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Effect of macrocytosis on erlotinib response in metastatic non-small cell lung cancer

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Ethics Committee Approval
The study was approved by Karadeniz Technical University Ethic Committee, 07/07/2022, with protocol number 20224/158.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Numerous studies have assessed the relationship between macrocytosis and responses to chemotherapeutic agents and TKIs such as sunitinib and imatinib. However, there is limited data in the literature regarding the prognostic or predictive value of macrocytosis in using erlotinib. If a relationship is detected, early response/resistance assessment can be performed before imaging time in the follow-up of treatments, and a more cost-effective, non-invasive method can be employed for response monitoring. This study aimed to elucidate the effect of macrocytosis on response rates in patients treated with erlotinib for non-small cell lung cancer.

Methods: Seventy-five individuals diagnosed with non-small cell lung cancer (NSCLC) and admitted to our institution were enrolled in this retrospective cohort study. Baseline demographics, time of diagnosis, previous treatment, and the initiation or cessation of erlotinib were recorded. Data of patients with and without macrocytosis were analyzed. Stable disease, partial and complete response rates, and progressive disease response were evaluated separately as response rates. Progression-free survival between drug initiation and discontinuation due to progression was interpreted using Kaplan-Meier curves.

Results: The distribution of the overall survival (OS) and progression-free survival (PFS) evaluations revealed that 84% (n=63) of the patients were deceased, and the progression rate was 94.7% (n=71). The median OS of the patients was 18 months, and the median PFS was 11 months. There was a statistically significant difference in overall survival in females, with a median OS of 25 months (95% CI 17–32 months) and a median OS of 13 months in males (95% CI 9–20 months) (P=0.008). PFS was 14.5 months (95% CI 11–21 months) in women and six months (95% CI 4–17 months) in men, and there was a statistically significant difference (P=0.02). A statistically significant difference was achieved between MCV values measured during diagnosis and the third month between age groups (P=0.044).

Conclusion: The outcomes of this research suggest a statistically significant difference between the MCV values measured at the time of diagnosis and the third month regarding age groups. Both OS and PFS in women were statistically significantly higher than in men.

Keywords: erlotinib, macrocytosis, non-small cell lung cancer

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Introduction

The mean corpuscular volume (MCV) is one of the most prevalent hematological laboratory parameters. Macrocytosis (identified by MCV >100 fl) is commonly associated with deficiencies in vitamin B12 and/or folic acid, hypothyroidism, alcoholism, and myelodysplastic syndromes. Recently, tyrosine kinase inhibitors (TKIs) have gained increasing employment in cancer treatment. These inhibitors target the ATP binding site of one or more constitutively activated tyrosine kinases within cancer cells [1]. The elevation in MCV induced by sunitinib and imatinib can be attributed to the inhibition of stem cell factor (c-KIT). Furthermore, various drugs bring about macrocytosis through distinct mechanisms [2].

In recent years, there has been a growing exploration of the prognostic and predictive implications of MCV in diverse solid tumors. Numerous studies have highlighted the prognostic and predictive significance of MCV in conditions such as colorectal cancer (CRC), advanced breast cancer, and esophageal cancer.

Macrocytosis can also manifest based on the therapeutic agents administered. While numerous mechanisms have been proposed, the underlying cause remains unidentified in most cases. Several studies have examined the correlation between macrocytosis and reactions to chemotherapeutic agents and TKIs like sunitinib and imatinib [3-7]. Certain studies have indicated that the utilization of capecitabine and/or bevacizumab is associated with macrocytosis [8]. Nevertheless, the outcomes concerning its predictive role in treatment could benefit from greater consistency [9].

Tracking tumor markers in the blood aids in this endeavor, although a definitive standard biomarker for lung cancer has not yet been established. The potential to forecast early resistance and progression lies in the ability to monitor patient responses through straightforward blood tests, such as MCV. While TKIs can yield sustainable responses, swift progression can emerge due to resistance, resulting in rapid deterioration. Patient assessments occur at 3-month intervals through imaging modalities. Nevertheless, an uncomplicated, cost-effective, and minimally invasive approach is still lacking for monitoring treatment response [10]. This study examines macrocytosis's impact on response rates among patients undergoing erlotinib treatment.

Materials and methods

In this retrospective cohort study, 75 individuals aged 18 and above who applied to our institution, underwent erlotinib treatment for a minimum of 3 months, and were diagnosed with NSCLC were included. At the commencement of the treatment, patients presenting macrocytosis due to alternative causes (e.g., alcoholism, hypothyroidism, megaloblastic anemia) were excluded.

Baseline demographics, time of diagnosis, previous treatments, and the initiation or discontinuation of erlotinib were recorded. MCV values were documented at the initiation of erlotinib and the third month of treatment. Data from patients with and without macrocytosis were subjected to analysis. Treatment outcomes included response rates, progression-free survival (PFS), and overall survival (OS). Response assessment was based on the RECIST (Response Evaluation Criteria In Solid Tumors) criteria (version 1.1) [11], categorizing responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Kaplan-Meier curves assessed PFS from drug initiation to discontinuation due to progression.

The procedures adhered to the ethical standards set by the responsible committee on human experimentation (institutional) and aligned with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Karadeniz Technical University Medical Faculty Scientific Research Ethics Committee on 07/07/2022 under protocol number 20224/158.

Statistical analysis

The data underwent analysis using IBM Statistical Package for the Social Sciences (SPSS) version 29.0 for macOS (IBM Corp., Armonk, NY) and MedCalc statistical software version 12.7.0.0 package programs (MedCalc Software, Ostend, Belgium). Categorical data were presented as frequencies and percentages. Descriptive statistics for continuous data included mean, standard deviation, median, minimum, and maximum. The normality of variables was assessed using the Kolmogorov-Smirnov test.

For normally distributed variables, the Paired Sample T-test evaluated differences between dependent measurements. Non-normally distributed variables were assessed using the Wilcoxon Test. The comparison of categorical variables employed either Fisher's Exact Test or the Chi-Square test.

The repeated measurements analysis of variance (ANOVA) test was performed to analyze the variation in MCV measurements between diagnosis and the third month. Gender-based assessments of overall and PFS utilized the Log-rank test, with plotting Kaplan-Meier curves. Results with a *P*-value below 0.05 were considered statistically significant.

Results

As part of the study, 75 patients were evaluated, comprising 53.3% (n=40) females and 46.7% (n=35) males. The patients' ages ranged from 27 to 82 years, with a mean age of 65 years. Table 1 presents the distribution of demographic and clinical findings among the patients.

The distribution of laboratory measurements, taken both at the time of diagnosis and at the third month, is outlined in Table 2. Analysis revealed no statistically significant differences between the laboratory parameters measured at diagnosis and those measured at the third month. Specifically, the parameters including hemoglobin, MCV, platelets, lymphocytes, neutrophils, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio yielded P values of 0.802, 0.775, 0.081, 0.467, 0.326, 0.318, and 0.447, respectively.

The distribution of patients' OS and PFS evaluations is displayed in Table 3. The median OS and PFS for the patients were 18 (14.4–21.6) months and 11 (6.8–15.2) months, respectively. Notably, the 6-month OS and PFS rates reached 81.3% and 64%, respectively (Figures 1 and 2).

Figure 1: Overall survival (OS) and progression-free survival (PFS) data of the study group.

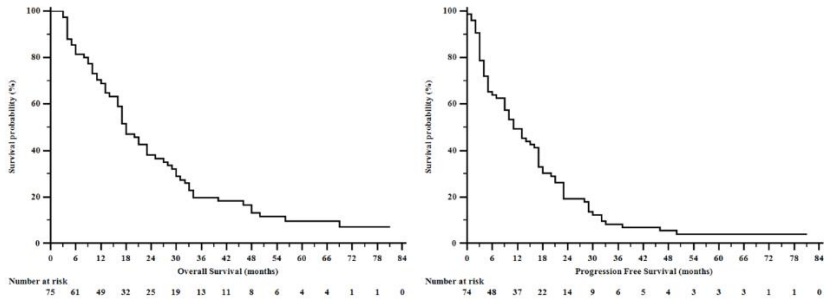

Figure 2: Overall survival (OS) and progression-free survival (PFS) distribution by gender of the patients.

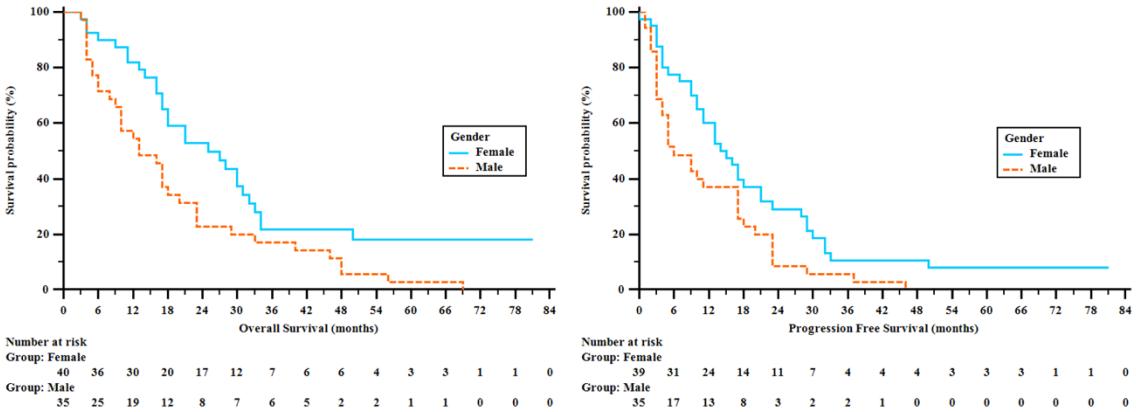

Table 1: Distribution of demographic and clinical findings of patients.

Variables	
Age (years), mean (SD)	62 (12)
Median (Min–Max)	65 (27–82)
	n (%)
Age <65	37 (49.3)
Age ≥65	38 (50.7)
Gender	
Female	40 (53.3)
Male	35 (46.7)
Histological subtype	
Adenocarcinoma	63 (84)
Squamous cell carcinoma	8 (10.7)
NOS	4 (5.3)
Smoking	
Non-smoker	51 (68)
Quit	4 (5.3)
Smoking	2 (2.7)
Unknown	18 (24)
Alcohol consumption	
None	49 (65.3)
Quit	0 (0)
Drinking	0 (0)
Unknown	26 (34.7)
Mutation	
Exon 19	15 (20)
Exon 21	13 (17.3)
Unknown	43 (57.3)
Negative	3 (4)
Other	1 (1.3)
Progression	71 (94.7)
Deceased	63 (84)
Treatment response	
Stable disease	26 (34.7)
Progression	24 (32.0)
Partial response	14 (18.7)
Complete response	7 (9.3)
Unknown	4 (5.3)

SD: Standard Deviation

Table 2: Distribution of diagnosis and third month laboratory measurements of the patients.

Laboratory	Mean (SD)	Median (Min-Max)	*P*-value
Hemoglobin (at diagnosis)	12.1 (1.8)	11.9 (8.8–17.7)	0.802
Hemoglobin (3rd month)	12.1 (1.5)	12.2 (8.4–14.8)	
MCV (at diagnosis)	90.7 (6.2)	89.8 (77–112.9)	0.775
MCV (3rd month)	90.6 (5.6)	90 (78.7–106.4)	
PLT (at diagnosis), $\times 10^3$	249.7 (98.9)	245.0 (61.0–558.0)	0.081
PLT (3rd month), $\times 10^3$	267.6 (97.3)	253.0 (65.0–554.0)	
Lymphocyte (at diagnosis)	1.8 (0.9)	1.7 (0.3–5.8)	0.467
Lymphocyte (3rd month)	1.8 (1.3)	1.6 (0.2–10.8)	
Neutrophil at diagnosis)	5.3 (3)	4.5 (1–13.5)	0.326
Neutrophil (3rd month)	5.9 (3.8)	4.3 (1.6–21.2)	
NLR (at diagnosis)	4.1 (3.9)	2.7 (0.5–23.6)	0.318
NLR (3rd month)	4.0 (3.0)	3.2 (0.4–16.4)	
PLR (at diagnosis), $\times 10^3$	186.3 (146.1)	150.4 (24.2–936.7)	0.447
PLR (3rd month), $\times 10^3$	207.4 (220.0)	162.0 (16.0–1825.0)	

SD: Standard Deviation, MCV: Mean Corpuscular Volume, PLT: Platelet, NLR: neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

Table 3: Progression-free survival and overall survival.

	Total Events / n	Total
Overall Survival (OS)	63/75	
Median (95% CI), month		18.0 (14.4–21.6)
6 months overall survival rate		81.3%
12 months overall survival rate		68.9%
24 months overall survival rate		38.1%
36 months overall survival rate		19.8%
Progression-free survival (PFS)	71/75	
Median (95% CI), months		11.0 (6.8–15.2)
6 progression-free survival rate		64.0%
12 progression-free survival rate		49.3%
24 progression-free survival rate		19.3%
36 progression-free survival rate		8.3%

Table 4 illustrates patients' demographic and clinical characteristics based on their treatment responses and progression status in the third month. Upon analysis of the table, it was observed that no statistically significant correlation existed between treatment response and the development of progression concerning demographic and clinical variables, including age (P=0.997), gender (P=0.092), histological subtype (P=0.131), smoking status (P=0.290), and driver mutations (P=0.290).

A statistically significant discrepancy in OS was evident between females and males, with females exhibiting a median survival of 25 months (95% CI 17–32 months), while males displayed a median survival of 13 months (95% CI 9–20 months,

P=0.008). In terms of PFS, women experienced a PFS of 14.5 months (95% CI 11–21 months), whereas men had a PFS of six months (95% CI 4–17 months), demonstrating a statistically significant distinction (*P*=0.02).

Table 4: Response rates of patients and distribution of demographic and clinical findings.

	Stable + Partial + Complete Response	Progression	*P*-value
	n (%)	n (%)	
Age			0.997
<65	22 (46.8)	12 (50)	
≥65	25 (53.2)	12 (50)	
Gender			0.092
Female	29 (61.7)	9 (37.5)	
Male	18 (38.3)	15 (62.5)	
Histological subtype			0.131
Adenocarcinoma	42 (89.4)	17 (70.8)	
Squamous cell carcinoma	3 (6.4)	5 (20.8)	
NOS	2 (4.3)	2 (8.3)	
Smoking			0.290
Non-smoker	34 (72.3)	14 (58.3)	
Quit	1 (2.1)	3 (12.5)	
Smoking	1 (2.1)	1 (4.2)	
Unknown	11 (23.4)	6 (25)	
Mutation			0.192
Exon 19	9 (19.1)	6 (25)	
Exon 21	11 (23.4)	2 (8.3)	
Unknown	24 (51.1)	15 (62.5)	
Negative	3 (6.4)	0 (0)	
Other	0 (0)	1 (4.2)	

No statistically significant difference was observed between the MCV measurements at the time of diagnosis and the third month concerning factors such as gender, histological subtype, smoking status, and mutation types.

The MCV value at the time of diagnosis decreased from 91.0 to 89.7 in individuals aged <65 years by the third month, while in individuals aged ≥65 years, it increased from 90.4 to 91.4. Although no statistically significant difference emerged in MCV measurements (*P*=0.775), a significant contrast was evident in MCV values between the diagnosis and the third month concerning different age groups (*P*=0.044). Notably, there was only one patient with macrocytosis (MCV >100) and no other underlying causes who also displayed a baseline MCV >100.

Discussion

Tyrosine kinases constitute a subgroup of protein kinases primarily responsible for facilitating the transfer of phosphate groups, typically derived from ATP, to target proteins. This process induces functional modifications within the protein structure. These molecules play a pivotal role in instigating tumor growth through diverse mechanisms. These mechanisms encompass cell proliferation, stromal expansion, angiogenesis, and tissue invasion. Genetic mutations leading to activating the pathways above are frequently identified in tumors. Instances encompass the overexpression of growth factors or hormones, their receptors, or the activation of tyrosine kinase receptors.

TKIs operate by impeding the signaling pathways of growth factors through various means. During chronic cancer treatment, the evolution of resistance mechanisms in cancer cells entails secondary mutations in the target site, the activation of alternative signaling pathways, and evasive maneuvers against the immune system. Among these mechanisms, the most prevalent is the occurrence of point mutations at the tyrosine kinase's binding site, resulting in a diminished affinity for TKIs. Given that TKIs necessitate prolonged administration, non-compliance with the prescribed treatment regimen is one of the foremost reasons for diminished efficacy [12].

Erlotinib is employed in treating non-small cell lung cancer (NSCLC) characterized by epidermal growth factor receptor (EGFR) mutations. The prevalent mutations comprise exon 19 deletion (del19) and exon 21 (L858R) substitution. Among the frequently encountered and controllable side effects are skin-related toxicities like rash, muscle and joint discomfort, diarrhea, and cough. In rare instances, more severe side effects may manifest, encompassing interstitial pneumonitis, gastrointestinal perforation, stroke, and corneal ulceration. The emergence of these side effects can be attributed to the inhibitory effects on EGFR.

MCV is a non-invasive, convenient, and cost-effective indicator for assessing red blood cells. This indicator can be readily obtained through a comprehensive analysis of the complete blood count. Macrocytosis, an emerging and frequent laboratory side effect, has been associated with prolonged treatment using the widely utilized TKI sunitinib [13]. The precise mechanism underlying sunitinib-induced macrocytosis remains elusive. Investigations have ruled out alternative causes such as vitamin B12 or folic acid deficiency, liver disease, or nutritional inadequacies. According to Rini et al. [13], sunitinib might directly trigger macrocytosis. A plausible explanation posits that sunitinib induces macrocytosis by inhibiting the c-KIT receptor of progenitor cells within the bone marrow. The restoration of MCV to normal levels following the discontinuation of the agent underscores the transient and reversible nature of this phenomenon. In contrast, sorafenib, a multikinase inhibitor with a potent impact on vascular endothelial growth factor (VEGF), does not affect MCV in renal cell carcinoma (RCC) patients due to its limited effect on c-kit [14].

In this investigation, no differences were detected in gender, histological subtype, smoking habits, or mutation types when comparing MCV measurements taken at the time of diagnosis and those obtained in the third month. However, variations in MCV values were noted between measurements taken solely at the diagnosis and those at the third month, stratified by age groups. Among individuals below the age of 65, the MCV value decreased at the time of diagnosis, while in the third month, an increase was observed among those aged 65 or older. Existing research has demonstrated that generally healthy individuals' MCV values rise with age [15]. Nonetheless, the observed MCV elevation in our study did not meet the criteria for macrocytosis. It is reasonable to consider that this outcome may not be linked to the treatment regimen.

The research conducted by Schallier et al. [16] revealed a notable elevation in mean MCV values from baseline with the administration of sunitinib and imatinib. They noted that neither sorafenib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, nor erlotinib, an EGFR inhibitor, exhibited an impact on MCV. The progression of macrocytosis was characterized by a gradual increase over time, a sustained elevation that remained statistically significant, and eventual plateauing after 6 months, all observed under the standard dose of sunitinib. However, our study lacked the necessary long-term patient follow-up to perform analyses spanning 6 months.

The underlying mechanism behind macrocytosis in TKI treatment remains elusive, though it is speculated to be linked to the inhibition of c-KIT in red blood cell progenitors within the bone marrow. This hypothesis is reinforced by the absence of macrocytosis when administering sorafenib, which exhibits a lower affinity for c-KIT. Nevertheless, it's plausible that inhibiting additional signaling pathways might also contribute to the emergence of macrocytosis [16,17]. Prior research has indicated that hematological progenitors are involved in regulating normal cell proliferation and differentiation within the bone marrow, displaying inherent signaling activity. Furthermore, the effects of newly developed signal transduction inhibitors warrant investigation [16].

Macrocytosis was identified in nearly half (42%) of gastrointestinal stromal tumors (GIST) patients undergoing treatment with the c-KIT inhibitor imatinib [14].

Limited literature exists investigating macrocytosis's potential prognostic or predictive significance in erlotinib usage. The discovery of any such correlation could pave the way for more extensive studies, enabling early assessment of treatment response/resistance prior to imaging and facilitating the adoption of a cost-effective and non-invasive method for monitoring treatment outcomes. The macrocytosis observed using TKIs is primarily believed to be associated with c-kit inhibition. Notably, erlotinib functions as an EGFR inhibitor without any known impact on c-kit. Hence, an inquiry was conducted to determine whether macrocytosis could emerge through unidentified mechanisms. Nonetheless, upon examining these findings, it was ascertained that erlotinib did not lead to the development of macrocytosis.

In this study, we additionally observed that gender exerted an influence on OS and PFS, with females exhibiting statistically significant superiority over males. Existing literature supports the notion that response rates are most prominent in cases of nonsquamous histology, particularly among women with no smoking history [18].

Limitations

The retrospective nature of our study constitutes a primary limitation, leading to inherent heterogeneity within the examined subgroups. Moreover, our analysis was confined to the third-month measurements due to the absence of extended follow-up data for certain patients. The potential for MCV elevations to manifest over an extended follow-up period is an additional constraint in our study. Consequently, assessing longer-term outcomes would hold significance and provide a more comprehensive understanding of the phenomenon.

Conclusion

Considering the outcomes of this study, in contrast to certain other TKIs like imatinib and sunitinib, there was no observed increase in MCV values at the third-month measurement. This finding supports the notion that macrocytosis associated with TKI usage can be attributed to c-kit inhibition, a mechanism not applicable to erlotinib. Distinct disparities in MCV values were noted between measurements taken at diagnosis and those at the third month, stratified by age groups. Notably, within the third month, MCV levels increased among individuals aged 65 and above, yet macrocytosis did not manifest. Furthermore, OS and PFS were more favorable in female patients than their male counterparts. In conclusion, this study suggests a lack of correlation between erlotinib use and the occurrence of macrocytosis, but it highlights the greater benefit experienced by female patients undergoing erlotinib treatment. It is important to note that these conclusions should be considered within the context of long-term follow-up results.

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