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ORIGINAL ARTICLE

The association of hematologic parameters on the prognosis of patients with metastatic renal cell carcinoma

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Summary

Purpose: *Metastatic renal cell carcinoma (mRCC) bears a poor prognosis. We investigated the prognostic significance of some hematologic parameters of patients with mRCC.*

Methods: *We retrospectively reviewed the records of 53 patients with mRCC . The mean follow up time was 34 months (range 5–142).We assessed the prognostic value of hematologic parameters (leukocytes ,neutrophils, lymphocytes, platelets, neutrophil to lymphocyte ratio/NLR, platelet to lymphocyte ratio/PLR), and other clinical parameters with univariate and multivariate analysis.*

Results: *Memorial Sloan-Kettering Cancer Center (MSKCC) risk group , lung metastases, sunitinib treatment, lymphocyte count, NLR, and anemia significantly correlated with median overall survival (OS) on univariate analysis. The median OS in patients with a NLR < 3.4 was 32.2 months , significantly higher than the 13.9 months in patients with a ratio ≥ 3.4 (p = 0.006) . Multivariate analysis revealed that MSKCC risk group and the NLR were independent predictors of OS.*

Conclusion: *Hematologic parameters may be associated with OS in mRCC. However, further studies are needed to establish their routine use.*

Key words: *hematologic parameters, metastatic renal cell carcinoma, prognosis, sunitinib*

Introduction

RCC originating from the renal cortex makes up 85% of the primary renal tumors. In those with localized RCC, surgical resection can be curative. RCCs can evoke an immune response, which occasionally results in dramatic, sustained remissions. Various immunotherapeutic strategies have been used to treat advanced disease. Studying the molecular pathogenesis of RCC has identified targets for therapeutic intervention. This led to the development of molecularly targeted therapies that have been integrated into the routine management of patients with advanced RCC.

On the other hand, in metastatic disease, long term survival can not be obtained. OS for stage IV disease is reported as 8 % [1]. However, it has been reported that having certain clinical properties increases survival in advanced-stage patients [2-4]. There are many factors that affect prognosis in patients with RCC (TNM stage, histopathology, clinical factors, etc) [2,5,6]. Five factors that predicted short survival with multivariate analysis of the results of 670 advanced stage RCC patients at Memorial Sloan-Kettering Cancer Center (MSKCC) have been defined [2]. Later, the same Center has defined that the period between the initial diagnosis to the beginning of interferon-alfa (INFa) treatment as an additional predictor for bad prognosis must be less than 1 year [7].

Recently, user-friendly and cheaper prognostic factors are being developed in many cancers. One of these is peripheral blood values. Changes in the peripheral blood such as neutrophilia, lymphopenia and thrombocytosis have been defined as responses to systemic inflammation [8-11]. Furthermore, NLR and PLR have also been

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evaluated as user-friendly responses to inflammation [11,12]. In the study of Beuselinck et al. it has been reported that neutrophil and platelet counts above normal limits are bad prognostic factors in addition to the bad prognostic factors of MSKCC [13].Several studies with NLR in metastatic and non-metastatic RCC have shown significance on prognosis [14-17]. In addition, the prognostic value of hematologic parameters has been shown in many types of cancers [18-21].

In this study we evaluated, on the basis of previous studies, the prognostic significance of some hematologic parameters in patients with mRCC.

Methods

Patient characteristics

Data of 53 mRCC patients presenting at the Medical Oncology Outpatient Clinic of Izmir Ataturk Training and Research Hospital between March 2006 and September 2011 were retrospectively evaluated. All patients had measurable metastatic lesions at least in one region. Hematologic parameters (leukocytes, neutrophils, lymphocytes, platelets, NLR,PLR) were registered at the time when metastases developed. The exclusion criteria included history of blood transfusion within the last 2 months, active bleeding, bleeding diathesis, hyper-or hypothyroidism, infections, steroid treatment, disseminated intravascular coagulation, heparin treatment or connective tissue disease. In patients with metastases, venous blood samples were drawn into ethylenediamine tetraacetic (EDTA)-containing tubes in order to test for the hematological parameters before treatment. Complete blood count was performed with impedance-based analyzer (CELL-DYN 3700 ABBOTT, USA). Furthermore, routine serum biochemistry was carried out. Low Karnofsky performance status (< 80%), high lactate dehydrogenase (LDH) levels (1.5 times the upper limit of normal), low hemoglobin levels (<10 mg/dl), high corrected serum calcium levels (> 10 g/dL) and less than 1 year between the initial RCC diagnosis and onset of IFN-α therapy, which are the MSKCC 5 risk factors predicting unfavorable prognosis, were evaluated. Those with no risk factors (zero risk factors) were grouped as favorable risk group, those with one or more risk factors as intermediate risk group and those with three or more risk factors as poor-risk group [7].

Hematologic parameteres

Regression tree analysis for censored data was used to find the best cut-off value of hematologic parameters.

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 < 3.4 and ≥3.4

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 <134 and ≥ 134.

Other parameters

Lymphocyte counts were divided as <1,815 and ≥1,815/mm^3, platelet counts as <312,000 and ≥312,000/mm^3, leukocyte counts as <6,020 and ≥ 6,020mm^3, hemoglobin levels as <10 and >10 mg/dl, LDH levels as normal and >1.5 times the upper limit of normal and Karnofsky performance status as <80 and >80.

Statistics

Descriptive statistics were used for mean and median values. We analysed hematologic parameters (leukocytes ,neutrophils, lymphocytes, platelets, NLR , and PLR) and other potential factors associated with OS, including gender, age, clear cell vs non-clear cell histology, time from initial RCC diagnosis to metastases, the presence of more than two metastatic sites, sites of metastases (lung ,liver, bone, central nervous system, lymph nodes), the presence of anemia, sunitinib treatment, therapy following sunutinib, and MSKCC risk groups. Regression tree analysis for censored data was used to find the best cut-off value of hematologic parameters. Factors with significant association in univariate analysis were included in multivariate Cox proportional hazards regression model to determine their independent effects. Survival probabilities and median survival times were estimated from Kaplan–Meier curves. Descriptive analyses were presented using means and standard deviations for normally distributed NLR variables. One-way ANOVA was used to compare these parameters among the MSKCC risk groups (favorable, intermediate, poor). Levene test was used to assess the homogeneity of the variances. An overall p-value of less than 0.05 was considered to show a statistically significant result. When an overall significance was observed , pairwise post-hoc tests were performed using Turkey's test.

Results

Patients

Data of 53 patients diagnosed with mRCC presenting at the Medical Oncology Department of Izmir Katip Celebi University Ataturk Training and Research Hospital, between March 2006 and

Table 1. Patient characteristics

Characteristics	*N (%)*
No.of patients	53 (100)
Median age, years (range)	61 (40-79)
Gender	
Male	39 (73.6)
Female	14 (26.4)
Histologic type	
Clear cell	44 (83)
Non-clear cell	9 (17)
Localization of metastasis	
Lung	37 (69.8)
Liver	5 (9.4)
Brain	5 (9.4)
Bone	11 (20.8)
Lymph nodes	15 (28.3)
Other	6 (11.3)
Number of metastatic sites	
1	33 (62.2)
2	15 (28.3)
≥3	5 (9.5)
MSKCC risk group	
Favorable	18 (34)
Intermediate	24 (45.3)
Poor	11 (20.8)
Therapy	
Palliative radiotherapy	17 (34)
Surgery	51 (96.2)
IFNα	44 (83)
Sunitinib	29 (54.7)
Post sunitinib therapy (molecular targeted therapy)	9 (16.9)

MSKCC: Memorial Sloan-Kettering Cancer Center, INFa: interferon alpha

September 2011 were retrospectively studied. Patient characteristics are summarized in Table 1.

Sunitinib treatment outcomes

The patients had received IFN-α therapy until progression or intolerance before sunitinib treatment. Sunitinib 50 mg/d was administered 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 toxicity. Sunitinib continued until disease progression, unacceptable toxicity, or withdrawal of consent. Median follow up time was 34 months (range 5–58). Sunitinib resulted in 1 (3.4%) complete response, 7 (24.1%) partial responses, 9 (31.0%) stable disease cases, and 12 (41.4 %) disease progression cases. Median progression free survival was 5 months (range 1–20) and median OS 9 months (range 1–35). At the time of analysis, 31/53 (54%) assessable patients had died.

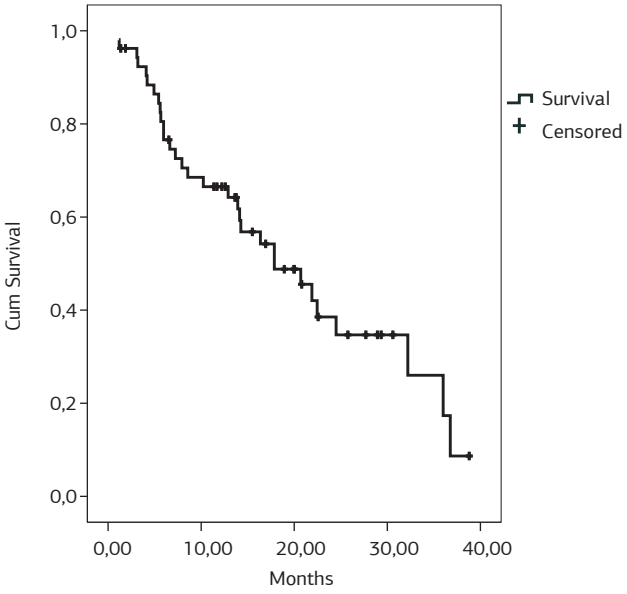

Figure 1. Overall survival of all patients.

Univariate analysis of factors associated with overall survival

The median OS for all patients after the establishment of metastases was 17.8 months (95% CI 10.2-25.5) (Figure 1). Lung metastases (p=0.021),MSKCC risk group (p<0.001;Figure 2), sunitinib treatment (p=0.006), lymphocyte count (p=0.025), NLR (p=0.006;Figure 3), MPV (p=0.018), and anaemia (p=0.026) were significantly associated with OS. Other metastatic sites, the number of metastatic sites,metastasis-free interval, age, gender, tumor histology, platelet count, neutrophil count, PLR, and post-sunitinib therapy were not associated with OS (Tables 2 and 3). The median OS was 13.9 months vs 24.5 months in patients with lymphocyte count <1,815 vs ≥ 1,815, respectively (p=0.025). The median OS was 7.2 months vs 21.9 months in patients with hemoglobin level <10 mg/dl vs ≥ 10 mg/dl, respectively (p=0.026).

Multivariate analysis of factors associated with overall survival

Factors associated with OS were MSKCC risk groups (poor risk group vs favorable risk group ; HR=15.4, p<0.001), pulmonary metastases (yes vs no; HR=3.08, p=0.047), NLR (<3.4 vs ≥ 3.4; HR=2.23, p=0.043) (Table 4). When compared according to

Table 2. Univariate analysis of overall survival according to the distribution of the clinicopathological risk factors

Risk factors	*Patients N*	*Median overall survival (months)*	*Log-rank p*
Age (years)			0.827
<65	38	20.7	
>65	15	26	
Gender			0.803
Female	14	21.9	
Male	39	17.8	
Tumor hıstology			0.527
Clear cell	44	17.8	
Non-clear cell	9	8.56	
Presentation with metastasis			0.613
Yes	18	17.8	
No	35	20.7	
Number of disease sites			0.058
≥2	20	12.9	
<2	33	24.5	
Lung metastases			0.021
Yes	37	14.2	
No	16	59% in 12 months*	
Bone metastases			0.131
Yes	11	14.1	
No	42	21.9	
Liver metastases			0.78
Yes	5	14.2	
No	48	20.7	
Lymph node metastases			0.152
Yes	15	8.5	
No	38	21.9	
CNS metastases			0.840
Yes	5	17.8	
No	48	21.9	
Metastasis-free interval (years)			0.193
≥1	25	20.7	
<1	28	14.1	
MSKCC risk group			<0.001
Favorable risk	18	36.0	
Intermediate risk	24	20.7	
Poor risk	11	5.96	
Treatment after sunitinib			0.295
Yes	9	21.9	
No	44	14.2	

*median overall survival not reached
MSKCC: Memorial Sloan-Kettering Cancer Center, CNS: central nervous system

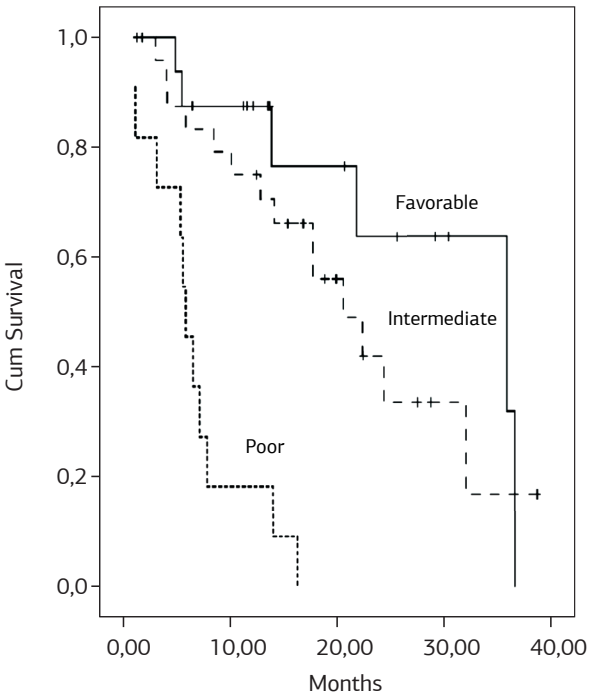

Figure 2. Overall survival according to MSKCC risk groups (Log-rank p<0.001).

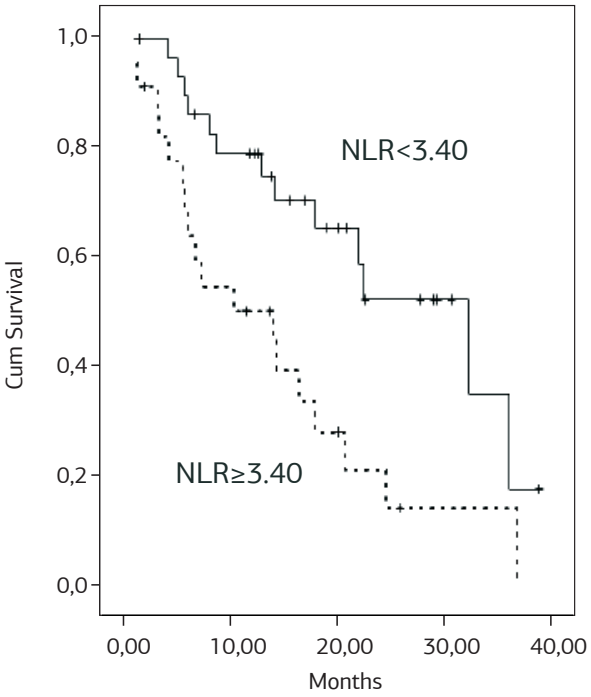

Figure 3. Overall survival of patients according to neutrophil to lymphocyte ratio (NLR) ≥ 3.4 and NLR < 3.4 (Log-rank p=0.006).

MSKCC risk group, the median OS for favorable-risk, intermediate-risk, and poor-risk patients was 36, 20.7, and 5.9 months, respectively. The median OS was 13.9 (95% CI 3.3-24.4) vs 32.2 (95% CI 18.6-45.7) months in patients with NLR >3.4 vs ≤ 3.4 (Figure 3). In patients with pulmonary metastases, the median OS was not reached and the 12-month survival was 59 %.

NLR values calculated when metastases were noted are given in Table 5 according to MSKCC risk groups. There was a significant difference be-

Table 3. Univariate analysis of overall survival according to hematologic parameters

Parameters	*Patients N*	*Median overall survival (months)*	*Log-rank p*
Neutrophils (mm^3)			0.171
<6020	30	36.0	
≥6020	23	17.8	
Lymphocytes (mm^3)			0.025
<1815	24	13.9	
≥1815	29	24.5	
Platelets (mm^3)			0.152
<312500	27	24.5	
≥312500	26	14.1	
Hemoglobin (g/dl)			0.026
<10	11	7.23	
≥10	42	21.9	
NLR			0.006
<3.40	30	32.2	
≥3.40	23	13.9	
PLR			0.233
<134	19	20.7	
≥134	34	16.3	

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

Table 4. Multivariate analysis of clinical and hematologic risk factors

Risk factors	*Categories compared*	*Hazard ratio*	*95% CI*	*Log-rank p*
MSKCC	Intermediate vs favorable	2.48	0.83-7.39	0.102
MSKCC	Poor vs favorable	15.47	4.3-55.2	<0.001
Lung metastases	Yes vs no	3.08	1.01-9.3	0.047
NLR	<3.4 vs ≥3.4	2.23	1.02-4.8	0.043

MSKCC: Memorial Sloan-Kettering Cancer Center, NLR: neutrophil to lymphocyte ratio

Table 5. Mean neutrophil to lymphocyte ratio by MSKCC risk groups

	Favorable risk	*Intermediate risk*	*Poor risk*
Mean	3.26	2.9	5.12
95% CI of the mean	2.5-4.0	2.3-3.5	3.9-6.7
Standard deviation	1.6	1.6	2.7

tween the mean values calculated by the one-way ANOVA test (F=6.07 p=0.004).

Discussion

The aim of this study was to assess the prognostic value of hematological parameters in patients with mRCC. Hematologic parameters (neutrophils, lymphocytes, platelets, hemoglobin ,NLR, PLR) were measured at the time when metastases developed and showed that the NLR values may be associated with patient OS. In this retrospective study, patients with NLR <3.4 had better OS after adjustment for other known prognostic factors. According to multivariate analysis , other hematologic parameters were not associated with OS.Clinical data suggest that inflammation plays a role in the pathogenesis of many cancers ,autoimmune disorders, infections, and trauma [22-24]. Previous studies indicate that inflammatory markers are associated with prognosis of RCC [25]. RCC cells have been shown to release some mediators which cause immunosuppression [26]. T-cell response is inhibited by mechanisms such as decrease of IL-2 production, changes in IL-2 receptor activity, inhibition of Jak-3 kinase activity and induction of T-cell apoptosis [26,27]. Furthermore, decrease of nuclear factor κB activation in lymphocytes is seen in RCC [28]. Increase in $CTLA4^+CD8^+$ T lymphocytes ratio, decrease in the number of dendritic cells and increase in granulocyte counts, and increase in $CD57^+$ T and NK cells have been detected in the blood of patients with RCC and these changes were associated with disease progression [29]. These changes in T cells, which can also be seen in inflammation, can cause lymphopenia in the peripheral blood [30]. All of these mechanisms cause persistent survival of tumor cells. While these changes lead to tumor growth, normal variation in hematologic parameters is disrupted (lymphopenia, granulocytosis etc). It is known that proinflammatory and prothrombotic factors [IL-1, ADP, thromboxane, thrombin, IL-1, TNF-α, vascular endothelial growth factor (VEGF), tissue factor (TF) and cancer procoagulant (CP)] are secreted by cancer cells [31,32] and cause changes in platelet count, shape and functions. These changes seen in hematologic parameters in cancer patients have been studied as prognostic factors in many cancer types [33-36]. The NLR may show the complex prognostic information of these two conditions (granulocytosis and lymphopenia), and be a very strong predictor of clinical outcome. Proctor et al. have

evaluated the effects on survival of NLR in 27031 patients with cancer [21]. In this study, the NLR was independently associated with survival in all cancers studied (all p<0.001).This study is important because it is the largest and most recent one. Wang et al. [18] confirmed that NLR was an independent prognostic factor in patients with bone metastasis. In another study [37] CRP, which is an inflammation marker, was preoperatively evaluated together with NLP in non-small cell lung cancer and showed that their combined use was an independent prognostic determinant. There are several studies dealing with the prognostic significance of NLR in RCC [14-17]. Ohno et al. have determined that the NLR change (a combination of the preoperative and postoperative ratios) was independent predictor of recurrence in RCC [15]. In another study in patients with RCC , NLRs were significantly lower in the FasL-negative group than in the positive group [16]. In the study by Keizman et al. it has been determined that the posttreatment NLR change was a significant prognostic factor for recurrence [38]. In our study multivariate analysis showed that MSKCC risk group and the NLR were independent predictors of OS (p=0.001 and p=0.043, respectively), whereas other hematologic parameters had no significant relationship with survival.

The limitations of this study include its retrospective nature which is associated with potential selection bias, incomplete data collection, and lack of pathology review. Despite these limitations, our observation that the NLR may be associated with OS of patients with mRCC is important. This parameter can be measured easily , it is cost-effective and can be used as a prognostic marker. Further studies with larger patient numbers are required to test and confirm our hypothesis.

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