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Improvement in survival end points of patients with metastatic renal cell carcinoma through sequential targeted therapy

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ABSTRACT

Survival of patients with metastatic renal cell carcinoma (mRCC) has improved since the advent of targeted therapy. Approved agents include the multi-targeted tyrosine kinase inhibitors (TKIs) sunitinib, sorafenib, axitinib, pazopanib, cabozantinib, and lenvatinib (approved in combination with everolimus), the anti-VEGF monoclonal antibody bevacizumab, the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus, and the programmed death-1 (PD-1) targeted immune checkpoint inhibitor nivolumab. The identification of predictive and prognostic factors of survival is increasing, and both clinical predictive factors and pathology-related prognostic factors are being evaluated. Serum-based biomarkers and certain histologic subtypes of RCC, as well as clinical factors such as dose intensity and the development of some class effect adverse events, have been identified as predictors of survival. Expression levels of microRNAs, expression of chemokine receptor 4, hypermethylation of certain genes, VEGF polymorphisms, and elevation of plasma fibrinogen or d-dimer have been shown to be prognostic indicators of survival. In the future, prognosis and treatment of patients with mRCC might be based on genomic classification, especially of the 4 most commonly mutated genes in RCC (*VHL*, *PBRM1*, *BAP1*, and *SETD2*). Median overall survival has improved for patients treated with a first-line targeted agent compared with survival of patients treated with first-line interferon-α, and results of clinical trials have shown a survival benefit of sequential treatment with targeted agents. Prognosis of patients with mRCC will likely improve with optimization and individualization of current sequential treatment with targeted agents.

Introduction

Survival of patients with metastatic renal cell carcinoma (mRCC) has improved since the advent of targeted therapy. Currently, 10 targeted agents are approved for first-line or later-line use in the treatment of patients with mRCC [1–3]. Among these agents, 1 is a monoclonal antibody targeting vascular endothelial growth factor (VEGF; bevacizumab), 6 are multi-targeted tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, axitinib, pazopanib, cabozantinib, and lenvatinib [approved in the US in combination with everolimus]), 2 target the mammalian target of rapamycin (mTOR) pathway (everolimus and temsirolimus) and 1 targets the immune checkpoint programmed death-1 (PD-1) pathway (nivolumab). Kidney cancer guidelines recommend first-line sunitinib, pazopanib, or bevacizumab (plus interferon-α [IFN-α]) for patients with clear cell histology and good or intermediate Memorial Sloan Kettering Cancer Center (MSKCC) prognosis (European Society for Medical Oncology [ESMO] level I evidence of activity and grade A recommendation) [1–3]. Temsirolimus is the only recommended first-line treatment for patients with a poor prognosis based on modified MSKCC criteria [3]. For patients who experience disease progression during (or who are intolerant to) treatment with a first-line VEGF receptor (VEGFR) TKI, subsequent treatments with the highest level of evidence include nivolumab, cabozantinib, axitinib, or everolimus [1,2]. Although sequential treatment with targeted agents is recommended, the optimal sequence has not been determined. The goal of therapy for patients with mRCC is to prolong survival while maintaining good quality of life, which should be taken into consideration when choosing second-line and

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later-line agents. Choosing a sequence of targeted agents with nonoverlapping safety profiles might improve quality of life by improving tolerability. Looking forward, identification of the optimal sequence of targeted agents might be achieved through identification of biomarkers and individualization of treatment for patients with mRCC.

The International mRCC Database Consortium (IMDC) model (Heng model) is being used more widely in clinical trials as a prognostic indicator of survival for patients with mRCC treated with targeted therapy. The externally validated IMDC model includes the following 6 independent predictors of short survival: Karnofsky performance status (KPS) <80%, time from diagnosis to treatment <1 year, hemoglobin level less than the lower limit of normal (LLN; i.e., anemia), corrected calcium level more than ULN (i.e., hypercalcemia), neutrophil count more than ULN (i.e., neutrophilia) and platelet count greater than ULN (i.e., thrombocytosis) [4,5]. The IMDC model stratifies patients into risk groups according to the number of prognostic factors: favorable = 0, intermediate = 1–2, and poor = 3 or more. The IMDC model has been validated for use in clear cell and non-clear cell mRCC and for use with second-line therapy [6,7]. Selection of patients for some clinical trials evaluating targeted therapy and novel immunotherapies in mRCC have utilized MSKCC prognostic criteria, which incorporates 5 independent predictors of short survival, 4 of which are in common with the IMDC model (KPS <80%, time from diagnosis to treatment less than 1 year, low serum hemoglobin level, and corrected calcium level more than 10 mg/dL), as well as a lactate dehydrogenase level more than 1.5 times ULN [8]. Patients with 0, 1–2, or $\geqslant$3 risk factors are stratified into MSKCC risk categories as favorable, intermediate, or poor risk, respectively. Patients treated in clinical practice are not always typical of those selected for participation in clinical trials, and prognostic criteria in addition to those identified in the MSKCC and IMDC models may prove to be valuable in identifying the most effective treatment strategy.

Clinical predictive factors

A number of clinical factors have been identified as potential predictors of treatment response, including dose variables, conditional survival, hypertension, serum biomarkers and disease characteristics. The results of a chart review of patients with mRCC who received first-line sunitinib demonstrated that overall survival (OS) was significantly shorter for patients with a dose intensity below 0.7 (hazard ratio [HR], 3.36) and for patients who discontinued treatment within the first 24 weeks because of adverse events (HR, 2.80) [9]. These results highlight the importance of good treatment tolerability and maintenance of dose intensity. Conditional survival, which accounts for elapsed time since treatment initiation, was also identified as a predictive measure of survival in mRCC in a study in which 2-year conditional survival improved over time from 44% (95% confidence interval [CI] 41.0–47.0) initially to 51% (95% CI, 46.0–55.0) for patients treated with a first-line VEGFR-TKI who had survived 18 months after initiation of therapy, irrespective of whether they were still receiving VEGF-targeted therapy [10].

A relationship has been observed between OS and the development of hypertension (defined as systolic blood pressure [SBP] $\geqslant$140 mmHg, or diastolic blood pressure [DBP] $\geqslant$90 mmHg) during treatment with a VEGFR-TKI in patients with mRCC. Results of pooled analyses showed prolonged OS in patients who developed hypertension, compared with those who did not, during treatment with first-line or second-line sunitinib (SBP $\geqslant$140 mmHg; 31.1 vs 18.2 months; $P < 0.001$ or DBP $\geqslant$90 mmHg 31.1 vs 23.0 months; $P = 0.013$) [11], and during treatment with second-line axitinib (DBP $\geqslant$90 mmHg; 25.8 vs 13.9 months) [12]. A post hoc landmark analysis of the AXIS trial showed that patients treated with second-line axitinib or sorafenib who developed hypertension (DBP $\geqslant$90 mmHg or SBP $\geqslant$140 mmHg) within the first 8 or 12 weeks of randomization had longer median OS than patients who did not develop hypertension [13]. Development of DBP $\geqslant$90 mmHg or SBP $\geqslant$140 mmHg was shown to be an independent predictor of OS on multivariable analyses, including baseline characteristics [13]. However, despite this compelling post hoc evidence, the role of treatment-related hypertension appears complex. A prospective dose-escalation study for axitinib showed improved objective response rate with dose-titration (54% vs 34%), but a single factor to guide dose titration was not identified [14]. Changes in BP were associated with longer progression-free survival (PFS), but only a weak correlation was found between axitinib exposure and DBP [15]. Neither pharmacokinetics (PK) nor treatment-related hypertension guided axitinib dosing exclusively. This study underlines the role of BP changes as a pharmacodynamic marker for VEGF inhibition, but also shows the limitations of a single marker in the clinical context.

Several serum-based biomarkers have also been identified as predictors of survival. For example, patients with mRCC who were poor risk and had pretreatment lactate dehydrogenase (LDH) levels greater than ULN experienced prolonged OS after treatment with temsirolimus compared with patients with pretreatment LDH greater than or equal to ULN ($P < 0.001$) [16]. In addition, results of a real-world study of patients with mRCC showed a significant association between serum alkaline phosphatase level and survival ($P = 0.003$) [17].

A number of other clinical characteristics have also been identified as potential predictive factors in RCC. In a study investigating the survival of patients with different RCC subtypes, patients with chromophobe histology experienced a lower risk of cancer-specific mortality than patients with clear cell histology (HR, 0.56; 95% CI, 0.40–0.78), whereas patients with collecting duct or sarcomatoid histology experienced a higher risk of cancer-specific mortality than patients with clear cell histology (HR, 2.26 and 2.07, respectively) [18]. Although the difference was not statistically significant, there was a trend toward a lower risk of cancer-specific mortality in patients with papillary histology compared with clear cell histology (HR, 0.85). In a study of patients with RCC who had undergone nephrectomy or nephron-sparing surgery, a shorter time to recurrence was an independent predictor of reduced cancer-specific survival after recurrence for up to 4 years after surgery ($P = 0.012$) [19]. A real-world study also found that KPS <80% (HR, 2.9), duration of mRCC <1 year (HR, 2.7), progression during first-line VEGFR-TKI (HR, 2.2), presence of liver metastasis (HR, 1.9), and clear cell histology (HR, 2.9) were predictive of shorter OS [20]. Taken together, results of these studies have identified serum-based biomarkers and certain clinical characteristics as being, or potentially being, predictors of survival. It remains to be determined if these markers will translate to the broader population of patients with mRCC. Based on what is currently known, there are multiple parameters that have the potential to affect survival, and individualization of therapy may be the key to improving survival of these patients.

Pathology-related prognostic factors

A number of studies have identified pathology-related prognostic factors in patients with mRCC (Table 1) [21–30]. MicroRNAs (miRNAs) were evaluated in several studies, which showed an association between expression levels of miR-21, miR-126, miR-221, miR-630, and miR-187 and the occurrence and progression of RCC [21–24]. Other studies showed an association of chemokine receptor 4 expression and hypermethylation of the secreted frizzled-related protein 1 (*SFRP1*) gene and the basonuclin 1 (*BNC1*) gene with poor survival in patients with RCC [25,26]. In