MINI-REVIEW

Review on Targeted Treatment of Patients with Advanced-Stage Renal Cell Carcinoma: A Medical Oncologist's Perspective

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Abstract

Renal cell carcinomas make up 3% of all cancers and one in four patients is metastatic at time of diagnosis. This cancer is one of the most resistant to cytotoxic chemotherapy. Studies have shown that the efficiency of interferon-alpha and/or interleukin-2 based immune therapies is limited in patients with metastatic renal cell carcinoma but latest advances in molecular biology and genetic science have resulted in better understanding of its biology. Tumor angiogenesis, tumor proliferation and metastasis develop by the activation of signal message pathways playing a role in the development of renal cell carcinomas. Better definition of these pathways has caused an increase in preclinic and clinical studies into target directed treatment of renal cell carcinoma. Many recent studies have shown that numerous anti-angiogenic agents have marked clinical activity. In this article, the focus is on general characteristics of molecular pathways playing a major role in renal cell carcinoma, reviewing clinical information onagents used in the target directed treatment of metastatic lesions.

Keywords: Renal cell carcinoma - targeted therapy - signal pathways - metastasis

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Introduction

Renal and renal pelvis tumors make up approximately 3% of all malignancies. Most of these cases are renal cell carcinoma (RCC) which are genetically and histologically different from renal pelvis tumors. It has been reported that currently the incidence of RCC has increased at a rate of 2.5-3.0% compared with the 1970s due to the advances in imaging techniques (Jemal et al., 2009; Ljungberg et al., 2011). Although approximately 60% of new cases are diagnosed by coincidence, nearly 25% are metastatic at the time of diagnosis (Ljungberg et al., 2011).

Radical or partial nephrectomy are still the standard therapies in localized RCC. On the other hand, recurrence occurs in approximately 1/3 of the patients. Anti-tumor activity of cytotoxic chemotherapeutic drugs is rather limited in patients with RCC. Previous studies have reported objective response rates of 15-30% obtained with interferon-α (IFN- α) or interleukin-2 (IL-2) based biological therapies. On the other hand, serious adverse effects and difficulties in compliance have been observed in patients receiving cytokin-based therapies (Bukowski, 2001; Ljungberg et al., 2011).

Many molecular pathways important for advanced RCC have been defined with the recent developments in molecular biology. The most important of these pathways is the angiogenesis pathway which also includes von Hippel-Lindau (VHL) gene in its regulation, and important targets in RCC treatment are growth factors associated with this pathway. VHL gene which is located on the chromosome 3p25-26 is the gene responsible for the regulation of hypoxia-inducible factor-1 (HIF-1) (Yazici et al., 2011). The products of this gene control cellular response which develops as a response against oxygen decrease. In the majority of patients with clear cell RCC, tumor suppressing VHL gene has become inactivated by deletion, mutation or methylation (Rini, 2005). Cytokines like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) and signal pathways like mammalian target of rapamycin (mTOR) have major importance in tumor angiogenesis and cell proliferation. Therefore, therapies aimed at inhibiting these targets are currently prominent in the treatment of RCC (Yazici et al., 2011). In this article, general characteristics of the targeted molecules in RCC pathogenesis and clinic data about the drugs targeting these molecules are reviewed.

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) is an important member of erbB cell surface receptor family (Wells, 1999; Yazici et al., 2011). Non-physiologic activation of EGFR causes uncontrolled cell division by intracellular activation of the ras pathway and consequently tumor growth. EGFR activation also leads

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to the activation of other intracellular pathways resulting in inhibition of apoptosis, stimulation of angiogenesis and metastasis/invasion (Price et al., 1996). These intracellular pathways include phosphatidyl-inositol 3-kinase, down flow protein-serin/treonin kinase (PI3K/Akt) pathways and Jak/Stat pathway (Mendelsohn et al., 2003; Yazici et al., 2011). Apoptosis can be blocked in cancer cells with increased EGFR-mediated signals and this allows increase of abnormal cells continuing to divide (Mendelsohn et al., 2003). Similarly, increased EGFR-mediated signals in cancer cells also stimulate the production of angiogenic factors like VEGF. EGFR activation causes metastasis particularly by increasing the invasion of tumor cells to the vascular endothelium (Yazici et al., 2005). However, 50-90% of RCCs express EGFR (Harari, 2004). In many human tumors, excessive EGFR expression is associated with poor prognosis (Mendelsohn et al., 2003).

Cetuximab

It is an anti-EGFR antibody and no partial or complete response has been observed in any patient in a phase II study including 55 patients with advanced stage RCC (Motzer et al., 2003).

Panitumumab

It is another anti-EGFR antibody and in a study administering panitumumab in the form of 8-week infusions to 31 RCC patients unresponsive to immunotherapy, partial response was reported in two patients (6%) and stable disease in 18 patients (58%) (Foon et al., 2004).

Vascular Endothelial Growth Factor

VEGF is a member of the PDGF family and is responsible for neovascularisation. VEGF is the most potent angiogenic factor specific for endothelial cells which causes endothelial cell proliferation, migration and tube formation and increases vascular permeability (Ferrara et al., 2003; Rini, 2005). In RCC, VEGF expression shows correlation with tumor vascularity and this can be considered to be a major prognostic indicator. In addition, VEGF can also affect hemostasis by increasing thrombomodulin and expression of tissue factor in endothelial cells. (Ferrara et al., 2003; Hicklin and Ellis; 2005; Yazici et al., 2011). VEGF is regulated by different growth factors (MAPK and PI3K) and oncogenes in the cellular signal transmission system (Harari, 2004).

Bevacizumab

It is a monoclonal antibody targeting VEGF and is applied parenterally. This antibody neutralizes all biologically active forms of the ligand by binding to VEGF-A (Presta et al., 1997; Escudier et al., 2007). On the other hand, it has no effect on other isoforms of VEGF and VEGFR. In a phase II study carried out by Yang et al. (2003), a total of 116 RCC patients previously treated twice with systemic therapy were randomized into three groups (placebo, bevacizumab 3 mg/kg and bevacizumab 10 mg/kg, respectively). At the termination of this study, median progression free survival was 2.5 months in the placebo group and 4.8 months in the bevacuzimab 10 mg/kg group (P<0.001). Toxicity was reported to be at a generally acceptable level but risk of intracerebral bleeding was increased in the bevacizumab arms and also third grade hypertension was reported in 36% of the patients receiving high dose bevacizumab (Yang et al., 2003). In addition, in two different randomized, double armed phase 3 studies on bevacizumab, efficiency of bevacizumab+IFN-α combination was studied in metastatic RCC patients without previous treatment (Escudier et al., 2007). Among these, in the AVOREN (AvastinR and RoferonR in Renal Cell Carcinoma) study (Escudier et al., 2007; Escudier et al., 2010, Bracarda et al, 2011), bevacizumab+IFN-α combination and placebo+IFN-α arms were compared in 649 patients diagnosed with RCC, while in the other study which was Cancer and Leukemia Group B (CALGB)-90206 (Rini et al., 2008; Rini et al., 2010), IFN-α and bevacizumab combination was compared with IFN-α therapy alone in 732 patients with metastatic RCC. Similar doses were used in both groups (bevacizumab every 2 weeks 10 mg/kg intravenously; IFN-α 3 times a week 9 MU) and treatment was resumed until disease progression or unexpected toxicity. In the interim evaluation of both studies, progression-free survival (PFS) was markedly longer in bevacizumab+IFN-α groups (AVOREN: 10.2 months vs. 5.4 months, P=0.0001; CALGB 90206: 8.5 months vs. 5.2 months, P<0.0001) (Yazici et al., 2011). In the CALGB study, PFS and overall survival (OS) were significantly longer in patients receiving combination therapy and developing grade 2 or higher hypertension when compared with patients not developing hypertension. Based on this conclusion, hypertension was suggested to be an indicator of response to treeatment. In the AVOREN study, objective response rates (ORR) were 31% in the bevacizumab+IFN-α group and 13% in the placebo+IFN-α group (P=0.0001); while in the CALGB 90206 study, objective response rates were 25.5% in the bevacizumab+IFN-α group and 13.1% in the IFN-α group (P<0.0001). It was shown in both studies that overall survival was prolonged by the addition of bevacizumab to IFN-α but this survival advantage thus obtained was not statistically significant.

Platelet Derived Growth Factor

PDGF is made up of PDGF-A, PDGF-B, PDGF-C and PDGF-D. These ligands bind to PDGF receptor alfa and beta (PDGFR-α, PDGFR-β) tyrosine kinase receptors and lead to the activation of intracellular signal pathways and consequently to angiogenesis and tumor growth. It has been shown that in human RCC cells PDGF-D expression is high and stimulates tumor growth, invasion and angiogenesis (Xu et al., 2005).

Tyrosine Kinases and Inhibitors

Activation of tyrosine kinase (TK) receptors by growth factors is an important step in the proliferation of tumor cells. These receptors are transmembrane glycoproteins which have an extracellular ligand binding piece and an intracellular TK piece. Receptors are inactive as

single units (monomer) but form active pairs (dimers) in the activation process of binding of the extracellular piece with ligands (EGF, PDGF, VEGF, amphiregulin, transforming growth factor-alfa, heparin-binding EGF, betacellulin, epiregulin and neuregulin G2b) (Harari et al., 2004). Dimer formation leads to the activation of the internal TK piece of the receptor and this catalyzes protein phosphorylation (Wells, 1999). Phosphorylation is followed by ras protein activation in the cellular cytoplasm and consequently MAPK (mitogen-activated protein kinase) phosphorylation and activation. This signal series extends to the nucleus and provides cell division mediated by cycline dependent kinases (Mendelsohn et al., 2003; Yazici et al., 2011).

Sorafenib

RAS/RAF/MEK/ERK which provides cell proliferation is a potent inhibitor of RAF-1 protein which has an active role in signal pathways. Moreover, it also inhibits TK receptors like VEGFR-2 and PDGFR-β which lead to angiogenesis (Willhelm et al., 2004). Previous animal studies have shown that it inhibits neovascularization and stops tumor proliferation. In a phase I study, it was shown that sorafenib dose of 200 mg and above is biologically active and decreases ERK phosphorylation in peripheral lymphocytes and sorafenib dose was established at 400 mg twice a day orally in the next clinical studies. In the phase II study by Ratain et al. (2006), sorafenib 800 mg daily was given for 12 weeks to 202 patients with metastatic RCC. At the end of twelve weeks, patients with tumor shrinkage of 25% or more (n=73) continued to receive sorafenib and those with tumor shrinkage of 25% or less (n=65) were randomized into sorafenib (n=32) and placebo (n=33) groups. In patients with progression, treatment was ended. At the end of twenty-four weeks, progression was not seen in 50% of the patients in the sorafenib group while this rate was reported to be 18% in the placebo group (P=0.0077). While median PFS was 6 weeks in the placebo group, it was found to be 24 weeks in the sorafenib group (P=0.0087). Adverse effects like hand-foot syndrome, rash, diarrhea and hypertension which are associated with sorafenib were stated to be manageable and reversible in this study (Ratain et al., 2006). International and multi-center TARGET (Treatment Approaches in Renal cell cancer Global Evaluation) study (Escudier et al., 2007; Escudier et al., 2009) is important because it is the first phase III study investigating the efficiency of TK inhibitors in RCC patients. In this study, 903 patients with unresectable or metastatic clear cell RCC diagnosed histologically were randomized into oral sorafenib (400 mg twice a day) (n=451) or placebo (n=452) groups. Patients with no benefit from previous therapies and with performance status of 0 or 1 in ECOG (Eastern Cooperative Oncology Group) were included in the study and primary target was overall survival and secondary target was PFS. While complete response was noted in 1%, partial response in 10% and stable disease in 78% of the patients receiving sorafenib, these rates were 0%, 2% and 53%, respectively, in the placebo group. Progression was seen in 12% of the patients receiving sorafenib and in 37% of those in the placebo group. Median PFS was reported to be 5.9 months in the sorafenib gruoup and 2.8 months in the placebo group (P<0.001). In the interim evaluation of this study, OS was 19.3 months in the sorafenib group and 15.9 months in the placebo group and in the final evaluation, these rates were 17.8 months and 15.2 months, respectively (Escudier et al., 2009). Drug related adverse effects were reported to be more common in the sorafenib group compared with the placebo group (hypertension 17% vs 2%; diarrhea 43% vs 13%; hand-foot skin reaction 30% vs 6%) (Escudier et al., 2007; Yazici et al., 2011).

In the phase II study carried out by Escudier et al. (2009), metastatic RCC patients did not receive primary systemic therapy following nephrectomy or radiotherapy were randomized into sorafenib (400 mg twice a day; total dose 800 mg/day) or IFN- α (9 MU/day three times a week) groups. Treatment dose of the patients receiving sorafenib 800 mg daily and showing progression were changed as 600 mg twice daily (total daily dose 1200 mg). On the other hand, patients in the IFN group who showed progression were shifted to the study group receiving 400 mg twice daily. Although PFS was found to be similar in patients receiving sorafenib (n=97) and IFN-α (n=92) (for sorafenib and IFN-α groups, 5.7 and 5.6 months, respectively) in the first stage of the study, tumor shrinkage was found to be greater in the patients receiving sorafenib (68.2% vs 39%). Following progression, tumor shrinkage was observed in 41.9% of 43 patients receiving 1200 mg sorafenib daily (median PFS 3.6 months). On the other hand, tumor shrinkage was seen at a rate of 76.2% in 50 patients showing progression while receiving interferon and shifting to the group treated with 800 mg sorafenib daily (median PFS 5.3 months). Based on the results of this study, it was concluded that shifting to sorafenib therapy (following interferon) in patients progressing during IFN therapy or increasing the drug dose in those progressing under sorafenib therapy may provide clinical benefit (Escudier et al., 2009).

In the SORCE study which is a phase III study belonging to the Medical Research Council (MRC), non-metastatic RCC patients at moderate or high risk for recurrence according to the Leibovich scoring system (Leibovich score 3-11) were randomized into 3 groups following primary tumor resection: patients to receive placebo for 3 years were included in Group 1, patients to receive sorafenib (800 mg/day) for 1 year and placebo for 2 years in Group 2 and patients to receive sorafenib (800 mg/day) for 3 years in Group 3. Patients in the first and second groups can be shifted into the third group in case of progression. The primary purpose of this study is to determine metastasis free survival and its secondary purpose is to determine OS and toxicity. Furthermore, biologic characteritics (VHL, VEGFR2, FGF2, B-RAF, MEK and ERK) of resected primary tumors will be established and accuracy of Leibovich risk model will be proved. 3-year metastasis free survival which is 64% in the moderate or high risk group is expected to rise to 71% with sorafenib therapy (Yazici et al., 2011).

Sunitinib

It is a selective, oral multi-tyrosine kinase inhibitor

which inhibits VEGFR-2, PDGFR-β, c-KİT and FLT-3 tyrosine kinases (Rini, 2005). Since it is known that expression of VEGF and PDGF receptors is increased in clear cell RCC, it has been possible to evaluate efficiency related with sunitinib in these patients. In preclinic studies with sunitinib, it has been shown that VEGFR-2 and PDGFR-β phosphorylation is inhibited in vivo, endothelial cell and fibroblast proliferation is inhibited in vitro and there is antitumor activity in mouse xenograft models (Mendel et al., 2003). Adverse effects like malaise, diarrhea, nausea, hematologic toxicity and rash associated with sunitinib monotherapy have been reported in published phase I studies. Malaise has been reported as the dose-limiting toxicity in these studies (Fiedler et al., 2005). As a result of phase II studies, sunitinib has been shown to be active in secondary treatment in patients with RCC. Oral sunitinib dose recommended for phase II studies is 50 mg daily and administration protocol is applying this drug in 6-week cycles by giving every day for 4 weeks and stopping for 2 weeks (Motzer et al., 2006a; 2006b; Gore et al., 2011). This recommended treatment protocol has been used in the two different phase II independent one-armed studies by Motzer et al. (2006a; 2006b). It has been shown in previous studies that hypertension is seen at doses above 75 mg and malaise increases as treatment is continued. The first study includes 63 patients with RCC (55 patients with clear cell RCC) with failed cytokine therapy (Motzer et al., 2006). While complete response was not seen in any patient, partial response was observed in 25 patients (40%) and in 18 patients (28%) the disease was stable for at least three months. Median time for obtaining partial response was 2.3 months, median response duration was 12.5 months and median time elapsed until progression was 8.7 months. Median OS was 16.4 months. The second study includes only patients with clear cell carcinomas histologically and showing radiologic progression during treatment with IFN, IL-2 or combination of both (Motzer et al., 2006). Evaluation by the researchers revealed a partial response rate of 45% (43 patients) to sunitinib, a complete response of 1% (1 patient) and an ORR of 44% (46 patients) in 105 patients (one patient with seminoma was excluded from evaluation) and the disease was stable in 4 patients (23%). Time to response was 2.3 months, duration of response was 9.9 months and time to progression was 8.1 months. Median OS could not be reached but rate of 6-month survival was reported to be 79%. In these two phase II studies on sunitinib, adverse effects were grade 2/3 malaise in 38% and 22% of patients, diarrhea in 24% and 16% of patients and nausea in 13% and 19% of patients, respectively. Motzer et al. (2006) have concluded that the drug is relatively well tolerated and a few patients with persistent response to therapy are still continuing to use the drug for more than two years. Moreover, in these two consecutive studies, sunitinib appears to have an important antitumor activity as a secondary treatment in metastatic RCC patients and the antitumor activity seen in the second study was supported by the first study.

In the multi-center phase III study by Motzer et al. (2007), 750 patients with no previous treatment and with metastatic RCC were randomized into sunitinib (oral 50 mg daily, the drug was given for 4 weeks and stopped for 2 weeks, n=350) or IFN-α (subcutaneous 9 MU three times a week, n=350) groups as 6-week cycles. Treatment was ended when the disease progressed, an unexpected toxicity was seen or according to patient choice. Primary purpose was PFS and secondary purpose was OS. In the interim evaluation, median PFS was found to be longer in the sunitinib group, independent of patient age, gender and MSKCC risk score (sunitinib 11 months, IFN-α 5 months; P<0.001). Objective response rates were 31% in the sunitinib group and 6% in the IFN-α group (P<0.001); this rate was also found to be higher in the sunitinib group (47% vs 12%) in the final evaluation. While treatment related grade 3/4 malaise was more prominent in the IFN-α group, diarrhea was more frequent in the sunitinib group (P<0.05). Better quality of life was reported by the patients in the sunitinib group (P<0.001). Due to the PFS advantage of sunitinib also shown in the second evaluation, patients on IFN-α were allowed to shift to the sunitinib group. Overall survival was longer in the sunitinib group although median survival was at statistical significance border (sunitinib 26.4 months, IFN-α 21.8 months; P=0.051). In the second evaluation, OS was markedly higher in the sunitinib group when effects due to the shift from the IFN-α group to the sunitinib group were overlooked (sunitinib 26.4 months, IFN-α 20 months; P=0.036) (Motzer et al., 2007). However, in recent randomized, phase II Renal EFFECT trial in metastatic RCC by Motzer et al. (2011), there was a trend toward inferior time to progression with 37.5 mg continuous sunitinib treatment. Additionally, in this study, ORR, OS, and adverse effects profiles were similar for the approved sunitinib 50 mg/daily dose on schedule 4 weeks on treatment/2 weeks off vs. 37.5 mg continuous dosing.

In the multi-center randomized phase III ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) study (NCT00326898) sponsored by ECOG, RCC patients without metastasis and with moderate or high risk for recurrence (pT1b, G3-4; pT2–pT4; any T stage, N+) were randomized into sorafenib or sunitinib groups as primary therapy following partial or radical nephrectomy (Yazici et al., 2011). Primary purpose of the study planned to evaluate approximately 1300 patients is to determine disease free survival and secondary purpose is determination of OS. Another study which evaluates adjuvant therapy following nephrectomy in high risk RCC patients without metastasis is the S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer) study (Yazici et al., 2011).

Pazopanib

It is an oral TK inhibitor which inhibits VEGFR, PDGFR and c-Kit. It is used as primary therapy in advanced stage RCC patients. In a randomized, double blind, placebo controlled phase 3 study on local advanced and/or metastatic RCC patients with previous cytokine therapy or no therapy, patients were divided into two groups of oral pazopanib (800 mg/day) (n=290) or placebo (n=145). In this study, primary purpose is determination of PFS, while secondary purposes are OS, ORR, duration of treatment response and quality of life. In the interim

evaluation of this study, patients showing progression in the placebo group were allowed to shift to the pazopanib group. Median PFS was found to be longer in the group receiving pazopanib (9.2 months vs. 4.2 months, P<0.0001). Long PFS obtained with the pazopanib therapy was reported to be independent of MSKCC risk score, age, gender and performance status. While rate of objective response was 30% in the group receiving pazopanib, this rate was found to be 3% in the placebo group (P<0.001) (Sternberg et al., 2010). In additionally, pazopanib has similar efficacy to sunitinib in first-line treatment of metastatic RCC, the results of the phase III randomized, open-label COMPARZ trial show (Motzer et al., 2012). The primary end-point was to establish non-inferiority of PFS, and safety and quality of life were evaluated as secondary end-points, as well, in this study. Additionally, in a randomized double-blind, placebo-controlled, cross-over study (PISCES study, NCT 01064310), patient preference between first-line 800 mg pazopanib for 10 weeks followed by a 2-week washout and 50 mg sunitinib for 10 weeks (4/2 weeks schedule) were investigated on 126 patients with advanced or metastatic RCC (Escudier et al., 2012). In this study, pazopanib was shown the better tolerability than sunitinib.

Axitinib

Is an oral TK inhibitor which inhibits VEGFR and PDGFR phosphorylation. In a multi-center phase II study by Rini et al., oral axitinib was given at a dose of 5 mg twice a day to metastatic RCC patients refractory to cytokine and 46% of the patients had partial responses (Rini, 2005). Treatment related adverse effects like hypertension, stomatitis, malaise and diarrhea were seen in 12% of patients (Grade 3/4 diarrhea 8%, hypertension 15%, malaise 8%). Furthermore, survival was reported to be longer in patients with diastolic blood pressures of 90 mmHg or above. In the phase 3 AXIS (axitinib as second line therapy for metastatic renal cell cancer) study, axitinib and sorafenib are compared as secondary therapy in patients developing progression following treatment with sunitinib, temsirolimus or bevacizumab/interferon (NCT00678392). First results of the study were declared in the ASCO 2011 meeting, and PFS was markedly longer in patients taking axitinib compared with sorafenib (6.7 months vs. 4.7 months, respectively) (Hutson, 2011; Rini et al., 2011). In final results of this study, the median PFS was 6·7 months with axitinib compared to 4·7 months with sorafenib (HR 0.665; 95%CI 0.544-0.812; p<0·0001) (Rini et al., 2011). Additionally, in the a randomized phase 2 trial by Rini et al. (2012), the efficacy and safety of axitinib dose titration from 5 mg BID to a maximum of 10 mg BID is evaluated as first-line treatment in patients with metastatic RCC. Axitinib is effective in first-line treatment of patients with RCC, with increased ORR and median PFS.

Tivozanib

It is an oral VEGFR TK inhibitor effective at picomolar concentrations. In a phase 2 placebo controlled study, efficacy and safety of tivozanib were investigated on 272 patients with local advanced or metastatic RCC (73% previously nephrectomized) (Bhargava et al., 2010). Median PFS was found to be 11.8 months and subgroup analysis revealed that patients with clear cell RCC pathology and previous nephrectomy had better response to therapy (PFS 14.8 months). In the randomized phase 3 TİVO-1 study (NCT01030783), tivozanib and sorafenib are compared in nephrectomized advanced stage clear cell RCC patients with no previous VEGF targeted therapy (Bhargava et al., 2010). The results of phase III rendomized, open-label, multicenter study were demonstrated significant improvement in median PFS (11.9 months for tivozanib vs. 9.1 months for sorafenib; HR 0.756, 95%CI 0.639-0.993; P=0.042) and ORR (33% for tivozanib vs. 23% for sorafenib; P=0.014) (Motzer et al., 2012).

Dovitinib

It is a selective oral inhibitor of fibroblast growth factor receptors and VEGFRs. Dovitinib was investigated in the phase I/II trial of 20 heavily pretreated patients. The results indicated a 10% ORR and preliminary median PFS duration was 5.5 months (Hutson, 2011).

Cabozantinib

It is a potent inhibitor of MET and VEGFR2 patways that is recently undergoing evaluation in treatment of several solid tumors. Cabozantinib was investigated together with rosiglitazone in the drug-drug interaction study of 25 patients with heavily pretreated RCC. Cabozantinib demostrates encouraging anti-tumor activity in patients with metastatic RCC with an adverse effect profile similar to other VEGFR thyrosin kinase inhibitors (Choueiri et al., 2012).

Regorafenib

It is a potent inhibitor of VEGF receptors 1, 2, and 3 and PDGF receptors like other anti-angiogenic multi-tyrosine kinase inhibitors approved for treatment of metastatic RCC. In a phase 2, open-label, non-randomized study (NCT00664326), efficacy and safety of regorafenib were evaluated on 49 patients with advanced RCC (Eisen et al., 2012). In this study, 48 patients were investigated for tumour response and 19 patients (39.6%, 90%CI 27.7-52.5) had an objective response, all of which were partial responses. Finally, regorafenib has an antitumour activity as first-line treatment for metastatic or advanced RCC (Eisen et al., 2012).

mTOR (mammalian target of rapamycin) Pathway and Drugs Targeting this Pathway

One of the major pathways playing a role in RCC pathogenesis is mTOR pathway. mTOR, is a member of the „TOR“ (target of rapamycin) protein family and is an important serine/threonine kinase in the PI3K/AKT signal pathway. This pathway is activated with the mediation of PI3K/Akt as a result of TK receptor phosphorylation (activation). mTOR is the most important kinase responsible for endothelial cell survival, proliferation and migration and regulated via Akt (Hanna et al., 2008). It exists in two different macromolecular

complexes sensitive to rapamycine and named mTORC1 and mTORC2. A strong tie has been shown between PI3K pathway and PTEN (phosphatase and tensin homologue) oncogene. Although rare in RCC, PTEN function loss as a result of mutation leads to activation of Akt/mTOR pathway and cellular protein synthesis is increased mediated by 4EBP1 (4E-binding protein) and S6K (S6 kinase). As for RCC, another product of mTOR pathway is inceased HIF-1a and HIF-2a expression (Radulovic and Bjelogrlic, 2007; Yazici et al., 2011). Therefore, considering that suppression of mTOR pathway would inhibit angiogenesis, randomized phase 3 clinical studies investigating the efficiency of mTOR inhibitors like everolimus and temsirolimus in metastatic RCC patients have been planned.

Temsirolimus

It is a rapamycin analogue inhibing mTOR and its antitumor activity has been shown in many animal models (Frost et al., 2004). In a phase II study on 111 advanced stage metastatic RCC patients, 3 different doses of temsirolimus (25, 75 or 250 mg once a week in 30-minute intravenous infusion) was tried as secondary therapy and partial or complete response was observed in 7% of patients (Atkins et al., 2004). Mean time to tumor progression was 5.8 months and median survival was 15 months. The most frequently encountered adverse effects were maculopapular rash (76%), mucositis (70%), malaise (50%) and nausea (43%). In a multi-center randomized phase III study published in 2007, 626 metastatic RCC patients with poor prognosis and no previous systemic therapy were randomized into 3 groups: 3 MU IFN-α 3 times a week s.c. (as to increase up to 18 MU) (n=207); temsirolimus 25 mg (n=209); temsirolimus 15 mg and 6 MU IFN-α 3 times a week s.c. combination (n=210). Presence of at least 3 of 6 indicators of short survival was determined as inclusion criteria. These criteria were serum LDH level 1.5 times higher than the upper limit, low hemoglobin level, serum calcium level above 10 mg/dl, diagnosis of less than 1 year, Karnofsky performance score of 60 or 70 and presence of more than one organ metastasis. Temsirolimus was administered once a week as 30-60-minute intravenous infusions. Treatment was ended when the disease progressed, symptoms worsened or an unexpected toxicity was seen. Primary purpose was determination of OS. Progression free survival was longer in those taking temsirolimus alone than those taking IFN-α alone (P<0.001) (median PFS was 3.8 months, 1.9 months and 3.7 months for temsirolimus, IFN-α and combination groups, respectively). Median OS was significantly longer in the temsirolimus group compared with IFN-α (temsirolimus 10.9 months, IFN-α 7.3 months; P=0.008) (Hudes et al., 2007). From this perspective, temsirolimus is the only agent significantly prolonging OS among target aimed agents. However, marked superiority of combination therapy has not been shown regarding OS, when compared with IFN-α; besides, adverse effects were more common in this group (median survival combination 8.4 months vs. IFN-α 7.3 months). Rash, peripheral edema, hyperglycemia and hyperlipidemia were more common in the temsirolimus group, while malaise was more common in the IFN-α group (Hudes et al., 2007). In the subgroup analysis of this study, temsirolimus (n=37) and IFN-α (n=36) therapies were also compared in extra-clear cell RCC patients (Dutcher et al., 2009). Progression free survival and OS were significantly longer in patients receiving temsirolimus (PFS, temsirolimus 7 months vs. IFN-α 1.8 months; OS, temsirolimus 11.6 months vs. IFN-α 4.3 months). Overall survival tends to be longer in patients with extra-clear cell RCC than in clear cell RCC in patients receiving temsirolimus (11.6 months vs 10.7 months). Temsirolimus is the only targeting agent whose clinic benefit has been shown with a phase 3 study in extra-clear cell RCC patients (Dutcher et al., 2009). In conclusion, when compared with IFN-α, temsirolimus has increased OS when given as primary therapy to metastatic RCC patients with poor prognostic indicators. Currently there are many ongoing studies on temsirolimus. Efficacy of bevacizumab, sorafenib and temsirolismus as secondary therapies are being investigated in many combinations. TORAVA was an open-label, multicentre randomized phase 2 study on 171 untreated metastatic RCC patients. In this study, the results were demonstrated that the toxicity of temsirolimus and bevacizumab combination was much higher than anticipated and limited treatment continuation over time. Finally, this combination treatment cannot be recommended for first-line treatment in patients with metastatic RCC (Négrier et al., 2011).

Everolimus

It is an oral mTOR inhibitor. In the randomized, double blind, placebo controlled phase 3 RECORD-1 (Renal Cell Cancer Treatment with Oral RAD001 given Daily) study, 416 metastatic RCC patients developing progression under VEGFR TK inhibitors therapy were randomized into everolimus (10 mg oral daily) and placebo groups (Motzer et al., 2008; 2010). In case of progression in patients receiving placebo, it was permitted to shift to the everolimus group. Primary purpose was PFS; OS, ORR, adverse effect profile and quality of life were also taken into evaluation. In the interim evaluation, double blind phase of the study was ended when median PFS was markedly longer in the everolimus group compared with placebo (4 months vs 1.9 months, P<0.0001). Disease stabilization was observed in 63% of patients receiving everolimus and in 32% of those receiving placebo. In the final analysis, PFS was found to be prolonged in favor of everolimus (4.9 months vs 1.9 months, P<0.0001). In patients in the everolimus group, decrease in Karnofsky performance score and symptomatic worsening occurred at a longer time than the placebo group. Although there was no statistically significant difference between the two groups regarding OS, when negative effects of shifting from placebo to everolimus were also calculated in post-hoc analysis, everolimus was shown to prolong survival 1.9-fold compared with placebo (Motzer et al., 2008; Motzer et al., 2010).

Targeted Therapy Algorithm in Patients with Renal Cell Carcinoma

Currently, targeted therapy in metastatic RCC patients

can be categorized as follows: previously untreated patients, patients refractory to immunotherapy and patients not benefiting from TK inhibitors therapy. One of the most important criteria in deciding the treatment of this patient population is Memorial Sloan- Kettering Cancer Center (MSKCC) prognostic risk determination system (Motzer et al, 1999). In this system, metastatic RCC patients were categorized according to 6 prognostic factors: serum LDH level 1.5 times higher than the upper limit, hemoglobin level below the lower limit, corrected serum calcium level above 10 mg/dl, diagnosis of less than 1 year, Karnofsky performance score of 60 or 70 and presence of more than one organ metastasis. Patients with no risk factors were included in the good prognostic group, those with 1 or 2 risk factors in the moderate prognostic group and those with 3 or more risk factors in the poor prognostic group (Motzer et al, 1999; 2004).

In patients with good or moderate prognosis and with no previous treatment, sunitinib or bevacizumab+IFN-α is recommended as primary therapy in the European and American guidelines. In selected patients with good prognosis, high dose IL-2 is presented as primary therapy in some guidelines. On the other hand, in patients with poor prognosis, first choice is temsirolimus. In patients previously treated with cytokine, although first choice is sorafenib, sunitinib is also recommended as secondary therapy in some guidelines. The other important group includes metastatic RCC patients unresponsive to TK inhibitors therapy. First choice is everolimus in these patients (Escudier and Kataja, 2010; Escudier et al., 2012).

Ongoing Trials of Combination Treatment with Targeted Molecules

Sequential treatment with targeted molecules is the recent standard approach in patients with metastatic RCC. However, combination therapy with targeted agents is under active investigation (Hutson, 2011). Ongoing trials in this topic are as follows;

INTORACT Trial (Trial number is NCT00631371) (ClinicalTrials.gov); Feature: Phase III study in 800 estimated untreated patients. Agents: Bevacizumab+temsirolimus versus bevacizumab+IFN-alfa. Primary end-point: PFS.

BeST Trial (Trial number is NCT00378703) (ClinicalTrials.gov); Feature: Phase II study in 360 estimated patients with no prior antiangiogenic treatment. Agents: Bevacizumab; Bevacizumab+temsirolimus; Bevacizumab+sorafenib; Sorafenib+temsirolimus. Primary end-point: PFS.

RECORD-2 Trial (Trial number is NCT00719264) (ClinicalTrials.gov); Feature: Phase II study in 360 estimated patients with no prior systemic therapy. Agents: Bevacizumab+everolimus; Bevacizumab+IFN-alfa. Primary end-point: PFS.

Conclusions

Absence of a biological marker able to predict tumor resistance or response in RCC which is resistant to cytotoxic chemotherapeutic drugs is an important obstacle in the evaluation and choice of targeted therapies. On the other hand, favorable results obtained with anti-angiogenic targeting drugs in patients with RCC has increased interest in the treatment of these patients. Planned studies on the use of targeting molecules alone or in combination and the ongoing clinical studies has extended the opinion that survival of these patients can be prolonged even more.

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