Systemic Treatment Options for Untreated Patients With Metastatic Clear Cell Renal Cancer

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The introduction of therapy targeting vascular endothelial growth factor (VEGF) and the mammalian target of rapomycin (mTOR) has significantly improved the outcome of patients with metastatic renal cancer. In this article a comprehensive overview of treatment choices for previously untreated patients with metastatic disease is given. Both established and emerging therapeutic options are discussed, as are prognostic factors predicting outcome.
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Renal cell carcinoma (RCC) is a malignancy of the kidney that originates in the proximal renal tubule and accounts for approximately 3% of all cancers. In 2012, an estimated 64,770 new cases of kidney and renal pelvis cancers are expected to be diagnosed in the United States with an estimated 13,570 deaths within the same group.[1] Surgical resection is the main treatment for tumors that are confined to the kidney. Approximately 20%–40% of patients with localized disease will eventually develop local recurrence or distant metastasis after nephrectomy.[2] In addition, about one third of patients with RCC have metastatic disease at diagnosis. The majority of these patients are candidates for systemic therapy.

Recently, an increased understanding of the pathogenesis of RCC has led to the development of novel drugs that target vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR). First-line treatment of metastatic renal cell carcinoma (mRCC) relies heavily on the use of small molecule targeted inhibitors. Phase III trials of these agents have demonstrated substantially better overall efficacy and fewer side effects than previously used cytokines and have assumed a predominant role in the standard management for mRCC.[3–9]

Patients with advanced RCC present with a wide spectrum of disease varying from asymptomatic or indolent disease to symptomatic or rapidly progressive disease. Several prognostic factors identified have led to the development of risk factor models that have proven to be instrumental in the design and interpretation of clinical trials and risk-directed therapy. Herein we review prognostic factors, clinical data for established first-line therapies, and emerging first-line therapy for advanced RCC.

PROGNOSTIC FACTORS

Prognostic factors are important for the purposes of clinical trial design, risk-directed therapy, and patient counseling. They can be divided into patient factors, tumor burden, inflammatory markers, and treatment factors. Many of these factors have been combined into multivariable models to assist the clinician in patient prognostication.[10]

Patient factors include symptoms such as night sweats and weight loss, Karnofsky performance status (KPS), and Eastern Cooperative Oncology (ECOG) performance status. A reflection of higher tumor burden includes the presence of anemia, an elevated lactate dehydrogenase (LDH) level, hypercalcemia, elevated alkaline phosphatase, and the sites and number of sites of metastatic disease. Additionally, a shorter disease-free interval or shorter time from diagnosis to treatment indicates more aggressive disease while longer ones depict more indolent disease. Inflammatory markers include and elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophilia, and thrombocytosis, which are all associated with poorer overall survival. Finally, treatment factors, including a prior cytoreductive nephrectomy, tend to be associated with a better prognosis.[11]

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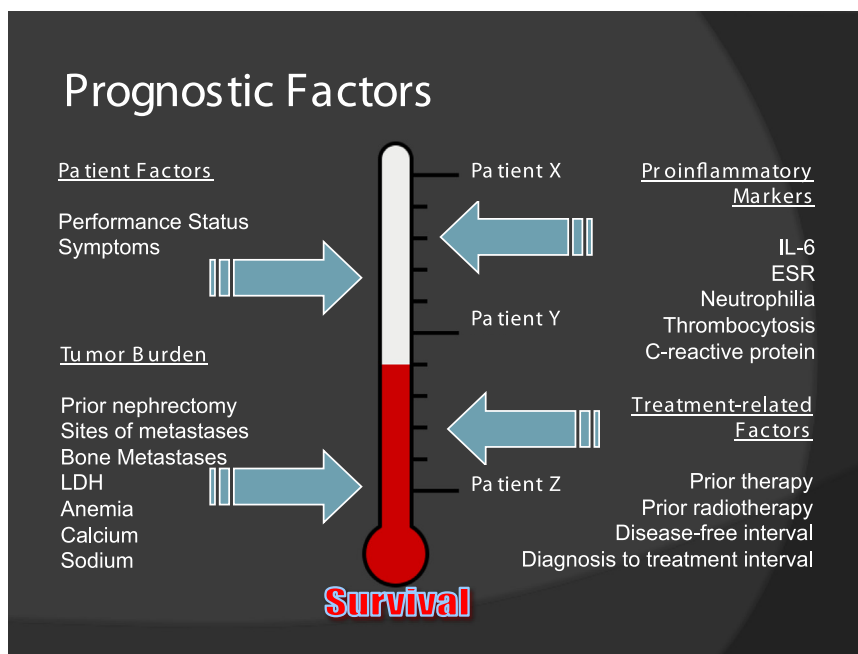[b]Tom Baker Cancer Center, Calgary, AB, Canada.
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Figure 1. Prognostic factors can be divided into patient factors, measures of tumor burden, proinflammatory markers, and treatment-related factors. Different patients may have different predicted outcomes based on these factors.

One of the first and most widely used prognostic models is from the Memorial Sloan-Kettering Cancer Center (MSKCC).[12,13] This model was developed using pooled data from patients in clinical trials treated with interferon-alpha accrued from 1982–1996. A KPS <80%, a diagnosis of RCC to treatment interval <1 year, anemia less than the lower limit of normal, LDH >1.5 times the upper limit of normal, and hypercalcemia >10 mg/dL were all independent predictors of poor overall survival. Patients with none of these risk factors were in the favorable group and had a median overall survival of 29.6 months. Patients with one or two of these risk factors were in the intermediate-risk group (median overall survival, 13.8 months). Patients with three or more risk factors were in the poor risk group (median overall survival, 4.9 months). This model has been externally validated[13] and is widely used in mRCC clinical trials.

Other models have been developed in the immunotherapy era, including that of the Groupe Francaise d'Immunotherapie,[14] which identified performance status, number of sites of metastases, disease-free interval, markers of inflammation, and hemoglobin as independent predictors of survival. A Japanese model developed in the era of immunotherapy includes time from initial visit to metastasis, ECOG performance status, hemoglobin, LDH, corrected calcium, and CRP.[15]

With the advent of targeted therapy, improvements in survival were observed. The International mRCC Database Consortium retrospectively collected population-based data on 645 patients with mRCC treated with targeted therapy.[16] It found six independent predictors of overall survival, which included a KPS <80%, a diagnosis of RCC to treatment interval <1 year, anemia less than the lower limit of normal, hypercalcemia (using institutional upper limits of normal), neutrophilia (greater than institutional upper limit of normal), and thrombocytosis (greater than institutional upper limit of normal). Patients with zero risk factors were in the favorable-risk group with a median overall survival that was not reached (44 months in the external validation cohort). Patients with one or two risk factors were in the intermediate-risk group (median overall survival, 27 months) and patients with 3 or more risk factors were in the poor risk group (median overall survival, 8 months). Although the prognostic criteria are slightly different, new benchmarks in overall survival were achieved in each of the prognostic categories compared to the MSKCC criteria. Median survivals have almost doubled and are a testament to the efficacy of targeted therapy. This model has been derived and externally validated[17] in the era of targeted therapy and can be used for patient counseling and risk stratification in clinical trials (Figure 1).

FIRST-LINE AGENTS

Four approved targeted agents have shown efficacy in randomized phase III trials as first-line treatment in patients with metastatic clear cell RCC (Table 1). The first three targeted agents, sunitinib, bevacizumab plus interferon (IFN-α), and temsirolimus were