5% of patients, respectively. Dose reductions, mainly due to HFS and diarrhea, occurred in 12% of Sorafenib recipients [51,55].

As in other combination trials the addition of IFNα increased the toxicity of Sorafenib. Compared with single-agent Sorafenib, the incidence of fatigue, diarrhea, nausea, and rash increased by ≥35%; however, these were predominantly grade 1–2 in severity. Dose reductions occurred in 48% of patients and were predominantly due to grade 3 rash (22%), grade 3–4 neutropenia (13%), or grade 2 fatigue/anorexia (13%) [55].

8. Targeting EGF

The effectiveness of disrupting EGFR-related signaling and hence tumor cell proliferation has been explored using three targeted agents, with limited success. In all clinical trials, agents were administered as monotherapy to patients with either advanced or metastatic RCC [56–58]. One agent tested was the orally administered small
molecule gefitinib (Iressa), a selective EGFR tyrosine kinase inhibitor. Although gefitinib has shown efficacy in non-small-cell lung cancer, it demonstrated no efficacy in RCC. None of the 18 examined patients had a complete or partial response. Assessment of the primary endpoint, progression-free survival, proved equally disappointing; after 4 months of treatment 81% of patients had progressed [44].

Studies with the recombinant mouse–human monoclonal antibody cetuximab (Erbitux) have also failed to demonstrate a response in RCC. In a mouse xenograft model of human RCC, cetuximab inhibited tumor growth and metastasis, and increased apoptosis, suggesting potential activity in humans. However, in a single-arm, phase II trial conducted in 55 patients with RCC, cetuximab failed to induce WHO-defined complete or partial responses, and the median time to progression was 57 days [44]. The results of these trials have effectively halted further investigation into the single-agent activities of gefitinib and cetuximab in the treatment of RCC.

An indication of some efficacy in targeting EGFR in RCC was found in a study investigating the high-affinity, human monoclonal antibody ABX-EGF. In a phase II dose-finding (1.0–2.5 mg/kg) study (n = 88), RECIST-defined major and minor responses occurred in three (including one patient with a complete response) and two patients receiving weekly administration of ABX-EGF, respectively. After 8 weeks, 50% of patients had stable disease and the median progression-free survival was 100 days [56,57].

ABX-EGF was generally well tolerated: the most frequently reported adverse event was skin rash, which occurred after 2–3 weeks of treatment and the severity gradually decreased despite continued treatment. Moderate-to-severe adverse events included asthenia (15% of patients), pain, back pain (both 13%), dyspnea (10%), cough (9%), diarrhea, constipation (both 6%) and nausea (5%) [56,57].

Although exaggerated EGFR signaling is one molecular characteristic of RCC, mutations in EGFR are rarely seen [59]. In contrast, EGFR mutations are common in non-small-cell lung cancer patients, and these patients are particularly responsive to gefitinib. In RCC, the VHL gene mutation results in the constitutive expression of mRNA encoding VEGF and TGF-α, which in turn may unregulate both VEGFR and EGFR signaling. Thus, it is possible that the inhibition of EGFR alone may not be sufficient to disrupt the signaling pathways involved in tumor proliferation and angiogenesis.

9. **Mammalian target of rapamycin (mTOR) inhibition**

The mammalian target of rapamycin (mTOR), a 250 kD protein kinase, has a key role in regulating translation of transcripts within the processes of angiogenesis and cell growth. Especially HIF alpha subunits are regulated by mTOR. Regulated by the PTEN/P13-AKT pathway it also induces cyclin D1 and cMyc. It also has a direct cytostatic effect by blocking cellular progression from the G1 to the S phase.

Temsolimus is a propyl ester analog of Sirolimus, also known as Rapamycin, a macrolide with antifungal and antitumor properties. Like the parent compound Sirolimus, Temsolimus inhibits mTOR. Sirolimus is known as oral immunosuppressor in transplant patients with a well known pharmacological profile. For the treatment of oncologic patients the i.v. application with Temsolimus is available.

In a single-agent, phase 2 study, Temsolimus (CCI-779, Wyeth, USA) administration to heavily pretreated patients (n = 111) with metastatic RCC resulted in a median overall survival of 15.0 months [60]. Retrospectively, 49 patients were categorized in a poor-risk group according to MSKCC risk criteria [52]. The Temsolimus-treated patients in this group had a 1.7-fold longer median overall survival than the first-line, IFNα-treated, poor-risk group reported by Motzer et al. [52,60].

Thus, a phase 3 study in first-line, poor-risk mRCC patients was initiated in July 2003. Patients with advanced RCC and no prior systemic therapy were enrolled if they had more than 3 of 6 risk factors (the 5 MSKCC criteria serum lactate dehydrogenase, serum calcium, haemoglobin, performance status, presence of nephrectomy where added with more than one metastatic disease site). Patients were randomized to three even arms. The first group received IFNα up to 18 MU s.c. tiw; the second group received Temsolimus at a dose if 25 mg i.v. once weekly and the third group received a combination of Temsolimus 15 mg i.v. once weekly combined with IFNα 6 MU s.c.tiw. The primary study endpoint was overall survival. As of 20 Mar 2006 preliminary data from an interim analysis performed by the IDMC is available. Of the 626 patients enrolled, 442 deaths occurred. Patients treated with Temsolimus had a statistically longer survival than those treated with IFNα only. The median overall survival in this group was 10.9 months (95% CI 8.6–12.7, hazard ratio 0.74 (95% CI 0.57–0.92)) versus 7.3 months (95% CI 6.1–8.9) in the IFNα treated group. There was no statistically different survival difference in patients treated with IFNα compared
to those in the combination arm (Temsirolimus plus IFNα). The time to progression in the IFNα only group of 1.9 months was statistically significantly lower compared to 3.9 months in both of the Temsirolimus treated groups (stratified log rank p-value 0.0001). First-line monotherapy with Temsirolimus in high risk patients not only doubled the time to progression compared to IFNα but also led to a significant longer overall survival by 49%.

9.1. Side effects

The most frequently occurring adverse events greater than grade three were asthenia, anemia, and dyspnea. Other important side effects, although mostly grade 2 or less, were rash, stomatitis, diarrhea, vomiting and peripheral edema in about 20–30% of the cases. Hematologic toxicities and laboratory abnormalities were mainly grade 2 and included hyperlipidemia, hyperglycemia, hypercholesteremia, creatinine increase, thrombocytopenia and, mainly with combination treatment, neutropenia.

10. Other anti-angiogenic agents

Response rates according to RECIST criteria were relatively low in patients with RCC receiving CC-5013, a thalidomide derivative, or ABT-510, a nonapeptide that mimics the anti-angiogenic activity of thrombospondin-1. Of the 36 evaluable patients who had received ≤1 prior therapy before receiving CC-5013, 32.5% had PFS of ≥6 months. Patients who received ABT-510 had received no prior antitumor activity and had a 6-month PFS rate of 36% [61,62]. Taken together these results are not very much promising compared to the TKIs.

11. Combining anti-angiogenic agents

There is a rationale for increased efficacy by combining agents that target different cellular angiogenetic and proliferative pathways. Bevacizumab (a VEGF inhibitor) in combination with erlotinib (an EGFR inhibitor) appear to have more activity than either agent alone; but the addition of imatinib (which targets PDGF-β) to this combination has no additional benefit in patients with metastatic RCC who had failed ≤1 prior systemic regimen. Response rates and median PFS were broadly similar between patients receiving bevacizumab plus erlotinib with or without imatinib. Similarly, PFS at 1 year was virtually identical between the two studies (43% of patients receiving bevacizumab plus erlotinib versus 47% of patients also receiving imatinib). Overall survival in patients receiving bevacizumab plus erlotinib was 60% at 18 months and was 70% at 9 months in patients also receiving imatinib.

The toxicity of bevacizumab plus erlotinib is considerably augmented by the addition of imatinib, particularly for grade 3–4 diarrhea (13% vs 29% of patients), rash (13% vs 27%), and fatigue (0% vs 6%) [63,64]. The marked increase in toxicities, combined with the lack of evidence suggesting imatinib increases response, precludes this regimen from further investigation in this group of patients.

12. Clinical experience with anti-angiogenetic drugs

In our own experience with actually 108 patients on anti-angiogenetic therapy the main challenge remains the control of the side effects, especially of the skin. About one third of the patients experience side effects affecting the skin. Most of them are described with the term “hand–foot-syndrome” compared to the changes associated with 5-FU therapy. In fact these changes are quite similar but different to this known syndrome. Mostly the feet and the hands show only a slight red efflorescence without any problems. This usually is reversible within 3–6 weeks under local therapy with urea-creme or some dermatopic fat applications. If this therapy is not helpful enough local cortisone treatment is indicated and mostly effective. Only in rare cases systemic antihistaminics or corticoids are needed. They have to be used if the patient suffers from swelling, pain, itching and blisters which are usually not superinfected. In some cases the skin reactions are hardly to differentiate from allergic skin lesions. In these cases the drug has to be withdrawn. In most of the other cases we try to keep the patient on therapy, as we have experienced, that complete withdrawal and later readministration leads to the same grade of adverse effect. With continuous application in reduced dose the side effects mostly diminish after 6 weeks and the full dose can be given again Figs. 3 and 4.

Another common side effect with clinical relevance is diarrhea, which mostly can be treated using loperamide or commonly used anti-diarrhoeics. In most patients this problem will not resolve the longer the therapy is given. There are some hints that the use of colestyramine might inhibit resorption of oral TKIs. In patients after bowel surgery, the likelihood of developing diarrhea under anti-angiogenetic therapy seems to be higher than in others.
Our patients also suffered from hypertension, erectile dysfunction, emesis, nausea pruritus and alopecia. Mostly, these problems were of minor clinical relevance. Although it is recommended to withdraw the drugs with grade 3 or 4 side effects and to reduce the dose in grade 2 adverse events, we have learned that it is better to keep the patient on treatment in reduced dose. Usually side effects will be controlled after the initial 3–6 weeks of treatment. If drug application was withheld side effects revolved with restart of therapy. With a continued lower dose this phenomenon can be avoided. So far we have no hints that severity of side effects correlates with effectiveness of the therapy.

13. Changing the paradigm of mRCC treatment

Given the new options to treat mRCC it seems that the strategic approach towards metastatic disease should be changed completely in the future. Standard therapy of metastatic disease should be nonetheless surgical removal of the metastases if technically feasible. After the surgical approach is no longer possible systemic therapy is indicated. There are several phase II and phase III studies with exciting good results that support angiogenetic therapy. Not only a proof of principle in treating mRCC was given but also high response rates (Temsirolimus, Sutent) can be achieved. A vast majority of patients benefits from stabilization of the disease (Sorafenib, Sutent, Temsirolimus), leading to a significant longer time to progression, which could be identified as a surrogate marker for survival in former RCC trials. Although this is not demonstrated with TKI treatment, it seems to be beneficial for the patients to suffer from slower growing tumors. So far there are only few complete responses reported. But with a lot of patients in stable disease or with remarkable response a positive influence on overall survival was proven with Temsirolimus and Sorafenib. These data are still pending for Sunitinib, but with a statistical significant and stable prolongation of the time to progression in Sunitinib patients, one can estimate that Sunitinib will also be able to prolong the patients survival in metastatic disease. Sunitinib and Sorafenib are commercially available in the U.S. and in Europe, which means that they can be imported by most of the nations even without approval of the local authorities.

The main challenge in the future will be to select those patients who will benefit from “classic” immuno- or immunochemotherapy and to distinguish them from those patients who will benefit from angiogenetic inhibition solely. So far no predictive factors are known that could foresee which patient will benefit from classic immuno-

<table>
<thead>
<tr>
<th>Indication</th>
<th>Therapy</th>
<th>Benefit</th>
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<tbody>
<tr>
<td>1st line</td>
<td>Surgical resection of metastasis or primary tumor</td>
<td>OS, CR, long term data available</td>
</tr>
<tr>
<td>1st line, good prognosis</td>
<td>Immunotherapy based on IFNa ± IL-2</td>
<td>Long term data available, beneficial OS</td>
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<tr>
<td>1st line, intermediate prognosis</td>
<td>Sorafenib</td>
<td>OS, PR, TTP</td>
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<tr>
<td>1st line, poor prognosis</td>
<td>Temsirolimus</td>
<td>OS, PR, TTP</td>
</tr>
<tr>
<td>2nd line</td>
<td>Sunitinib (phase II) Sorafenib</td>
<td>PR, TTP OS, TTP</td>
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OS: overall survival, TTP: time to progression, PR: partial response, CR: complete response.
chemotherapy and for whom angiogenetic inhibition would be best. Generally, modern treatment strategies for patients should carefully focus on this point.

With the given results of targeted therapies, second line therapy should be based on TKI. In first line therapy risk stratification should be performed. Low risk patients can be treated with a regimen consisting of IL-2 or IFNα or a combination of the two substances for 2 cycles. If restaging afterwards cannot prove response, TKI treatment is indicated. In intermediate risk patients, or patients with multiple bone and or liver metastasis TKI treatment should be standard. As first line data for Sorafenib are lacking, Sutent should be first choice in these patients. In high risk patients or patients with low performance status Temsirolimus can be recommended. A treatment scheme for mRCC patients based on phase II and phase III data is shown in Table 2.

Although data on TKI treatment are promising there are only few complete responses, rendering these therapies palliative in most cases.

So far no evidence on the effect of switching the targeted drug after progression is available. According to our own experience it is effective to switch a progressing patient from one TKI to another. Withdrawal of medication should be avoided even in progressive disease, because rebound effects and accelerated aggressive tumor growth are seen. The mechanism of acceleration of the course of the disease by withdrawal of TKI is not yet understood and should be invested in the future. Although side effects mostly are described as manageable and tolerable this is not true for every patient and there are many pitfalls. Therefore treatment of mRCC patients should only be performed in association with a high-volume mRCC center Table 3.

Further evaluation of the new drugs should stress combination therapies and adjuvant treatment of high risk patients.

References


CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. Metastatic clear cell renal cell carcinoma is characterized by a variety of molecular changes. Some of them are of therapeutic consequence. Please select correct statement(s):
   A. Ki67 is an important risk indicator and can be suppressed by targeted therapies.
   B. Expression of Carboanhydrase IX is elevated in IL-2 responding patients.
   C. VEGFR and PDGF are important regulators of Angiogenesis and can be blocked by specific drugs in various ways.
   D. B + C.

2. High risk patients are characterized by clinical factors and biochemical changes. Therapy of these patients mostly is discouraging.
   A. So far, no therapeutic regimen for high risk patients is successful.
   B. Temsirolimus, Sutent and Sorafenib have shown efficacy in high risk patients with prolonged time to progression.
   C. Temsirolimus has shown improved overall survival in high risk patients with no substantial benefit in time to progression.
   D. Sutent or Sorafenib should be considered standard therapy in high risk patients.

3. Under normoxic conditions, HIF is expressed at low levels and undergoes hydroxylation at the alpha subunit. VHL gene regulates HIF expression.
   A. Following the hydroxylation of HIF, the β domain of the VHL complex binds to HIFβ. Under hypoxic conditions, HIF undergoes hydroxylation and initiates the transcription of hypoxia-inducible genes.
   B. VHL gene mutation results in the expression of mRNA encoding hypoxia-inducible genes such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-α (TGF-α), erythropoietin (EPO), glucose transporter 1 (GLUT-1), and carbonic anhydrase IX (CAIX).
   C. Biosynthesis of HIF-1α is not regulated by growth factors through the phosphatidylinositol 3-kinase-AKT, mTOR, IGF, EGF and PTEN.
   D. RCC overexpresses growth factors, which sustain tumor cell proliferation and angiogenesis. So far no correlation with the likelihood of tumor metastases, pathological stage of renal cancer and survival was seen.

4. Regulation of angiogenesis is regulated in several steps. Please select the WRONG answer.
   A. Upon ligand binding growth factor receptors undergo autophosphorylation. Specific intracellular tyrosine kinase activity and intracellular signal transduction pathways is mediated by phosphoinositide 3-kinase (PI3K)/AKT and ras/raf/MEK/ERK.
   B. PI3K/AKT pathway can be repressed by Temsirolimus and is regulated by PTEN.
   C. VEGF-1, VEGF-2, and VEGF-3 expression in RCC correlates with the possibility of tumor metastases, pathological stage and survival.
   D. RCC is characterized by a loss of CAIX expression.

5. Mechanisms of action of Tyrosin Kinase inhibitors do NOT include:
   A. Bevacizumab binds to VEGF, depleting plasma stores of soluble VEGF and depriving VEGF receptors of its ligand.
   B. PTK787 (Schering) is a selective promoter of VEGFR-1, VEGFR-2 and VEGFR-3 tyrosine kinases.
   C. Sunitinib inhibits tyrosine kinases of PDGFR, VEGFR-1, -2, -3, KIT, CSF-1R, FLT-3 and RET. A comparable mechanism is used by AG-013736.
   D. Sorafenib is a kinase inhibitor of VEGFR-2, VEGFR-3, PDGFR-β, Raf-1, b-raf, Flt-3, c-KIT and RET.

6. In clinical trials tyrosin kinase inhibitors showed substantial therapeutic efficacy. Which of the following findings is true?
   A. Complete response by systemic therapy is achieved in a significant portion of patients with sorafenib or sunitinib monotherapy.
   B. Every patient with metastatic disease and first line indication should be treated with sunitinib.
   C. Second line treatment should be based on sorafenib.
   D. Metastasectomy following nephrectomy should be considered in all patients, not only in curative but also in palliative intent.