Clinical Oncology: Case Reports

EDITORIAL

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Kidney Cancer Overview

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Abstract

Every year, more than 65,000 Americans receive a kidney cancer diagnosis, and about 13,000 people pass away from the condition. Kidney cancer is made up of several different cancer kinds, each of which has a unique histology, clinical course, and response to treatment, as well as being brought on by a separate gene. Kidney cancer is now understood to be a metabolic illness as a result of research into the thirteen genes that are known to cause kidney cancer. New areas of strong interest in the investigation of the underlying genetic basis of kidney cancer have been made possible by recent discoveries of chromatin remodeling/histone modifying genes, such as PBRM1 and SETD2. Ipilumumab, a CTLA4 inhibitor, and other novel immunotherapy strategies have opened up intriguing new avenues for clinical studies. The foundation for the creation of efficient treatments for this condition will hopefully be laid by a variety of fresh drugs that target VEGF receptor signaling, the mTOR pathway, and HIF2.

Keywords: Kidney; Cancer; Metabolic; Disease.

Introduction

The condition known as kidney cancer is actually a collection of several malignancies, each of which has a unique histology, clinical course, and underlying genetic etiology. It is possible to create efficient treatment options for kidney cancer by understanding the genetic underpinnings of the disease. Targeting the VHL pathway in clear cell kidney carcinoma has made significant strides. There are now six authorized medications being used to treat advanced kidney cancer patients. Although thousands of patients with advanced kidney cancer benefit clinically from these targeted medicines, the majority of patients eventually progress on targeted treatments due to resistance.

A metabolic illness is kidney cancer: Marston Linehan gave an overview of the genetics of kidney cancer and mentioned that at least twelve well-studied genes, including VHL, MET, FLCN, fumarate hydratase, succinate dehydrogenase B, succinate dehydrogenase D, TFE3, TFEB, MITF, TSC1, TSC2, and PTEN, are currently known to be responsible for kidney cancer. The ability of the cell to perceive oxygen, iron, nutrition, or energy is governed by each of these genes, leading one to the conclusion that kidney cancer is primarily a metabolic illness. A fresh strategy for the creation of potent treatments for kidney cancer is to target the metabolic pathways in this illness. Linehan addressed two cases of kidney cancer that are defined by mutations of Kreb's cycle enzymes, Hereditary Leiomyomatosis and Renal Cancer and Succinate Dehydrogenase Kidney Cancer, in order to illustrate the possibilities for addressing the metabolic foundation of kidney cancer [1].

Fumarate hydratase kidney cancer: A genetic cancer syndrome known as genetic Leiomyomatosis and Renal Cell Carcinoma (HLRCC) puts people at risk for developing kidney cancer as well as cutaneous and uterine leiomyomas. Fumarate hydratase, an enzyme involved in the Krebs cycle, has a germline mutation that defines HLRCC. Patients with HLRCC run the risk of developing an extremely aggressive type of bilateral, multifocal, early-onset kidney cancer. Patients with HLRCC-associated kidney cancer should not be managed with active monitoring since the disease can spread when the tumor is extremely small (less than 2 cm). Instead, surgical excision is advised as soon as a solid tumor is found. Patients with HLRCC should undergo imaging every year, and at-risk individuals should begin genetic testing and abdominal imaging at age 8. The germline allele and the somatic allele of the tumor suppressor gene fumarate hydratase are both inactivated in kidney cancers connected to HLRCC. Fumarate builds up when fumarate hydratase-the Krebs cycle enzyme that converts fumarate to malate is insufficient. Prolyl hydroxylase is inhibited by the extra fumarate, which prevents the VHL complex from locating and destroying hypoxia-inducible factor [2]. HIF builds up, causing a rise in the production of VEGF (which gives the tumor more blood vessels) and GLUT 1 (which increases the transfer of glucose into the cell).

Fumarate hydratase loss also severely reduces ATP synthesis and mitochondrial activity. The metabolism of fumarate hydratase-deficient kidney cancer switches to aerobic glycolysis; as a result, the electron transport chain is compromised and the tumors absorb little to no oxygen, impairing their ability to perform normally oxidative mitochondrial functions. These malignancies switch to aerobic glycolysis, which results in an increase in glucose transport and glycolysis and a dependence of the cells on glycolysis for ATP production. The key energy sensor of the cell, AMPK activation, is reduced, while mTOR and fatty acid production are elevated. In addition, it has been demonstrated that FH-deficient kidney cancer is characterized by a reductive, glutamine-dependent pathway in which the typical Krebs cycle events are switched around to produce bigger lipid pools necessary for quick cell division. These findings open up the possibility of creating brand-new methods for attacking the metabolic underpinnings of cancers that exhibit aerobic glycolysis, such as metformin-like drugs that target AMPK, fatty acid synthesis, or glutamine metabolism [3].

Succinate dehydrogenase kidney cancer: Another inherited kind of kidney cancer is Succinate Dehydrogenase Kidney Carcinoma (SDH-RCC), which is distinguished by germline mutation of a Krebs cycle enzyme. Pheochromocytomas, paragangliomas, and kidney cancer can all develop in SDH-RCC patients. Similar to FH-deficient kidney cancer, patients with SDH-RCC have hereditary mutations of succinate dehydrogenase B or D, and these tumors exhibit aerobic glycolysis. When kidney lesions are tiny (less than 3 cm), SDH-RCC can also manifest with an early beginning, and the tumors are more likely to spread.

Targeting the metabolic basis of kidney cancer: Kidney tumors with advanced HLRCC grow quickly and are resistant to conventional

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chemotherapeutic and targeted treatments. Ramaprasad Srinivasan reported on a pilot trial using bevacizumab and erlotinib to treat patients with advanced HLRCC-associated kidney cancer by targeting the metabolic pathway. HLRCC tumors have a relatively high rate of glucose transfer when compared to other cancers, making them particularly PET-avid. These tumors may be exceptionally sensitive to medicines that target the tumor vasculature, such as bevacizumab, just as they are to glucose. There were several patients who saw objective partial responses and one patient who experienced a complete response to therapy, according to a preliminary examination of the outcomes from this pilot research. Bevacizumab and erlotinib are being examined in a formal trial in individuals with advanced HLRCC-associated kidney cancer [4].

JNK pathway overexpression in kidney cancer: A novel JNK pathway component was discovered to be overexpressed in clear cell kidney carcinoma, according to an elegant series of research on which Kevin White reported. To assess transcription factors involved in the process of embryonic segmentation, White and colleagues built a sizable functional network model in the Drosophila species. In this model, researchers looked at SPOP, a component of the ubiquitin E3 ligase complex that directs the breakdown of the Jun kinase phosphatase Puckered, a protein that triggers tumor necrosis factor-dependent apoptosis. SPOP protein expression on tissue arrays from 20 tumors from 18 different organs was evaluated by White and colleagues to ascertain whether or not SPOP is connected to human cancers. They discovered that although normal kidney tissue was negative, SPOP was expressed by 85% of renal cell carcinomas. 77% of the RCC samples in a tissue array they examined for SPOP expression were positive, they discovered. Only a relatively small number of papillary RCC tumors tested positive for SPOP, compared to the 86% of chromophobe RCC samples and 99% of clear cell RCC samples that did. 97% of verified RCC metastases stained with SPOP were found to be positive, suggesting that SPOP staining can be helpful for identifying clear cell RCC metastases. This study reveals SPOP as a new marker for clear cell kidney carcinoma and may provide the groundwork for cutting-edge treatment modalities.

The treatment of renal cell carcinomas has seen a lot of advancements. The majority of management strategies for localized disease have been on lowering morbidity and mortality during surgical techniques that have been shown to deliver appropriate oncologic control. The development of safe and efficient partial nephrectomy techniques occurred parallel with the only randomized study to be conducted to compare partial with radical nephrectomy, particularly in the context of managing localized kidney malignancies. It was difficult to randomly assign patients based on their surgical plans, therefore it is unlikely that such a study could ever be taken seriously in the modern period. Dr. Van Poppel attentively presents the sole randomized data addressing this crucial subject, which fails to demonstrate a survival and recurrence benefit to the partial nephrectomy arm despite being underpowered and having multiple sources of bias. Only a few of the more than 500 patients who were randomly assigned to the study have perished from metastatic cancer, demonstrating the remarkable local control with either strategy. Adapting immunotherapy, creating highly selective VEGF receptor targeted therapy, and uncovering novel new targets for therapeutic development have all seen significant advancements in the management of metastatic disease. Dr. David McDermott reviewed immunotherapy approaches and looked at specific issues related to tumors and hosts that more recent immune therapy methods can address. To be more precise, inhibiting co-stimulation offers a highly practicable method for teaching the host immune system to overcome tolerance and go after tumor cells [5].

Ipilumumab, a CTLA4 inhibitor that was just recently approved for the treatment of melanoma, is currently being studied in the treatment of renal cell carcinoma. Additionally, because the PD-1/PD-1L interaction has received significant attention, many pharmaceutical companies are prioritizing the development of PD-1 inhibitory therapeutics for the treatment of renal cell carcinoma. Phase II trials are currently looking into this target after phase 1 data showed promise in 16 of 18 patients treated in the RCC group, with several complete and lasting responses. Targeting VEGF receptor signaling has become the cornerstone of treatment for renal cell carcinoma, but Dr. Robert Motzer, a global expert in the development of these therapeutic alternatives, discussed how this route can be modulated. Axitinib and tivozanib, two brand-new medications with extremely high affinity to the VEGF receptor 2, are soon to be available. The licensed medications sunitinib, sorafenib, and pazopanib also complicate the already crowded field of VEGF receptor inhibitors, although these new, very effective on target options come with less off target adverse effects. Axitinib is further along than sorafenib, and it will shortly be assessed for FDA approval based on second-line randomized evidence showing its superiority to produce response and duration of progression-free survival after sunitinib failure [6].

While patients receiving tivozanib showed a progression-free survival of more than 15 months, longer than that seen with any of the previous tyrosine kinase inhibitors, the data for tivozanib is primarily restricted to data from a randomized discontinuation trial. It will be exciting to see how this agent performs in phase III. Last but not least, novel VEGF receptor tyrosine kinase inhibitors are also being developed. They concurrently target the Fibroblast Growth Factor Receptor (FGFR), showing early signs of action and offering an intriguing new paradigm to observe.

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