

RESEARCH ARTICLE

Prognostic and Predictive Value of Hematologic Parameters in Patients with Metastatic Renal Cell Carcinoma: Second Line Sunitinib Treatment Following IFN-alpha

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Abstract

Background: Long-term survival is a problem with locally advanced and metastatic renal cell carcinomas. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor, but data on sunitinib use as a second line treatment in metastatic renal cell carcinoma (mRCC) are limited. Prognostic and predictive value of peripheral blood markers has been shown for many cancers. **Materials and Methods:** Efficacy and safety profiles of sunitinib after interferon alpha (IFN- α) were evaluated based on retrospective data for 23 patients with mRCC. Hematological parameters (neutrophils, lymphocytes, platelets, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio) were recorded at the time of metastasis. It was evaluated whether hematological parameters were prognostic and predictive factors. **Results:** Median progression-free survival (PFS) time was 16.5 months (95% CI: 0-34.5). Median overall survival (OS) time was 25.7 months (95% CI: 10.8-40.0). Most common side effects were neutropenia (52.2%), stomatitis (26.1%) and hand-food syndrome (26.1%). PFS was found 3.13 vs 17.1 months in patients with neutrophil / lymphocyte ratio (NLR)>3 vs NLR \leq 3 (p:0.012). Median OS was 6.96 vs 27.1 months in patients with NLR>3 vs NLR \leq 3 (p:0.001). While 75% of patients who responded to sunitinib had NLR \leq 3, in 72% of patients with no response to sunitinib NLR>3 was detected (p:0.036). The association between the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria and NLR was statistically significant (p:0.022). **Conclusions:** Data on second line sunitinib treatment following cytokine in mRCC are limited. In our study, we observed second line sunitinib treatment following IFN- α to be effective and tolerable. NLR appeared to have prognostic and predictive value.

Keywords: Metastatic renal cell carcinoma - sunitinib - hematologic parameters

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Introduction

Surgery may be curative in local RCC. However most of the patients have recurrence after surgery. No long-term survival can be achieved in locally advanced and metastatic renal cell carcinoma and prognosis in these patients is poor. It is reported that 5 year survival in Stage IV RCC is 8% (AJCC, 2010). Surgical removal of primary tumor in mRCC has impact on metastatic focus suggesting that immune mechanism play a role in disease pathogenesis (Vogelzang et al., 1992; Gleave et al., 1998).

With RCCs, interleukin-2 and IFN- α have been used for immunotherapy. Molecular targeted treatment has been applied after the molecular pathogenesis of the disease has been clarified. Sunitinib, oral VEGF receptor tyrosine kinase inhibitor is one of the targeted treatments in RCC.

Efficacy of sunitinib in mRCC has been proved in Phase II and Phase III studies and it is used as first line treatment (Mekhail et al., 2005; Motzer et al., 2006; 2007; 2009). Data on second line sunitinib treatment in mRCC are, however, limited.

Many factors (TNM stage, histopathology, clinical factors) affect the prognosis in patients with RCC (Motzer et al., 2005; Patard et al., 2005; Kidney, 2009). Recently, prognostic value of peripheral blood markers has been shown in many cancers (Ohno et al., 2010; Keizman et al., 2011). In the present study, we therefore aimed to evaluate the efficacy and safety profiles of second line sunitinib treatment using retrospective data and in addition to clarify the prognostic/predictive value of different peripheral blood parameters in association with the treatment efficacy.

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Materials and Methods

Patients

Data obtained from 23 mRCC patients admitted to the outpatient clinic of Izmir Atatürk Training and Research Hospital Medical Oncology between May 2006 and March 2011 were evaluated retrospectively. All patients had histologically confirmed RCC and at least one measurable metastatic lesion. Eastern Cooperative Oncology Group (ECOG) performance status was between 0 and 2. Pre-treatment evaluation included a complete medical history, physical examination, complete blood cell counts, serum biochemistry, thyroid function tests, urine analysis and abdominal and thoracic CT to evaluate the target lesions. If necessary, target lesions were evaluated by Positron Emission Tomography–Computed Tomography. Bone metastases were evaluated by magnetic resonance imaging and/or bone scintigraphy. Five risk factors determined as indicator of poor prognosis by MSKCC were also evaluated: low Karnofsky performance status (<80%), high lactate dehydrogenase levels (1.5 times ULN), low hemoglobin levels (<10 mg/dl), high corrected serum calcium levels (>10 g/dL) and <1 year of time between RCC diagnosis and initiation of IFN α . Risk groups were determined as favorable, intermediate and poor according to the having risk factors 0, 1-2 or ≥ 3 , respectively (Motzer et al., 2004).

Treatment plan

All patients had received IFN- α therapy until progression or intolerance before sunitinib treatment. Sunitinib 50 mg per day was administered in repeated 6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off. Dose reduction for toxicity was allowed to 37.5 mg/d and then to 25 mg/d, according to a nomogram for grade 3-4 severity. Sunitinib treatment had been continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were evaluated for hematological and nonhematological toxicities and were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria.

Response evaluation

Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST) as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) (Eisenhauer et al., 2009; Therasse et al., 2009).

Hematologic parameters

Hematological parameters (leukocyte, neutrophil, lymphocyte, thrombocyte, MPV) obtained at the time of metastases were recorded. Patients with blood transfusion, active bleeding, infection, connective tissue disease, steroid treatment, heparin anticoagulant therapy during the previous three-month period of hematologic evaluation were excluded. Complete blood count was performed with impedance-based analyzer (CELL-DYN 3700, Abbott, USA).

Neutrophil /Lymphocyte Ratio (NLR)

Before treatment NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. This calculated value was divided into two groups as ≤ 3 and >3 (Keizman et al., 2011).

Platelet/Lymphocyte Ratio (PLR)

Before treatment PLR was calculated as platelet count divided by lymphocyte count. The calculated value was divided into two groups as <160 and ≥ 160 (Smith et al., 2008; Aliustaoglu et al., 2010).

Mean Platelet Volume (MPV)

Mean MPV value in the adult Turkish population has been determined as 8.9 fl (Demirin et al., 2011). However, there is no definite value for this. In our study, MPV values of our patients were divided as <8.9 and ≥ 8.9 .

Other parameters

Lymphocyte counts were divided as $<1.500/\text{mm}^3$ and $\geq 1.500/\text{mm}^3$ and platelet counts as <400.000 and $\geq 300.000/\text{mm}^3$ (Rodriguez et al., 1994; Shimada et al., 2004; Yamanaka et al., 2007).

Statistics

PFS and OS were calculated by Kaplan-Meier method. SPSS (Statistical Package for Social Sciences, v.15.0) was used for the statistical analysis. Associations between survival and potential prognostic factors were assessed by using the log-rank test. Associations between the baseline clinical features/hematologic parameters and treatment response; MSKCC groups and hematological parameters were assessed by 2-tailed Fisher exact or Pearson Chi-square according to the sample size.

Results

Patient characteristics

Data obtained from 23 mRCC patients admitted to the outpatient clinic of Izmir Atatürk Training and Research Hospital Medical Oncology between May 2006 and March 2011 were evaluated retrospectively. 73.9% of the sample was male. Median age was 59 (range 43-76). ECOG performance status was between 0 and 2. 76.2% and 23.8% of patients had clear cell and non-clear cell histology, respectively. All patients had at least one metastatic lesion. Three patients (13%) had metastasis during the diagnosis. Distribution of metastatic lesions were lung (n:14; 60.9%), bone (n:5; 21.7%), abdominal lymph nodes (n:8; 34.8%), liver (n:1; 4.3%), brain (n:1; 4.3%) and other (n:2; 8.7%). Rate of having one, two or ≥ 3 metastatic lesions were 69.6% (n:16), 21.7% (n:5) and 8.7% (n:2), respectively. Table 1 presents a summary of patient characteristics. Favorable, intermediate and poor risk groups had 9 (39.1%), 10 (43.5%) and 4 (17.4%) patients, respectively.

Treatment and adverse events

All patients underwent nephrectomy. In addition, all patients had received subcutaneous IFN- α therapy prior to the treatment with sunitinib. The median duration of sunitinib treatment was 6.43 months (range 0.1-19,

Table 1. Patient Characteristics

		No. (%)
No. of patients		23
Median age (range)		59 (43-76)
Sex	Male	17 (73.9)
	Female	6 (26.1)
Histological type	Clear cell	18 (78.2)
	Non-clear cell	5 (21.8)
Localization of metastasis	Lung	14 (60.9)
	Liver	1 (4.3)
	Brain	1 (4.3)
	Bone	5 (21.7)
	Lymph nodes (intraabdominal)	8 (34.8)
	Other	2 (8.7)
Number site of metastasis	1	16 (69.6)
	2	5 (21.7)
	≥3	2 (8.7)
MSKCC	Favorable	9 (39.1)
	Intermediate	10 (43.5)
	Poor	4 (17.4)

Table 2. Treatment Related Toxicity

Toxicity	Grade 1-2		Grade 3-4		Total	
	No	%	No	%	No	%
Hematology						
Neutropenia	12	52.2	0	0	12	52.2
Anemia	4	17.4	0	0	4	17.4
Thrombocytopenia	4	17.4	4	17.4	8	34.8
Nonhematologic						
Stomatitis	4	17.4	2	8.7	6	26.1
Diarrhea	1	4.3	2	8.7	3	13.0
Vomiting	2	8.7	0	0	2	8.7
Nausea	4	17.4	0	0	4	17.4
Fatigue	3	13.0	2	8.7	5	21.7
Hand-foot syndrome	4	17.4	2	8.7	6	26.1
Hypothyroidism	3	13.0	0	0	3	13.0
Hypertension	1	4.3	0	0	1	4.3
Epistaxis	4	17.4	0	0	4	17.4

Table 3. Clinical Response Rates

Clinical Response (no:)	no (%)
CR	1 (4.3)
PR	7 (30.4)
SD	8 (34.8)
PD	7 (30.4)

*CR: Complete Response; PR: Partial Response, SD: Stable disease, PD: Progressive disease

6), respectively. In fourteen (60.8%) patients sunitinib treatment was interrupted due to the progressive disease. Third line molecular target treatment was administered in eight patients. In one patient sunitinib treatment was interrupted due to the adverse effect. Dose reduction was applied in 12 patients (57.1%) because of side effects related to sunitinib. Dose decreased to 25 mg and 37.5 mg in five patients (21.7%) and seven patients (30.4%), respectively. Dose decreased in two patients because of grade 3-4 hand-foot syndrome; two patients had grade 3-4 diarrhea, two patients had grade 3-4 stomatitis; four patients had grade 3-4 thrombocytopenia; two patients had grade 3-4 fatigue.

All side effects related to sunitinib treatment are summarized in Table 2.

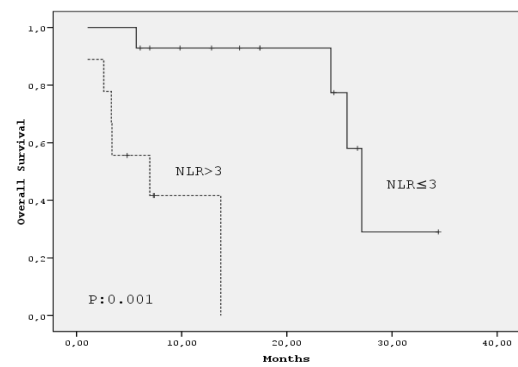


Figure 1. Kaplan-meier Estimates of Overall Survival. NLR≤3 and NLR>3

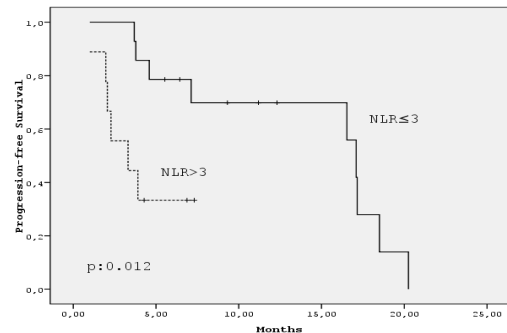


Figure 2. Kaplan-Meier Estimates of Progression-free Survival. NLR≤3 and NLR>3

Response evaluations

For sunitinib treatment: Overall response rate (ORR) was 34.8% (7 Partial Response, 1 Complete Response). Clinical response rates were presented in Table 3. Of five patients with non-clear cell histology; SD, PR and PD were found in 1, 3 and 1 patients, respectively.

Survival analysis

Median follow-up was 13.43 months (range 1.97-40.91). Median PFS time was 16.53 months (95%CI, 1-34.5 months). Median OS time was 25.71 months (95%CI, 10.82-40.01 months). At the time of data record, 10 (43.5%) patients were dead. Median OS was 2.5, 6.9 and 27.1 months in poor (17.4%), intermediate (43.5%) and favorable (39.1%) risk groups, respectively. The difference between the three groups was statistically significant (log rank, p<0.001). Median OS in patients with or without bone metastases was 3.37 (95%CI: 3.24-3.50 months) and 27.12 months (95%CI, 24.99-29.25 months), respectively. Patients with bone metastasis had received palliative radiotherapy and zoledronic acid treatment based on creatinine clearance. The median OS was significantly different between the two groups (log rank, p=0.001). Between the other metastatic lesions there was no difference in terms of survival.

Hematologic parameters

Median OS was 27.12 vs 6.96 months in patients with NLR ≤ 3 (14; 60.9%) vs NLR > 3 (9; 39.1%) (log rank; p:0.001, Figure 1). Median PFS was 17.09 vs 3.13 months in patients with NLR ≤ 3 vs NLR > 3 (log rank; p:0.012, Figure 2). Median OS was 6.9 vs 27.1 months in patients with lymphocyte counts <1500/mm³ (6; 26.1%) vs lymphocyte counts ≥1500/mm³ (17; 73.9%) (log rank;

$p=0.035$). No survival difference was found for other hematologic parameters. In favorable risk group (n:9) 7 patients had $NLR \leq 3$ and 2 patients had $NLR > 3$; in intermediate risk group (n:10) 7 patients had $NLR \leq 3$ and 3 patients had $NLR > 3$; in poor risk group (n:4) all patients had $NLR > 3$ ($p:0.022$). In patients responded sunitinib treatment (PR,SD,CR) (n:16), 12 patients had $NLR \leq 3$ (75%) and 4 patients had $NLR > 3$ (25%); in patients with (progressive disease (n:7) 2 patients had $NLR \leq 3$ (28%) and 5 patients had $NLR > 3$ (72%) ($p:0.036$). 4 of 5 patients with bone metastasis (80%) had $NLR \leq 3$ ($p:0.05$).

Discussion

Approximately 65-75% of RCC cases are the clear cell carcinoma. The loss of heterozygosity of the von Hippel-Lindau (VHL) gene located on chromosome 3p25 was observed in 75-80% of clear cell renal carcinomas. This especially causes overproduction of vascular endothelial growth factor (VEGF) (Latif et al., 1993; Maxwell et al., 2001; Barry et al., 2004; Kim et al., 2004; Sufan et al., 2004). VEGF is an important growth factor in tumor angiogenesis and has an important role in tumor growth and spread.

Based on these mechanisms, small molecule tyrosine kinase (TK) inhibitors (sunitinib, sorafenib, pazopanib) interrupting VEGF pathway by blocking intracellular domain of VEGF receptor have been used in patients with RCC. Most of the studies were conducted in patients with clear cell histology. Data for the other histological forms are limited. In two phase II studies conducted in cytokine resistant patients receiving second line sunitinib treatment, Motzer et al. (2006) reported tumor response rates as follows: PR 34-40%, SD 27-29% PD 33-37% and CR 0-1% (Motzer et al., 2006). The same authors reported tumor response rates as PR 36-44%, SD 40-47%, PD 7-16%, CR<1-3% in two phase III study of patients treated with sunitinib as first line treatment (Motzer et al., 2007; 2009). In our study, tumor response rates were as follows: PR 30.4%, SD 34.8%, PD 30.4% and CR 4.3%. These results were consistent with the phase II studies of Motzer et al. (2006) mentioned above. In comparison with the phase III studies of the same authors PD was higher in our study (30.4% vs 7-16%). However, other tumor response rates were similar. PD rates were also higher in phase II studies than in phase III studies mentioned above. In our study and the phase II studies, sunitinib was used as second line in cytokine resistant patients. In these two phase II studies PFS and OS were reported as 8.7-8.3 m. and 16.4 ay -79% (OS has not been reached), respectively. Motzer et al. (2007) reported PFS as 11 month and OS 26.4 month -87% (OS has not been reached) in two phase III studies (Motzer et al., 2007). In our studies PFS and OS were 16.5 month and 25.7 month. OS in our study is consistent with the OS found in phase III studies but better than in phase II studies. This result may be explained by the third line treatment that we offered to eight patients.

In our study, grade 3-4 hematological toxicity of sunitinib therapy was only thrombocytopenia (17.4%). Grade 1-2 hematologic toxicity included neutropenia (52.2%; 12), anemia (17.4%; 4) and thrombocytopenia

(17.4%; 4). Motzer et al. (2007) reported Grade 1-2 hematologic toxicity as neutropenia (26-32%), anemia (20-27%) and thrombocytopenia (15-18%); Grade 3-4 hematologic toxicity as neutropenia (12-16%), anemia (4-10%) and thrombocytopenia (6-8%) in their phase II-III studies (Motzer et al., 2007). Incidence of Grade 1-2 neutropenia was higher and incidence of grade 3-4 neutropenia and anemia were lower in our study. Grade 3-4 non-hematologic side effects in our study were stomatitis, diarrhea, fatigue, hand-foot syndrome with the incidence each of 8.7% (n:2). Non-hematologic adverse reactions reported in our study were consistent with the literature. RCC prognostic and predictive factors developed a lot of patients receiving therapy.

Many prognostic and predictive factors have been developed in RCC patients receiving cytokine and targeted therapy. These factors include MSKCC criteria, corrected calcium values, number of metastatic sites (one or more than one), thrombocytosis, LDH level, presence of liver metastases and bone metastases (Motzer et al., 1999; 2008; Therasse et al., 2000; Mekhail et al., 2005; Heng et al., 2009; Patil et al., 2009; Sahi et al., 2010; Sahi et al., 2010). In our study, prognostic value of MSKCC criteria have been showed (log rank; $p<0.001$). Furthermore, bone metastasis has been determined as an indicator for poor prognosis (median OS 3.37 m vs 27.12 m; log rank; $p:0.001$). Recently, a number of studies in which the prognostic value of peripheral blood markers was shown in many cancers were conducted. In RCC, it has been showed that especially neutrophilia, thrombocytosis and NLR rates may be prognostic and predictive (Heng et al., 2009; Ohno et al., 2010; Keizman et al., 2011). In other study, PFS and OS were reported as 4 month vs 15 month and 14 month vs 29 month in patients with $NLR > 3$ vs $NLR \leq 3$, respectively ($p<0.001$, $p:0.043$). In our study, PFS and OS were found 3.13 month vs 17.09 month and 6.96 month vs 27.12 month in patients with $NLR > 3$ vs $NLR \leq 3$, respectively ($p:0.012$, $p:0.001$). It has been showed that in patients with high NLR, OS and sunitinib response were poor. In our study, sunitinib response was better in patients with $NLR \leq 3$ ($p:0.036$). In assessing the association between MSKCC criteria and NLR rate, all patients in poor risk group had $NLR > 3$; 77% and 70% of patients in favorable and intermediate risk groups had $NLR \leq 3$ ($p:0.022$).

No phase III clinical data related to the second line sunitinib treatment following cytokine therapy are available. Data from phase II studies are limited. Our results showed that the second line sunitinib treatment following cytokine therapy was generally as effective as the first line sunitinib treatment and there was no difference in term of side-effect profile. The value of MSKCC criteria and bone metastases as prognostic factors were also emphasized in our study. In terms of hematological parameters standing out as a cost effective indicator, it has been showed that NLR may have prognostic and predictive value.

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