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Seminar article

Metastatic clear cell renal cell carcinoma: Circulating biomarkers to guide antiangiogenic and immune therapies

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Abstract

Background: The therapeutic armamentarium for metastatic renal cell carcinoma has rapidly expanded over the past decade to include a number of anti-angiogenic therapies and more recently, an immunotherapy. Biomarkers in the peripheral circulation are easily accessible, can provide important prognostic value, and have the potential to give important information about disease progression and treatment sensitivity or response.

Main Findings: Herein, we review a variety of circulating markers including circulating protein markers (VEGF-A, inflammatory cytokines, and LDH), circulating nucleic acids (cell free DNA and micro RNAs), and circulating cellular factors (circulating tumor cells, circulating endothelial cells, and immune cell subsets). We discuss these biomarkers in the context of their ability to provide prognostic and predictive information to anti-angiogenic and immunotherapeutic agents.

Principal Conclusions: While promising, there is still much work to be done, and prospective evaluation of any potential predictive biomarker for these therapies is greatly needed.

Keywords: Metastatic renal cell carcinoma; Circulating biomarkers; Circulating tumor cells; Circulating tumor DNA; VEGF therapies; Immunotherapy

Introduction

Metastatic renal cell carcinoma (mRCC) is one of the top 10 malignancies affecting both men and women in the United States, with more than 62,000 new cases and more than 14,000 deaths expected in 2016 [1]. As more therapies become available to treat mRCC, it is important to understand the patient and disease characteristics that predict benefit from these treatments. Currently in the United States, there are 6 antiangiogenesis agents (sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and sorafenib), 2 mammalian target of rapamycin (mTOR) therapies (temsirolimus and everolimus), and 2 immune therapies (high-dose interleukin (IL) 2 and nivolumab) approved for the treatment of mRCC. Having specific, noninvasive biomarkers that can predict better responses to these therapies would allow clinicians to more precisely select from this variety of treatment options.

Biomarkers serve in this capacity and can be important indicators of disease prognosis, progression, and therapeutic benefit. The different classes of biomarkers can be used in a variety of settings such as to assess patient risk, to evaluate progression of disease, or to predict response to certain treatments. For purposes of this review, prognostic biomarkers refer to the likelihood of disease recurrence, progression, or death, independent of any therapeutic intervention. In contrast, predictive biomarkers refer to the likelihood of therapeutic benefit or resistance to certain treatments. In some cases, a biomarker may have both prognostic value for disease outcome and predictive value for a treatment response. Classically, prognosis of RCC is based on pathologic staging, both from gross pathology as well as from common histologic subtypes. Clinical factors have also been identified as important elements of prognostication across large series of patients with RCC. Importantly, through technological advances in molecular biology, a wide array of circulating biomarkers (including

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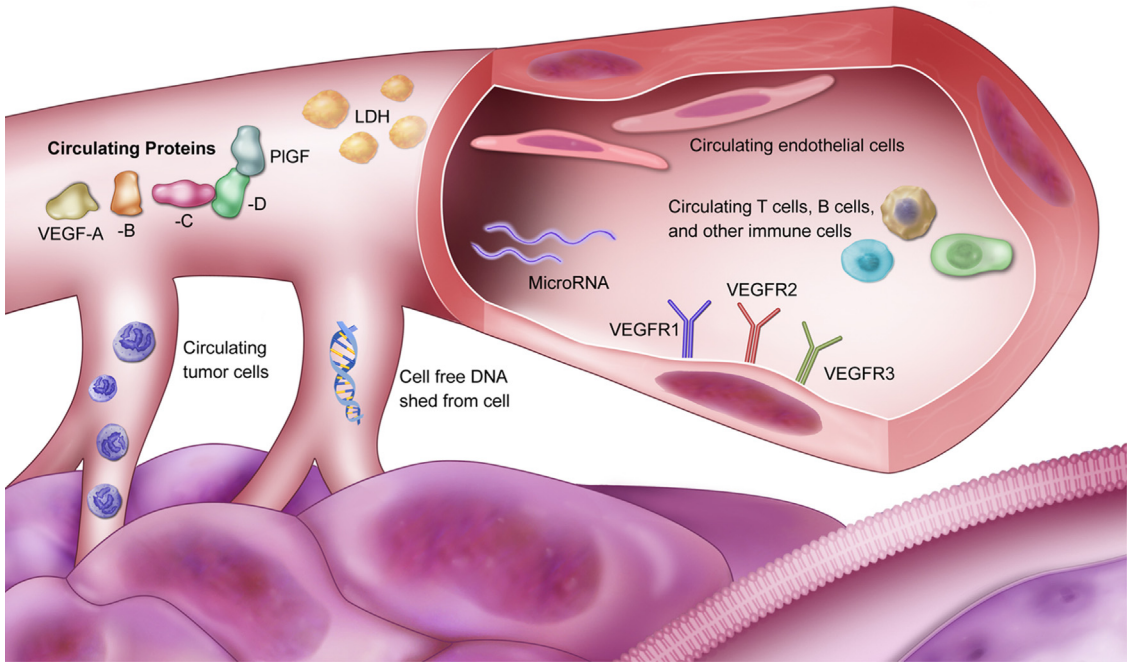

Fig. Circulating biomarkers in metastatic clear cell renal cell carcinoma. Circulating proteins include vascular endothelial growth factor A (VEGF-A), VEGF-B, VEGF-C, VEGF-D, placental growth factor (PlGF), and lactate dehydrogenase (LDH). Circulating nucleic acids that can be captured in the bloodstream include cell-free DNA and microRNA. Cellular elements in the peripheral circulation include circulating tumor cells, circulating endothelial cells, and circulating T cells, B cells, and other immune cells. (Color version of figure is available online.)

proteins, circulating tumor cells [CTCs], microRNA (miRNA), and circulating cell-free DNA [cfDNA]) have now been identified as potential prognostic or predictive biomarkers or as both (Fig.). This review first addresses classic prognostication of RCC through clinical factors and then delves into the prognostic and predictive significance of specific biomarkers including proteins, circulating nucleic acids (cfDNA and miRNA), and circulating cells (tumor cells and subsets of immune cells) (Table).

Clinical factors

Patients with RCC have many clinical characteristics that can be independent prognostic factors [2]. Patients can have paraneoplastic phenomena, humoral hypercalcemia, cachexia, anemia, hepatic dysfunction, and fevers, all of which can negatively affect disease-specific survival [3–5]. All of these factors affect a patient's performance status. Using the Eastern Cooperative Oncology Group score, Fuhrman's histologic grade and TNM system, one can place a patient in 1 of 5 survival stratification groups based on the University of California Los Angeles Integrated Staging System, an older prognostication system [6]. Overall, the 5-year survival rates for patients in groups I through V are as follows: 94%, 67%, 39%, 23%, and 0%. These survival rates are based on data collected before the advent of antiangiogenic agents.

More recently, multivariate models have been established as novel prognostic indicators. The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score is a widely used score in clinical prognostication of patients who present with metastatic disease. The MSKCC score is based on a cohort of 670 patients treated with interferon alfa, IL-2, or chemotherapy. Motzer et al. [7] found that performance status (Karnofsky score $>$ 80%), high lactate dehydrogenase (LDH $>$ 1.5 upper limit of normal), low hemoglobin (less than lower limit of normal), hypercalcemia (Ca $>$ 10), and the absence of nephrectomy were associated with shorter survival in a multivariate analysis. Patients with none of these risk factors had a median survival of 20 months, compared with only 4 months for patients with 3 or more risk factors. As antiangiogenic agents targeting vascular endothelial growth factor (VEGF) have become standard of care for mRCC, the Heng criteria have become a useful model for prognostication as well [8]. Developed a decade after the MSKCC criteria, the Heng prognostic nomogram was based on data from 645 patients who were treated with first-line VEGF-targeting agents (bevacizumab, sorafenib, and sunitinib). Hypercalcemia, performance status, and anemia were independent predictors of survival among patients treated with VEGF-targeted agents, whereas neutrophilia and thrombocytosis replaced elevated LDH as prognostic indicators more commonly checked in clinical practice [8]. It is theorized that patients with increased tumor burden often display neutrophilia and thrombocytosis as clinical markers of increased inflammation. LDH was included but, given the other clinical factors, did not independently factor into prognosis. In addition, LDH may not have been checked as often as a routine complete blood count and therefore may not have been a prognostic marker in the Heng criteria [8].