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Available markers in the diagnosis and prognosis of kidney cancer

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SUMMARY

Introduction and purpose:

Renal cell carcinoma (RCC) is the most common kidney cancer that has no symptoms for a long time. It is most often diagnosed accidentally during abdominal ultrasound or abdominal computed tomography, performed primarily due to non-specific clinical symptoms. Despite progress in treatment, late detection is associated with poor prognosis. The aim of the study is to analyze literature (database PubMed) for potential prognostic markers and those used in RCC diagnostics.

A brief description of the state of knowledge:

The most common RCC subtype is clear cell renal cell carcinoma(ccRCC). Metastatic ccRCC is associated with poor prognosis. The pathogenesis of ccRCC includes, among others, disorders of miRNA change. These molecules are described as a promising marker of both diagnostic and prognostic. Detection of CD163 + antigen on cancer cells may be useful in assessing the clinical course of ccRCC patients. In clinical diagnosis of RCC, the presence of mutations and epigenetic inactivation of the von Hippel-Lindau (VHL) gene, vascular endothelial growth factor (VEGF) and carbonic anhydrase IX (CAIX) genes are particularly important. Plasma CAIX levels are described as not only a diagnostic and prognostic marker, but also lymph node involvement. There are studies on molecular markers that can also be a

therapeutic target, including Caveolin-1 (CAV1), CCL5. Recent research results show a link between PDL1 expression and high-grade tumors. PDL-1 may also be an important prognostic factor.

Conclusions:

Research on molecular markers is a promising personalized diagnostic and prognostic route. The limitation is the nonspecificity of molecular markers, so research on new and current markers is needed.

Key words: renal cell carcinoma; targeted treatment; molecular markers

Introduction and purpose

Malignant neoplasms constitute 2% on a global scale and their incidence is increasing [1]. According to statistical data from 2016 in Poland, the incidence of kidney cancer in men is 3.8% and women in 2.5% among malignant tumors respectively [2]. Renal cell carcinoma (RCC) accounts for about 90% of all malignancies of this organ, and the disease gives no symptoms for a long time. Specific markers can lead to early diagnosis, so further research are very important [3]. In 2018, an increase of 63,000 new cases and 15,000 deaths from kidney cancer is expected in the United States, and around 350,000 new cases worldwide [1]. Kidney cancer's incidence is often associated with exposure to environmental factors. Potential risk factors include: use of painkillers, smoking, obesity, hypertension, advanced kidney disease, and genetic factors containing phenacetin [4,5]. Currently, in most cases, kidney cancer is diagnosed during abdominal ultrasonography or abdominal computed tomography, performed primarily due to non-specific clinical symptoms [6]. Early kidney cancer often shows no symptoms. Renal cell carcinoma symptoms at later stages include: haematuria, loss of appetite, weight loss, fatigue, palpable tumor, lumbar pain [7]. Obesity and aging of the population lead to an increase in morbidity. For this reason, the frequency of ccRCC is expected to increase significantly over the next decade. Therefore, new therapies are aquired. Not only new therapeutic methods are needed, but also predictive markers that will allow to make the right treatment decisions [1]. This work is an analysis of the available PubMed literature of currently used markers in the diagnosis and prognosis of kidney cancer.

Description of the state of knowledge

CLASSIFICATION OF RENAL CELL CARCINOMA (RCC)

Renal cell carcinomas exhibit significant morphological heterogeneity and it is often difficult to determine the type of cancer, especially in the rarer cancer subtypes. Differentiation between benign and malignant oncocyctic tumors remains a particular challenge. There are many histological subtypes of kidney cancer with a different molecular picture. According to the WHO 2016 classification, the main subtypes of renal cell carcinoma (RCC) include: ccRCC (clear cell renal cell carcinoma) 65-75%, PRCC (papillary renal cell carcinoma) 15-20%, ChRCC (Chromophobe renal cell carcinoma) 5-7 % [8].

The WHO 2016 classification of kidney tumors is based on a combination of morphological, molecular and genetic characteristics. CCRCC is most common in 65–70% of all RCCs. Macroscopic lesions of CCRCC are often yellow with signs of necrosis and hemorrhage. Microscopically ccRCC consists of transparent/eosinophilic cells with thin-walled vessels. The ccRCC cytoplasm usually consists of accumulated glycogen and lipids. Immunohistochemically ccRCC shows positive results for CAIX and CD10, and negative for CK7 and AMACR. Loss of VHL gene function at 3p25-26 is almost always presented. In 90% of sporadically occurring ccRCC's one copy of the VHL gene is either mutated or

silenced, while the other copy has 3p deletions, detected in ccRCC's line comprehensive molecular profiling by The Cancer Genome Atlas (TCGA) [9].

Despite the progress in the treatment of kidney cancer over the last decade, many patients with ccRCC disease have progression after surgery and/or combination therapy [10,11]. Therefore, learning about new factors associated with disease progression is critical to improving treatment outcomes and patient survival [12].

PROGNOSTIC AND PREDICTIVE FACTORS

VHL

In renal cell carcinoma, the most mutated gene is the VHL suppressor gene (located on chromosome 3). VHL is a component that recognizes the substrate of the E3 ligase complex that ubiquitinates HIF-1 α and HIF-2 α to proteasome-mediated degradation. Thus, the loss of VHL leads to abnormal accumulation of HIF proteins despite a properly oxygenated tissue microenvironment, which in turn results in the uncontrolled activation of HIF target genes, that regulate angiogenesis, glycolysis and apoptosis. Loss of VHL alone is insufficient for RCC induction, as evidenced by the long latency (> 30 years) in individuals who carry germline mutations. The results suggest that additional genetic (or epigenetic) events are probably needed for the development of RCC [13].

3p chromosome loss occurs in more than 90% of sporadic ccRCC. This results in the simultaneous loss of one copy of four tumor suppressor genes. They are also mutated individually at high frequency in ccRCC (i.e. VHL, 80%; PBRM1, 29% to 46%; BAP1, 6% to 19%; and SETD2, 8% up to 30%). Pathogenic 3p loss probably represents the first genetic event that occurs in sporadic ccRCC and the second genetic event in hereditary ccRCC mutated VHL [14].

CAIX

Carbon anhydrase (CA) IX is considered a marker of tumor hypoxia, and its inhibitors have been proposed as a new class of anti-cancer drugs. Expression of some CAs, in particular CA IX and CA XII isoforms, has been correlated with aggressiveness and tumor progression in several cancers, including renal cell carcinoma. In 2018, studies revealed that CA IX expression and the VEGF proangiogenic factor levels were strongly increased in ccRCC compared to control. Both of factors are hypoxia responsive proteins. Test results show that CA IX plasma level, but not total CA activity, can be considered as a diagnostic marker for ccRCC. In addition, plasma CA IX levels may also be potential predictors of treatment response [15]. In subsequent studies from 2018, the CAIX result was predictive for disease-free survival, overall survival and lymph node involvement [16].

The results of the meta-analysis conducted in 2019 under the direction of Samberkar S. also prove that measuring this marker can be beneficial for determining the course of the disease. It is expected that CAIX may be developed as a specific tissue biomarker for RCC in the near future [17].

VEGF

High expression of vascular endothelial growth factor (VEGF) increases angiogenesis along with increased signaling from growth factor receptors in endothelial cells in a tumor microenvironment (including fibroblast growth factor (FGF) and hepatocyte growth factor (HGF)). Together, these changes provide targets for therapeutic measures that inhibit tumor growth [18].

CD163+

In 2018, Ma C., Horlad H., Ohnishi K. et al. performed an immunohistochemical analysis of renal cell carcinoma cells. CD163-positive cancer cells were detected in 35% of patients. The dependence of observing higher CD163 expression in patients with high T classification (in TNM) and in women was clearly visible. High expression of this molecule turned out to be significantly associated with shorter progression-free survival and lower overall survival. Macrophages displaying CD163 on their surface were more frequently detected in tumor areas with high content of CD163 positive cancer cells. Therefore, detection of CD163 antigen on cancer cells may be a useful marker for assessing the clinical course of patients with ccRCC [19].

HIF

With the VHL protein (pVHL) function loss, the factor induced by hypoxia α (HIF- α) accumulates in the tumor cell and dimerizes with HIF- β . The HIF- α /HIF- β complex transcriptionally activates hundreds of genes, promoting adaptation to hypoxia that is involved in cancer development. There are more and more proofs that the HIF-2 α subunit plays a central role in ccRCC over HIF-1 α . PT2385 and PT2399 are primary, orally available low molecular weight HIF-2 inhibitors that selectively interfere with HIF-2 α heterodimerization with HIF-1 β . Preclinical and clinical data indicate that these new molecules are effective in blocking cancer cell growth, proliferation and angiogenesis of ccRCC-specific tumors. Treatment with specific HIF-2 α antagonists, alone or in combination with immunotherapy or other anti-angiogenic agents, may in the future change therapeutic options in this cancer [20]. HIF-2 is involved in angiogenesis and many other processes. Angiogenesis is the main focus of drugs such as sunitinib, a tyrosine kinase inhibitor. In 2016, a research group led by Chen W. analyzed the effect of PT2399, a selective HIF-2 antagonist on kidney cancer. PT2399 was found to dissociate HIF-2 in human ccRCC cells and inhibited cancer by 56%. PT2399 was more active than sunitinib, was effective in progressive cancers and was better tolerated. Surprisingly, some ccRCC mutated VHLs were resistant to PT2399. Resistance occurred despite the dissociation of HIF-2 in tumors. Long-term treatment with PT2399 led to resistance. The mutations in the binding site and the second site suppressor in HIF-2 α and HIF-1 β were identified. These researchers began to study HIF-2 as a target in ccRCC that potentially may be used in biomarker-based clinical practice [21].

NON-SPECIFIC MARKERS: mTOR, cytokines CCL5 i CXCL9, caveolin-1

MicroRNA (miRNA) is a family of short, non-coding RNAs that regulate gene expression, which has been identified as one of essential biological modulators. One of the oncogenic mechanisms in the pathogenesis of RCC involves the activation of the PI3K/AKT/mTOR pathway. This regulates cell metabolism and tumor cell proliferation. Several studies have described the role of miRNA dysregulation in the pathogenesis and progression of ccRCC. These molecules can be considered as potential diagnostic and prognostic biomarkers to monitor response to treatment [22].

In recent years studies proved that caveolin-1 (CAV1) plays a role in carcinogenesis in many cancers, including clear cell kidney cancer. Its potential function is still not fully explored. The 2017 study by Ruan H. et al. showed that high CAV1 expression was associated with a lower disease-free survival rate, and thus could serve as a useful diagnostic indicator in patients with ccRCC at various clinical-pathological stages. Their results provided information on the effect of CAV1 on carcinogenesis - a decrease in CAV1 inhibited cell migration and invasion, while overexpression of CAV1 had the opposite effect. In addition, high CAV1 expression was associated with pronounced sunitinib resistance. Therefore,

suppression of CAV1 function may be a promising clinical treatment strategy in patients with metastatic renal cancer and sunitinib resistance [23].

Immunotherapy and targeted therapy are particularly effective in the treatment of ccRCC. Expression of ten genes (LCK, CD2, CD3D, CD3G, IRF1, IFNG, CCR5, CD8A, CCL5 and CXCL9) were identified as significantly elevated in tumor tissues and correlated with tumor progression. In 2020, the research of Lin J. et al. CCL5 was selected as a prognostic biomarker. Decreased CCL5 expression was found to correlate with less cell proliferation and invasion in the ccRCC cell line. CCL5 is therefore a potential biomarker and therapeutic target associated with renal cell carcinoma [24].

PDL-1 AS HIGHWAY RISK RCC BIOMARKER

PDL-1 is the transmembrane cell surface protein. It is expressed on tumor cells and appears to play a major role in inhibiting the T-cell immune response. It is essential to improve the host immunity by targeting the PD1/PDL1 pathway, thereby destroying the tumor progression. In the study of Chandrasekaran D. et al. positive PDL-1 expression was observed in 44% of tumors, thus a significant relationship between high WHO ISUP and positive PDL-1 expression. It was noticed in 75% RCC of the sarcomatoid type and 46.8% ccRCC. Blocking the pathway appears to PD1/PDL-1 as an effective way in the immunotherapy of cancer, in particular renal cell carcinoma. The study seems to confirm the significant association between PDL1 expression and high-graded tumors, which proves that PDL-1 is an important prognostic factor [25].

In analysis of tissue biomarkers, George et al. also stated that PDL1 expression may have prognostic value in a group of patients: in patients treated with placebo, disease-free survival (DFS) was shorter in patients with PDL1(+) tumors than in patients with PDL1(-) tumors. Among all patients with tumors PDL1(+) DFSs were longer for those receiving sunitinib than for those receiving placebo [26].

CURRENT CLINICAL POSSIBILITIES

According to the current guidelines of the Polish Society of Clinical Oncology (from 2013), the standard treatment of renal cell carcinoma is surgery. Renal-sparing resection in early stage of cancer (IA and IB) is associated with a prognosis comparable to nephrectomy. Systemic treatment as palliative therapy is used in patients who are not eligible for radical surgery. Interferon alpha immunotherapy is valuable in selected patients. Classic CTH is ineffective. Cytokine immunotherapy for a long time was the basis for systemic treatment of the advanced stage of this tumor, although the overall survival median of patients undergoing treatment increased by only 4 months compared with the control group. [27]

In addition, symptomatic treatment, including hemodialysis and peritoneal dialysis, is used in patients with renal cell carcinoma. Patients with metastatic renal cell carcinoma and end-stage renal disease (SNN) function in daily clinical practice. Scientific evidence regarding the efficacy and safety of e.g. nivolumab in these patients is scarce. In 2020, Osmań-García I. et al. described the cases of patients with RCC with SNN treated with second-line nivolumab. Nivolumab has been shown to be safe for dialysis patients as for patients without renal impairment. [28]

OPPORTUNITY FOR THE FUTURE - NEW DIAGNOSTIC AND PROGNOSTIC MARKERS

The therapeutic effects in patients with renal cell carcinoma (RCC) have changed significantly over the past few years. Surgical operations ("total" and partial nephrectomy) remain the primary intervention in a locally advanced RCC, but systemic treatment is the basis for the treatment of relapses and metastases. Prior to 2005, systemic treatment protocols

for this cancer were limited to cytokine therapies that were significantly toxic and effective in a small number of patient patients. In the following years other agents were incorporated into clinical practice, including kinase inhibitors and drugs that target immune checkpoints. Interest in modern sequencing and molecular identification of biomarkers to personalize treatment in order to develop targeted therapy - individual treatment directed at a specific patient [29].

Personalized treatment is the goal that modern medicine aspires to. It is also a chance for patients with cancer, and at the same time it is the opportunity to avoid the adverse effects of traditional methods of treatment. Extensive research on cancer stem cells (CSCs) has also been underway in recent years. Emerging evidence suggests that renal carcinogenesis and RCC resistance may be derived from kidney cancer stem cells (CSCs) with unrestricted proliferative capacity. A better understanding of the underlying mechanism of CSC would enable the development of treatment targeting CSC renal angiogenesis pathways, immunosuppression signaling pathways, surface biomarkers, and microRNAs. Therefore, CSCs are another potential and innovative therapeutic option in renal cell carcinoma [30].

Conclusions:

Molecular markers identified in recent years are an excellent opportunity to develop a personalized and predictive approach to patient stratification and to create a treatment strategy. The fact that they are mainly non-specific markers still makes it impossible to make an early diagnosis. Modern targeted treatment is an opportunity for RCC patients to improve their quality of life and extend their disease-free time. However, further research is still needed to prove their effectiveness and safety.

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