CASE REPORT

NEW TRENDS IN THE THERAPEUTICAL OPTIONS OF RENAL CELL CARCINOMAS

Alexandru Nesiu[1,2], Ahmed Adile[1,2], Alin Mihu[1,2*], Ioan Ioiart[1,2]

[1]Clinical Country Emergency Hospital, 2-4 A Karoly, Str., 310037, Arad, Romania
[2]West University Vasile Goldis, 94 Revolutiei Blvd., 310130, Arad, Romania
*Corresponding Author

ABSTRACT

Renal cancer is the 9th most frequent cancer worldwide causing aproximately 334.000 new cases per year. From this group of cancers, renal cell carcinomas are the most frequent malignant tumours representing 85% of newly diagnosed renal cancer cases. This cancer causes 95000 deaths anually. Renal cell carcinomas are a group of cancers that derive from the renal tubular cells. Due to the major advances in molecular and histopathological characterization of these cancers, major chances were made to the management and therapies in the last 20 years. The aim of the present paper is to review the latest medical literature in order to clearly go trough these new classifications and therapies and postulate what the future holds.

KeyWords: renal cell carcinoma, angiogenesis, cancer, treatment, imunotherapy.

INTRODUCTION

RRC (Renal cell carcinoma) comprise a heterogeneous group of cancers derived from renal tubular epithelial cells. Major advances in molecular and histopathological characterization of renal cancer over the past two decades have led to major revisions in the classification of renal cancer. RCC management has undergone major changes and this is largely due to the progress made in discovering new therapeutic targets that can be successfully targeted for the benefit of patients (1).

Tumor angiogenesis is the process of formation of new vessels and the distinguishing sign of tumor progression (2). Tumor angiogenesis is the proliferation of a network of blood vessels that penetrate cancerous growths providing nutrients and oxygen. Tumor angiogenesis begins with the release of molecules by the tumor cells. These tumor cells transmit signals to the surrounding normal host tissue and activate certain genes to produce proteins that encourage the growth of new blood vessels (3).

RCC are very well-vascularized tumors. Due to this phenomenom along with their rapid progression they are difficult to manage with current antiangiogenic and anti-vascular therapies. Over time they establish resistence to the treatment.

Tumors can develop a vascular network in two ways: 1) by angiogenesis (germination of endothelial cells from nearby blood vessels) and 2) by vasculogenesis (formation of blood vessels from circulating cells) (4). Tumors cannot grow in size without the formation of new blood vessels so they secrete an angiogenic factor that stimulates neovascularization. If this process of angiogenesis could be stopped, the tumor would stop growing. This has paved the way for many antiangiogenic therapies, with several antiangogenic drugs being approved for use in RCC by the Food and Drug Administration (FDA) such as: Bevacizumab, Sunitinib, Sorafenib, Pazopanib, Axitinib and Tivozanib (5).

Although in the last 10 years, the treatment of renal cancer has been continously improved with the advent of antiangiogenic drugs and tyrosine kinase inhibitors, these drugs rarely cause lasting tumor responses and most patients will experience disease progression. Due to this reason is important to discover new therapeutic targets to improve overall survival (6).

Our goal in this review is to take a look at each drug and procedure used for therapy, where it can be used, the prognosis that follows and to assess what the future holds in developing further treatment options and maybe, even a cure.

The main treatment and management options for RCC are: surgery, thermal ablation, radiation therapy, imunotherapy, molecular-targeted therapy and active surveillance.

TREATMENT OF LOCALIZED RENAL CANCER

Classic nephrectomy (radical or partial)

Surgical therapy remains the main treatment for patients with stage I renal carcinoma, because the resection of primary tumors tends to be curative, providing the most effective oncological outcome (7).

For patients with stage I renal cancer, surgical therapy should be considered as a primary treatment option, so radical nephrectomy has been considered the gold standard of surgical treatment since the 1960s (8). The disadvantage of radical nephrectomy was highlighted by the development chronic kidney disease and increased risk of cardiovascular disease in patients who underwent the procedure. Thus, the recent preference in surgical treatment for patients with stage I

and T1a (≤4cm) renal cancer is partial nephrectomy (9). 9

Laparoscopic nephrectomy

The laparoscopic procedure stands out because it offers an improved post-operative recovery for the patients and offers a better visibility of the surgical field, benefiting the operator. According to current guidelines the standard procedure for partial nephrectomy is open surgery, because partial laparoscopically treated nephrectomy is associated with a higher incidence of complications and a longer ischemic time (10).

Radical laparoscopic nephrectomy showed a significant benefit compared with open radical nephrectomy by reducing intraoperative bleeding, postoperative complications and reducing hospitalization time (11).

There are less invasive treatment options for small renal masses. Renal masses can be treated by radiofrequency ablation, cryoablation, microwave ablation and stereotactic radiotherapy (12).

Local recurrence after thermal ablation therapy is observed more frequently than after surgical therapy. A major advantage of thermal ablation is keeping the renal function in the upper limits, following the procedure. Thermal ablation is recommended for elderly patients with severe comorbidities, small kidney tumors or multiple hereditary tumors, for patients with solitary kidney or bilateral tumors and those who are at high risk of complete loss of renal function if the chosen treatment is surgery (13).

For patients with stage II renal cancer it is recommended to perform laparoscopic radical nephrectomy. Classical radical nephrectomy is also recommended, but it has a greater loss of blood and longer hospitalization compared to laparoscopic radical nephrectomy. Partial nephrectomy is difficult to perform in most cases of T2 RCC, where the tumor exceeds 7 cm. In a therapeutic study it has been shown that partial nephrectomy for tumors greater than 7 cm has acceptable functional, technical and oncological results (14).

Lymphadenectomy

In a prospective randomized clinical trial performed in patients with renal carcinoma, no therapeutic benefit was demonstrated following lymphadenectomy (15).

Lymphadenectomy should be performed for accurate staging, if the imaging examination describes associated adenopathy (13).

Ipsilateral adrenalectomy

In a review, the risk factors of adrenal metastasis were examined, and patients with upper pole tumors larger than 7 cm were reported as suitable candidates for adrenectomy (16). Current guidelines recommend that ipsilateral adrenelectomy be performed only if radiological imaging reveals the possibility of metastatic lesions in the adrenal glands (13).

Interferon α immunotherapy

In a clinical study, it was noted that the administration of natural interferon α for 1 year after radical nephrectomy in patients with stage II and III renal carcinoma showed no improvement in progression-free survival of the disease (17).

TREATMENT OF METASTATIC RENAL CANCER

In a review written by Gupta K. et. al. related that despite recent scientific advances in diagnosis and treatment, around 25-30% of patients with renal cancer have metastases at first diagnosis and in another review conducted by Uzma A. et. al. was related that 20-30% of patients with local disease who have been operated, develop metastases with a medium-term up to at recurrence of about 15-18 months (18,19).

Surgical treatment

In most patients the established practice is to perform citoreductive nephrectomy before starting systemic treatment. Cytoreduction nephrectomy is followed by treatment with a combination of 8 FDA-approved agents, including antiangiogenic agents, immunotherapeutic drugs, and mTOR (mammalian target of rapamycin) inhibitors. In a randomized control trial, improvement in survival was demonstrated in patients with metastatic renal cancer who had undergone cytoreduction nephrectomy prior to interferon α treatment. Cytoreduction nephrectomy is recommended for patients with good status, in patients with symptomatic primary lesion and in those with large primary tumors (20).

Adjuvant therapies

Adjuvant therapies are treatments administered in addition to the main or initial treatment to maximize their effectiveness.

Immunotherapy

1) IFN α (Interferon α)

IFN α was the first cytokine therapy approved for the systemic treatment of metastatic renal cancer. IFN α is a glycoprotein expressed by leukocytes acting as follows: 1) it stimulates Natural Killer Cells, 2) it decreases cell proliferation by inhibiting cyclin-dependent kinases (CDK), 3) it increases tumor cell immunogenicity and 4)

it inhibits angiogenesis (21,22).

IFN α treatment as monotherapy

Although IFN α treatment had a promising start in the treatment of advanced or metastatic clear cell renal cell carcinoma, in a review conducted by Canil et. al. in 2010, eight randomized clinical studies were performed in patients with inoperable renal carcinoma, showing that there is a response rate limit of up to 20% in patients treated with IFN α compared to the control group treated with placebo (23).

In addition, this drug has a high toxicity, manifesting the following conditions: inadequacy, nausea/vomiting, fatigue, chills, depressive states, lack of energy and xerostomia after four weeks of treatment with IFN α. Use of IFN α treatment has been limited, with several drug combinations being tried with other antitumor agents as first- or second- line therapy in metastatic renal cell carcinoma (24).

IFN α as an adjuvant treatment

In an article described by Flanigan et. al. in 2001, the median overall survival of patients treated with IFN α after nephrectomy citoreduction increased to 11.1 months, and in patients treated only with IFN α the median overall survival was 8.1 months (25).

In a study conducted by Mickisch in 2001, overall survival was observed up to 17 months in radically nephrectomized patients treated with INF α, compared to the group of patients treated with IFN α only, who had a 7-month overall survival (26).

IFN α may be considered for the treatment of patients at increased risk of tumor recurrence after surgery, but due to the high toxicity of this drug makes its use difficult and limited in most cases.

2) IL-2 (Interleukin-2)

IL-2 is a growth factor of T cells and regulates the activity of monocytes, macrophages, T cells and Natural-Killer Cells. IL-2 affects tumor growth by activating lymphoid cells in vivo, without directly affecting tumor proliferation (27).

IL-2 as monotherapy

In a clinical trial conducted by Law T. et. al. was described that the high dose of IL-2 may induce a lasting remission of the disease, but in a small number of patients (28).

In a study by Fisher, et. al., the average duration of treatment response for all partial responses was 20 months, and the average survival time for all patients included in the study was 16.3 months, and it was estimated that 10% to 20% of patients live between 5 and 10 years after treatment. Due to the serious adverse effects of this treatment have limited its use. High doses of IL-2 have toxic effects, such as: increased vascular permeability and secondary cytokine secretion (IL-1, tumor necrosis factor, nitric oxide and interferon gamma) (29,30).

IL-2 as an adjuvant treatment

In a study conducted by Clark et. al., in 2003, the results showed no difference in overall survival after a high dose cycle of IL-2, being added as adjunctive treatment in patients with advanced and metastatic local disease after they were completely reset (31). Due to this reason the role of IL-2 in nephrectomized patients remains controversial.

TARGETED THERAPIES

Systemic therapy of advanced renal cell carcinoma was not satisfactory, as this treatment demonstrated limited efficacy as well as high toxicity.

Due to this, a better understanding of the cellular signaling pathways involved in the development of renal carcinoma has led to the development of new therapies that specifically target the abnormal pathways that aid in the development of cancer.

VEGF (Vascular endothelial growth factor) / VEGFR (Vascular endothelial growth factor receptor) inhibitors

Bevacizumab (BEV)

Bevacizumab is a humanized monoclonal antibody that interacts with circulating VEGF and blocks its binding to its receptor (VEGFR), thus inhibiting angiogenesis in clear cell renal cell carcinoma (32).

The AVOREN study and the CALGB 90206 study compared BEV + IFNα with IFNα alone. The objective therapeutic response rate (ORR) was 28.4% vs. 12.9% for BEV + IFNα versus IFNα or IFNα + placebo, and progression-free survival was 10.2 months versus 5.4 months for BEV + IFNα versus IFNα or IFNα. + placebo. As demonstrated, response to therapy was substantially improved when there was a combination of BEV + IFNα versus IFNα alone or in combination with placebo (33,34).

Sunitinib

Sunitinib is an oral drug that inhibits multiple tyrosine kinase receptors, binding to VEGFR-1/2/3, PDGFR-α/β (Platelet derived growth factor receptor alpha and beta), FLT3 (fms-like tyrosine kinase 3), c-KitR (tyrosine-protein kinase KIT) and CSF1-R (Colony stimulating factor 1 receptor) (35).

The pivotal Phase 3 clinical trial NCT83889, included patients with previously untreated metastatic renal cell carcinoma, with a predominantly favorable or intermediate prognosis, showed that average progression-free survival of the disease was significantly higher in patients treated with Sunitinib than in patients treated with IFN α (11 months versus 5 months) (36).

Sorafenib

Sorafenib is a "multitarget" drug, having kinase inhibitory activity, suppressing cell proliferation and angiogenesis (37). Sorafenib inhibits tyrosine kinase receptors (VEGFR-1, VEGFR-2, VEGFR-3, c-kit, PDGFR-β and FLT3) and serine / threonine kinases (C-Raf and B-Raf) in tumor cells and tumor vascular cells (38).

In a clinical study by Escudier et. al., the efficacy of sorafenib in patients with advanced renal carcinoma was evaluated. The number of patients treated with sorafenib was 335 and the number of patients treated with placebo was 337. The sorafenib-treated group had 7 patients with partial response (2%), 261 patients with stable disease (78%) and 29 patients with disease progression (9%), and for the remaining 38 (11%) patients the data was missing. The placebo group had 186 patients with stable disease (55%), 102 patients with disease progression (30%), for 49 patients (15%) data were mising and no patients with partial response. Significantly more patients in the sorafenib group than in the placebo group had stable disease or partial responses (39).

Pazopanib

Pazopanib is a tyrosine kinase inhibitor and through interaction with PDGFR-β / α, VEGF-1/2/3 and C-kit receptors, suppresses angiogenesis. In a clinical study by Sternberg et. al., Pazopanib demonstrated a significant improvement in tumor response and PFS (Progression-free survival) compared with patients receiving placebo, and the therapeutic response rate was 30% with pazopanib and 3% with those receiving placebo (40).

Cabozantinib

Cabozantinib is a multiple tyrosine kinase inhibitor which blocks VEGFR-1/2/3, TRKB, RET, KIT, FLT-3, AXL, TIE-2, with additional potential to inhibit c-MET (41). Choueiri et. al., conducted a clinical study comparing cabozantinib and everolimus in patients with advanced RCC. Cabozantinib treatment significantly increased overall survival (21.4 months in those treated with cabozantinib and 16.5 months in those with everolimus), and progression-free survival was improved (7.4 months in patients in the cabozantinib group compared to 3.8 months in patients in the everolimus group) (42).

Axitinib

Axitinib is a tyrosine kinase inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3, being 50-450 times more potent than the first generation of VEGF inhibitors (43).

In a randomized phase III clinical trial (AXIS), they compared the efficacy of axitinib with sorafenib in advanced renal cell carcinoma in a group of 723 patients, of whom 361 received axitinib and 362 received sorafenib. The mean progression-free survival was 6.7 months in those receiving axitinib compared with 4.7 months in those treated with Sorafenib (44).

Temsirolimus

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). Treatment of cancer cells with this agent induces cell cycle arrest and inhibition of angiogenesis by regulating VEGF, which in turn is regulated by hypoxia inducible factor (HIF-1) (45).

It was approved by the FDA for the treatment of advanced renal cell carcinoma in 2007, based on a prospective phase III study, including 626 patients with metastatic renal cell carcinoma, with a poor prognosis. Intravenous administration of temsirolimus (25 mg/week) was compared with subcutaneous administration of interferon alfa (3 ml units 3 times weekly). In patients treated with temsirolimus the overall survival was 10.9 months compared to 7.3 months in those treated with interferon alfa and the progression-free survival of the disease was 5.5 months in the group treated with temsirolimus compared to 3.1 months in those treated with interferon α (46).

Everolimus

Everolimus was approved by the FDA in 2009 for the treatment of patients with metastatic renal cell carcinoma, whose disease progressed after treatment with sorafenib, sunitinib or both. Approval was based on a randomized phase III clinical trial in 410 patients, the group of 272 patients received 10 mg everolimus daily and the group of 138 patients received placebo. The progression-free survival of the disease was 4.0 months for patients treated with everolimus compared to 1.9 months in patients receiving placebo. Everolimus is used as a second or third line treatment (47).

Promising therapies in RCC

PD1/PD-L1

Programmed death 1 (PD-1) is a 288 amino acid type I transmembrane protein. PD-1 functions as a receptor expressed by activated T cells (48). There are two known ligands of PD-1. The first, PD-L1 (also known as CD274), is a 290 amino acid type I transmembrane protein. PD-L1 is expressed on antigen-presenting cells and tumor cells, and is primarily responsible for the immunosuppressive effects of PD-1 (49). PD-L2 (also known as CD273) is the second ligand for PD-1; it also functions to inhibit T-cell activation (50).

PD-1/PD-L1 interaction is an important regulator of tumor immune tolerance and tumor growth in RCC. Blocking the interaction of PD-L1 (expressed on RCC cells) with PD-1 (expressed on T cells) might reverse tumor-induced immune tolerance. This mechanism of action can serve as an attractive approch for RCC therapy (51).

In metastatic ccRCC, unprecedented OS (overall survival), PFS (progression-free survival), and response rates were reached using a combination of ICI (immune checkpoint inhibitors), like anti-CTLA-4 and anti-PD1 for poor and intermediate risk patients. The PFS was even improved by the combination of ICI with antiangiogenic drugs. With ICI combination was reched the best complete response rate (52).

CAR T cell therapy

One of the most promising advances in cancer immunotherapy is the use of chimeric antigen receptor (CAR) T cells. A CAR T cell is a T cell that has suffered genetical engineering in order to express a antigen-specific non-MHC restricted receptor that is composed of a single chain variable fragment of an antibody fused to a

a transmembrano domain and a intracellular signaling domain (53). Adoptive T cell therapies for RCC patients using ex vivo expanded tumor-infiltrating lymphocytes has shown some succes (54,55). In one of the few studies done on humans using CAR T cells, two of the three patients suffered from liver toxicity that promptly necessited lowering of the CART dose and a pretreatment with CAIX monoclonal antibodies G250 to prevent further liver toxicities (56).

CLIC 1

CLIC1 (chloride intracellular channel 1) is a protein that belongs to the family of ion channels of chlorine. This protein is naturally expressed in the human body and is involved in many cellular processes, such as cell volume regulation, regulation of membrane potential, cell cycle regulation, cell proliferation and cell differentiation (57).

A potential involvement of CLIC1 in tumor development is suspected both for its role in cell cycle regulation as well as for its functional expression during oxidative stress. CLIC1 is expressed in the normal kidney in the glomerular structures and also on the apical domain of proximal tubules' epithelial cells (26), however, its role of in renal cancer is yet to be elucidated (58).

Our experimental data, obtained using the chorioallantoic membrane of eggs to implant human tumour cells in order to visualise their behaviour, on HE stained sections a significant difference between the the specimens treated with CLIC 1 antibodies and the control group. The differences consist of both tumour cell density and morphology.

CONCLUSIONS

The treatment strategy for renal cancer has changed dramatically in recent decades, due to the development of new technologies for surgery and the advent of molecular therapy. Better prognosis and longer life spans were obtained with the new therapies but current data suggests we are far from a cure. Further research is need to prolong the life span even longer and maybe, eventually, developing a cure.

Corresponding Author:

Alin Mihu[1],[2]*

[1] Clinical Country Emergency Hospital, 2-4 A Karoly, Str., 310037, Arad, Romania

[2] West University Vasile Goldis, 94 Revolutiei Blvd., 310130, Arad, Romania

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