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Recommendations for the Management of Rare Kidney Cancers

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Abstract

Context: The European Association of Urology Renal Cell Carcinoma Guideline Panel recently conducted a systematic review of treatment options for patients with advanced non–clear-cell renal cell carcinomas (RCCs), which showed a substantial lack of evidence for management recommendations.
Objective: To improve the outcomes of patients with rare kidney cancers (RKCs), we performed a subsequent unstructured review to determine current treatment strategies and druggable pathways, involving key stakeholders with a global perspective to generate recommendations.
Evidence acquisition: Based on the systematic review, literature was queried in Pubmed, Medline, and abstracts from proceedings of European Society for Medical Oncology and American Society of Clinical Oncology, in addition to consulting key opinion leaders and stakeholders. A conventional narrative review strategy was adopted to summarize the data.
Evidence synthesis: The systematic review showed an absence of evidence for treating RKCs, with data only supporting sunitinib or MET inhibitors for some specific subtypes. However, a growing body of evidence implicates druggable pathways in specific RKC subtypes. To test hypotheses, the small patient numbers in each subtype require coordinated multicenter efforts. Many RKC patients are currently excluded from studies or are not analyzed using subtype-specific parameters, despite their unmet medical need.
Conclusions: We recognize the need for additional multicenter studies and subtype-specific analyses; however, we present management recommendations based on the data available. Web-based tools facilitating subtype-specific global registries and shared translational research resources will help generate sufficient data to formulate evidence-based recommendations for guidelines.

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Patient summary: Patients confronted with rare kidney cancers are often treated the same way as clear-cell renal cell carcinoma patients, despite little evidence from randomized trials. Molecular characterization of tumors to stratify patients may improve outcomes. Availability of potential agents and trials remain a problem. Collaboration among medical centers is important to pool scarce data.

1. Introduction

Renal cell carcinoma (RCC) is a relatively rare cancer, although it is estimated that there are >338 000 new cases annually, with a 22% increase projected by 2020 [1]. RCC is characterized by distinct histological subtypes defined by the 2016 World Health Organization classification [2]. Among the malignant tumors, clear-cell RCC (ccRCC) accounts for approximately 75% of kidney cancer. Subtypes making up the remaining 20–25% RCCs are papillary types (pRCC) 1 and 2, chromophobe (chRCC), collecting duct, translocation, medullary, and other very rare RCCs; collectively, these variants of kidney cancer are often termed "non-ccRCCs". Like ccRCCs, these entities may be hereditary or sporadic [3]; however, unlike ccRCCs, limited data are available for evidence-based treatment management, largely due to a lack of trials specific to this population. As "non-ccRCC" is a nondesignation, we employ the inclusive nomenclature "rare kidney cancers" (RKCs).

The European Association of Urology (EAU) RCC Guideline Panel recently performed a systematic review of management strategies for "non-ccRCCs" [4]. The outcome of this process revealed an almost complete lack of evidence. In response to this systematic review, the authors of this paper met in San Francisco, USA, to reach a consensus on "how to improve outcomes for 'rare kidney cancer' patients as a global effort." Specialists (urologists, medical oncologists, and nephrologists) focused on the care of patients with RKCs, as well as patient advocates and two RKC survivors, unanimously agreed on the urgent need for improved medical management of RKCs. This paper is a call to action to appreciate the burden of RKCs and move forward with a roadmap to improve the outcome for these patients with well-coordinated clinical trials and translational research efforts.

2. Evidence acquisition

In addition to the search results derived from the systematic review, we queried the relevant literature in Pubmed, Medline, abstracts from proceedings of European Society for Medical Oncology, and American Society of Clinical Oncology(-GU) until February 18, 2017, in addition to consulting key opinion leaders and stakeholders. A conventional narrative review strategy was adopted to summarize the data, available online (Appendices A and B).

3. Evidence synthesis

The evidence for systemic treatment of metastatic non-ccRCC shows a trend toward favoring vascular endothelial growth factor (VEGF) pathway–targeted therapy over inhibitors of the mammalian target of rapamycin (mTOR), although statistical significance was not reached [4]. The lack of strong evidence calls for experimental data and recommendations from experts in the field of RKCs as well as key stakeholders to help generate informed management strategies [5].

3.1. Definition of RKCs

RKCs comprise a broad spectrum of over a dozen histopathological entities [2]. Papillary RCCs (pRCC types 1 and 2) and chRCCs are more common than the other RKCs. Distinguishing genomic characteristics help characterize RKCs (Supplementary Tables 1 and 2). An estimated 5–8% of RCCs have a strong hereditary component, and 13 distinct hereditary RCC syndromes are known, each associated with specific germline mutations, RCC histology, and nonrenal manifestations [6]: von Hippel–Lindau syndrome (VHL; MIM193300), hereditary pRCC (MIM605074), Birt–Hogg–Dubé (BHD; MIM135150) syndrome, hereditary leiomyomatosis and renal cell cancer (HLRCC; MIM150800), tuberous sclerosis (TS; MIM191100), germline succinate dehydrogenase (SDH) mutations, hyperparathyroidism–jaw tumor syndrome (MIM145001), phosphatase and tensin homolog (PTEN) hamartoma syndrome (MIM601728), constitutional chromosome 3 translocation (MIM144700), *BAP1* hereditary cancer predisposition syndrome (MIM614327), and *MITF*-associated susceptibility to melanoma and RCC syndrome (MIM614456). The current best practice is to consider genetic counseling for individuals suspected of having a hereditary predisposition including early age of onset (age <46 yr), since timely diagnosis could prevent or identify comorbidities at an early stage [7]. Somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC <45 yr and 20–45% of children and young adults with RCC (MIM300854). Even though some hereditary RCC syndromes, such as VHL, predispose to ccRCC and not to one of the RKC subtypes, all hereditary RCC syndromes should be considered as RKCs since they typically require specialized care.

3.2. Current treatment options

Cytoreductive nephrectomy should be considered carefully in RKC patients, with the exception of pRCC type 1, where it is considered beneficial [8]. In the metastatic setting, limited available data suggest that RKCs are less responsive to single-agent VEGF pathway–targeted therapy or mTOR inhibitors than ccRCCs (Table 1). In a retrospective study including 252 patients with RKCs and 1963 patients with ccRCCs treated with targeted therapies, the median overall

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