Outcome of Patients With Metastatic Sarcomatoid Renal Cell Carcinoma: Results From the International Metastatic Renal Cell Carcinoma Database Consortium

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Abstract

Outcome and prognosis of metastatic sarcomatoid renal cell carcinoma (sRCC) in the targeted therapy era are not well described. In this retrospective series of 230 patients with metastatic sRCC, we examined the role of anti–vascular endothelial growth factor (VEGF) agents as a treatment option. The validity of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model in patients with metastatic sRCC was confirmed. Sarcomatoid histology was found to be an independent factor for adverse prognosis.

Background: Sarcomatoid renal cell carcinoma is associated with poor prognosis. Data regarding outcome in the targeted therapy era are lacking. **Patients and Methods:** Clinical, prognostic, and treatment parameters in metastatic renal cell carcinoma patients with and without sarcomatoid histology treated with targeted therapy were retrospectively analyzed. **Results:** Two thousand two hundred eighty-six patients were identified (sRCC: n = 230 and non-sRCC: n = 2056). sRCC patients had significantly worse IMDC prognostic criteria compared with non-sRCC (11% vs. 19% favorable risk; 49% vs. 57% intermediate risk, and 40% vs. 24% poor risk; $P < .0001$). Time from original diagnosis to relapse (excluding synchronous metastatic disease) was shorter in the sRCC group (18.8 vs. 42.9 months; $P < .0001$). There was no significant difference in the incidence of central nervous system metastases (6%-8%) or underlying clear cell histology (87%-88%). More than 93% of patients received VEGF inhibitors as first-line therapy; objective response was less common in sRCC whereas primary refractory disease was more common (21% vs. 26% and 43% vs. 21%; $P < .0001$, for both). sRCC patients had significantly less use of second- ($P = .018$)

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and third-line ($P < .0001$) systemic therapy. The median progression-free survival (PFS)/overall survival (OS) was 4.5/10.4 months in sRCC patients and 7.8/22.5 months in non-sRCC patients ($P < .0001$ for both). Sarcomatoid histology was associated with a significantly worse PFS and OS after adjusting for individual IMDC risk factors in multivariable analysis (hazard ratio, 1.5; $P < .0001$ for both). **Conclusion:** Patients with sRCC have a shorter time to relapse, worse baseline prognostic criteria, and worse clinical outcome with targeted therapy. Additional insight into the biology of sRCC is needed to develop alternative therapeutics.

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Introduction

Renal cell carcinoma (RCC) is a histologically heterogeneous disease.[1] Clear cell carcinoma comprises the most common subtype (approximately 70%-80% of all cases) followed by other less common histologies such as papillary (10%-15%), chromophobe (3%-5%), medullary and unclassified (4%-6%).[2] Each histologic type arises from different parts of the nephron and possesses distinct genetic profiles, clinical characteristics, and prognosis.[2]

Sarcomatoid is a term used to describe morphologic changes within an RCC tumor similar to sarcomas—like elongated, spindle-shaped cells, high cellularity and cellular atypia, and can be recognized in association with every histologic type of RCC. According to the 2004 World Health Organization classification of renal tumors of adults,[2] RCCs with sarcomatoid differentiation are not considered a distinct subtype and they are classified according to the underlying histology; when no epithelial elements can be recognized, those tumors are categorized as unclassified.[3,4] Sarcomatoid differentiation is observed in approximately 5% to 10% of all RCC and it is believed to represent a clonal expansion of tumor cells with greater accumulation of genetic alterations and cellular dedifferentiation.[5-7] Clinically, tumors with sarcomatoid changes carry a poor prognosis with rapid tumor growth, high rates of metastasis at the time of diagnosis, poor response to historical treatment, and shorter overall survival (OS).[8-14]

This study was performed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). The aim of the current study was to identify patients with metastatic RCC with sarcomatoid differentiation (sRCC) and compare their clinical characteristics, prognostic factors, and targeted therapy treatment outcomes with patients with metastatic RCC without sarcomatoid features (non-sRCC). Additionally, the applicability of the IMDC prognostic model to patients with sRCC was investigated.

Patients and Methods

Study Population

The IMDC database includes cancer centers from Canada, the United States, South Korea, Japan, Denmark, Greece, and Singapore. Eighteen academic institutions that participate in the IMDC contributed consecutive series of patients with metastatic RCC treated with targeted therapy. Data were retrospectively collected from August 15, 2008, until January 28, 2013. At the time of the analysis, the database contained information about sarcomatoid histology for 2286 patients. Two hundred thirty patients were found to have tumors with sarcomatoid differentiation, whereas 2056 patients did not have sarcomatoid features identified. All centers obtained local institutional review board approval before collecting data for this large retrospective study. Baseline patient characteristics included demographic and clinicopathologic characteristics, and laboratory data as described in the development study of IMDC or Heng et al model.[15] Survival data were retrospectively collected from medical charts and electronic records. Standardized data collection templates were used to ensure consistent data collection across all study centers. Most patients in the study received standard-of-care treatment; a small proportion of patients received treatment in the context of a clinical trial.

Statistical Analyses

The primary end point of our study was to compare the overall response rate (ORR) to anti−vascular endothelial growth factor (VEGF) agents and the progression-free survival (PFS) and OS between metastatic RCC patients with and without sarcomatoid differentiation. PFS was measured in months and was defined as the time from initiation of treatment to documented disease progression according to investigator-assessed Response Evaluation Criteria in Solid Tumors 1.1 (RECIST),[16] treatment cessation, death, or censored at last follow-up. OS was measured in months and was defined as the time between initiation of treatment and death or censored at last follow-up. The secondary end point of this analysis was to confirm the validity of the IMDC (Heng et al)[15] prognostic model in patients with metastatic sRCC. The end points were compared using Kaplan−Meier curves. Proportional hazards regression was used to adjust censored outcomes to known predictors of poor OS according to the IMDC criteria: anemia, thrombocytosis, neutrophilia, hypercalcemia, time from diagnosis to treatment interval < 1 year, and Karnofsky Performance Status < 80%.

Results

Baseline Characteristics

The study cohort included 2286 patients with metastatic RCC (Table 1). Overall, 230 patients (10%) had sRCC and 2056 (90%) had non-sRCC. The mean age at diagnosis was 58 years in both groups ($P = .2617$) and most patients had underlying clear cell histology (88% vs. 87%; $P = .5372$). Patients with sRCC had a significantly worse IMDC prognostic score (11% vs. 19% favorable, 49% vs. 57% intermediate, and 40% vs. 24% poor; $P < .0001$) and significantly higher Furman nuclear grade (2% vs. 4% grade 1, 5% vs. 30% grade 2, 17% vs. 46% grade 3, and 21% vs. 76% grade 4; $P < .0001$) compared with their non-sRCC counterparts. Both groups included similar numbers of patients with > 1 site of metastatic disease (73% for both groups; $P = .9786$), and there was no