Sarcomatoid Dedifferentiation in Metastatic Clear Cell Renal Cell Carcinoma and Outcome on Treatment With Anti–Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors: A Retrospective Analysis

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Abstract

In order to describe the impact of sarcomatoid dedifferentiation on outcome in metastatic clear cell RCC treated with first-line anti-VEGFR-TKIs, we retrospectively reviewed 124 patients files. An important sarcomatoid component, defined as ≥25% involvement of the primary tumor, was associated with poor outcome. Analysis of the extent of sarcomatoid features in resected metastases can also provide additional prognostic information.

Introduction: This study aimed to assess the efficacy of anti–vascular endothelial growth factor receptor tyrosine kinase inhibitors (anti-VEGFR-TKIs) in patients with metastatic clear cell renal cell carcinoma (m-ccRCC) with sarcomatoid dedifferentiation. **Patients and Methods:** The files of all patients with m-ccRCC consecutively treated with first-line anti-VEGFR-TKIs at the authors' institution were retrospectively reviewed. Pathology slides from nephrectomy and metastasectomy were assessed for the presence and extent of sarcomatoid dedifferentiation. **Results:** A total of 124 patients were included; nephrectomy and metastasectomy specimens were available in 117 and 35 patients, respectively. Thirty percent of the primary nephrectomy specimens had sarcomatoid features, and the median involvement of the sarcomatoid component was 21% (range, 1%-95%). Patients with an important sarcomatoid component, defined as $\geq$ 25% involvement of the tumor, had a very poor outcome: progression-free survival (PFS) and overall survival (OS) were 3 and 6 months, respectively, and no partial responses (PR) were observed. Patients without sarcomatoid dedifferentiation or with sarcomatoid involvement $<$ 25% had a PFS of 12 months ($P < .0001$; hazard ratio [HR], 51; 95% CI, 12.58-207.3), an OS of 22 months ($P < .0001$, HR, 10.72; 95% CI, 3.56-32.25), and a PR rate of 50% ($P = .0015$). Patients with a sarcomatoid component $\geq$ 25% in the metastasectomy also had a poorer PFS and OS on anti-VEGFR-TKIs compared with patients with $<$ 25% of sarcomatoid features at these sites. **Conclusion:** Patients with m-ccRCC whose tumors contain a component of sarcomatoid dedifferentiation of $\geq$ 25% of the total tumor volume have a very poor outcome when treated with anti-VEGFR-TKIs. Analysis of the extent of sarcomatoid features in resected metastases can provide additional prognostic information.

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Introduction

At initial diagnosis, up to one-third of patients with renal cell carcinoma (RCC) present with metastatic disease, and 40% of patients with primary nonmetastatic disease who undergo a nephrectomy with curative intent will ultimately relapse or develop metastases.[1] Therapies targeting the vascular endothelial growth factor (VEGF) pathway (the tyrosine kinase inhibitors [TKIs] sunitinib, sorafenib, pazopanib, and axitinib and the monoclonal antibody bevacizumab) or inhibiting the mammalian target of rapamycin pathway (everolimus and temsirolimus) have almost completely replaced cytokines as first- and second-line treatment of metastatic RCC (mRCC).

In the pivotal trial in previously untreated patients with m-ccRCC, half of the patients treated with sunitinib experienced a partial response (PR), 43% had stable disease, and 7% had progressive disease (PD) at first evaluation. Median progression-free survival (PFS) and overall survival (OS) were 11 and 26.4 months, respectively.[2,3] In the sorafenib pivotal trial in patients with m-ccRCC pretreated with cytokines, 10% of patients achieved a PR, 74% had stable disease, and 16% had early PD, with a median PFS and OS of 5.5 and 17.8 months, respectively.[4] In previously untreated patients predominantly with ccRCC, pazopanib showed a median PFS of 11.1 months and 33% PR, 42% stable disease, and 16% early PD as best response.[5] Despite this major breakthrough in the treatment of mRCC, eventually all patients will relapse owing to acquired secondary resistance. Several mechanisms of resistance have been proposed, but reliable biomarkers predictive of anti-VEGFR-TKI sensitivity or primary/secondary resistance are still lacking.[6] Baseline serum lactate dehydrogenase (LDH), hemoglobin, corrected calcium, neutrophil, platelet, and C-reactive protein (CRP) levels, bone metastases, the number of metastatic sites, prior nephrectomy, Eastern Cooperative Oncology Group performance status (ECOG PS), and the interval between diagnosis and systemic therapy were found to be associated with PFS, OS, or both in mRCC treated with anti-VEGF-targeted therapy.[7-10]

RCCs of all histologic subtypes can present with sarcomatoid dedifferentiation, a growth pattern characterized by variable degrees of spindle-shaped cell histology.[11,12] Most sarcomatoid RCC presents as a biphasic lesion with both mesenchymal (sarcoma-like) and epithelial (carcinoma) elements; rarely, the sarcomatoid dedifferentiation affects the whole tumor. Sarcomatoid dedifferentiation is associated with a more aggressive disease and poor outcome after nephrectomy or on immunotherapy.

The 2 major trials that defined the benefit of anti-VEGFR-TKIs included patients with clear cell histology[2] or predominantly clear cell histology[5] but did not provide details on the percentage of tumors displaying sarcomatoid elements nor on the percentage of sarcomatoid involvement of the tumors. In 2 retrospective series with patients with mRCC with sarcomatoid dedifferentiation, PRs on VEGF-targeted therapies were seen, but outcome seemed globally poorer than in patients with mRCC without sarcomatoid dedifferentiation, although a direct comparison was lacking.[13,14] Moreover, both series included also non-ccRCCs, in which anti-VEGFR-TKIs are less active.[15,16]

The present authors aimed to study the effect of sarcomatoid dedifferentiation on outcome on anti-VEGFR-TKIs in clear cell RCC in the metastatic setting.

Patients and Methods

In the database of the University Hospitals Leuven, the authors searched for patients with m-ccRCC treated with sunitinib, sorafenib, or pazopanib as first-line anti-VEGFR-TKIs between November 2005 and August 2013 and with available tissue blocks or representative slides from nephrectomy or metastasectomy specimens. Patients for whom only biopsies were available were not considered for inclusion.

In these patients, anti-VEGFR-TKIs were started at the labeled dose: 50 mg/d, 4 weeks on 2 weeks off, for sunitinib and 800 mg/d continuously for sorafenib and pazopanib. Previous immunotherapy or chemotherapy was allowed, but previous targeted therapy was prohibited. The study was approved by the ethics committee of the authors' institution. Signed consent was obtained from all patients. In some cases, biologic material and clinical data were used from patients who had already died and for whom a general positive advice for the utilization of remaining tissue was foreseen by the institutional board.

The following clinical data were assessed: patient age at diagnosis, gender, prior treatment, baseline Karnofsky PS, number and sites of metastases (bone, liver, lung, lymph nodes), platelet count, neutrophil count, LDH level, hemoglobin, corrected calcium, C-reactive protein, and time between nephrectomy and start of systemic treatment. Patients underwent follow-up computed tomography (CT) scans (chest and abdomen) every 2 to 3 months during TKI treatment.

All available pathology slides were reviewed by an expert genitourinary pathologist (E.L.) blinded to patient outcome. The classification of RCC subtypes and the presence of sarcomatoid dedifferentiation were assessed following the 2004 World Health Organization Classification of Renal Tumors. The percentage of sarcomatoid elements in each nephrectomy or metastasectomy sample compared with the total available tumor extent was estimated by examining every slide from each case individually. The area of the sarcomatoid component relative to the tumor or metastasis was estimated on each slide. The mean percentage of sarcomatoid component relative to the tumor or metastasis from each slide was added to obtain the total estimated sarcomatoid percentage for each patient. Samples with sarcomatoid dedifferentiation in the original tumor were classified Fuhrman grade 4 by definition, because sarcomatoid dedifferentiation is believed to represent transformation of the RCC to higher grade.

Endpoints of the study were PFS, OS, and response rate (RR). PFS was defined as the time between the first day on sunitinib and the date of radiologic progressive disease or death. Patients who had not progressed at database closure were censored at last follow-up. OS was defined as the time between the first day on sunitinib and the date of death or last date of follow-up. An objective response was defined according to Response Criteria in Solid Tumors (RECIST), version 1.0. Patients who had PD at the first CT scan evaluation were considered as having early PD. Patients who stopped therapy for toxicity before reaching the first evaluation by CT scan were discarded. PFS and OS distributions were estimated using the Kaplan-Meier product-limit method. *P* values were calculated with the log-rank Mantel-Cox test. The association between the sarcomatoid component and outcome was studied with a Cox proportional hazards model to obtain an optimal cutoff for OS.