Current Status of Targeted Therapy in Metastatic Renal Cell Carcinoma

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1. Introduction

Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies and is the third most frequent urologic malignancy after prostate and bladder cancer [1]. In 2004, almost 60,000 individuals in the European Union were diagnosed with RCC, and almost 30,000 individuals died from the disease [2]. RCC is highly resistant to conventional cytotoxic chemotherapy and the prognosis for patients with advanced disease is poor. Although the majority of patients (70%–80%) present with localised RCC, around half of these will develop metastatic disease [1,3]. Patients with metastatic disease have a median survival of just 1 yr and an expected 5-yr survival of <20% [3,4].

Spontaneous remissions have been reported with RCC, probably as a result of immune responses and have been the rationale to develop immunotherapeutic therapies [3,5,6]. Cytokine therapy is the only immunotherapeutic approach that has so far been integrated into routine clinical practice for RCC. The most widely used and extensively studied cytokines for the treatment of RCC are interferon-α...
(IFN-α) and interleukin-2 (IL-2). Response rates of between 10% and 20% have been reported with these therapies, and some patients do achieve complete long-lasting remission, especially when treated with high dose IL-2 [7]. However, the antitumour activity of cytokine therapy is generally small and many patients derive little or no benefit from these agents [7]. In addition, cytokine therapy may be poorly tolerated, particularly intravenous IL-2, which is sometimes associated with serious and, in some instances, life-threatening toxicities. A major spin off from the randomised trials in the cytokine era has been the recognition of prognostic factors. At present the most frequently used model is the one developed by Motzer (Memorial Sloan-Kettering Cancer Center [MSKCC] criteria) [8,9]. Three patient groups were discerned on the basis of five factors (Karnofsky performance status, lactate dehydrogenase, haemoglobin level, corrected serum calcium, and nephrectomy). The median time to death in the 25% of patients with no risk factors (good risk) was 20 mo. Fifty-three percent of the patients with one or two risk factors (intermediate risk) had a median survival of 10 mo. Patients with three or more risk factors (poor risk), comprising 22% of the patients, had a median survival time of 4 mo. If prognostic factors are taken into account, there is sufficient evidence to support the view that poor-risk patients do not benefit from cytokine-based treatment. Furthermore it can be deduced from the survival curves that, within the good-prognosis group, there is a cohort of patients who live beyond 5 yr. It is however unclear if this survival is related to the natural history of the disease, medical interventions, or both.

The recent data from the French Immunotherapy Group [10] revealed no difference in median survival between medroxyprogesterone acetate (MPA), subcutaneous IFN-α, and subcutaneous IL-2 or combination cytokine therapy in patients with an intermediate-risk profile (not identical with the MSKCC criteria) and does not support a major role for subcutaneous cytokine treatment in this risk group. Next to the above-mentioned clinical parameters, additional tools may become available to better select our patients. Positive responses to IL-2 seem almost exclusively related to the clear-cell histology subtype and good risk features, and within this group, those patients who have a high expression of carbonic anhydrase IX (CAIX) [11]. This enzyme, whose expression is mediated by the hypoxia-inducible factor (HIF) transcriptional complex, which is upregulated with von Hippel-Lindau (VHL) inactivation, has been observed in clear-cell RCC [12]. The CAIX protein is associated with an improved overall survival independent of other factors [13]. Importantly, CAIX expression in >85% of tumour cells ("high" CAIX expression) was associated with a higher objective response rate in IL-2-treated patients. CAIX is thus an example of a molecular marker that might be able to appropriately select patients for IL-2 therapy. The validity of this concept is currently being evaluated in a prospective trial in the United States. Other examples are the positive correlation between cyclooxygenase-2 expression in primary tumour and an objective response on IFN-α treatment [14], as well as the observation that a high blood neutrophil count (>6.0 × 10⁹/l; hazard ratio: 2.0; p = 0.015), the presence of intratumoural neutrophils (>0 cells/mm² tumour tissue; hazard ratio: 2.3; p = 0.001), and low intratumoural CD57+ natural killer cell count (<50 cells/mm² tumour tissue; hazard ratio: 2.1; p = 0.01) were independent poor prognostic factors [15]. These three independent immunologic parameters had significant discriminatory power as supplemental risk factors in prognostic models based on the clinical risk factors, identifying three subgroups within the favourable clinical group with estimated 5-yr survival rates of 60%, 25%, and 0%, respectively.

Irrespective of these observations, there remains a clear need for well-tolerated and effective treatments to prolong survival of patients with RCC. Recent insights in the process of angiogenesis in RCC and the availability of specific inhibitors provided an excellent opportunity to explore this approach in this disease.

2. Angiogenesis in RCC

Clear-cell RCC is clinically recognised as a highly vascularised tumour. VEGF messenger RNA expression correlates with this vascularisation, and VEGF is overexpressed in the vast majority of patients with adenocarcinomas of the clear-cell subtype. This VEGF overexpression is related to mutations found in the VHL gene, which is found in more than 75% of sporadic clear-cell RCC [4]. VHL is a tumour suppressor gene that, under normoxic circumstances, will bind HIF1-α to form a complex with VHL tumor suppressor protein (pVHL). This complex will be ubiquinated and subsequently degraded in the proteasomes. In conditions of hypoxia or defective/mutated pVHL function, however, this interaction is dysfunctional, resulting in accumulation of HIF1-α [16]. Subsequently, HIF1-α translocates to the nucleus and dimerises with HIF1-β, resulting in the transcription of several hypoxia-inducible genes including various growth factors such as VEGF, platelet-derived growth factor (PDGF),...
basic fibroblast growth factor, erythropoietin, and transforming growth factor α (TGF-α) [17,18]. HIF1-α also induces the expression of several membrane proteins including the G250 membrane protein, an isoenzyme of the carbonic anhydrase family, which plays a role in the pH regulation of the cell [19]. VEGF and PDGF will bind with specific receptors, which results in stimulation of receptor tyrosine kinases, leading to endothelial cell proliferation, survival, and angiogenesis, and thus contributing to the typical hypervascular histology of clear-cell RCC.

Because angiogenesis is infrequent in the adult, there is the potential to develop very specific therapies with minimal toxicities except during times of wound healing, inflammation, ovulation, pregnancy, or ischemia. Vessels within tumours can be inhibited by blockade of the endothelial growth factor receptors through false ligands, by receptor protein kinase inhibitors, or by neutralisation of the ligand by means of monoclonal antibodies (Fig. 1).

For this reason growth factors such as VEGF and their receptors are interesting targets for drug therapy, especially in clear-cell RCC because of its already mentioned abundant VEGF overexpression.

3. Clinical studies

The new compounds that have become available are bevacizumab, sunitinib, sorafenib, and temsirolimus. The most relevant data will be briefly reviewed.

3.1. Bevacizumab

Bevacizumab is a recombinant, humanised, monoclonal antibody targeting the angiogenic factor VEGF-A. Bevacizumab has a linear pharmacokinetic profile with a half-life of 21 d, and the 10 mg/kg dose is considered safe and well tolerated [20]. A randomised phase 2 placebo-controlled, double-blind study with bevacizumab in patients with metastatic RCC (mRCC) was the first study published that showed a significant clinical benefit [21]. One hundred and sixteen patients were randomised to one of three arms: placebo (n = 40), or bevacizumab 3 mg/kg (n = 37) or 10 mg/kg (n = 39) every 2 wk. Patients receiving placebo were allowed to cross over to the bevacizumab 3 mg/kg arm after disease progression. The median time to progression was
studies with IFN-α being evaluated in two large double-blind phase 3 studies with advanced RCC. Patients receive either IFN-α alone three times weekly or IFN-α2b plus avastin 10 mg/kg on days 1 and 15 of a 4-wk cycle. The primary end point is survival. The trial is expected to last 3 yr.

3.2. Sunitinib

Sunitinib is a novel, oral, multitargeted receptor tyrosine kinase inhibitor. It has antitumour and antiangiogenic activity via targeting the VEGFR, PDGFR, KIT, and FLT3R tyrosine kinases [23]. Two recently published phase 2 studies on cytokine failures with 50 mg sunitinib for 4 wk followed by 2 wk of rest revealed a 40% [24] and 34% [25] response rate in 63 and 106 patients, respectively. An additional large proportion of patients (27% and 29%) had disease stabilisation for more than 3 mo, resulting in a “clinical benefit ratio” in 67% and 63% of the patients (= objective response + stable disease). The most frequently observed treatment-related adverse events were fatigue, diarrhoea, nausea, dyspepsia, hand–foot syndrome, stomatitis, anaemia, leucopenia, and thrombocytopenia [23,24]. Recently the results of a randomised phase 3 study in previously untreated patients with mRCC comparing sunitinib with IFN-α have been published [25]. All patients had clear-cell histology, and 94% had either good- or intermediate-risk features according to the MSKCC risk model. The objective and independently evaluated response rate was 31% versus 6%, with a doubling of the progression-free survival from 5 to 11 mo (p < 0.001). Reliable overall survival data are not yet available. The toxicity profile was as predicted from the phase 2 studies.

3.3. Sorafenib

Sorafenib is an oral inhibitor of RAF, but it recently has been demonstrated also to inhibit other targets such as the receptor kinases of VEGFR2 and VEGFR3, FLT-3, PDGFR, and c-KIT. In a phase 2 randomised discontinuation trial [26], the effects of sorafenib 400 mg twice daily were evaluated in patients with metastatic RCC. Of 202 patients treated during the run-in period, 73 patients had tumour shrinkage of ≥25%. Sixty-five patients with stable disease at 12 wk were randomly assigned to sorafenib (n = 32) or placebo (n = 33). Median progression-free survival from randomisation was significantly longer with sorafenib (24 wk) than placebo (6 wk, p = 0.009). Common adverse events were skin rash/desquamation, hand–foot reaction, and fatigue. Nine percent of patients discontinued therapy, and no patients died from toxicity [26]. A subsequent randomised placebo-controlled phase 3 trial [27] of sorafenib versus placebo in cytokine-refractory or cytokine-unfit patients resulted in a statistically significant improvement of the progression-free survival from 2.8 mo to 5.5 mo (p < 0.01). The objective response rate was low (10% vs. 2%), but 74% of patients had stabilisation of their disease resulting in the observed progression-free survival benefit. After release of these initial results, patients were allowed to cross over (48%), a decision that might compromise a precise estimation of the impact on overall survival. A similar efficacy has been seen after crossover, which might suggest that a certain delay is not necessarily detrimental.

3.4. Temsirolimus

Temsirolimus is a specific inhibitor of mammalian target of rapamycin (mTOR), which has antitumour activity in preclinical studies. In phase 1 studies, CCI-779 displayed manageable and reversible adverse events such as acne, rashes, mucositis/stomatitis, asthenia, and nausea [28]. In a phase 2 study of 111 patients with advanced refractory RCC, an objective response was observed in 7% and minor responses in 26% [29]. The essential difference compared to angiogenesis inhibitors is that mTOR inhibitors have a direct effect on the tumour cell instead of the infrastructure. Based on a series of phase 1 and 2 studies [29,30], a randomised phase 3 study [31] in poor-risk mRCC patients has been completed; it compared single-agent IFN-α, single-agent temsirolimus (25 mg), or both agents combined. More than 70% of the patients had poor-risk features according to the MSKCC risk score. Patients treated with temsirolimus monotherapy experienced a median overall survival of 10.9 mo versus 7.3 for IFN-α (p = 0.007) and 8.4 (NS) for the combination. Median progression-free survival was 3.7 versus 1.9 and 3.7 mo, respectively. The response rate was low (9% vs. 7% and 11%, respectively). The most prominent side-effects
attributable to temsirolimus were stomatitis, peripheral oedema, and rash.

4. What is the present place of these new approaches?

First of all, the natural history of the disease is variable. A small proportion of patients will have a very protracted course of their disease irrespective of therapeutic interventions. This is one reason to observe patients after a tumour nephrectomy prior to the start of any treatment. Patients with good-risk features, but especially those with unresectable pulmonary metastases only, should be considered for cytokine treatment. In most centres, this would be IFN-α or standard dose IL-2. Some centres may offer high-dose IL-2 to suitable patients although there are no supportive randomised data yet available. After discontinuation of cytokine treatment, responding patients can again have a variable course, which should be regarded. A positive effect of angiogenesis inhibitors after cytokine failure is well documented [20]; data regarding a reverse order are not available. The hypothesis that patients can be better selected for high-dose IL-2 is presently being evaluated in a prospective manner and is crucial to advocate this approach on the basis of solid scientific data.

The presently available results with the targeted agents are relevant for patients with mRCC in view of the influence on progression-free survival and in one instance on survival. The second observation is that, so far, rarely complete responses have been seen, which suggests modification of biology but not cure of this still fatal disease. This points at the necessity of long-term treatment at least until progression. Although long-term application of these compounds seems feasible, in general our knowledge regarding prolonged treatment is very limited. The majority of patients do become resistant to the inhibition of neoangiogenesis by mechanisms that are still poorly understood. Furthermore from in vivo models, it is known that discontinuation of the inhibition results in a rapid regrowth of the neovasculature and the tumour, even within days. This finding does raise questions regarding maintenance therapy irrespective of documented progression. This issue is not yet addressed and cannot be answered with certainty.

If we consider the limitations of the performed large randomised studies [25,26,31], the following observations can be made.

The first-line study with sunitinib was restricted to patients with clear-cell histology, although in the first phase 2 study [23] a response in a patient with papillary carcinoma has been described. Furthermore the number of poor-risk patients was only 6%, which does not allow a relevant subgroup analysis on both progression-free survival and toxicity for this patient category. Second-line data are available in a nonrandomised fashion and reveal progression-free survivals of 8.7 and 8.3 mo [23,24]. It should be realised that more side-effects will surface with prolonged treatment. In sunitinib-treated patients with gastrointestinal stromal tumors, abnormal serum thyroid-stimulating hormone (TSH) concentrations were documented in 26 of 42 patients (62%), of whom 15 (36%) developed persistent, primary hypothyroidism, 4 (10%) developed isolated TSH suppression, and 7 (17%) experienced transient, mild TSH elevations. The risk for hypothyroidism increased with the duration of sunitinib therapy. Six of 15 (40%) hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism, suggesting thyroiditis [32]. Motzer et al [25] found a decrease in left ventricular ejection fraction. The decrease did not cause clinical symptoms, but this parameter was required to be normal prior to the start of treatment and may become more relevant over time or when patients are treated with less strict entry criteria. Last but not least, survival data are not yet available and are still an important standard for efficacy.

Sorafenib was evaluated predominantly in second line with 17% of patients being cytokine-naïve. Clinical benefit for this first-line subgroup seems comparable but cannot be translated as proof for first-line efficacy.

First- and second-line data of sufficiently sized randomised studies with bevacizumab monotherapy are lacking, which makes it impossible to place this agent in the presently available strategies. This might change when the first-line data of the randomised studies with IFN-α become available.

The majority of patients treated with temsirolimus were poor risk and, although previous phase 2 data did suggest similar efficacy over risk strata, the available data provide no proof of efficacy beyond the poor-prognosis patient population selected for the phase 3 study.

The toxicity profile of both sunitinib and sorafenib, certainly when compared with chemotherapy and cytokines, is favourable but still not negligible for long-term treatment. There are no data allowing head-to-head comparison between sorafenib and sunitinib, but the profile of the two components seems different. Fatigue, diarrhoea, mucositis, hypertension, and bone marrow suppression seem more prominent with sunitinib than with sorafenib.
The rationale for combination therapy is sound, but preliminary data certainly indicate enhanced toxicity without leading to a next step, that is, higher complete response rate or a striking further improvement of the progression-free survival. It might be more logical to look for sequential therapy. Early nonrandomised data suggest the absence of cross-resistance, which would be an argument for sequential instead of combined approaches [33]. These considerations require further carefully executed randomised studies and are, at present, only a hypothesis without definitive proof. The availability of these new compounds will confront many physicians with demands from patients to be treated with this new class of agents outside the proven indication. It will be our task to fill the gaps of knowledge with adequately designed trials instead of trying to give everything to everybody.

5. Conclusion

From a review of these data, it is obvious that we are moving to a new era for patients with mRCC, but there is no reason to sit back because the achievements reflect more a modification of the natural course of the disease than a method to cure. Past achievements should not be neglected but applied on the basis of available insights. Selected patients (with clear-cell histology) should still be offered cytokine therapy. Fortcoming data on the use of CAIX as a marker to predict benefit may mean that this continues to include high-dose IL-2. For intermediate-risk patients, sunitinib is the treatment of choice. For the poor-risk patients, temsirolimus has today provided the most convincing data; however, its availability is limited. Data for sorafenib and sunitinib in the poor-risk group are still anecdotal. After cytokine failure, sorafinib is the treatment of choice. Although phase 2 data with sunitinib in second line are strong, they are nonrandomised. The toxicity profile of the two most extensively studied angiogenesis inhibitors is different and might guide certain patient groups with known cardiovascular comorbidity towards a choice of sorafenib. Although the early signs suggest that there might be no or limited cross-resistance, no sufficient data are available to give solid treatment advice regarding sequential use. Patients should preferably be treated in the framework of clinical trials to find the answers to unanswered questions. It is well-known that the strict entry criteria used within the clinical studies are applied very flexibly when drugs are available after approval by the authorities. These aspects require a very careful follow-up to ascertain optimal use and to prevent misuse. Finally the costs of prolonged treatment will be enormous, and only meaningful survival advantages for our patients will convince the health authorities to make these new treatments available for all our patients.

References

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