Sunitinib for Patients with Metastatic Non-clear Cell Renal Cell Carcinoma: A Multicenter Retrospective Turkish Oncology Group Trial

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Abstract. Aim: This study aimed to assess the clinical efficacy and toxicity of sunitinib, a targeted-agent, for non-clear cell renal cell carcinoma. Patients and Methods: Sixty-three patients with complete clinical data from 13 oncology Centers were retrospectively evaluated. Outcomes analyzed were objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and adverse events. Results: The median age of all patients, 38 men (60.3%) and 25 women (39.7%), was 63 years (range=25-82 years). Histological subtypes included 46 (88%) cases of papillary RCC, 10 of chromophobe, and 7 unclassified cases. Median treatment duration was seven months (range=2-86 months). At the time of this analysis, 52 patients had discontinued treatment, 33 of whom had died. Treatment discontinuation was due to disease progression in 43 patients, and toxicity in nine. Dose interruption was necessary in 22 (34.9%) patients, and dose reduction in 27 (42.9%). The objective response rate and disease control rate were 11.1% and 63.5%, respectively. The median PFS and OS were 7.6 months (95% confidence interval (CI)=5.5-9.7 months) and 22.0 months (95% CI=13.4-30.6 months), respectively, with 1-year rates of 64.7% and 33.7%, respectively. Conclusion: Clinical outcome of the metastatic non-clear cell RCC patients with sunitinib treatment seemed to be worse than the historical data of clear cell RCC patients, in terms of PFS, OS and objective response. New and more effective targeted-therapies and better understanding of the underlying molecular processes are necessary to improve survival outcome for these patients.

Renal cell carcinoma (RCC) is distinguished into several distinct subtypes (1), including clear (conventional), papillary (types 1 and 2), chromophobe, collecting duct, medullary, and unclassified type (2). These subtypes differ in pathogenetic mechanism, histological appearance, and clinical course. Clear cell RCC is the predominant subtype, accounting for 75% of all renal epithelial tumors. All other histological subtypes are collectively identified as non-clear cell RCC. Except for collecting duct carcinoma, which is sensitive to platinum-based chemotherapy, metastatic non-clear cell RCC is resistant to both immunotherapy and cytotoxic chemotherapy, resulting in poor patient prognosis (3).
In the past decade, targeted therapies that block angiogenic activity mediated by the vascular endothelial growth factor (VEGF) signaling pathway (sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab) or by the mammalian target of rapamycin (mTOR) signaling pathway (temsirolimus and everolimus) have shown profound effects on the clinical outcome of patients with advanced RCC (4, 5). However, due to the relatively high prevalence of clear cell RCC, clinical trials for targeted-agents have typically focused on this patient population while frequently excluding those with non-clear cell histology. The optimal treatment for patients with non-clear cell RCC, including the role of targeted therapy, thus remains uncertain and is under investigation (4). To date, the phase III trial for temsirolimus with non-clear cell RCC accounting for 20% of its study cohort, is the largest investigated targeted agents in such patients (6).

Non-clear cell RCC consists of multiple histological subtypes, each with a distinct molecular profile. Although VEGF and mTOR inhibitors are commonly used in the management of these patients, a histological diagnosis of non-clear cell type does not appear to be related to the von Hippel-Lindau gene. However, VEGF receptors and their ligands are overexpressed in papillary RCC and chromophobe RCC (7, 8). In addition, overexpression of KIT (CD117), a kinase effectively inhibited by sunitinib, has been observed in chromophobe RCC (9). Furthermore, activating mutations of mesenchymal-epithelial transition factor (c-MET) have been observed in RCC of hereditary papillary type 1, whereas inactivating mutations of fumarate hydratase have been reported in RCC of hereditary papillary type 2 (5, 10). To date, however, the significance of these pathogenetic pathways has not been validated in sporadic non-clear cell RCC.

Sunitinib, one of the first tyrosine kinase inhibitors to emerge for the treatment of RCC, is currently standard first-line therapy for the disease. Retrospective studies, phase II trials, and expanded access data suggest that sunitinib might also exert efficacy in patients with non-clear cell RCC (11-13). In the present work, we therefore evaluated the efficacy and safety of sunitinib in Turkish patients with metastatic non-clear cell RCC.

Patients and Methods

Patients. Clinical data of 63 patients from 13 oncology Centers were retrospectively analyzed. Clinicopathological characteristics such as age, sex, RCC histological subtype, Eastern Cooperative Oncology Group performance status (ECOG PS), prior treatments, metastatic sites, laboratory findings, and patient survival were recorded. The inclusion criteria were proper bone marrow function (white blood cell count $\geq 3,000/\text{mm}^3$, hemoglobin $\geq 9$ g/dl, and platelet count $\geq 100,000/\text{mm}^3$) and proper liver function (total bilirubin $\leq 1.5$ mg/dl with alanine and aspartate transaminase levels no greater than twice the upper limit of normal). Patients were included if they were diagnosed with the non-clear cell histological subtype and had received no prior anti-VEGF treatments. However, patients with ECOG PS of 4 and those with severe concomitant medical illnesses were excluded.

Baseline evaluation. The pre-treatment assessment included a medical history, a physical examination with ECOG PS evaluation, cardiac function testing with electrocardiography and echocardiography, and laboratory examinations such as complete blood count and serum biochemistry. Computed tomography (CT), magnetic resonance imaging (MRI), or positron-emission tomography was performed when indicated. Each patient was classified according to the Memorial Sloan-Kettering Cancer Center risk scoring system (14).

Treatment, toxicity, and response evaluation. Sunitinib was administered orally at a continuous daily dose of 37.5 mg or an intermittent dose of 50 mg. Treatment cycles of 28 days in duration each were repeated every four weeks on an outpatient basis unless disease progression or severe toxicity was observed.

Hematological and non-hematological toxic effects were graded according to the Common Terminology Criteria for Adverse Events version 3.0 (15). Toxicity evaluations were conducted on days 1, 14, and 28 of the first treatment cycle and on days 1 and 28 of each subsequent cycle. A dose reduction of sunitinib to 25 mg was allowed depending on the type and severity of the observed adverse event. If grade 3 hematological toxicity was recorded, treatment was withheld until either recovery to grade 2 or less, or the blood counts returned to baseline, after which sunitinib treatment was resumed at the original dose. In the case of grade 4 hematological or grade 3 or 4 non-hematological toxicity, treatment was withheld until recovery to grade 2 or 1, respectively. The sunitinib dose was then reduced from 37.5 to 25 mg daily. When grade 4 hematological or grade 3 or 4 non-hematological toxicity recurred despite such a dose reduction, treatment was usually discontinued, and the affected patients were treated with inhibitors of either tyrosine kinase or mTOR.

All patients underwent physical examinations, complete blood cell counts, and serum biochemistry tests on the first day of every treatment cycle. Complete blood cell counts were also performed on day 14 of the first cycle. A CT or MRI was performed at baseline and every three treatment cycles to assess clinical response according to the Response Evaluation Criteria in Solid Tumors version 1.0 (16). Treatment was discontinued in patients with disease progression and in those experiencing severe toxicity even after sufficient dose reduction.

Statistical analysis. Quantitative data are presented as means, standard errors, medians, minimums, and maximums as appropriate, whereas the results of qualitative analyses are presented as frequencies and percentages. Overall survival (OS) was calculated from the date of the first sunitinib dose to that of death, the final follow-up visit, or the end of this study as appropriate. Progression-free survival (PFS) was calculated from the date of the first sunitinib dose to that of death of any cause or disease progression. Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used for their comparison. All statistical tests were two-sided, and $p$-values of $<0.05$ were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical features. The clinical characteristics of all participating patients are listed in Table I. The median age was 63 years (range, 25–82 years), and the sample comprised of 38 men (60.3%) and 25 women (39.7%). Forty-six (73%)
patients were diagnosed with papillary RCC, whereas the others were diagnosed with chromophobe (n=10) or were unclassified (n=7) RCC. Approximately half of the patients had an ECOG PS of 1. Most patients (89%) had undergone nephrectomy. Metastasectomy, including that of the lungs and retroperitoneal areas, had been performed in five patients (7.9%).

Adherence to treatment. Twenty-four (38.1%) patients received sunitinib as first-line systemic treatment. The median treatment duration was seven months (range=2-86 months), and treatment was on-going for 11 patients (19%). At the time of this analysis, treatment had been discontinued in 52 patients, 33 of whom had died. The reasons for treatment withdrawal were disease progression in 43 patients (68.3%) and toxicity in nine (14.3%).

Response rates. Patients were evaluated for their response to treatment (Table II). Out of the 63 patients with measurable lesions, seven (11.1%) achieved a confirmed partial response; 33 (52.4%) had stable disease, and 23 (36.5%) experienced progressive disease. The disease control rate (including complete response, partial response, and stable disease) was 63.5%.

Survival analysis. The median follow-up duration was 21 months (range=2-78 months). At the time of the analysis, 52 patients had discontinued treatment, 33 (52.4%) of whom had died. The median PFS was 7.6 months [95% confidence interval (CI)=5.5-9.7 months] (Figure 1), and the median OS was 22 months (95% CI=13.4-30.6 months) (Figure 2). The OS rate was 64.7% (95% CI=52.9-76.5%) at one year, 47.0% (95% CI=31.2-62.7%) at two years, and 23.5% at three years (95% CI=7.8-39.2%). The 1-year PFS rate was 33.7% (95% CI=20.0-47.4%).

Adverse effects. The toxicity profiles of all 63 patients are summarized in Table III. Twenty-two patients (34.9%) experienced dose interruptions, and 27 (42.9%) required dose reductions. The most frequently reported hematological toxicities were anemia, thrombocytopenia, and leukopenia (Table III). In particular, grade 3 or 4 anemia occurred in 22% of the patients. The most frequent non-hematological adverse events of grade 1 or 2 were fatigue, stomatitis, anorexia, hypertension, hypothyroidism, dyspepsia, nausea, hand–foot syndrome, and diarrhea (Table III), whereas the most frequent grade 3-4 adverse events were fatigue, hypertension, and hand–foot syndrome.

Twenty-three patients with bone metastases and 11 with brain metastases received radiotherapy while undergoing
sunitinib treatment. No grade 3 or 4 hematological or non-hematological toxicity occurred during radiotherapy.

Discussion

In the present analysis, we assessed the efficacy of sunitinib treatment in patients with advanced non-clear cell RCC. Our results on median PFS (7.6 months), OS (22 months), and disease control rate (63.5%) were comparable to those previously reported (11-13, 17). However, compared to the findings of previous studies on anti-VEGF-based treatments for clear cell RCC (18, 19), our survival results and objective response rates seem inferior. Additionally, when we compared our survival results with the outcome of a similar study including mostly patients with clear cell RCC, we found that the benefit of sunitinib was also inferior in patients with non-clear cell RCC (20).

The histological diversity of non-clear cell RCC presents unique challenges. Except for collecting duct carcinoma, which shows some sensitivity to cisplatin-based cytotoxic chemotherapy, non-clear cell RCCs have been considered to be resistant to immunotherapy and cytotoxic chemotherapy. Patients with metastatic non-clear cell RCC often have a worse response to immunotherapies than those with clear cell RCC (3). Motzer et al. reported a median OS of 9.4 months in a cohort of patients with non-clear cell RCC treated with several types of cytokines (21).

The introduction of therapeutic agents targeting the VEGF and mTOR pathways to clinical practice has revolutionized the treatment of metastatic RCC. However, despite recent advances, there remains a lack of effective systemic options directly applicable to advanced and metastatic non-clear cell RCC. While targeted-agents mark a major advance in the treatment of clear cell RCC, nearly every trial in which they were tested excluded other RCC subtypes, providing clinicians and their patients little guidance when selecting a systemic treatment for non-clear cell RCC. Fortunately, the same methodology of studying the genetic and molecular characteristics of hereditary and sporadic non-clear cell RCC tumors, which account for approximately 20-25% of all patients with RCC, has identified promising novel pathways that are amenable to targeted therapy.

Research on the molecular characteristics of RCC has identified different gene expression patterns associated with various histological and macroscopic morphological profiles of the many sub-groups of this tumor type, most of which are regularly combined under the generic term ‘non-clear cell RCC’. Given these differences, it would be unreasonable to assume a similar efficacy and safety profile for clear cell and non-clear cell RCC treated with targeted agents. Nonetheless, the available data suggest that targeted agents currently approved for clear cell RCC are active to a certain degree in non-clear cell RCC. Temsirolimus has demonstrated therapeutic advantages over interferon-α in patients with non-clear cell RCC.
non-clear cell RCC according to data from a phase III study (6), and expanded-access studies (12) for everolimus, sunitinib, and sorafenib have all confirmed the activity of these agents in non-clear cell RCC (10).

Furthermore, the expanded access program of sunitinib in RCC also provided evidence for its potential efficacy in non-clear cell RCC. Out of 437 patients with non-clear cell RCC treated with sunitinib, the overall response rate was 11%, with an additional 57% of the patients having stable disease and a median PFS of 7.8 months (12). A retrospective review of 20 patients with metastatic papillary or chromophobe RCC showed that sunitinib prolonged their PFS (11.9 months), although the response rate was generally low (13%) (11). Data from several prospective phase II studies on sunitinib in advanced non-clear cell RCC have been presented or published. For the most part, there was a low response rate to sunitinib (0-7%), although most patients typically experienced stable disease (52-73%) (22, 23). In contrast, a Korean phase II study on sunitinib in patients with non-clear cell RCC reported a 36% overall response rate, including eight cases of partial response among 22 patients with papillary RCC, and a median PFS of 6.4 months (95% CI=4.2-8.6 months) (13). The median OS was not available, but the 1-year survival rate was 65%. These conflicting data suggest that ethnic differences may explain the variable responses to sunitinib in non-clear cell RCC.

Most pivotal phase III trials for molecular-targeted agents in patients with metastatic RCC have excluded those with non-clear cell disease. The only exception was a trial for temsirolimus. A subset analysis showed that temsirolimus significantly enhanced the OS in patients with non-clear cell RCC (hazard ratio=0.55; 95% CI=0.33-0.90) (6). In addition, the results of a phase II trial for foretinib, a dual inhibitor of c-MET and VEGF, may provide further information and open new avenues for papillary RCC treatment (n=74). The overall response rate was 13.5%, the median PFS was 9.3 months, and the median OS was not reached. The presence of a germline MET mutation was highly predictive of a response (5/10 vs. 5/57 patients with and without germline MET mutations, respectively) (17).

The toxicity and safety profile of our study was found to be similar to our recent trial including mostly patients with clear cell RCC in the same population (20). The most common grade 3-4 hematological toxicity was anemia, whereas frequent non-hematological toxicities included fatigue, hypertension, hypothyroidism, and hand–foot syndrome. In addition, it was possible to perform radiotherapy for bone or brain metastases safely without the need to discontinue or interrupt sunitinib treatment in the present study.

In summary, non-clear cell histology represents an uncommon and heterogeneous group of RCC for which effective treatments have not yet been established. Sunitinib was generally well tolerated in Turkish patients with metastatic RCC and demonstrated promising activity in those with non-clear cell RCC. In future trials for novel agents for non-clear cell RCC, in-depth characterization of the molecular features underlying these subtypes could help identify rational therapeutic strategies targeting relevant pathways.

### Conflicts of Interest

The Authors have no conflicts of interest that are directly relevant to the content of this study.

### Funding

This study received no financial support.

### Acknowledgements

We thank all the patients and their families for participating in this study. We also thank the investigators and their staff from all participating sites.
References