RESEARCH ARTICLE

Prognostic Value of Hematologic Parameters in Patients with Metastatic Renal Cell Carcinoma Using Tyrosine Kinase Inhibitors

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Abstract

Background: The prognostic significance of the neutrophil-to-lymphocyte ratio for progression free survival in patients with metastatic renal cell carcinoma is unclear. Materials and Methods: We retrospectively reviewed 45 patients diagnosed with metastatic RCC previously treated with tyrosine kinase inhibitors from two centers, Akdeniz University Hospital and Afyon Kocatepe University. The prognostic value of the pretreatment neutrophil-tolymphocyte ratio, and other clinical and laboratory parameters were assessed by univariate and multivariate analysis. Results: Median progression free survival (PFS) was 13.9 months [95% CI for HR (6.88-20.91)] and overall survival figure of 16.6 months [95% CI for HR (7.23-26.03)] Univariate analysis revealed that PFS was significantly affected by hemoglobin level [p=0.013 (95% CI for HR (0.71-0.96))], eosinophil count [p=0.031 (95% CI for HR (0.20-0.92))], ratio of neutrophil lymphocytes (NLR) [p=0.007 (95% CI for HR (1.47-11.74))] and calcium level [p=0.006 (95% CI for HR (0.15-0.73))]. However, only NLR [p=0.031 (95% CI for HR (1.15-18.1))] and calcium levels [p=0.018 (95% CI for HR (0.20-18.1))] retained significance with multivariate analysis. Median PFS was 23.9 vs 8.6 months in patients with NLR ≤2 vs NLR >2 (Log rank; p= 0.040). Conclusions: This study showed that increased pretreatment NLR is an independent prognostic factor for patients with metastatic RCC using tyrosine kinase inhibitors.

Keywords: Metastatic RCC - tyrosine kinases inhibitor - neutrophil-to-lymphocyte ratio - prognosis

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Introduction

The incidence of kidney cancer has been increasing worldwide, accounting for approximately 2% of all cancers (Mathew et al., 2002). In 2010, 287,421 new cases and 122,302 deaths were estimated and, by 2015, 325,433 new cases and 138,629 deaths are expected to ocur (Ferlay et al., 2010). Five-year survival rates approximate 8% for patients with metastatic renal cell carcinoma (RCC). (AJCC Cancer Staging Manual, 2010) Chemotherapy is ineffective in treating kidney cancer; immunotherapy with high-dose interleukin-2 or interferon-alfa (INF-α) is effective in some patients (Yang et al., 2003). These agents are associated with low response rates (<15%) and significant toxicities, which often limit their use and affect patient quality of life (QoL) (Kapoor and Hotte, 2007).

Vascular endothelial growth factor (VEGF) is primarly targeted in antiangiogenic treatment of solid tumors (Willett et al., 2004). Clinical trials showed antiangiogenic agents (such as sorafenib, sunitinib, bevasizumab and pazopanib) in advanced RCC have reported consistent prolongation of progression-free survival (PFS) and, in some cases, overall survival (OS) in both treatment-naive and previously treated patients (Cohen and Oudard, 2012). This targeted agents needs to new prognostic markers. Many factors, such as anatomic extent of disease, histopathology, clinical factors, affect the prognosis in patients with RCC (Heng et al., 2009). Prognositic value of peripheral blood markers has been present in many cancers (Ohno et al., 2010; Zheng et al., 2013).

The purpose of this study was to examine retrospectively the survival data of our patients with metastatic renal cell cancer who received tyrosine kinase inhibitors and to determine the prognostic value of different peripheral blood parameters in association with the treatment efficacy.

Materials and Methods

Patients

The medical files of the patients with metastatic renal cell cancer (RCC) were reviewed retrospectively. The study included 45 patients diagnosed with metastatic RCC previously treated with tyrosine kinases inhibitors from two center. These centers were Akdeniz University Hospital and Afyon Kocatepe University.

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Treatment plan

All patients had received IFN-α therapy until progression or intolerance before tyrosine kinases inhibitors. Sunitinib, sorafenib and pazopanib were used in metastatic RCC treatment as tyrosine kinases inhibitors.

The disease progression status of patients was defined as increase in the dimensions of existing lesions or development of new metastases, as demonstrated by radiological imaging.

Statistical analysis

Overall survival (OS) was defined as the duration between the date of onset of a treatment and the date of death. Progression-free survival (PFS) was defined as the period of time between the initial administration of a treatment and the detection of the first tumor progression based on radiological criteria, or death. Survival was analyzed by the Kaplan-Meier survival analysis and the univariate Cox regression analysis. Variables with a value of p<0.10 in univariate analysis were also evaluated by multivariate analysis. A p value of less than 0.05 (p<0.05) was considered as statistically significant.

Results

Patient, disease and treatment characteristics

In this study, we evaluated the data of 45 patients diagnosed with metastatic RCC. The study group consisted of all patients with metastatic RCC from two centers between of May 2009 and September 2013. The median follow-up period was 23.9 months. The median age of the patients was 63 years (ranging from 41 to 90). The patients with ECOG performance status ≤2 were 78.9%.

Twenty patients (44.4%) had metastasis during the diagnosis. The patients had developed metastases after diagnosis a median time of 8.2 months. While 8 of the patients had bone metastasis (17.8%), 24 patients had visceral metastasis (53.3%), 8 patients bone and visceral metastasis (17.8%).

Table 1. Basaline Characteristics of Patients

Characteristic		No (45)	%
Sex	Female	11	24.4
	Male	34	75.6
Age	Median	63	
	Range	41-90	
ECOG Performance Status	0	5	13.2
	1	14	36.8
	2	11	28.9
	3	8	21.1
Nephrectomy	Present	31	68.9
	Absent	14	31.1
Metastases area	Visseral	24	53.3
	Bone	8	17.8
	Bone and Visseral	8	17.8
	Missing	5	11.1
Tyrosine Kinase Inhibitors	Sunitinib	35	77.8
	Sorafenib	5	11.1
	Pazopanib	5	11.1
Baseline Hgb (g/dl)	Median	11.2	
	Range	7.5-16.6	
Baseline WBC(/mm^3)	Median	6220	
	Range	1030-13120	
Baseline Eosinophil (/mm^3)	Median	60	
	Range	10-1160	
Baseline Calcium (mg/dl)	Median	9.1	
	Range	7.9-10.4	
Baseline NLR	≥2	13	28.2
	≤2	32	71.2

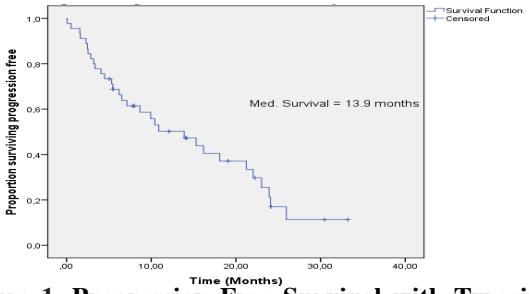

Figure 1. Progression Free Survival with Tyrosinc Kinases Inhibitors

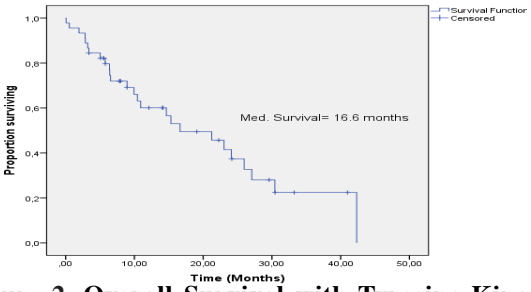

Figure 2. Overall Survival with Tyrosinc Kinases Inhibitors

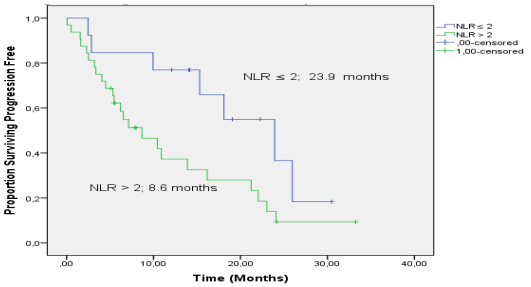

Figure 3. Progression Free Survival in Patients with NLR ≤2 vs NLR >2

The patients with underwent nephrectomy were 31 (68.9%). In addition all patients had received subcutaneous IFN-α therapy prior to the treatment with oral tyrosine kinases inhibitors. In 77.8% of the patients were use sunitinib, 11.1% of them were use sorafenib and other patients were use pazopanib. Refer to Table 1 for the details.

Survival analysis

The median follow-up period was 23.9 months. During the treatment with tyrosine kinases inhibitors, the patients had a median PFS of 13.9 months [95% CI for HR (6.88-20.91)] and overall survival figure of 16.6 months [95% CI for HR (7.23-26.03)] (Figures 1 and 2).

We did not find any significant relationships between PFS and age, history of nephrectomy, white blood cell count prior to the treatment, neutrophil count, platelets (PLT) count, lactate dehidrogenaselevel (LDH) or alanine aminotransferase (ALT) levels. Univariate analysis revealed that PFS is significantly affected by hemoglobine level [p=0.013 (95% CI for HR (0.71-0.96))], eosinophil count [p=0.031 (95% CI for HR (0.20-0.92))], ratio of neutrophil lymphocyte (NLR) [p=0.007 (95% CI for HR

(1.47-11.74))] and calcium level [p=0.006 (95% CI for HR (0.15-0.73))]. However, NLR [p=0.031 (95% CI for HR (1.15-18.1))] and calcium levels [p=0.018 (95% CI for HR (0.20-18.1))] retained significance with multivariate analysis.

Median PFS was 23.9 vs 8.6 months in patients with NLR≤2 vs NLR>2 (Log rank; p=0.040) (Figure 3). Median PFS was 18.1 vs 5.3 months with calcium level ≥9 g/dl vs <9 g/dl (Log rank; p=0.04).

Discussion

The results of our study showed that value of NLR was a prognostic for the patients with RCC who use tyrosine kinases inhibitors.

The systemic treatment of metastatic renal cell carcinoma (mRCC) has dramatically developed during recent years. Vascular endothelial growth factor (VEGF) pathway inhibitors are important agents in the treatment of RCC. Several studies have demonstrated the efficacy of VEGF-targeted agents in previously untreated patients with advanced or metastatic RCC and patients with RCC who have progressed after prior therapy (Motzer et al., 2007; Sternberg et al., 2010). Clinical efficacy has been reported for these agents associated with a median overall survival (OS) of 22.9-26.4 months, PFS of 8-9 months for sunitinib or sorafenib in first line treatment (Al-Marrawi et al., 2010; Motzer et al., 2011; Porta et al., 2011). Otherhand, patients with metastatic RCC and progression on first-line cytokine therapy median time to progression was 8.7 months with sunitinib (Motzer et al., 2006). In our study, the median progression-free survival was 13.9 months [95% CI for HR (6.88-20.91)] in patients treated with tyrosine kinases inhibitors , and overall survival was 16.9 months [95% CI for HR (7.23-26.03)] in secondline settings.

Neutrophilia maybe markers of inflammation related to the overproduction of cytokines as a result of increasing tumor burden or aggressive tumor biology. NLR is other marker of systemic inflammatory response. The prognostic role of tumor-infiltrating neutrophils, elevated blood neutrophils and elevated blood neutrophil/lymphocyte ratio has been associated with poor clinical outcome in several human cancers, such as in renal cell carcinoma, melanoma, colorectal cancer, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, GIST, gastric, esophageal, lung, ovarian and head and neck cancer (Ohno et al., 2010; Donskov et al., 2013; Unal et al., 2013). Hanninen et al. (1996) reported the first report of neutrophils as an adverse prognostic factor for patients with metastatic renal cell carcinoma (mRCC). The recent studies have evaluated the association of pre-treatment neutrophil to lymphocyte ratio (NLR) with response rate, PFS and OS in patients treated with sunitinib for mRCC. This trials showed that a low baseline blood NLR ≤3 was independently correlated with response to sunitinib, and independently correlated with favorable PFS and OS (Hanninen et al., 1996; Dirican et al., 2013). We determined that PFS is significantly affected by NLR [p=0.031 calcium levels (p=0.018) with multivariate analysis. Median PFS was 23.9 vs 8.6 months in patients with NLR ≤2 vs NLR >2 (p=0.040). Our results indicate that NLR levels below 2 and calcium level below 9 mg/dl increase PFS in patients with metastatic RCC who used tyrosine kinases inhibitors. Therefore, both of these should be considered to be positive predictive factors for survival. Morever in our study, we did not detect a significant relationship between the PFS and its predictive factors such as age, history of nephrectomy, white blood cell count before the treatment, neutrophil count, PLT count, eosinophil count and ALT levels.

In conclusion, anti VEGF targeted therapy is important for mRCC. This targeted agents needs to new prognostic markers. Metastatic RCC patients should have an assessment of degree of systemic inflammation at the prior the treatment. NLR is an easily measurable and cost effective parameter for show the systemic inflammation. This study shows that increased pretreatment NLR independent prognostic for in patients with metastatic RCC who use tyrosine kinases inhibitors.

References

Al-Marrawi MY, Rini BI, Harshman GA, et al (2011). The association of clinical outcome to front-line VEGF-targeted therapy with clinical outcome to second-line VEGF-targeted therapy in metastatic renal cell carcinoma (mRCC) patients (Pts.). *J Clin Oncol*, **29**, 4555.

AJCC Cancer Staging Manual, Seventh Edition (2010). published by Springer New York, Inc.

Cohen RB, Oudard S (2012). Antiangiogenic therapy for advanced renal cell carcinoma: management of treatment-related toxicities. *Invest New Drugs*, **30**, 2066-79.

Dirican A, Kucukzeybek Y, Erten C, et al (2013). Prognostic and predictive value of hematologic parameters in patients with metastatic renal cell carcinoma: second line sunitinib treatment following IFN-alpha. *Asian Pac J Cancer Prev*, **14**, 2101-5.

Donskov F (2013). Immunomonitoring and prognostic relevance of neutrophils in clinical trials. *Sem Cancer Biol*, **23**, 200-7.

Ferlay J, Shin HR, Bray F, et al (2010) International Agency for Research on Cancer. The GLOBOCON Project. http://globocan.iarc.fr.

Hanninen LE, Kirchner H, Atzpodien J (1996). Interleukin-2 based home therapy of metastatic renal cell carcinoma: risks and benefits in 215 consecutive single institution patients. *J Urol*, **155**, 19-25.

Heng DY, Xie W, Regan MM, et al (2009). Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*, **27**, 5794-9.

Kapoor AK, Hotte SJ (2007). Current status of cytokine therapy in management of patients with metastatic renal cell carcinoma. *Can Urol Assoc J*, **1**, 28-33.

Mathew A, Devesa SS, Fraumeni JF, et al (2002). Global increases in kidney cancer incidence, 1973-1992. *Eur J Cancer Prev*, **11**, 171-8.

Motzer RJ, Hutson TE, Tomczak P, et al (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*, **356**, 115-24.

Motzer RJ, Michaelson MD, Redman BG, et al (2006). Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*, **24**, 16-24.

Motzer RJ, Hutson TE, Olsen MR, et al (2011). Randomized phase II multicenter study of the efficacy and safety of sunitinib on the 4/2 versus continupus dosing schedule as first-line therapy of metastatic renal cell carcinoma: renal EFFECT trial. *J Clin Oncol*, **29**, 308.

Ohno Y, Nakashima J, Ohori M, et al (2010). Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol*, **184**, 873-8.

Ohno Y, Nakashima J, Ohori M, et al (2012). Followup of neutrophil-to-lymphocyte ratio and recurrence of clear cell renal cell carcinoma. *J Urol*, **187**, 411-7.

Porta C, Procopio G, Carteni G, et al (2011). Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. *BJU Int*, **108**, 250-7.

Sternberg CN, Davis ID, Mardiak J, et al (2010). Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*, **28**, 1061-8.

Unal D, Eroglu C, Kurtul N, Oguz A, Tasdemir A (2013). Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? *Asian Pac J Cancer Prev*, **14**, 5237-42.

Zheng YB, Zhao W, Liu B, et al (2013). The blood neutrophil-to-lymphocyte ratio predicts survival in patients with advanced hepatocellular carcinoma receiving sorafenib. *Asian Pac J Cancer Prev*, **14**, 5527-31.

Yang JC, Sherry RM, Steinberg SM, et al (2003). Randomized study of high-dose and low-dose interleukin-2 in patients withmetastatic renal cancer. *J Clin Oncol*, **21**, 3127-32.

Willett CG, Boucher Y, di Tomaso E, et al (2004). Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med*, **10**, 145.