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Original contribution

Sarcomatoid features, necrosis, and grade are prognostic factors in metastatic clear cell renal cell carcinoma with vascular endothelial growth factor–targeted therapy☆,☆☆

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Summary Various clinical and laboratory parameters are used to determine the prognosis of patients with renal cell carcinoma (RCC), but the prognostic significance of histologic features has not been fully examined in patients with metastatic clear cell RCC receiving vascular endothelial growth factor (VEGF)/tyrosine kinase inhibitor (TKI; VEGF-TKI)–targeted therapy. To define prognostic clinicopathological factors, 83 such patients were retrospectively analyzed. Of these patients, 38 (45.8%) showed response to VEGF-TKI, whereas 45 (54.2%) were nonresponsive. Response to VEGF-TKI was associated with less than 10% sarcomatoid features and less than 10% tumor necrosis. Multivariate analysis showed that tumor necrosis was independently prognostic of VEGF-TKI response. During a median follow-up of 18 months (range, 1-62 months), 54 patients (65.1%) showed disease progression and 44 (53.0%) died. Shorter progression-free survival and overall survival (OS) were associated with a period less than 1 year from initial diagnosis to VEGF-TKI initiation, high Fuhrman grade, at least 10% sarcomatoid features, and at least 10% tumor necrosis. In addition, thrombocytosis was associated with shorter OS. Multivariate analysis showed that sarcomatoid features was independently prognostic of progression-free survival, whereas time from initial diagnosis to VEGF-TKI initiation and sarcomatoid

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features were independent prognostic factors of OS. In summary, sarcomatoid features, tumor necrosis, and tumor grade are histologic prognostic factors and should be considered in determining whether to initiate targeted treatment in patients with metastatic clear cell RCC.

1. Introduction

Metastatic renal cell carcinoma (RCC) is resistant to conventional anticancer treatment regimens. However, the recent development of drugs that target vascular endothelial growth factor (VEGF) signaling pathways has revolutionized the management of metastatic RCC, and these drugs are recommended as a first-line treatment option in patients with this disease [1]. Small molecule tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, pazopanib, and axitinib inhibit VEGF-signaling pathways by binding to vascular VEGF receptors and platelet-derived growth factor receptors.

A major challenge in the treatment for patients with metastatic RCC is the selection of patients who may benefit from targeted therapy. These drugs are effective in a limited number of patients, with the highest objective response rate observed, to date, being 45% [2]. These drugs are generally unable to induce durable complete responses, making long-term treatment necessary and imposing a considerable economic burden on patients [2]. Although generally less toxic than conventional chemotherapeutic and immunotherapeutic drugs, these TKIs have a toxicity profile that includes fatigue, mucositis, hand-foot skin reaction, diarrhea, hypothyroidism, and hypertension [3]. Therefore, identifying prognostic factors prior to initiating targeted therapy may help predict treatment response to anti-VEGF drugs and help select those patients who may benefit from these agents.

Various clinical and laboratory parameters have been suggested from previous studies and are being used as prognostic factors. Reduced overall survival (OS) is associated with anemia, hypercalcemia, neutrophilia, thrombocytosis, low Karnofsky performance status, and short time (<1 year) from diagnosis to treatment [4,5]. However, histologic features of RCC have not been fully appreciated as prognostic factors partly because central pathology review was not available in the previous studies [4,5]. This study was therefore designed to identify clinicopathological factors, especially histologic features, prognostic of response to TKIs and survival in patients with metastatic clear cell RCC.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the Asan Medical Center Institutional Review Board (2012-0788). The initial cohort consisted of 194 patients with metastatic RCC who were treated with first-line TKI at Asan Medical Center from June 2006 to March 2011. Because most patients had clear cell subtype, only those patients were included. Sixteen patients with non–clear cell subtype, including 8 with papillary RCC, 4 with unclassified RCC, and 1 each with chromophobe RCC, collecting duct carcinoma, medullary carcinoma, and thyroid follicular carcinoma-like carcinoma, were excluded, as were 5 patients without tissue confirmation prior to TKI therapy. In addition, 90 patients whose RCC specimens were nonnephrectomy were excluded (40, needle biopsy of a kidney mass; 31, metastatic tumor biopsy; 19, metastatectomy). Therefore, 83 patients with clear cell RCC diagnosed on radical (78) or partial (5) nephrectomy specimens were included in the final analysis.

Patients' clinical information was obtained from electronic medical records and/or hospital charts. Tumor response was assessed according to the Revised Response Evaluation Criteria in Solid Tumors guideline (version 1.1) [6]. Patients with complete or partial response were considered responders, whereas those with stable or progressive disease were considered nonresponders.

2.2. Sampling of renal tumors

During the gross examinations, at least 1 section of tumor was sampled for every 1 cm of its greatest diameter. Additional sampling was done in areas other than the golden yellow color of clear cell RCC. The average slide number of the tumor sections was 7.1 (median, 6; range, 1-18).

2.3. Pathology review

All available pathologic materials from each patient were reviewed for diagnostic reassessment and histologic subtyping according to the 2004 World Health Organization Tumor Classification [7]. Each tumor was graded according to the Fuhrman grading system [8,9].

The sarcomatoid features were subclassified into spindle, rhabdoid, and other types. Microscopic coagulative tumor necrosis was evaluated in each patient. The extent of sarcomatoid features and the extent of tumor necrosis were estimated semiquantitatively by the naked eye and recorded as percentages relative to each tumor. Tumor-associated inflammatory reactions were assessed as absent, mild, moderate, and severe. Patients with absent to mild inflammation were categorized as the low inflammation group, whereas those with moderate to severe inflammation were categorized as the high inflammation group (Supplementary Fig. 1A and B).