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Review Article

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TARGETED THERAPY FOR RENAL CELL METASTATIC CANCER

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ABSTRACT

Renal cell carcinoma (RCC) accounts for 2-3% of all malignancies in adults, while the incidence increases in most developed countries: the annual increase is 2.3%.[1] In Russia, in 2017, RCC was first diagnosed in 13556 patients. The standardized incidence rate was 16.87 per 100,000 populations, and the increase in incidence over 10 years was 42.63%. In terms of the rate of increase in the incidence of RCC, it is second only to prostate and thyroid tumors.[2] In 2018 in Uzbekistan, RCC was first diagnosed in 717 patients. The standardized incidence rate was 2.2 per 100 thousand populations.[3] Despite the fact that the majority (up to 70%) of patients with RCC are detected at the stage of localized tumor process, more than half of patients develop metastases after surgical treatment.[4]

INTRODUCTION

The prognosis of the course of the disease during the development of metastatic process in patients with RCC is extremely poor: in the absence of specific treatment, the period before progression is 2-4 months, and the average life expectancy after detection of metastases is no more than 10-13 months.[5] Various factors related to the characteristics of the patient and the tumor are used to assess the prognosis of RCC: neoplasms of the morphological type (light-cell chromophobic, papillary), the degree of differentiation by Furman, the stage of the disease, the location and number of metastatic foci, the age and status of the patient at the time of detection of the disease. In clinical practice and research in patients with metastatic RCC (mRCC), the mskcc prognostic scale (sum of points), proposed by Motzer, is widely used and includes an assessment of the level of lactate dehydrogenase, hemoglobin and calcium, as well as the patient's status on the ECOG or Karnofsky scale and the presence or absence of a history of nephrectomy.[6] Based on the presence of prognostic factors, there are groups of low (no risk factors), moderate (1 or 2 risk factors) and high (3, 4 or 5 adverse prognostic factors) risk of progression. Determining the individual prognosis of a patient with mRCC is currently of great importance in determining the most effective treatment tactics. Treatment of metastatic renal neoplasms is extremely difficult, since RCC refers to tumors that are virtually insensitive to chemotherapy and radiation therapy. In most clinical studies on the effectiveness of cytostatics in patients with mRCC, the total response to treatment was no more than 0-6%.[8] Studies that demonstrate a higher level of antitumor effect (10-25%) are not numerous, they included a small number of patients, and in subsequent studies the effectiveness of the described schemes was not confirmed. Randomized trials have shown that chemotherapy has no effect on patient survival. The average life expectancy of patients is only 6 months.[8] One of the most studied mechanisms that explain the resistance of renal tumors to chemotherapy is the overexpression of a multi-drug-resistant protein (MDR-1, p-glycoprotein).[9] MDR-1 belongs to the family of transmembrane pump proteins belonging to the so-called adenosine triphosphate linked (ABC) conveyor. Overexpression of MDR-1 in RCC may be due to the fact that this protein is normally produced in the cells of the proximal tubules of the renal, from which tumors most often develop.[10] Several studies using MDR - pump inhibitors have been carried out to overcome drug resistance of RCC, but none of them have increased the effectiveness of cytostatic therapy, which is probably due to the presence of additional mechanisms of drug resistance (overexpression of glutathione, Bcl-2 protein, survivin, etc.).[11] Resistant to radiation therapy and cytostatic Therapy, renal tumors have certain sensitivity to immunogenic effects. The phenomenon of "spontaneous regression" of RCC metastases is known, as well as cases of long-term remission in the absence of specific treatment, which indirectly indicates the immune dependence of tumor cells.[12] Immunotherapy with cytokine drugs (interferon-alpha-IFN-α and interleukin-2-IL-2) is not currently the main method of treatment for ipcr. The use of cytokines makes it possible to achieve partial and less often complete regression of metastases in some patients, but the total objective response to treatment does not exceed 5-15%.[13] IL-2 was for many years the only drug approved by the FDA in the treatment of mRCC. However, treatment with IL-2 leads

to clinical remission and long-term survival in a very small number of patients with RCC, mostly with a favorable prognosis. In addition, to date, no controlled trials have shown a survival advantage in Il-2 therapy compared to placebo or other treatment options.[14] In this regard, the development and application in clinical practice of a new variant of drug treatment — targeted therapy, which has become possible due to the success of molecular biology and affects certain intracellular structures, is currently the main direction associated with improving the results of treatment of patients with common RCC. Angiogenesis is an important pathogenetic mechanism for the growth of malignant neoplasms and the dissemination of the tumor process. Therefore, one of the main goals of antitumor targeted therapy is intracellular targets involved in the process of stimulating angiogenesis and tumor growth. The signaling pathogenetic pathway associated with the loss of activity of the VHL (von Hippel-Lindau) gene as a result of mutation or methylation has been well studied in RCC. VHL encodes a cytoplasmic protein that acts as an oxygen sensor and is a multiprotein complex that, in a state of normoxia and normal VHL function, binds to a hypoxia-induced factor (HIF1), thereby reducing its amount. In a state of hypoxia, the VHL complex is destroyed, resulting in the accumulation of HIF1, which causes overexpression of genes encoding vascular endothelial growth factor (VEGF), platelet growth factor (PDGF), transforming growth factor (TGF-α), stimulating the process of angiogenesis.[15] VHL disease is an autosomal dominant syndrome caused by embryonic mutations in VHL. This hereditary syndrome is quite rare, but at the same time it has been established that complete inactivation of VHL is observed in more than 76% of sporadic cases of light-cell renal cancer.[16] Loss of VHL expression leads to the accumulation of HIF1-α in the normoxic state, which in turn stimulates the overexpression of proangiogenic factors and, accordingly, stimulates the proliferation of tumor cells and angiogenesis. VEGF plays a Central role in angiogenesis overexpression of this growth factor ensures the growth of new blood vessels. At the same time, excess PDGF production occupies a key place in the process of endothelial stabilization due to stimulation of pericytes.[17] TGF-α is an important factor in autocrine growth stimulation and is also able to interact directly with the epithelial growth factor receptor (EGFR), which is overexpressed in 50-90% of RCC cases.[18] Activation of EGFR and VEGF receptors initiates a downstream cascade of signals that include the Raf/MEK / ERK pathway of Raf kinase — a key molecular component of this signaling pathway. Experimental studies have shown the relationship of its activity with cell survival and apoptosis disorders, which is why Raf kinase is considered as another important goal of systemic therapy in RCC.[19] To date, many drugs have been developed that affect various intracellular targets related to the pathogenetic pathway associated with VHL inactivation. Drugs that affect cell proliferation include cetuximab (cetuximab), panitumumab (panitumumab), lapatinib (lapatinib), gefitinib (gefitinib). Drugs that inhibit angiogenesis include bevacizumab, sunitinib, and pazopanib. Bevacizumab is a recombinant human monoclonal antibody that binds to VEGF and inhibits its biological activity both in vitro and in vivo.[20] The drug in combination with cytostatics is currently approved in the United States and European countries for the treatment of non-small cell lung cancer and metastatic colorectal cancer. Pazopanib is an oral tyrosine kinase inhibitor and inhibits angiogenesis by interacting with VEGF-1, VEGF-2, and VEGF-3 receptors.[21] Sunitinib (Sutent) is a low-molecular-weight inhibitor of tyrosine kinase VEGFR and PDGFR, which is approved as a monotherapy drug for common RCC in the United States and in some European countries.[22] mTOR (mammalian target of rapamycin), a serintreonine kinase that plays an important role in the regulation of cell growth and proliferation, as well as increases the expression of the HIF1a gene, and as a result, stimulates angiogenesis, is also a target for anti-tumor therapy in patients with RCC. To drugs, the mTOR inhibitors include temsirolimus (temsirolimus) and RAD001 (everolimus).[23] The most versatile in the class of targeted drugs is Sorafenib (Nexavar), which has the activity of a multikinase inhibitor that suppresses both cell proliferation and angiogenesis. The drug can act on receptor tyrosine kinases (VEGFR-2, VEGFR-3, PDGF-β, RET, c-KIT), as well as inactivate serine/threonine kinases (C-Raf, B-Raf) in tumor cells and in tumor vessel cells.[24] Studies of inhibitors of other control points, such as PD-1/PD-L1, have demonstrated even greater efficacy and a more favorable toxic profile. In particular, checkpoint inhibitors have been shown to be highly effective in more than 15 types of cancer, including renal cell carcinoma.[25] The FDA approved inhibitors: PD-1/ PD-L1 nivolumab - for the treatment of renal cell carcinoma. Thus, the use of targeted drugs is a new promising direction in the treatment of patients with mRCC, which allows increasing the effectiveness of therapy in this category of patients.

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