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The Clinical Significance of Erythrocytic Macrocytosis in Metastatic Renal Cell Cancer and Sarcoma Patients Treated with Pazopanib

Pazopanib ile Tedavi Edilen Metastatik Renal Hücreli Kanser ve Sarkom Hastalarındaki Eritrositer Makrositoz'un Klinik Önemi

ABSTRACT

Objective:
Pazopanib is a multi-kinase inhibitor used in metastatic renal cell carcinoma or sarcomas (mRCC or mSTS). We aimed to investigate the relationship between pazopanib and macrocytosis and evaluate the clinical significance of this effect in mRCC or mSTS.

Material and Methods:
Patients diagnosed with mRCC and mSTS and have been treated with pazopanib were included. Drug-induced macrocytosis was defined as MCV >100 fL during any mount of treatment. ΔMCV was defined as difference between MCV during pazopanib treatment and baseline MCV. Data was collected retrospectively.

Results:
Fifty patients were included the study. During the pazopanib treatment, significant increase in MCV levels was observed and the mean MCV at the 0, 1, 3, 6, and 9 months were found as 86.7±7.6 fL, 87.8 ± 7.5, 92.4 ± 8.9, 94.8 ± 11.1 and 99.0 ± 10.7 fL, respectively (p<0.001). In the group with ΔMCV3 ≥ 5fL, median PFS was found as 48.0 months (95% CI, 26.3-69.9); in the group with ΔMCV3 <5, it was 25 months (95% CI, 14.6-35.4) (p:0.036). Median PFS was 21.0 months (%95 CI, 0-46.3) for macrocytic patients compared to 4.0 months (%95 CI, 2.0-5.9) in normocytic patients (p:0.023). There was no statistically significant difference between the groups for overall survival.

Conclusion:
A significant increase in MCV values or the development of macrocytosis during the pazopanib treatment in mRCC and mSTS, can be used as an important biomarker for progression-free survival.

Key Words:
Mean Corpuscular Volume (MCV), Macrocytosis, Pazopanib, Progression-free Survival

ÖZ

Amaç:

Pazopanib, metastatik renal hücreli karsinom (mRHK) ve metastatik yumuşak doku kanserlerinde (mYDK) kullanılan multi-kinaz inhibitörüdür. Çalışmamızda pazopanib tedavisinin ortalama eritrosit hacmi (MCV) üzerine etkisinin ve progresyonsuz sağkalım süresi (PSS) ve genel sağkalım süresi (GSS) üzerine etkilerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler:

Çalışmamız tek merkezli, retrospektif olarak planlandı ve mRHK veya mYDK tanılı ve pazopanib kullanan hastalar dahil edilmiştir. ΔMCV, tedavinin belli bir ayındaki MCV ile başlangıç MCV arasındaki fark; makrositoz ise tedavinin herhangi bir ayında MCV >100 fL olarak tanımlanmıştır. MCV artışı ve makrositoz ile sağkalım ilişkisi istatiksel olarak analiz edilmiştir.

Bulgular:

Hasta sayısı 50 idi. Pazopanib ile 0.ay, 1.ay, 3.ay, 6.ay ve 9.ay ortalama MCV değerleri sırasıyla 86.7 ± 7.6, 87.8 ± 7.5, 92.4 ± 8.9, 94.8 ± 11.1 ve 99.0 ± 10.7 fL olarak hesaplandı ($p<0.001$). Yirmi iki hastanın (%44) üçüncü MCV'si 5 fL ve üzeri artmış olarak bulundu. Hastaların 14' ünde (%28) makrositoz gelişti. Üçüncü ayda ΔMCV 5 fL ve üstü olanların mPSS 48.0 ay (%95 CI, 26.3-69.9) iken; 5'in altı olanlarda mPSS 25 ay (%95 CI, 14.6-35.4) olarak bulundu (p:0.036). Makrositoz olmayan hastalarda mPSS 4.0 ay iken (%95 CI, 2.0-5.9); makrositoz gelişen hastalarda mPSS 21.0 ay (%95 CI, 0-46.3) olarak bulundu (p: 0.023). ΔMCV ve makrositoz gelişimi ile GSS arasında istatiksel anlamlı bir fark bulunmadı.

Sonuç:

Pazopanib ile tedavi edilen mRHK ve mYDK' de, MCV değerlerindeki anlamlı artışın veya makrositoz gelişiminin, prospektif çalışmalar ile valide edildiği takdirde önemli bir gösterge olabileceğini düşünmekteyiz.

Anahtar Kelimeler:

Ortalama eritrosit hacmi (MCV), Makrositoz, Pazopanib, Progresyonsuz Sağkalım

INTRODUCTION

Pazopanib, a tyrosine kinase inhibitor (TKI) is frequently used in anti-cancer treatment. It is an oral small-molecule multi-kinase inhibitor that mainly inhibits vascular endothelial growth factor receptors 1,2 and 3, platelet endothelial growth factor receptor-alfa, and beta, and the stem-cell factor receptor c-kit. Although pazopanib has been investigated for various solid tumors, it is currently approved for metastatic renal cell carcinoma (mRCC) and some subtypes of metastatic soft-tissue sarcomas (mSTS) (1).

A significant number of different clinical and laboratory side effects such as hypertension, hand-foot syndrome, and fatigue with different degrees of severity are known with TKIs (2). Historically, TKI-induced adverse events such as hand-foot skin reaction and hypertension, have been evaluated as potential pharmacodynamic biomarkers of treatment effectiveness for different TKIs (3,4). Specific to pazopanib, in an Asian study, Huang et al demonstrated that hand-foot skin reaction is an independent predictive factor for better treatment outcomes in chemotherapy-refractory recurrent or metastatic soft tissue sarcoma who had received pazopanib treatment (5). Despite these studies, unfortunately, a major issue for clinicians is the inadequacy of validated predictive pharmacodynamic biomarkers for TKIs such as pazopanib that have been successfully used in routine clinical practice.

Macrocytosis defined as a mean corpuscular volume (MCV) greater than 100 fL, occurs in approximately 3 percent of the general population. It is usually seen in patients with vitamin B12 or folic acid deficiency, chronic alcoholism, and hypothyroidism (6,7). In the absence of such conditions, sometimes drug-induced macrocytosis can be also seen. Increases in MCV are defined with different drugs such as hydroxyurea, methotrexate, and capecitabine (8-10). In the last 10 years, macrocytosis after drug-using was described with different TKIs, especially with sunitinib and imatinib (2,7,11). The biggest hypothesis about this subject, the increase in MCV in patients treated with sunitinib or imatinib might be caused by inhibition of the stem cell factor (c-KIT). It is known that c-KIT is expressed on the surface of haematopoietic progenitor cells, where it regulates the proliferation, differentiation, and survival of the erythrocytes. So, inhibiting this pathway may be related to drug-induced macrocytosis (2,7). Pazopanib may also be related with macrocytosis, as it inhibits c-KIT like sunitinib. Contrary to sunitinib and imatinib, the data is very limited about the relationship between pazopanib, MCV, and macrocytosis (7,12). In our current trial, we aimed to investigate the relationship between pazopanib and macrosytosis in metastatic renal cell carcinoma or sarcomas. Moreover, we aimed to evaluate the clinical significance of this effect.

MATERIALS and METHODS

Patients diagnosed with metastatic renal cell carcinoma or metastatic soft tissue sarcomas and who have been treated with pazopanib were included in this study if at least one baseline MCV and one more MCV during treatment were available. Patients younger than 18 years old and with known brain metastases were excluded. Data were retrospectively obtained from the hospital database. Demographic characteristics of patients, laboratory values such as hemoglobin (Hb), MCV and related-factors, and oncological survival outcomes were recorded. MCV levels were collected at baseline, during the first mount, 3rd mount, 6th mount and 9th mount of pazopanib treatment.

Drug-induced macrocytosis was defined as MCV >100 fL during any mount of treatment. ΔMCV was defined as difference between MCV during pazopanib treatment and baseline MCV. Progression-free survival (PFS) was defined as the time between first day of treatment and the day of progressive disease or death from any cause. Overall survival (OS) was defined as the time between the first day of treatment and the date of death from any cause. If progression or death had not

occurred or the patient was lost to follow-up, PFS and OS were censored at the date of last follow-up.

The statistical package software system version 21.0 (SPSS Inc, Chicago, IL) was used for all data analyses. Descriptive analyses were presented using mean±SD, median (min–max) or n (%), where appropriate. The normality assumptions were controlled by the Shapiro–Wilk test. Categorical data were compared with the Pearson chi-square test. ANOVA and t-test were used to analyze numerical data. Survival curves were generated by the Kaplan–Meier method and the log-rank test was performed to compare overall and progression-free survival between the groups. A two-sided p value less than 0.05 was considered statistically significant.

This research was designed and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (Approval Date/No. 23.02.2021/125). In our study, research and publication ethics were complied with.

RESULTS

A total of 50 patients were included the study. The number of patients diagnosed with mRCC and mSTS were 20 (40%) and 30 (60%), respectively. In general the mean age was 58.4 ± 13.4, and 19 (38%) patients were male. When baseline conditions such as vitamin B12 level, folat level, hypothyroidism, and alcohol using were evaluated for the patients, there was no significant condition that could cause macrocytosis. The metastasis regions of patients were also recorded. The baseline characteristic of the patients are shown detail in Table I.

Table I. Patients' Demographic Characteristics (n:50)

Diagnosis	
• mRCC	20 (40%)
• mSTS	30 (60%)
Gender	
• Male	19 (38%)
• Female	31 (62%)
Age, mean ± SD, (year)	58.4 ± 13.4
Lung Metastasis	
• No	11 (22%)
• Yes	39 (78%)
Liver Metastasis	
• No	39 (78%)
• Yes	11 (22%)
Bone Metastasis	
• No	33 (66%)
• Yes	17 (34%)
Other Metastasis	
• No	44 (88%)
• Yes	6 (12%)
Baseline Vitamin B12 Level	
• Low	3 (6%)
• Normal	31 (62%)
• Unknown	16 (32%)
Baseline Folate Level	
• Low	6 (12%)
• Normal	21 (42%)
• Unknown	23 (46%)
Hypothyroidism	
• No	33 (66%)
• Yes	3 (6%)
• Unknown	14 (28%)
Alcohol Using	
• No	44 (88%)
• Yes	6 (12%)

The baseline mean hemoglobin for all patients was 11.9 ± 2.0 gr/dL. The baseline mean MCV was 86.7±7.6 fL. When subgroups were evaluated it was found as 87.3± 8.0 fL and 86.3 ± 7.4 fL for mRCC and mSTS, respectively. During the pazopanib treatment, a significant increase in MCV levels was observed and the mean MCV at the 1, 3, 6, 9 months were found as 87.8 ± 7.5, 92.4 ± 8.9, 94.8 ± 11.1 and 99.0 ± 10.7 fL, respectively (p<0,001) (Table II).

Table II. Baseline and on-treatment levels

• Baseline Hb, mean ± SD, g/dL	11.9 ± 2.0
• Baseline MCV mean ± SD , fL	86.7 ±7.6
• 1.months MCV mean ± SD , fL	87.8 ± 7.5
• 3.months MCV mean ± SD , fL	92.4 ± 8.9
• 6.months MCV mean ± SD , fL	94.8 ± 11.1
• 9.months MCV mean ± SD , fL	99.0 ± 10.7

As mention before, ΔMCV was defined as difference between MCV during pazopanib treatment and baseline MCV. ΔMCV3 was defined as MCV difference between 3 months on-treatment and baseline MCV level. The MCV of 22 patients (44%) at 3. months was found to be increased by 5 fL or more. In the group with ΔMCV3 ≥ 5fL, median PFS was found as 48.0 months (95% CI, 26.3-69.9); conversely, in the group with ΔMCV3<5, it was found as 25 months (95% CI, 14.6-35.4) (p:0.036) (Figure1).

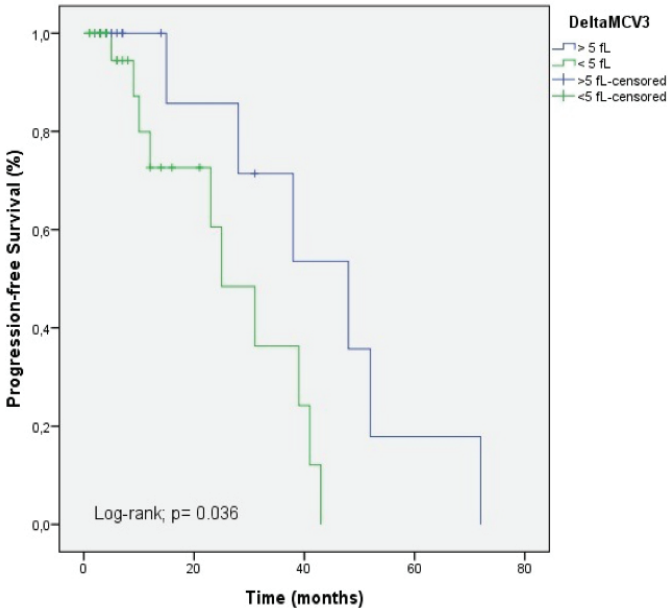

Figure 1: Progression-free survival graphic according to DeltaMCV3

Moreover, there was no statistically significant difference between the groups when evaluated in terms of overall survival (p:0.41). During the pazopanib treatment macrocytosis (MCV >100 fL) developed in 14 (28%) patients and they were defined as macrocytic patients. Macrocytic and normocytic patients were divided into 2 groups and survival analysis was performed. Median PFS was 21.0 months (95% CI, 0-46.3) for macrocytic patients compared to 4.0 months (95% CI, 2.0-5.9) in normocytic patients (p:0.023) (Figure 2).

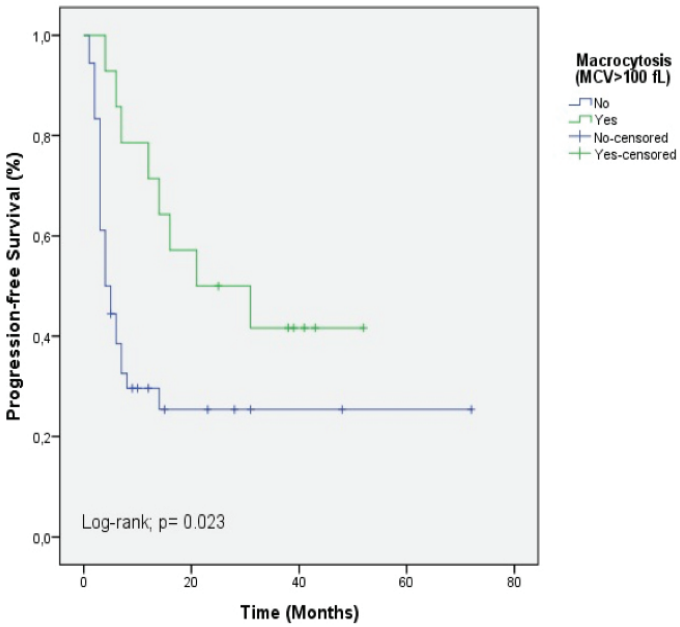

Figure 2: Progression-free survival graphic according to macrocytosis

Additionally, median OS was 42.0 months (95% CI, 33.4-50.5) for macrocytic patients compared to 22.0 months (95% CI, 12.4-31.5) in normocytic patients. There was no statistically significant difference between the groups (p:0.47).

Subgroup analyzes were performed for mRCC and mSTS. In the subgroup of mRCC, mPFS in the ΔMCV3 ≥ 5fL and Δ MCV3<5 groups were 16.0 months (95% CI, 0-37.0) and 3.0 months (95% CI, 1.0-4.9), respectively (p:0.01). For STS patients, it was found as 4.0 months (95% CI, 0-12.3) and 7.0 months (95% CI, 0-28.2), respectively (p:0.36). There was no statistically significant relationship between the ΔMCV3 and overall survivals in both subgroups. Furthermore, due to the small number of patients, subgroup analyzes were not performed in patients who developed macrocytosis because they would not be reliable. Finally, patients were also grouped for metastasis regions such as lung metastatic, liver metastatic and bone metastatic patients. There was no notable significant difference between the groups.

DISCUSSION

During the treatment with pazopanib for mRCC and mSTS, we observed a significant increase in MCV values after pazopanib treatment, and also in some of them macrocytosis was developed. In this retrospective analysis, we aimed to investigate the clinical significance of these effects. We demonstrated that there was a close and significant relationship between the increasing MCV or macrocytosis and progression-free survival. A similar relationship with increasing MCV or macrocytosis and overall survival was not demonstrated.

In our current study, during the pazopanib treatment, significant increase in MCV levels was observed and the mean MCV at the 0, 1, 3, 6, 9 months were found as 86.7±7.6 fL, 87.8 ± 7.5, 92.4 ± 8.9, 94.8 ± 11.1 and 99.0 ± 10.7 fL, respectively (p<0.001). When baseline conditions such as vitamin B12 level, folat level, hypothyroidism, and alcohol using were evaluated for the patients, there was no significant condition that could cause these increases. So, these increases can be clearly considered as pazopanib-related. The increase in MCV in patients treated with sunitinib, imatinib, and other TKIs was shown in different previous research with small numbers of patients (2,7,13-15). Contrary to sunitinib and imatinib, the data is very limited about the relationship between pazopanib, MCV and macrocytosis. To the best of our knowledge, this effect was investigated in a small-scale study with 35 patients in 2015, and the authors considered that MCV changes may be a biomarker of pazopanib antitumor effects (12). Moreover, Kloth JSL et al., designed a study with several TKIs and in the subgroup of pazopanib-treated patients (n:66), they showed that the rise in MCV levels occurs roughly after 3 months of treatment (7). Similarly, we observed significant increase in MCV levels especially in the 3rd month of the pazopanib treatment.

In our current study, roc analysis was performed for the determining the most appropriate cut-off value for survival analysis and it was 5 fL (ΔMCV3). In the patients group with Δ MCV3 ≥ 5fL, median PFS was found as 48.0 months (95% CI, 26.3-69.9); conversely, in the group with ΔMCV3 <5, it was found as 25 months (95% CI, 14.6-35.4) (p:0.036). But, there was no statistically significant difference between the groups when evaluated in terms of overall survival (p:0.41). Relationship between substantial increase in MCV levels after start of sunitinib-treatment and overall survival was shown in a study before (7). In the same trial, there was no relationship between the overall survival and pazopanib-induced MCV increase. Furthermore, to our knowledge, there is no study which have investigated pazopanib-induced MCV increase and survival except this study mentioned above. So, it can be clearly said that, our current study is the first study showed that 5 fL or more increasing MCV levels in the 3rd month of the pazopanib-treatment may be a strong potential biomarker for progression-free survival in mRCC and mSTS patients, if validated prospectively. Despite low number of patients, this relationship was also shown in mRCC subgroups. The same relationship was not shown for overall-survivals.

During the pazopanib treatment macrocytosis (MCV >100 fL) developed in 14 (28%) patients and they were defined as macrocytic patients. Median PFS was 21.0 months (95% CI, 0-46.3) for macrocytic patients compared to 4.0 months (95% CI, 2.0-5.9) in normocytic patients (p:0.023). Although median overall survival was numerically longer in macrocytic patients, there was no statistically significant difference (p:0.47). There were some studies about TKI-induced macrocytosis and clinical significance of these effects. Bourlon et al., investigated clinical significance of sunitinib-associated macrocytosis in mRCC in 2016. In this study, mPFS was higher among patients with macrocytosis compared to normocytic patients during sunitinib treatment (21 m vs. 4 m, respectively, p= 0.0001). The authors hypothesized that sunitinib-induced macrocytosis may have a role as a predictive biomarker for sunitinib (11). In another small-scale study, Kucharz et al., also designed a study with 27 mRCC patients. Patients who had macrocytosis after 3 treatment cycles had significantly longer PFS than those whose

MCV stayed less than 100 fL (not reached vs.11.2 months, p: 0.001) (15). Furthermore, Kloth JSL et al., performed a study with a big number of patients (n:533) with several TKIs such as sunitinib, imatinib, sorafenib, pazopanib and vemurafenib. In this study, it was shown that in sunitinib-treated patients with RCC, the occurrence of macrocytosis could potentially be accepted as a positive prognostic factor for survival. But with other TKIs, especially with pazopanib this relationship was not shown in this study (7). It can be clearly understood from these studies that sunitinib-induced macrocytosis are well known and could potentially serve as a positive prognostic factor for survival. But data is limited for pazopanib-induced macrocytosis. In our knowledge, this is the first study about clinical significance of pazopanib-associated macrocytosis in mRCC and mSTS. In our study, we exhibited that this phenomenon could help clinicians to predict PFS during pazopanib treatment for mRCC and mSTS, but unfortunately our sample was small, more studies are essential.

Thus far, the mechanism of pazopanib-induced macrocytosis or MCV increases is still unclear. Our study was not planned to determine mechanism of macrocytosis. Nevertheless, the most important hypothesis about this subject is related with c-KIT. It is known that, c-KIT is expressed on the surface of haematopoietic progenitor cells, where it regulates differentiation, proliferation, and survival of the erythrocytes. So, inhibiting this pathway may be related with drug-induced macrocytosis (2,7). Pazopanib may also be related with macrocytosis, as it inhibits c-KIT like sunitinib, imatinib etc. Further research are necessary.

Retrospective design and relative small number of patients can said to be the most important limitations for our study. Despite baseline conditions such as vitamin B12 level, folate level, hypothyroidism, and alcohol using were evaluated and there was no significant condition that could cause macrocytosis in our study; other rare causes which can affect MCV levels were not recorded and it can be confusing.

CONCLUSION

In our study, we demonstared that a significant increases in MCV values or the development of macrocytosis during the pazopanib treatment in metastatic renal cell carcinoma and metastatic soft tissue sarcomas can be used as an important biomarker for progression-free survival if validated by prospective studies.

Ethics Committee Approval:
This study was approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (Approval Date/-No. 23.02.2021/125).

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Conflicts of Interest:
The authors declare that they have no conflicts of interest in relation to this study.

Patients' Consent:
Because this study was retrospective, the condition of patients' consent was waived.

Authors' Contributions:
Y.I wrote the manuscript. YI, MFO were involved in the study design and data interpretation. The study concept was developed by SSG, AMT and HSC. YI analyzed the data. Manuscript was reviewed and edited by SSG. All authors read and approved the final version of the manuscript.

Presented at Congress:
The abstract of our study had been sent to 9th Turkish Medical Oncology Congress and accepted for poster presentation.

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