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Seminar article

Precision medicine for metastatic renal cell carcinoma[1]

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Abstract

Objectives: This review provides a broad overview of emerging data that provide hope that rational precision medicine for metastatic renal cell carcinoma (RCC) may be possible.

Methods: PubMed and major conferences were searched for studies reporting potential predictive biomarkers for the therapy of metastatic RCC.

Results: The availability of multiple new agents for the therapy of advanced RCC poses new challenges in terms of optimal selection of patients for the appropriate drug. Prognostic stratification based on routine histopathologic, clinical and laboratory factors have been utilized to broadly select individuals based, i.e. high-dose interleukin (IL)-2 or vascular endothelial growth factor (VEGF) inhibitors for good and intermediate risk patients and temsirolimus for poor risk patients. While multiple candidate predictive molecular biomarkers suggest that rational selection of patients for high-dose interleukin (IL)-2, and VEGF and mammalian target of rapamycin (mTOR) inhibitors may be possible, none have been validated for use in the clinic. Tumor heterogeneity and standardization of tissue collection and analysis are massive challenges that need to be addressed. Predictive molecules derived from tumor tissue, plasma and host tissue may all be predictive for therapeutic benefit. Moreover, gene expression may be modulated by multiple factors including epigenetics, transcription factors and post-transcriptional and post-translational modifications. Indeed, study of the interaction of molecular factors from all of these sources with environmental and clinical factors may be necessary to develop a unified profile composed of a panel of factors predictive of benefit from specific agents (i.e. sustained response, limited toxicity and overall a positive benefit/risk ratio).

Conclusions: Conducting clinical trials with 1) prospective incorporation of promising candidate predictive molecular biomarkers, 2) novel biomarkers endpoints, and 3) mandatory biopsies of metastatic sites at different time points on therapy, are potential important steps in developing the concept of "the right medication for the right patient".

Keywords: Renal cell carcinoma; Biomarkers; Prognostic; Predictive

1. Introduction

Multiple vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors have been shown to improve median progression-free survival (PFS) for renal cell carcinoma (RCC) in the first- and second-line settings. High-dose (HD) interleukin (IL)-2 is a valid option for selected good- and intermediate-risk patients with clear cell histology owing to durable complete responses seen in a small minority of patients [1]. When employing VEGF and mTOR inhibitors, RCC is incurable; the median overall survival (OS) of good- and intermediate-risk disease is approximately 2 to 2.5 years, and the median OS of poor-risk disease is less than a year [2,3]. In addition, VEGF and mTOR inhibitors produce toxicities and sometimes no benefit at all, which entails appropriate patient selection. Combinations of targeted agents in unselected patients have generally been plagued by toxicities and have not yielded increments in outcomes [4–9]. Hence, the identification of patients with tumors that are most likely to respond is important. Conversely, given that most patients benefit to variable extents with stability or response, it may be more critical to identify tumors likely to be inherently resistant to a particular agent, i.e. tumors that progress without initial stability or response. In this study, we review the available data supporting personalized targeted therapy for RCC (Fig.).

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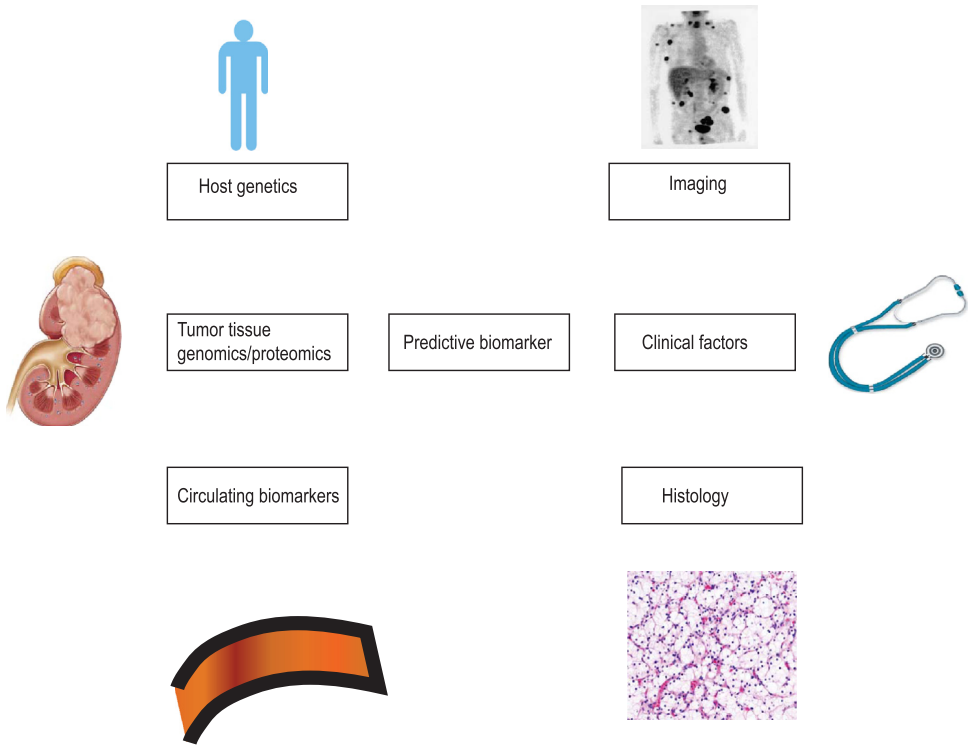

Fig. Potential predictive biomarkers in metastatic RCC.

2. New insights into tumor biology

2.1. Clear cell (CC)-RCC

Our understanding of RCC tumor biology has been growing exponentially, although the translation of these new insights into robust therapeutic advances including cures requires vigorous clinical investigation in this post–VEGF and mTOR inhibitor era. A major impediment is the complexity of tumor biology, which is highlighted by the substantial intrapatient and interpatient heterogeneity, i.e. the presence of diverse histologies and molecular alterations [10]. Acquisition of new somatic mutations that could confer drug resistance and differences in detection of somatic alterations depending on the sample (primary tumor vs. metastasis) and influence of host genetics are major confounders of tumor tissue studies. CC-RCC is characterized by somatic loss secondary to mutation or silencing by methylation of the von Hippel-Lindau (*VHL*) tumor suppressor gene in most of the tumors. These VHL aberrations lead to the up-regulation of hypoxia-inducible factor (HIF), a transcription factor that amplifies multiple proangiogenic molecules including VEGF [11]. *VHL*-deficient CC-RCCs may be distinguished on the basis of differential HIF-1α and HIF-2α expression, with HIF-2α-expressing tumors displaying enhanced c-Myc activity than those coexpressing both HIF-1α and HIF-2α or *VHL* wild-type tumors [12]. In contrast, HIF-1α and HIF-2α-coexpressing and *VHL* WT tumors displayed increased activation of Akt/mTOR and ERK/MAPK1, suggesting these may be more angiogenic and may respond to VEGF and mTOR inhibitors. CC-RCC tumors have been recently found to harbor inactivating mutations of histone modification genes (*SETD2*, *JARID1C*, and *UTX*), a chromatin remodeling complex gene, polybromo 1, and genes implicated in deubiquitination (BAP1) and the ubiquitin-mediated proteolysis pathway [13–16]. Intriguingly, polybromo 1 and *BAP1* mutations appeared to be mutually exclusive, with *BAP1* mutant tumors exhibiting aggressive pathological features and poorer survival. In addition, familial forms of CC-RCC may occur with congenital mutations in *VHL*, succinate dehydrogenase-B, and tuberous sclerosis (*TSC*)-1 and 2 genes [17,18].

Knowledge regarding molecules that engender resistance has been accumulating, which may help select appropriate combinations and second-line therapy. Other proangiogenic molecules, such as IL-8, fibroblast growth factors and ephrin, and those involved in the angiopoietin-Tie pathway and pathways that promote tumor cell survival, proliferation, invasion, and metastasis, including epidermal growth factor, hepatocyte growth factor-*MET*, insulin-like growth factor, and PI3K/AKT/mTOR, may engender resistance to VEGF inhibitors [19,20]. In addition, immune mechanisms of resistance and growth may be mediated by intratumoral myeloid-derived suppressor cells and amplification of T-lymphocyte checkpoints, cytotoxic T-lymphocyte antigen-4, and programmed death (PD-1) [21].

2.2. Non-CC RCC

Non-CC RCC includes the papillary, chromophobe, and collecting duct/medullary subtypes. The papillary subtype is