Research Results in Pharmacology

Research Results in Pharmacology 4(1): 17–25
UDC: 575, 571.21, 61
DOI 10.3897/rrpharmacology.4.25251

Research Article Rus

Renal cell carcinoma drug and cell therapy: today and tomorrow

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Academic editor: *Konstantin Reznikov* ♦ **Received** 25 September 2017 ♦ **Accepted** 19 March 2018 ♦ **Published** 28 March 2018

Citation: Pushkin AA, Burda YE, Sevast'yanov AA, Kulikovskiy VF, Burda SY, Golubinskaya PA, Zvyagina AK Kulyushina NV (2018) Renal cell carcinoma drug and cell therapy: today and tomorrow. Research Results in Pharmacology 4(1): 17–25. https://doi.org/10.3897/rrpharmacology.4.25251

Abstract

Today, considerable progress in the renal cell carcinoma (RCC) treatment has been made due to development of targeted and immunotherapeutic approaches to the RCC treatment, especially in metastasising carcinoma. In the early stages of RCC, it is possible to use partial or total surgical nephrectomy, but in metastases development, the range of efficient treatment methods is dramatically limited. Appearance of targeted drugs like PD-1 and CTLA-4 receptors and their ligands' inhibitors in clinical practice has significantly increased the total survival rate of patients with renal cell carcinoma. Emergence of adoptive cell therapy has opened new possibilities and prospects in RCC treatment. Previously activated *in vitro* cells are used there, which provides antineoplastic activity. For example, it could be antigen-specific cytotoxic T-lymphocytes (CTL), lymphokine-activated natural killers (LAK-NK-cells) and tumour-infiltrating lymphocytes (TILs). In this review, the authors specified the main molecular markers, associated with RCC; and signalling pathways (VEGFR- and EGFR-signalling pathway), which directly take part in carcinogenesis. The paper also looks at clinically applicable targeted immune drugs and the principle of their effect on tumorous cells. Besides, modern clinical studies of cell drugs have been considered. At the moment, there are a number of variants of targeted and immune drugs for the metastatic RCC treatment. Patients have no opportunity to use all the available agents because of their cost and toxicity level. For the most efficient treatment of patients with diagnosed metastatic RCC, it is necessarily to carry out risk stratification and prognostic factors for the response to treatment.

Keywords

renal cell carcinoma, renal cancer, targeted therapy, immunotherapy, cancer cell therapy, immune system.

Introduction

The problem with oncological diseases throughout the world still remains precarious. Annually, 12 million new cases of the disease are registered in the world with about 210,000 of the new cases being renal cell carcinoma (RCC). An annual increase of RCC cases in advanced countries is 1.5 – 5.9%. Renal cancer in Russia ranks 10th for the incidence of malignant tumours and only prostate cancer has a higher growth rate (Davydov et al. 2011).

Highest incidences of the disease are observed amongst the 55–60 age group; RCC is twice as frequent in men than in women. Most cases of RCC do not clinically show and they are not diagnosed until RCC reaches an advanced stage or metastasises. A considerable number of RCC cases are diagnosed accidentally. A high metastatic potential leads to the fact that metastases are diagnosed in 25% of patients at the time when the diagnosis was made. Fifty percent of patients have locally advanced cancer and 25% have localised forms. The disease progression and patient's general condition deterioration are observed in 20–40% of cases after nephrectomy. The prognosis of the disease course in patients with the metastasising RCC is extremely unfavourable: without a specific treatment, within a period where the disease progression is 2–4 months, the average life-span after metastases are detected is less than 10–13 months (Keane et al. 2007).

As has been proven, smoking tobacco is one of the most significant risk factors for development of various malignant tumours. The renal tumour emergence risk in smokers of both sexes increases by 30% when compared with non-smokers. The unfavourable influence of being overweight on the renal cancer development probability is also confirmed. Obesity leads to an increase of RCC morbidity rate by 20%. RCC emergence is associated with diabetes mellitus and the use of diuretics (Chow et al. 2010).

The first classification of RCC was presented in 1826 and, since then, the approach to this nosology classification has repeatedly changed. Today, the renal cell carcinoma classification singles out four cancer forms, each of which has specific genetic changes conditioning different clinical process and sensitivity to the treatment undertaken. Based on this classification, four forms of renal cell carcinoma are distinguished: non-papillary carcinoma or clear cell carcinoma (75% of RCC cases), papillary or chromophilic cancer (7–14% cases), chromophobic cancer (4–10%) and also collecting-duct carcinoma (1–2% of RCC cases) (Matveev 2011).

There are a number of renal cell carcinoma treatment methods: surgical treatment, ablative method, chemotherapy, radiotherapy, vessels embolisation, photodynamic therapy, immunotherapy and targeted therapy (Matveev 2011). Surgical treatment has been used for quite some time and it is represented mainly by a radical nephrectomy and an adrenalectomy. Until recently, a nephrectomy was considered the "gold standard", but it is efficient only in patients with an early stage of the localised disease. Ultimately, a significant number of the patients develop a recurrent tumour. The prognostic factors of RCC recurrence or metastasising are: the Karnofsky index score, a high level of lactate dehydrogenase (LDH), a low level of haemoglobin and high concentration of blood calcium. Ablation is an alternative to surgical treatment for small renal tumours. Radiotherapy is applied in patients with metastatic RCC, who have unresectable symptomatic brain or bones affections resistant to the systemic therapy. Radiotherapy after a nephrectomy does not have any advantages even in patients with metastases in lymph nodes or after non-radical surgery (Davydov et al. 2011). Development of the immunotherapeutic approach has reached the level of an important medicinal approach in patients with diffuse renal carcinoma. The following immunotherapeutic approaches are distinguished: non-specific immunotherapy with application of cytokines (interferones and interleukines) and other biological reactions modifiers; immune checkpoint inhibitors therapy, adoptive cell immunotherapy by using autolymphocytes, lymphokine-activated killers (LAK-cells) and tumour-infiltrating lymphocytes (TILs); specific immunotherapy (vaccinotherapy, using dendritic cells use) and gene therapy (Matveev 2011).

Kidney cancer targeted therapy

Targeted therapy is a personalised modern approach to the medicinal treatment which is formed according to the factors, which predict its efficiency. In order to understand the meaning and the mechanism of targeted therapy effect, it is necessary to examine molecular markers of renal cell carcinoma. Most of the clear cell carcinomas are characterised by a VHL oncosuppresor gene inactivation owing to mutations, allelic deletions and/or methylation of this gene (Banks et al. 2006). Furthermore, a mutated VHL gene underlies Hippel-Lindau disease. Loss or disorder of the VHL expression is observed in 50–80% of clear cell RCC cases. Probably, the disorder of VHL gene activity and intracellular signalling pathways controlled by it, is one of the early and key oncogenesis mechanisms in RCC and other nosologies. Under physiological conditions, VHL, which is an oncosuppresor (Kim et al. 2010), provides intracellular regulation of the HIF-1α (hypoxia-induced factor) transcriptional factor level. VHL protein is an intrinsic part of the ubiquitin ligase complex, by which HIF-1α degradation is carried out (Bausch et al. 2013). The above-mentioned disorders lead to blocking or disturbance of the VHL expression. There is an excess of HIF-1α in a cell, which initiates gene expression (VEGF, PDGF, TGF-α and others) induced by hypoxia, participating in positive regulation of both cell proliferation and neoangiogenesis, which allows the cell to temporarily adapt to hypoxia induced by fast and unlimited proliferation. It is known, that VEGF plays a central role in angiogenesis and this growth factor hyper-expression provides new vessels formation (Richard et al. 2013). TGF-α is an important factor of autocrine growth stimulation and it can immediately interact with the epithelial growth factor receptor (EGFR), which is hyper-expressed in 50–90% of kidney tumour cases (Mikami et al. 2015). EGFR and VEGF receptors activation initiates one of the main mitogenetic signal cascades, namely, Raf / MEK / ERK signalling pathway, contributing, in particular, to the uncontrolled proliferation of tumour cells.

At the moment, about 15 molecules claiming to be diagnostic and prognostic markers of kidney tumours are described in literature. Depending on the analysed material, the following groups of renal cell carcinoma potential diagnostic markers are identified: VHL, VEGF, HIF-1, survivin, mTOR, carbonic anhydrase 9 (CA9), PTEN, tyrosine kinases Akt and S6K, CCL5 and CXCL9, caveolin-1 and others; blood markers (VEGF, CA9) and the urine marker NMP-22 (Kovaleva et al. 2014). Almost all of the above-mentioned proteins are not specific for this pathology. For example, survivin, an inhibiting protein of apoptosis, is expressed in all types of cancers, but its expression is absent in normal differentiated cells. A high quantitative expression of survivin is a bad prognostic marker in RCC (Zamparese et al. 2008). PTEN phosphatase is one of a few negative regulators of the PI3K/AKT/mTOR-signalling pathway, which makes it an oncosuppresor. Reduction of PTEN phosphatase expression is observed in many oncological pathologies – gliomas, meningiomas, melanomas, tumours of the kidney, liver, uterus, mammary gland and prostate, - but it does not make this marker specific for RCC. Akt and S6K tyrosine kinases are included in the mTOR signalling pathway, which regulates different proteins within a cell. In assessing the pAkt and pS6K activity, it is possible to determine the significance of targeted therapy with temsirolimus (Cho et al. 2007). Caveolin-1 takes part in most of the intracellular signals transduction and its expression increase correlates with the unfavourable course in oncological pathologies of prostate, oesophagus, lungs, mammary glands as well as RCC (Hehlgans and Cordes 2011; Campbell et al. 2008). Under normal conditions, CA9 regulates the acid-base balance level (pH) in the extracellular matrix by ions binding the H+ ion with sodium bicarbonate (Zukov 2013). The CA9 expression is observed in non-small-cell lung cancer, cervical cancer, colon cancer and ovarian cancer, this being a negative prognostic factor. CA9 is considered to allow a tumour cell to adapt to acidotic conditions which develop along with the uncontrolled cells proliferation. After that, the tumour is characterised by a more aggressive status. CA9 expression is observed in 90% of clear cell RCC cases and, to a lesser extent, it is observed in a papillary and chromophobic cancer (Span et al. 2003). There are also PBRM1, BAP1 and SETD2 oncosuppresors, which often mutate in RCC. They are not for direct therapeutic purposes, but the signalling pathways regulated by them are being studied for developing new therapeutics (Brugarolas 2013).

Since the discovery of microRNA, a number of microRNA markers associated with oncogenesis, including in RCC, have been identified. Thus, in clear cell renal carcinoma, a high expression of microRNA-28, -185, -27 and let-7f-2 has been found. So far, a multitude of microRNA associated with RCC subtypes and the course of the disease have been identified (Heinzelmann et al. 2014). Probably, a change of expression in one or another microRNA associated with RCC by specific inhibitors can have a positive therapeutic effect.

As VHL inactivation is a fundamental event in RCC, these tumours are characterised by intensive growth of vessels. Due to that, in the first- and second-line treatments in metastatic RCC, tyrosine kinases inhibitors directed at the whole VEGFR-signalling pathway are used. Such inhibitors are sorafenib, sunitinib, pazopanib, axitinib, lenvatinib and cabozantinib. Furthermore, combinations of lenvatinib and everolimus or bevacizumab (anti-VEGF antibodies) and interferon alpha are used (Escudier et al. 2007; Motzer et al. 2015). Each drug depresses VEGFR (VEGFR-1, VEGFR-2, VEGFR-3) to varying degrees. Differences in efficiency can be explained both by different activity and toxicity of each drug and by an individual response of each patient's organism. Taking into account the mTOR importance in RCC progression, mTOR inhibitors – everolimus and temsirolimus, – are used in the first- and second-line therapies in patients with a low risk level of recurrence (Motzer et al. 2008, Hsieh et al. 2017).

Modern strategies of advanced or metastatic RCC treatment include VEGFR and mTOR inhibitors as the first-line therapy (Choueiri et al. 2016). In the AXIS research, axitinib, which is a powerful inhibitor for all three VEGF receptors, increases the median survivability without progression in comparison with sorafenib (a multikinase inhibitor; 8.3 months against 5.7 months) in patients previously taking sunitinib (a multikinase inhibitor), bevacizumab (antibody to VEGF) with interferon alpha, temsirolimus (an mTOR inhibitor) and cytokines (Motzer et al. 2013). In the METEOR research, cabozantinib exceeds everolimus both in the median survivability rates (7.4 months against 3.8 months) and in the average total survivability rates (21.4 months against 16.5 months) (Choueiri et al. 2016). In phase 2 of CABOSUN research, cabozantinib (antibody to VEGFR) was compared with sunitinib in the first-line treatment of patients with RCC. The therapy with cabozantinib increases the median survivability (8.2 months against 5.6 months) (Motzer et al. 2013). Pazopanib is another kinase inhibitor demonstrating efficiency in the first-line treatment. In comparison with the placebo, pazopanib considerably prolongs recurrence-free survivability. When comparing pazopanib with sunitinib, a similar efficiency is observed, but pazopanib is better tolerated by a patient's organism (Motzer et al. 2014).

Combining the targeted drugs can become an alternative strategy to developing more powerful drugs. This approach is based on the fact that VEGFR inhibition is not always efficient. This is due to the fact that tumours "use" signalling pathways not only those connected with VEGFR but also those running in parallel with VEGFR signalling pathways. These pathways also stimulate oncogenic and metastatic signals, which develop resistance to some or other targeted drugs. The combination of lenvatinib (antibody to VGFR) and everolimus (antibody to mTOR) can be considered a successful example of such a strategy. Such a therapy prolongs the median survivability in comparison with everolimus (14.6 months and 5.5 months). On the other hand, the combination therapy has a strong toxic effect (Motzer et al. 2015). Combination therapy is being quite actively developed. It is known that CD105 (endolgin) is a strong angiogeneses factor taking part in VEGFR inhibition. The combination of a monoclonal antibody to CD105 (TRC105) and axitinib or bevacizumab is clinically efficient in the first phase of the research. Currently this combination is being tested in the second phase of clinical studies in patients with advanced and metastatic RCC (Choueiri et al. 2014). Dalantercept, inhibiting ALK-1 and being a receptor playing a crucial role in pathological angiogenesis, is actively studied in connection with axitinib in advanced RCC.

Even though targeted drugs affect the key elements of oncogenesis, currently available drugs do not have an equally positive effect for each patient. Different response of patients is conditioned by individual biological factors. The introduction of a new generation of sequencing can help to discover genomic and/or transcriptomic variations, which can predict the degree of positive response to a specific therapy. This approach can lead to the individual therapy after diagnosing metastatic RCC. A retrospective analysis of patients' tissues revealed the expected predictive markers of response to the treatment. In a sample of 79 patients receiving mTOR, inhibitors sequencing showed that mutations in mTOR, TSC1 or TSC2 occurred more often in patients responding to therapy (Kwiatkowski et al. 2016). In a clinical study comparing everolimus with sunitinib in clear cell RCC, it was found that mutations in the PBRM1 locus were related to longer survivability in patients receiving everolimus. At the same time, this mutation does not affect a response in patients receiving sunitinib (Hsieh et al. 2017). These biomarkers can be useful when selecting personalised drugs.

At the moment, there are many variants of targeted drugs for the metastatic RCC treatment. Patients have no opportunity to use all of the available drugs because of their cost and toxicity level. For the most efficient treatment of patients with diagnosed metastatic RCC, it is necessary to carry out risk stratification and identify prognostic factors of a response to treatment. Taking into account the range of therapeutic possibilities available to patients, defining a treatment strategy should be undertaken based on individual characteristics, so that the therapy selection should become more personalised.

Kidney cancer immunotherapy

Immunotherapy is often perceived as a new method for the treatment of oncological diseases. However in the late 19th century, surgeon William Coley administered an injection of inactivated bacteria into a sarcoma's inoperable tissue, which subsequently led to the tumour reduction. Later, he developed a mixed bacterial vaccine and achieved long remission in some patients with sarcoma and other types of tumours (Kienle 2012). Later, it was determined that cancerous cells expressed tumour antigens capable of stimulating cell and/or humoural immunity. These antigens' expression paves the way for treatment of oncological diseases using methods of immunotherapy (Kit et al. 2016). Peptides derived from tumour antigens are represented by class I and class II epitopes of the major histocompatibility complex (MHC) and they can stimulate CD8+ and CD4+ T-cells. Binding a T-cell receptor (TCR) with the MHC peptide requires additional co-stimulatory signals. Binding activates signalling pathways leading to the secretion of pro-inflammatory cytokines. The binding amplitude and quality are regulated by a balance between co-stimulatory and inhibitory signals – "immune checkpoints" (Pardoll 2012).

The human immune system has an inherent ability to adapt to different pathologies like infections or cancer creating a varied repertoire of effector T-cells. Cancerous cells can increase the expression of apoptosis inhibitors and expression on the cell surface of molecules killing cytotoxic T-cells. Tumours are capable of releasing factors inhibiting inborn and acquired immunity and they also can accumulate regulatory cells for creating the immuno-suppressing microenvironment. All of these factors prevent the natural human immunity from fighting a tumour.

RCC has long been recognised as a malignant neoplasm, which can be treated with stimulating the immune system by cytokines: recombinant interferon alpha and high concentration of interleukin 2 (IL 2) (Klapper et al. 2008). Interferon and high concentration of IL 2 have been used to treat metastatic RCC since the 1990s, before the use of sunitinib (McDermott et al. 2005). The high toxicity of IL 2, however, often limits its use, despite cases of complete remission in some patients (Hutson et al. 2016). Patients taking interferon alpha have problems with depression and thrombocytopenia (McDermott 2009). Introduction of new methods of treatment has led to the lower frequency of cytokines use.

To prevent an autoimmune response, the organism has immune checkpoints: T-lymphocyte-associated protein-4 (CTLA-4) and ligand 1 of programmed cell death (PD-L1). CTLA-4 is situated on the T-cell surface and counteracts a CD28 co-stimulatory receptor. CTLA-4 and CD28 bind with similar ligands CD80 and CD86, but CTLA-4 has the higher affinity for these ligands and due to this makes a strong competition to CD28. Moreover, CTLA-4 can sequester CD80 and CD86 from CD28, which also leads to suppressing the T-cell response (Pardoll 2012). PD-1 is a transmembrane protein, which is more widely expressed than CTLA-4 and it is found on T-cells, B-cells and NK-cells. PD-1 binds with both ligands PD-L1 and PD-L2, which are usually expressed on the surface of tumour cells. The interaction between PD-1 and ligands inhibits kinases activating T-cells, induces anergy amongst antigen-specific T-cells and converts effector T-cells into regulatory T-cells (Amarnath et al. 2011). Cancerous cells use these factors for masking from cellular immunity (Schreiber et al. 2011). Blocking this interaction demonstrated an impressive tumour remission in different types of solid tumours including RCC, melanoma, non-small-cell lung cancer and colorectal cancer (Brahmer et al. 2010).

PD-L1 and CTLA-4 inhibition promotes T-cells activation. Subsequently, it was discovered that the use of PD-L1 and CTLA-4 blockers was efficient against malignant tumours and, in doing so, they have a lower toxicity level than cytokines (interferon alpha and interleukin-2). These rates led to the creation of many antineoplastic immune agents, such as anti-CTLA-4-antibodies (ipilimumab, tremelimumab), anti-PD-1-antibodies (nivolumab, pembrolizumab) and anti-PD-L1-antibodies (atezolizumab, avelumab, durvalumab). These drugs have been approved for treatment of melanoma, lung cancer and bladder cancer (Balar 2017). Currently new CTLA-4 inhibitors (tremelimumab) and PD-1 inhibitors (pidilizumab) are being developed for RCC treatment (Drake et al. 2014).

Nivolumab is the first PD-1 inhibitor approved by the FDA for mRCC treatment after therapy with VEGFR inhibitor. In the CheckMate research, patients taking VEGFR inhibitors received nivolumab or everolimus (an mTOR inhibitor). Research shows the difference in total survivability in favour of nivolumab (25 months against 19.6 months, p=0.002). However, the response frequency was only 25% and most of the patients receiving therapy did not respond to treatment (Motzer et al. 2015).

Despite the beneficial effects and low toxicity of new inhibitors, these agents did not show a sufficient number of complete remission cases (Escudier et al. 2017). Tumours with a higher mutation load are characterised by a good reaction and a longer clinical response (Voron 2015). The immunotherapy effect can be reinforced by inhibiting the secondary immune checkpoints. This idea led to development of a series of new inhibitors and new targets: TIM 3, VISTA, LAG-3, IDO-1, KIR, B40, GITR, OX40L, CD137 and ICOS. All these targets, such as molecules, antigenes, receptors etc., take part in immune checkpoints and are under active development for treating oncological pathologies including metastatic RCC (Dempke et al. 2017).

As well as with targeted drugs, combining immune checkpoint inhibitors can reinforce the positive effect of the therapy. In phase 1 of the research, the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) increased the positive response to the treatment in metastatic RCC (Hammers et al. 2017). Taking into account positive effects of immune checkpoint inhibitors in RCC treatment, it is necessary to identify patients susceptible to the therapy with these agents. It was considered that PD-L1 expression in tumours and immune cells could be considered a prognostic factor, but studies showed that a low expression or no expression of PD-L1 did not guarantee the absence of a response to the therapy with PD-1 or PD-L1 inhibitors (Callea et al. 2015). Combination of immunotherapy with targeted drugs, such as VEGFR inhibitors, is currently being tested (Voron et al. 2015).

Toxic effects of proangiogenic signalling pathways inhibitors differ from toxic effects of immune checkpoint inhibitors in RCC treatment. VEGFR inhibitors are associated with hypertension, hand-foot syndrome and other side effects (Motzer et al. 2013). Immune checkpoint inhibitors are relatively non-toxic, but they can induce an autoimmune response, which can negatively affect the organism's endocrine, gastrointestinal, respiratory systems and skin (Larkin et al. 2015). Another widespread and early toxicity form is dermatological disorders, but they are easily treated with corticosteroids. Diarrhoea and colitis are also common side effects, which are more often encountered in anti-CTLA-4-antibodies therapy. Hepatotoxicity and endocrinopathy are possible (Liu et al. 2017). Different inhibitors in RCC, which are being clinically tested, are described in Table 1.

The significance of immunotherapy in treating RCC has dramatically increased since the beginning of this century. Previously, therapy with IL-2 and IFN-α cytokinins was incorporated as a basis for mRCC immunotherapy. However, the effect was largely negative, considering all toxic effects when using cytokines. Immune checkpoint inhibitors became an important element in RCC treatment. These agents are gradually being introduced into treatment of mRCC and other cancer types, such as melanoma, non-small-cell lung cancer, Hodgkin's disease and head and neck cancer. Nivolumab is approved and available for patients with mRCC. PD-1 inhibitors demonstrate long remissions and tolerable toxicity profile. To optimise a treatment strategy, it is also necessary to determine and use predictive biomarkers of response to the treatment.

Kidney cancer cell therapy

Different vaccines for RCC treatment are currently being actively developed. Vaccines are used for treating a primary tumour, but not for preventing an onco-

Table 1. Immune drugs in RCC are currently being clinically tested (Liu et al. 2017).

Drug	Target	Phase of the clinical trial	Line of therapy	Source of information or NCT
Nivolumab	CTLA-4	4	2	NCT02596035
Atezolizumab	PD-L1	3	1	NCT02420821
Avelumab	PD-L1	3	1	NCT02684006
Nivolumab + Ipilimumab	PD-1 CTLA-4	3	1	NCT02231749
Ipilimumab	CTLA-4	2	1	NCT00057889
Pembrolizumab	PD-1	1/2	1/2	NCT02014636
Pembrolizumab + Ipilimumab	PD-1 CTLA-4	1	2	NCT02089685

logical disease. Clinical trials are conducted to assess the effectiveness of different vaccines, but none has so far demonstrated an increase in the survivability rate. High immunogenicity of cancerous antigens provides the possibility for a wide range of studies for these agents aimed at antineoplastic vaccination (Vodolazhskii et al. 2017).

AGS-003 is a vaccine based on dendritic cells (DCs), where DCs are electroporated by amplificated tumour mRNA and synthetic CD40L-RNA. It is considered that CD40L expression on DC surfaces promotes CD8-positive T-cells recruitment through co-stimulatory signals induction (IL-2). The phase 2 research included 21 patients with an intermediate or clear prognostic category of metastasis risk. The efficiency of combining AGS-003 with sunitinib (a growth factor receptors inhibitor) was assessed. Nine patients had a partial response, in four patients the disease was stabilised, and eight patients had the disease progression. Treatment with this combination provided the average survivability without progression for 11.2 months and the total survivability for 30.2 months with 5 patients having a survivability rate over 5 years. Based on these results, the phase 3 research, in which patients with mRCC are being treated with sunitinib or a combination of sunitinib with AGS-003, is being conducted (ClinicalTrials.gov 2017).

IMA-901 is a vaccine consisting of peptides associated with tumours and expressed in cancer tissue (Rini et al. 2016). In the phase 2 research of combining the cyclophosphamide (B-cells inhibitor), IMA-901 and GM-CSF, it was demonstrated that this combination stabilised disease development in 31% of patients receiving cytokines therapy after 6 months and in 14% of patients previously receiving tyrosine kinases inhibitors (Walter 2012). In separate research of phase 3 involving 339 patients, the efficiency of combination therapy with sunitinib, IMA-901 and GM-CSF was assessed. Addition of IMA-901 to sunitinib did not show any effects (Rini et al. 2015).

TroVax is a therapeutic vaccine aimed at a carcinoembryonic antigen 5T4. This tumour-associated antigen is hyper-expressed in most RCC cases (Griffiths et al. 2005). In phase 3 of TRIST research, TroVax in combination with interferon alpha, interleukin 2 or sunitinib, as the first-line treatment, demonstrated a significant increase in the total response concerning the therapy without TroVax (Amato et al. 2010).

Another type of vaccines is the lysate of autologous tumour cells. Based on the lysate of autologous tumour cells, this vaccine stimulates antigen-presenting cells (APC) which, in turn, promote the cytotoxic T-lymphocytes response to the antigens expressed on RCC cells (Wittke et al. 2016). The vaccine based on the lysate of autologous tumour cells prolonged the survivability without progression in the phase 3 clinical research in patients with RCC (May et al. 2010).

There are a few perspective trials of vaccines based on dendritic cells. For example, there is a trial of a DC-based vaccine being conducted, where autologous DCs are loaded with a hybrid gene structure of GM-CSF and carbonic anhydrase IX (ClinicalTrials.gov 2017). A trial of pidilizumab (anti-PD-1) and activated by RCC cells on DCs is also underway (ClinicalTrials.gov 2017). There has also been a study using DCs in combination with LAK-cells in mRCC (ClinicalTrials.gov 2017).

An encouraging immunotherapy method is adoptive cell therapy which uses cells previously activated *in vitro* and which provides antineoplastic activity. For example, it could be antigen-specific cytotoxic T-lymphocytes (CTL), lymphokine-activated natural killers (LAK-NK-cells) or tumour-infiltrating lymphocytes (TILs) (Perica et al. 2015; Tang et al. 2013). A series of adoptive cell therapy studies in patients with mRCC showed that the median survivability level was 10.2 months and a five-year survival rate was observed in 15% of patients (Combe at al. 2015). In any case, the significance of the cell therapy in mRCC is still not clear.

Conclusions

New ideas of cancer development have led to the creation of new immunomodulatory agents. The ways of treating mRCC develop quite fast for new target agents with different treatment regimens being developed, which, in turn, are being optimised. The results of recent clinical trials of immunotherapeutic agents prove that immunotherapy, such as the monotherapy or in combination with other agents, can provide a long-term response and significant total increase in survivability.

As immunotherapy use is becoming increasingly widespread in oncology, a number of related problems and questions arise. For example, important factors are long-term side effects and mechanisms for developing resistance to these drugs in different tumours (Khunger et al. 2017). Further studies and experience in this area will allow to better determine strategies for using immunotherapeutic agents not only in RCC, but also in many other malignant neoplasms.

There is some preclinical evidence for combining immunotherapy with anti-VEGF inhibitors. Furthermore, development and clinical implementation of prognostic biomarkers can be crucial for applying immunotherapy. Preliminary studies, especially of PD-L1 expression by an immunohistochemical test in tumour cells, do not predict a tumour response to immune drugs.

Using immunotherapy in RCC has great potential after the use of inhibitors for the immune checkpoint has been started. In the future, immunotherapy by itself or together with other treatment methods, is likely to cause a paradigm shift in the clinical treatment of patients with mRCC.

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