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Factors influencing the prognosis in Braf wild-type metastatic malignant melanoma and the role of novel inflammation indices

Braf wild tip metastatik malign melanomda prognozu etkileyen faktörler ve yeni enflamasyon indekslerinin rolü

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Abstract

Background and Design: This study aims to investigate the prognostic factors in BRAF wild-type metastatic cutaneous melanoma and the prognostic role of inflammation indices.
Materials and Methods: Metastatic BRAF wild-type cutaneous melanoma patients who presented to our clinic between 2011 and 2021 were enrolled. To investigate their prognostic roles, age, gender, performance status, first immunotherapy regimen received by the patient, metastatic sites, and seven inflammation indices [C-reactive protein (CRP)/albumin ratio (CAR), neutrophil lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and advanced lung cancer inflammation index (ALI) and hemoglobin, albumin levels, lymphocyte and platelet counts (HALP)] were studied.
Results: Fourty-seven patients, consisting of 22 (46.8%) females and 25 (53.2%) males, were included in this study. Mean patient age was 54 (18-88) years. In our study, there were 16 (34%) patients with liver metastasis, 17 (36.2%) patients with lung metastasis, and 9 (19.1%) patients with brain metastasis. As immunotherapy, 34 (72.3%) patients had received Nivolumab, while 13 (27.7%) patients had received Ipilimumab therapy. When the relationships of the prognostic variables with overall survival were inspected in univariate and multivariate analyses, brain metastasis was found to be an independent prognostic factor (p=0.02). Lung metastasis approached the threshold of statistical significance in univariate analysis (p=0.09) and liver metastasis in multivariate analysis (p=0.07). The seven inflammation indices examined in the analyses [CAR, NLR, PNI, PLR, SII ALI and HALP] were found to have no prognostic role in both univariate and multivariate analyses.
Conclusion: Our study determined that brain metastasis is an independent poor prognostic factor in BRAF wild-type metastatic melanoma. Prognostic roles of the CAR, NLR, PNI, PLR, SII ALI and HALP indices could not be demonstrated.
Keywords: BRAF wild, metastatic melanoma, inflammation indices, prognosis

Öz

Amaç: Bu çalışma BRAF wild tip metastatik melanomda prognostik faktörleri ve enflamasyon indekslerinin prognostik rolünü araştırmayı amaçlamaktadır.
Gereç ve Yöntem: Kliniğimize 2011-2021 yılları arasında başvuran metastatik evre BRAF wild tip melanom hastaları dahil edildi. Prognostik rolleri araştırılmak üzere; yaş, cinsiyet, performans durumu, aldığı ilk immünoterapi ve metastaz alanları ile birlikte 7 enflamasyon indeksi [C-reaktif protein (CRP)/albumin oranı (CAR), nötrofil lenfosit oranı (NLR), prognostik nütrisyonel indeks (PNI), platelet lenfosit oranı (PLR), sistemik immün-enflamasyon indeks (SII), ileri akciğer kanseri enflamasyon indeksi (ALI) ve hemoglobin, albumin düzeyi, lenfosit ve platelet sayısı skoru (HALP)] incelendi.
Bulgular: Çalışmamıza 22 (%46,8) kadın, 25 (%53,2) erkek olmak üzere toplam 47 hasta alındı. Hastaların ortalama yaşları 54 (18-88) yıl idi. Çalışmamızda 16 (%34) hastada karaciğer metastazı, 17 (%36,2) hastada akciğer metastazı, 9 (%19,1) hastada ise beyin metastazı mevcuttu. İmmünoterapi olarak 34 (%72,3) hasta Nivolumab, 13 (%27,7) hasta ise Ipilimumab tedavisi almıştı. Genel sağkalım ile potansiyel prognostik değişkenlerin ilişkisine bakıldığında tek ve çok değişkenli analizde beyin metastaz varlığı bağımsız prognostik faktör olarak tespit edildi (p=0,02).

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Tek değişkenli analizde akciğer metastaz varlığı (p=0,09), çok değişkenli analizde karaciğer metastaz varlığı (p=0,07) istatistiksel anlamlılık sınırına yakındı. Analizlerde incelenen 7 enflamasyon indeksinin [CAR, NLR, PNI, PLR, SII ALI ve HALP] hem tek hem çok değişkenli analizde prognostik rollerinin olmadığı gözlendi.
Sonuç: Çalışmamızda beyin metastaz varlığı BRAF wild tip metastatik melanomda bağımsız kötü prognostik faktör olarak tespit edildi. CAR, NLR, PNI, PLR, SII ALI ve HALP indekslerinin prognostik rolleri gösterilemedi.
Anahtar Kelimeler: BRAF wild, metastatik melanom, enflamasyon indeksleri, prognoz

Introduction

Malignant melanoma is considered the most aggressive type of skin cancer and is the fifth most prevalent type of cancer[1]. While it is curable in the early stages, it displays an aggressive course at the metastatic stage. BRAF mutation constitutes the most frequent gene mutation in malignant melanoma. Particularly, a targetable BRAF V600 mutation is common[2,3]. Immunotherapy is included among the current treatment approaches for patients without BRAF gene mutations[4]. Although the poor prognostic factors in early-stage melanoma patients have been well elucidated, the controversial areas concerning the prognostic factors in advanced-stage patients remain unresolved[5]. After lung and breast cancer, malignant melanoma is the third most common type of cancer that progresses to brain metastasis[6]. While the risk of brain metastasis is around 10% in all melanoma patients, the rate of brain metastasis reaches approximately 40 to 60% at the metastatic stage[7-9]. Brain and lung metastases are associated with a poor survival rate[5,10].
As is the case in multiple diseases, the current inflammation indices have also been investigated in malignant melanoma. Of inflammation indices, the majority are computed using blood count parameters, albumin and body mass index parameters; the roles of C-reactive protein (CRP)/albumin ratio (CAR), neutrophil lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and advanced lung cancer inflammation index (ALI) have been investigated in melanoma patients[11-15]. Meanwhile, the hemoglobin, albumin levels, lymphocyte, and platelet counts (HALP) score have been studied in certain malignancies other than melanoma[16].
In this study, we investigate the role of potential prognostic parameters and inflammatory indices in predicting the prognosis of BRAF mutation-negative metastatic malignant melanoma.

Materials and Methods

Patients

This study included adult patients with a diagnosis of metastatic-stage BRAF wild-type cutaneous malignant melanoma, who presented to Dicle University Medical Oncology Clinic between 2011 and 2021. Only cutaneous melanoma patients were included in the study. Besides demographic characteristics, patients' clinical findings, laboratory parameters, and the treatments they received were reviewed through the hospital archiving system. Patients' gender data, stages at initial diagnosis, and Eastern Cooperative Oncology Group performance status (ECOG PS), age, weight, height, BRAF mutation status at the first metastatic manifestation, the first treatments they received in the metastatic phase as immunotherapy, and the metastatic sites were recorded. Furthermore, from the patients' laboratory parameters from the early metastatic phase, hemoglobin level, neutrophil count, platelet count, lymphocyte count, albumin, and CRP levels were investigated. Staging followed the American Joint Committee on Cancer manual, 8th edition.
An ethical approval was granted by the Dicle University Faculty of Medicine Ethics Committee (approval number: 356, date: 06.05.2021).

Formulae for the calculation of the indices

Patients' inflammation index values were obtained using the laboratory and clinical parameters from the first 28 days of metastatic disease progression. The following formulae were used in the calculation of the listed indices: body mass index (BMI) = weight (kg)/height^2 (m^2), CAR = CRP (mg/dL)/serum albumin (g/dL), NLR = absolute neutrophil count (10^3/microL)/absolute lymphocyte count (10^3/microL), ALI = BMI x serum albumin (g/dL) / NLR, PNI = [(10x serum albumin (g/dL)) + (0.005x absolute lymphocyte count (count/microL))], HALP = hemoglobin (g/L) x serum albumin (g/L) x absolute lymphocyte count (10^3/microL)/absolute platelet count (10^3/microL), PLR = absolute platelet count (10^3/microL)/absolute lymphocyte count (10^3/microL) and SII = absolute neutrophil count (10^3/microL) x absolute platelet count (10^3/microL)/absolute lymphocyte count (10^3/microL)

Analyzed variables

Age, gender, ECOG PS, received treatments, and metastatic sites were considered potential variables that could influence the prognosis of malignant melanoma in light of the literature. Besides these, seven indices, namely CAR, NLR, ALI, PNI, HALP, PLR, and SII, were included in survival analysis. The associations of the potential prognostic variables and inflammation indices with overall survival were investigated using univariate and multivariate analyses. Overall survival was calculated as the time from diagnosis of metastatic disease to death.

Statistical analysis

The PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, USA) software was utilized for statistical analysis of the data. Descriptive statistics were used to evaluate patient characteristics and frequencies of the parameters. Pearson's correlation and Spearman's correlation were used for analysis of normally distributed variables and non-normally distributed variables, respectively. Survival was analyzed using the Kaplan-Meier method; the Log rank P value was taken as the basis. In survival analyses, Cox regression analysis was used for univariate and multivariate analyses. The enter method was used in univariate analysis, and the backward stepwise likelihood ratio method was used in multivariate analysis. A 95% confidence interval and a two-tailed significance level of p<0.05 were taken.

Results

A total of 47 patients, consisting of 22 (46.8%) females and 25 (53.2%) males, were included in this study. Mean patient age was 54 (18-88) years. At progression to metastatic disease, ECOG PS was 0-1 in 43 (91.5%) patients and >1 in 4 (8.5%) patients. Fifteen (31.9%) patients had already presented with metastatic disease at the time

of presentation. Of the remaining patients, 8 (17%) had presented with stage-II disease and 24 (51.1%) with stage-III disease, developing metastasis later (all patients were in the metastatic stage when included in the study). When the metastatic sites were considered, there were 17 (36.2%) patients with lung metastasis, 16 (34%) patients with liver metastasis, and 9 (19.1%) patients with brain metastasis. When evaluated with respect to the type of immunotherapy they received, 34 (72.3%) patients had received Nivolumab as first-line immunotherapy, while 13 (27.7%) patients had received Ipilimumab therapy. The general characteristics of the patients and mean values of inflammation indices are presented in Table 1.

Table 1. Baseline characteristics of patients

		n (%)
Age (median, range)		54 (18-88)
Gender		
Female		22 (46.8)
Male		25 (53.2)
ECOG PS		
0-1		43 (91.5)
>1		4 (8.5)
Stage at diagnosis		
II		8 (17)
III		24 (51.1)
IV		15 (31.9)
Metastasis area*		
Liver		16 (34)
Lung		17 (36.2)
Brain		9 (19.1)
First line immunotherapy option		
Nivolumab		34 (72.3)
Ipilimumab		13 (27.7)
	Mean	**Max-min**
CAR	0.52	0.1-4.2
NLR	3.1	0.8-22.5
ALI	46	4-191
PNI	47.7	25.3-64.5
HALP	41.7	8-81.1
PLR	155	65-743
SII	837	219-6,198

ECOG PS: Eastern Cooperative Oncology Group performance status, CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, ALI: Advanced lung cancer inflammation index, PNI: Prognostic nutritional index, HALP: Haemoglobin, albumin levels, lymphocyte and platelet counts, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index, max: Maximum, min: Minimum, *All patients were in the metastatic stage when included in the study.

When the associations between the inflammation indices were inspected, a strong negative correlation was found between ALI-NLR and PLR-HALP. A moderate positive correlation was determined between PNI-ALI and SII-HALP, while a strong positive correlation was determined between SII-PLR (Table 2). When the variables were evaluated in univariate analysis with respect to the prognosis, inflammation indices (CAR, NLR, ALI, PNI, HALP, PLR and SII), age, gender, ECOG PS, the choice of first-line immunotherapy, and the presence of liver metastasis did not have a statistically significant relationship with overall survival (OS).

The median OS time was 16 months in patients who were administered Ipilimumab and 12 months in patients who were administered Nivolumab as the first-line immunotherapy. These two groups were not significantly different (p=0.80).

Although the presence of lung metastasis was not statistically significant in univariate analysis, it was a poor prognostic factor approaching the threshold of statistical significance (p=0.09). The presence of brain metastasis had a statistically significant association with a shorter survival rate. The median overall survival time was 10 months in those with brain metastasis as opposed to 26 months in those without brain metastasis [(Log-rank p=0.034), (heart ration (HR): 2.30; 95% confidence interval (CI): 1.02-5.18)] (Figure 1). The presence of liver metastasis had a relationship with OS that approached the threshold of statistical significance in multivariate analysis [(HR: 1.95; 95% CI: 0.93-4.09), (p=0.07)], while the presence of brain metastasis had a significant relationship with OS [(HR: 2.53; 95% CI: 1.11-5.76), (p=0.02)]. In our study, the presence of brain metastasis was a poor prognostic factor for BRAF wild-type metastatic cutaneous melanoma (Table 3).

Discussion

In localized-stage melanoma, prognostic factors, such as age, gender, Clark level, tumor site, lymph node metastasis, and tumor thickness, have been previously identified[17]. In advanced melanoma, the presence of lung metastasis and brain metastasis are poor prognostic factors[5]. In this study, we investigated the prognostic factors in BRAF wild-type metastatic cutaneous melanoma and the prognostic role of inflammation indices that are currently being extensively investigated in several types of cancer.

The presence of brain metastasis was reported to be a poor prognostic marker for melanoma, and the median OS is approximately 6 months in these patients[18,19]. Zhang et al.[10] determined the median OS as 5 months in patients who had brain metastasis and 28 months in those who did not. In our study, the rate of brain metastasis was 19.1%, consistent with the literature. Patients with brain metastasis had a median OS of 10 months, whereas the median OS was 26 months in the group without brain metastasis. The median OS was remarkably longer in patients without brain metastasis, and the relationship of brain metastasis with OS was consistent with the rates reported in literature.

The presence of lung metastasis is a poor prognostic factor for melanoma[5]. In our study, While the presence of lung metastasis and liver metastasis approached the level of statistical significance, only the presence of brain metastasis reached a significant relationship with a poor OS.

Table 2. Relationship between inflammation indices

		CAR	NLR	ALI	PNI	HALP	PLR
NLR	**r**	0.546	–	–	–	–	–
	p	<0.001	–	–	–	–	–
	n	47	–	–	–	–	–
ALI	**r**	-0.419	**-0.871**	–	–	–	–
	p	0.003	**<0.001**	–	–	–	–
	n	47	47	–	–	–	–
PNI	**r**	-0.090	-0.441	**0.607**	–	–	–
	p	0.548	0.002	**<0.001**	–	–	–
	n	47	47	47	–	–	–
HALP	**r**	-0.125	-0.440	0.464	0.575	–	–
	p	0.404	0.002	0.001	<0.001	–	–
	n	47	47	47	47	–	–
PLR	**r**	0.194	0.467	-0.436	-0.438	**-0.935**	–
	p	0.191	0.001	0.002	0.002	**<0.001**	–
	n	47	47	47	47	47	–
SII	**r**	0.443	**0.714**	-0.555	-0.156	**0.657**	**0.746**
	p	0.002	**<0.001**	<0.001	0.294	**<0.001**	**<0.001**
	n	47	47	47	47	47	47

CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, ALI: Advanced lung cancer inflammation index, PNI: prognostic nutritional index, HALP: Haemoglobin, albumin levels, lymphocyte and platelet counts, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index

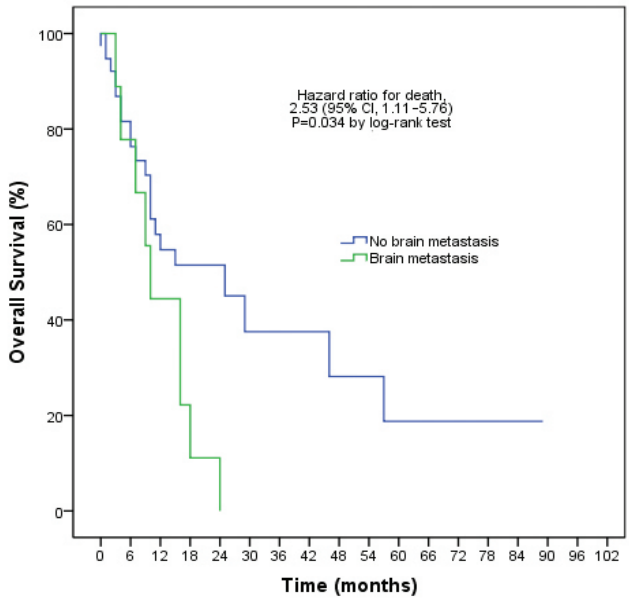

Figure 1. Overall survival according to brain metastasis status

When Nivolumab was compared with chemotherapy (dacarbazine) in advanced melanoma patients without BRAF mutation, immunotherapy offered an advantage in terms of OS and progression-free survival (PFS)[20]. From checkpoint inhibitors, the combination of programmed cell death 1 (PD-1) inhibitors (Nivolumab, pembrolizumab) with ipilimumab is associated with more favorable response rates and PFS outcomes compared with single-agent PD-1 in advanced-stage melanoma patients. A combination of nivolumab and ipilimumab offers better survival outcomes than single-agent ipilimumab[21,22]. Meanwhile, in BRAF wild-type melanoma, the survival outcomes of single-agent nivolumab are comparable to those of combination immunotherapy[23]. Due to the inclusion of older patients and the national pharmaceutical reimbursement policies, 13 (27.7%) patients had used single-agent ipilimumab, and 34 (72.3%) patients had used single-agent nivolumab. Median OS outcomes were 16 months in the ipilimumab arm and 12 months in the nivolumab arm. The two agents had similar survival outcomes in terms of overall survival.

Although CAR has been evaluated as a prognostic biomarker in several types of cancer, to our knowledge, it was not studied as a prognostic factor in malignant melanoma patients. However, elevated CRP levels were reported to indicate a poor OS and melanoma-specific survival rate[11,24,25]. In our study, there was no statistically significant association between CAR and the prognosis in advanced BRAF wild-type melanoma. CAR levels did not have a significant relationship with survival rate.

In a study conducted by Capone et al.[12] on 97 patients diagnosed with stage-IV malignant melanoma who received nivolumab, a high NLR was reported to be associated with poor survival outcomes. In their study, they emphasized that patients with NLR ≥5 had particularly poorer survival outcomes[12]. Different studies have suggested different cut-off values for NLR[26,27]. There were also studies that could not demonstrate a significant relationship between NLR and survival in

Table 3. Examining the effects of parameters on overall survival, univariate and multivariate analysis results

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P value****	**HR**	**95% CI**	**p value*****
Gender (Female*/male)	1.66	0.79-3.47	0.17			
Age	1.02	0.99-1.04	0.19			
ECOG PS (0-1*/ >1)	1.88	0.56-6.34	0.30			
Metastasis area						
Liver (no*/yes)	1.77	0.85-3.68	0.12	1.95	0.93-4.09	0.07
Lung (no*/yes)	1.87	0.90-3.90	0.09			
Brain (no*/yes)	**2.30**	**1.02-5.18**	**0.04**	**2.53**	**1.11-5.76**	**0.02**
First line immunotherapy option (Nivo*/İpi)	0.90	0.40-2.03	0.80			
CAR	1.02	0.68-1.51	0.91			
NLR	0.94	0.79-1.12	0.52			
ALI	0.99	0.98-1.01	0.59			
PNI	0.98	0.93-1.03	0.45			
HALP	0.99	0.97-1.01	0.40			
PLR	1.00	0.99-1.01	0.87			
SII	1.00	0.99-1.00	0.59			

*Reference category, **Cox regression analysis Enter method, ***Cox regression analysis Backward stepwise likelihood ratio method, ECOG PS: Eastern Cooperative Oncology Group performance status, CAR: C-reactive protein albumin ratio, NLR: Neutrophil lymphocyte ratio, ALI: Advanced lung cancer inflammation index, PNI: Prognostic nutritional index, HALP: Haemoglobin, albumin levels, lymphocyte and platelet counts, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index, Nivo: Nivolumab, İpi: Ipilimumab, CI: Confidence interval

their multivariate analyses[28]. Similarly, our study did not determine a statistically significant relationship between NLR and OS.

Studies that have examined PNI in melanoma are quite scarce. Among systemic inflammation indices, a high PNI and low SII were reported by Mirili et al.[28] to be associated with better PFS and OS. However, this study enrolled melanoma patients regardless of disease stage. Meanwhile, a study by Hannarici et al.[13] did not show PNI and SII levels to be related to survival in the multivariate analysis. Our study included metastatic-stage BRAF mutation-negative patients. Consistent with the study by Hannarici et al.[13], PNI and SII did not display a statistically significant relationship with OS in our study.

Conflicting results have been reported concerning PLR levels in the prediction of the prognosis of malignant melanoma. In a meta-analysis conducted by Zhang and Gong[14] that included the results of nine studies, it was suggested that high PLR levels could indicate a poor prognosis and that PLR should be assessed in the preoperative period. Most studies in this meta-analysis also included patients in early stages. A study performed by Qi et al.[29] on 140 stage II-IV patients reported high PLR levels to be associated with poor survival outcomes. However, their multivariate analysis did not incorporate important prognostic factors, such as the metastatic sites[29]. In our study, PLR levels were not found to have a relationship with survival.

ALI is an inflammation index predominantly studied for the prediction of prognosis of lung cancer[15]. Cheng et al.[30] and colleagues investigated the role of ALI in predicting the treatment response in malignant melanoma patients who received immunotherapy as second-line treatment. This study proposed that ALI could predict the response to immunotherapy in the second-line treatment of malignant melanoma[30]. The prognostic role of ALI in malignant melanoma is unknown. In our study, ALI did not have a significant association with the prognosis in univariate and multivariate analyses.

The HALP score has not been previously evaluated in melanoma patients. It was reported to predict overall survival with NLR in small-cell lung cancer[16]. In this study, we investigated the relationship of the HALP score, which is among the scores that are being popularly studied, with the prognosis in malignant melanoma. In our study, the HALP score was not found to have a statistically significant relationship with OS.

When the associations between inflammation indices were evaluated in our study, most were found to show negative or positive correlations with each other at varying degrees. This was thought to arise from the use of similar parameters in the calculation of these inflammation indices.

Most inflammation indices, the prognostic values of which are currently being studied in various types of cancer, are obtained using CRP, albumin, BMI, and blood count parameters. Since these parameters are quite sensitive to acute inflammatory events and infections, we reason that they may prove insufficient in the prediction of long-term prognosis. We think the investigation of parameters that reflect the specific characteristic features of the disease that might be associated with treatment response and that would either not be influenced by acute events or show a minimal effect as prognostic markers will contribute to the literature.

Study Limitations

The limitations of the present study include its single-center nature, the low number of patients, and the heterogeneity of the patient population.

Conclusion

In this study, the presence of brain metastasis was determined to be an independent poor prognostic factor. From novel popular inflammation indices, CAR, NLR, PNI, PLR, SII, HALP, and PNI were not found to have a significant relationship with overall survival.

Ethics

Ethics Committee Approval: An ethical approval was granted by the Dicle University Faculty of Medicine Ethics Committee (approval number: 365, date: 06.05.2021).

Informed Consent: Our study has a retrospective design and was conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Z.K., Z.O., Y.S., Z.U., M.K., M.A.K., A.I., Concept: S.E., Z.K., Z.O., Y.S., Z.U., M.K., M.A.K., A.I., Design: S.E., Z.K., Z.O., Data Collection or Processing: S.E., Z.K., Z.O., Y.S., Z.U., Analysis or Interpretation: S.E., Z.K., Z.O., Y.S., Z.U., M.K., M.A.K., A.I., Literature Search: S.E., Z.K., Z.O., Y.S., Z.U., Writing: S.E., Z.K., Z.O.

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