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Original Article

Are they all the same? Different effects of opioid types on survival in metastatic NSCLC receiving nivolumab

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Abstract: The aim of this study was to evaluate the effects of concurrent opioid analgesic (OA) use and types of OA on progression-free survival (PFS) and overall survival (OS) in non-small cell lung cancer (NSCLC) patients receiving nivolumab. This observational, retrospective study included patients with pathologically confirmed, driver mutations negative metastatic NSCLC at five different hospitals in Turkey between 2018 and 2024. A total of 209 patients were included in this study. Of these patients, 113 (54.1%) used OA. 86 (41.1%) patients were using tramadol, and 48 (23.4%) were using fentanyl. The median survival of the group without OA was significant in the univariate analysis compared to that of the group with OA PFS (7 vs. 4 months, P = 0.006) an OS (8 vs. 14 months, P = 0.003). The group with bone metastases had worse OS than the group without bone metastases [7 vs. 15 months, HR (95% CI) = 1.810 (1.064-3.079), (P = 0.029)]. In the group without bone metastases, patients on tramadol had worse PFS than patients not on tramadol [5 vs. 8 months, HR (95% CI) = 2.260 (1.097-4.655), (P = 0.027)]. In conclusion, OA use was associated with poor PFS and OS. Fentanyl use led to worse OS in the group with bone metastases, whereas tramadol use led to worse PFS in the group without bone metastases. The prognostic impact of OA may differ according to the site of metastasis; therefore, prospective studies that include the type of OA are needed.

Keywords: Opioid analgesic, immune checkpoint inhibitors, tramadol, fentanyl, NSCLC

Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide. The 5-year survival rate was <20% [1]. Although the discovery of immune checkpoint inhibitors (ICI) and monoclonal antibodies in non-small cell lung cancer (NSCLC) has been a beacon of hope in recent years, it is important to determine the factors that affect prognosis [2, 3].

Pain is one of the most feared symptoms in cancer patients and is difficult to control [4]. A meta-analysis showed that 64% of patients with metastasis experienced lifelong pain [5]. Opioid analgesics (OA) are the most important analgesic drugs used to treat moderate or severe cancer pain [6].

Several mechanisms have been identified to explain the positive association between opioid exposure and tumor growth. A study in human lung cancer cell culture showed increased expression of mu (μ) opioid receptor (MOR) and morphine-induced epidermal growth factor receptor (EGFR) [7, 8]. OAs have also been shown to increase angiogenesis and tumor growth in cell cultures via MOR [9]. OAs also contribute to tumor growth by facilitating mesenchymal transport of cancer stem cells [10]. A study on lung cancer cells showed that fentanyl increased cisplatin sensitivity by increasing apoptosis [11].

Drug-drug interactions (DDI) are important because of the possibility of toxicity resulting from the narrow therapeutic index of anticancer

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agents. Concomitant drugs may have increased toxicity and decrease efficacy [12]. Studies have revealed that the use of proton pump inhibitors, systemic antibiotics, and systemic steroids with some ICIs worsens prognosis [13, 14]. In a study evaluating the effect of concomitant drug use on survival in patients with NSCLC receiving nivolumab, steroid use was found to worsen prognosis [15]. Advances in DDI have led to new restrictions on the use of other medications in patients receiving ICIs. ICIs may lead to different outcomes in different patient.

Thus, OAs may play an important role in ICI resistance. This is because the immune cells contain opioid receptors. Specifically, MOR-1 and MOR-2 are subtypes, each of which is involved in the modulation of analgesia and immune responses. Opioids acting through mu receptors have been reported to exert immunomodulatory effects that can suppress immune responses depending on several factors, including the type of opioid and dosage [16, 17]. This dual nature poses a challenge in integrating opioid therapy with immunotherapeutic strategies because certain opioids can potentially impair the immune response to treatments such as anti-PD-1/PD-L1 agents [18]. Modulation of T cell activation and cytokine production by mu receptors can significantly influence the immune environment within tumors and affect the overall efficacy of immunotherapies. Therefore, understanding the mechanisms underlying these interactions is crucial for developing innovative therapeutic approaches that enhance both pain management and enhanced immune responses [19]. In vitro studies have shown that morphine increases lymphocyte proliferation by binding to μ receptors. OA, especially morphine, increases interleukin (IL) -2 levels and decreases IL-4 levels in T cells, leading to decreased T cell activity and therefore may affect the response to immunotherapy [20]. Morphine and fentanyl increase Treg numbers [18]. OAs may reduce the therapeutic efficacy of ICIs by altering the intestinal microbiota, cytokine production, and T cell activity [21]. In the literature, there are studies including different ICIs in heterogeneous cancer populations. OA use has been associated with poor survival [13, 22, 23].

Due to the different effects of OA types on the immune system, no study has investigated the effect of OA types on survival. The effect of the OA type on the effectiveness of ICIs, if supported by strong evidence, will contribute to the literature in terms of both pain relief and prognosis. We conducted this study to determine whether there is a relationship between OA types and survival in patients with metastatic NSCLC who received nivolumab.

Materials and methods

This observational retrospective study included patients with pathologically confirmed EGFR, ALK, ROS-1 negative adenocarcinoma or squamous cell carcinoma (SCC), and metastatic NSCLC in six different hospitals in Turkey between 2018 and 2024. Patient and hospital databases were also reviewed. Patients with adequate follow-up and appropriate imaging to assess treatment responses were included. Patients who received nivolumab as neoadjuvant or adjuvant treatment, had a history of additional malignant tumors, received immunotherapy in metastatic 1st line, had active infection at the time of diagnosis, or had missing data were excluded from the study. Various details were recorded, including patient demographics, histologic subtypes of cancer, locations of metastases, use OA, date of OA onset, types of OA used (fentanyl, codeine, morphine, or tramadol), and date of the last follow-up.

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were presented as numbers and percentages for categorical variables, and mean, standard deviation, minimum, maximum, median, and interquartile range for numerical variables when normal distribution conditions were met. Survival rates were calculated using Kaplan-Meier analysis. Risk factors were analyzed using Cox Regression Analysis. The statistical significance was set at $P<0.05$. Progression-free survival (PFS) is measured as the time interval between the initation of immunotherapy and disease advancement, death, or the final patient visit. Overall survival (OS) is calculated as the duration from the initiation of immunotherapy until either death or the last patient visit.

The research was designed and implemented in compliance with Good Clinical Practice guidelines and the Helsinki Declaration. It received approval from the ethics committee at Alanya Alaaddin Keykubat University on September

Table 1. The features of study population

Age (years)	Mean		Median	
	63.4		64	
Gender N%	Male		Female	
	182 (87.1)		27 (12.9)	
ECOG n%	0	1	2	3
	50 (24)	104 (50)	51 (24.5)	3 (1.5)
Metastasis Type n%	Denovo		Recurrent	
	120 (57.4)		89 (42.6)	
Histologic Types n%	Adenocarcinoma	SCC	Others	
	78 (37.3)	124 (59.3)	7 (3.4)	
Smoking n%	Never		Former/Current	
	34 (17.1)		165 (82.9)	
Opioid Using n%	No		Yes	
	96 (45.9)		113 (54.1)	
Lung Metastasis n%	No		Yes	
	72 (34.4)		137 (65.6)	
Lymph Node Metastasis n%	No		Yes	
	35 (16.7)		174 (83.3)	
Liver Metastasis n%	No		Yes	
	169 (80.8)		40 (19.2)	
Bone metastasis n%	No		Yes	
	99 (47.4)		110 (52.6)	
Brain Metastasis n%	No		Yes	
	172 (82.3)		37 (17.7)	
Tramadol n%	No		Yes	
	123 (58.9)		86 (41.1)	
Morphine n%	No		Yes	
	201 (96.2)		8 (3.8)	
Fentanyl n%	No		Yes	
	160 (76.9)		48 (23.1)	
Codein %	Negative		Positive	
	153 (73.6)		55 (26.4)	

ECOG, Eastern Cooperative Oncology Group; n, patient; SCC, squamous cell carcinoma.

11, 2024 (approval number 10354421-2024/20-04).

Results

Patient characteristics

The study included 209 participants, with ages ranging from 36 to 81 years and a median age of 64. Of these, 182 (87.1%) were male. A total of 154 (74%) patients had an A score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance status scale was 154 (74%). While 120 (57.4%) patients were de novo metastatic, 89 (42.6%) were recurrent metastatic. 124 (59.3%) were SCC, and 78 (37.3%) were adenocarcinoma. While 137 (65.6%) patients had metastases in the opposite lung, 110 (52.6%) had bone metastases, and 40 (19.1%) had liver metastases.

Of these patients, 113 (54.1%) used OA. Of the patients, 86 (41.1%) used tramadol, 55 (26.4%) used codeine, 48 (23.4%) used fentanyl, and only 8 (3.8%) used morphine. Patient characteristics are shown in **Table 1**.

Progression-free survival analyzes

Univariate analyses: The median PFS of the adenocarcinoma group was 7 (95% CI: 4.75-

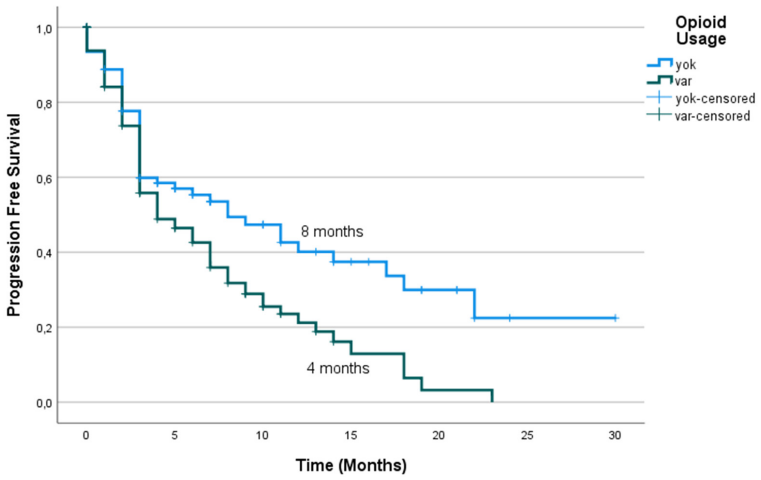

Figure 1. PFS according to opioid analgesic usage.

9.25) months, significantly longer than the median PFS of the SCC group at 6 (95% CI: 2.73-9.27) months (P<0.001). In patients with bone metastases, the median PFS was 5 months (95% CI: 2.38-7.62), while in those without bone metastases, it was 6 months (95% CI: 2.28-9.72). No significant difference was observed between these two groups (P = 0.93).

The median PFS was 8 (95% CI: 3.38-12.62) months in the group OA-free group and 4 (95% CI: 1.72-6.28) months in the OA receiving group, and the median PFS of the OA-free group was significantly longer than that of the OA receiving group (P = 0.006), as shown in **Figure 1**.

Analysis of the OA types revealed differences in PFS. The tramadol-free group showed a median PFS of 7 months (95% CI: 2.44-11.56), while the tramadol receiving group had a median PFS of 4 months (95% CI: 1.85-6.15). The tramadol receiving group median PFS was significantly shorter than the tramadol-free group (P = 0.023). For fentanyl receiving group, the median PFS was 6 months (95% CI: 3.69-6.84), in the fentanyl-free group 4 months (95% CI: 1.46-6.54). No statistically significant distinction was observed between the two groups (P = 0.254). The results of the univariate analysis for PFS are displayed in **Table 2**.

When the group without bone metastases was evaluated, The median PFS was 8 (95% CI: 0.87-15.13) months in the tramadol-free group and 5 (95% CI: 1.23-8.77) months in the tramadol receiving group, with no significant difference between the two groups (0.118), as shown in **Figure 2** The median PFS was 7 (95% CI: 3.41-10.59) months in the fentanyl-free group and 3 (95% CI: 1.02-4.97) months in the fentanyl receiving group, the median PFS in the fentanyl-free group was numerically better than the fentanyl receiving group but not significant (P = 0.062).

In the cohort with bone metastases, analysis revealed a median PFS of 8 months (95% CI: 4.25-11.76) for patients OA-free group, compared to 4 months (95% CI: 1.37-6.63) for OA receiving group. The OA-free group demonstrated a significantly higher median PFS (P = 0.011). For patients tramadol-free group, the median PFS was 7 months (95% CI: 2.06-11.94), while for tramadol receiving group was 4 months (95% CI: 1.38-6.62). Although the tramadol-free group showed a numerically superior PFS, the difference was not significant (P = 0.088). Patients fentanyl-free group had a median PFS of 5 months (95% CI: 1.88-8.12), whereas fentanyl receiving group had 6 months (95% CI: 1.22-10.78), with no significant difference observed between these groups (P = 0.942). **Table 3** presents the univariate PFS results stratified by the presence or absence of bone metastasis.

To determine the independent factors that might predict PFS, a multivariate Cox regression analysis was conducted.

Multivariate analyses: Multivariate analysis for PFS showed no difference between the adenocarcinoma and SCC group [HR (95% CI) = 0.809 (0.482-1.359), (P = 0.423)]. Patients without bone metastases had better PFS than patients with bone metastases [HR (95% CI) = 0.598 (0.361-0.992), (P = 0.046)].

There was no significant difference between the OA receiving group and patients OA-free group [HR (95% CI) = 3.166 (0.413-24.254), (P = 0.267)]. There was no significant difference between the patients treated with tramadol receiving and tramadol-free group [HR (95%

Table 2. The univariate analysis of risk factors for PFS and OS

		PFS			OS		
		Median (months)	Confidence Interval (95%)	*p* value	Median	Confidence Interval (95%)	*p* value
Overall		6	3.83-8.17		10	6.56-13.44	
Histologic subtype	Adenocarcinoma	7	4.75-9.25	<0.01	15	NR	0.005
	SCC	6	2.73-9.27		8	5.19-10.81	
Gender	Man	5	2.45-23.51	0.083	9	6.32-11.67	0.52
	Woman	13	2.64-7.36		NR	NR	
Cigarette	No	7	1.67-12.31	0.95	8	0-21.25	0.91
	Yes	7	3.72-10.29		11	6.49-15.51	
	Ex-smoker	5	3.86-8.14		9	6.11-13.89	
ECOG	0	9	4.93-10.07	0.327	12	5.86-18.15	0.31
	1	4	2.61-5.4		10	4.34-15.66	
	2	3	0-6.25		7	3.34-10.66	
	3	1	0-2.6		3	0-7.8	
Lung Metastasis	Yes	6	3.61-6.39	0.808	10	5.01-14.99	0.75
	No	6	3.23-8.77		10	6.94-13.06	
Lenf Node Metastasis	Yes	6	3.33-8.67	0.557	10	6.72-13.28	0.569
	No	7	2.88-11.12		17	0.77-33.23	
Liver Metastasis	Yes	3	0.59-5.42	0.084	7	1.63-13.38	0.232
	No	6	3.88-8.12		10	5.56-14.44	
Bone Metastasis	Yes	5	2.38-7.62	0.93	7	4.29-9.71	0.021
	No	6	2.28-9.72		15	8.31-21.69	
Opioid Using	Yes	4	1.72-6.28	0.006	7	3.56-10.44	0.03
	No	8	3.38-12.62		14	9.05-18.95	
Tramadol	Yes	4	1.85-6.15	0.021	6	2.32-9.77	0.047
	No	7	2.44-11.56		11	6.79-15.71	
Morphine	Yes	3	0-12.98	0.75	3	NR	0.948
	No	6	3.88-8.12		10	7.01-12.97	
Fentanil	Yes	4	1.46-6.54	0.254	7	2.94-11.06	0.37
	No	6	3.69-8.34		10	6.52-13.48	
Codein	Yes	6	3.1-8.9	0.51	10	2.89-17.11	0.783
	No	6	2.96-9.04		10	5.81-14.19	

ECOG, Eastern Cooperative Oncology Group; OS, Overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

CI) = 1.255 (0.639-2.467), (P = 0.51)]. There was no significant difference between the fentanyl-free group and fentanyl receiving group [HR (95% CI) = 0.608 (0.333-1.111), (P = 0.106)]. The results of the multivariate analysis for PFS are shown in **Table 4**.

In a multivariate analysis of the group without bone metastases, tramadol receiving group had worse PFS than patients tramadol-free group [HR (95% CI) = 2.260 (1.097-4.655), (P = 0.027)]. There was no significant difference between patients fentanyl receiving group and fentanyl-free group [HR (95% CI) = 0.836 (0.288-2.427), (P = 0.742)].

In a multivariate analysis in the group with bone metastases, there was no significant difference between patients OA-free group and OA receiving group [HR (95% CI) = 1.018 (0.045-23.128), (P = 0.991)]. There was no difference between tramadol-free group and tramadol receiving group [HR (95% CI) = 1.268 (0.495-3.251), (P = 0.621)]. There was no significant difference between the patients fentanyl-free group and fentanyl receiving group [HR (95% CI)

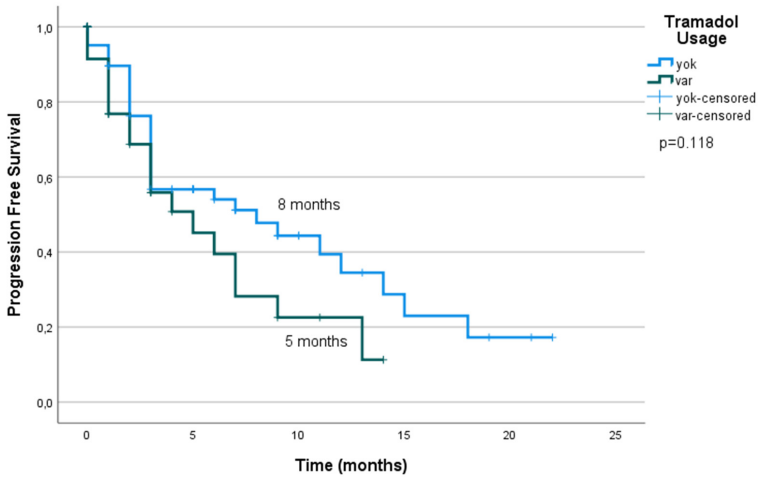

Figure 2. PFS in the tramadol-receiving group without bone metastases.

= 0.524 (0.219-1.256), (P = 0.147)]. Multivariate PFS results according to the presence or absence of bone metastases are shown in **Table 5**.

Overall survival analyzes

Univariate analyses: The median OS was 15 months (95% CI: NR) for the adenocarcinoma group and 8 months (95% CI: 5.19-10.81) months for the SCC group. The median OS of adenocarcinoma was longer than SCC, and there was a significant difference between the groups (P = 0.005). The median OS was 15 (95% CI: 8.31-21.69) months in the group without bone metastases and 7 (95% CI: 4.29-9.71) months in the group with bone metastases. The median OS of the group without bone metastases was longer than that of the group with bone metastases, with a significant difference between the groups (P = 0.021).

The median OS was 14 (95% CI: 9.05-18.95) months in the OA-free group and 7 (95% CI: 3.56-10.44) months in the OA receiving group. The median OS of the OA-free group was significantly longer than that of the OA receiving group (P = 0.03), as shown in **Figure 3**.

When opioid types were evaluated, the median OS was 11 (95% CI: 6.79-15.71) months in the tramadol-free group, median OS was 6 (95% CI: 2.32-9.77) months in the tramadol receiving group, and the median OS of the tramadol receiving group was shorter than tramadol-free group and significant (P = 0.047). The median OS was 10 (95% CI: 6.52-13.48) months in the fentanyl-free group and 7 (95% CI: 2.94-11.06) months in the fentanyl receiving group, and there was no significant difference between the two groups (P = 0.254). The univariate analysis results for OS are shown in **Table 2**.

When the group without bone metastases was evaluated, the median OS was 21 (95% CI: 3.86-38.15) months in the group OA-free group and 15 (95% CI: 10.7-19.31) months in the OA receiving group. The median OS of the OA-free group was significantly longer than the OA receiving group (P = 0.049). The median OS was 15 (95% CI: 10.48-19.52) months in the tramadol-free group and 7 (95% CI: 0-16.5) months in the tramadol receiving group, the median OS of the tramadol-free group was numerically better than the tramadol receiving group but not significant (P = 0.096). The median OS was 17 (95% CI: 8.6-21.4) months in the fentanyl-free group and 3 (95% CI: 0.27-5.73) months in the fentanyl receiving group, the OS of the fentanyl-free group was significantly better than the fentanyl receiving group (P<0.01).

When the group with bone metastases was evaluated, the median OS was 11 (95% CI: 0-23.86) months in the OA-free group and 5 (95% CI: 2.17-7.83) months in the OA receiving group, there was no significant difference between the two groups (P = 0.529). Median OS was 8 (95% CI: 4.96-11.04) months in the tramadol-free group and median OS was 5 (95% CI: 1.6-8.4) months in the tramadol receiving group, with no significant difference between the 2 groups (P = 0.484). The median OS was 10 (95% CI: 0-21.03) months in the fentanyl-free group, the median OS was 7 (95% CI: 4.16-9.84) months in the fentanyl receiving group, and there was no significant difference between the 2 groups (P = 0.139). As shown in **Figure 4** univariate OS results according to the presence or absence of bone metastasis are shown in **Table 3**.

Table 3. Univariate survival results according to the presence or absence of bone metastases

		PFS			OS		
Without Bone Metastasis		Median (months)	Confidence Interval (95%)	*p* value	Median	Confidence Interval (95%)	*p* value
Opioid Using	Yes	5	2.7-7.3	0.203	15	(10.7-19.31)	0.049
	No	8	1.48-14.19		21	(3.86-38.15)	
Tramadol	Yes	5	(1.23-8.77)	0.118	7	0-16.5	0.096
	No	8	(0.87-15.13)		15	10.48-19.52	
Morphine	Yes	1	NA	0.781	1	NA	0.219
	No	7	(3.82-10.18)		15	8.29-21.71	
Fentanyl	Yes	3	(1.02-4.97)	0.062	3	(0.27-5.73)	<0.01
	No	7	(3.41-10.59)		17	8.6-21.4	
Codein	Yes	6	1.48-10.59	0.794	NA	NA	0.607
	No	7	2.17-11.83		15	(8.45-21.57)	
With Bone Metastasis (n: 110)							
Opioid Using	Yes	4	1.37-6.63	0.011	5	2.17-7.83	0.529
	No	8	4.25-11.76		11	(0-23.86)	
Tramadol	Yes	4	1.38-6.62	0.088	5	1.6-8.4	0.484
	No	7	2.06-11.94		8	4.96-11.04	
Morphine	Yes	5	2.45-7.59	0.546	7	4.05-9.96	0.366
	No	19	NA		NA	NA	
Fentanyl	Yes	6	1.22-10.78	0.942	7	4.16-9.84	0.139
	No	5	1.88-8.12		10	0-21.03	
Codein	Yes	7	3.72-10.28	0.574	7	(0-15.49)	0.759
	No	5	1.74-8.26		7	(4.53-9.47)	

ECOG, Eastern Cooperative Oncology Group; OS, Overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

Table 4. The multivariate analysis of risk factors for survivals

	PFS		OS	
	HR (95 CI)	*p*-value	HR (95 CI)	*p*-value
Histologic subtype				
SCC	Ref	0.423	1.606 (0.928-2.777)	0.090
Adenocarcinoma	0.809 (0.482-1.359)		Ref	
Gender				
Woman	Ref	0.201	Ref	0.609
Man	1.684 (0.758-3.742)		1.266 (0.513-3.124)	
Liver Metastasis				
No	Ref	0.675		0.748
Yes	1.122 (0.655-1.921)		1.115 (0.575-2.161)	
Bone Metastasis				
Yes	Ref	0.046	1.810 (1.064-3.079)	0.029
No	0.598 (0.361-0.992)		Ref	
Opioid Using				
No	Ref	0.267	0.798 (0.096-6.618)	0.835
Yes	3.166 (0.413-24.254)		Ref	
Tramadol				
No	Ref	0.510	Ref	0.350
Yes	1.255 (0.639-2.467)		1.402 (0.691-2.846)	

Morphine				
No	0.977 (0.289-3.306)	0.970	0.925 (0.242-3.534)	0.909
Yes	Ref		Ref	
Fentanyl				
No	0.608 (0.333-1.111)	0.106	0.675 (0.359-1.270)	0.223
Yes	Ref		Ref	
Codein				
No	Ref	0.474		0.694
Yes	1.256 (0.673-2.343)		1.148 (0.577-2.287)	

HR, hazard ratio; OS, Overall survival; PFS, progression-free survival; Ref, reference; SCC, squamous cell carcinoma.

Table 5. Multivariate survival results according to the presence or absence of bone metastases

	PFS		OS	
Without bone metastasis	HR (95 CI)	*p*-value	HR (95 CI)	*p*-value
Opioid Using				
Yes	NR		NR	
No	NR		NR	
Tramadol				
No	Ref	0.027	Ref	0.231
Yes	2.260 (1.097-4.655)		2.577 (0.547-12.134)	
Morphine				
Yes	Ref	0.742	3.009 (0.756-11.98)	0.118
No	0.836 (0.288-2.427)		Ref	
Fentanyl				
Yes	1.725 (0.318-9.361)	0.527	1.53 (0.144-16.208)	0.724
No	Ref		Ref	
Codein				
No	Ref	0.572	Ref	0.39
Yes	1.963 (0.19-20.315)		3.865 (0.177-84.385)	
With bone metastasis				
Opioid Using				
Yes	1.018 (0.045-23.128)	0.991	Ref	0.62
No	Ref		0.551 (0.052-5.823)	
Tramadol				
No	Ref	0.621	Ref	0.275
Yes	1.268 (0.495-3.251)		1.622 (0.68-3.86)	
Morphine				
Yes	Ref	0.719	Ref	0.844
No	0.739 (0.143-3.834)		0.86 (0.191-3.869)	
Fentanyl				
Yes	Ref	0.147	Ref	0.019
No	0.524 (0.219-1.256)		0.38 (0.169-1.854)	
Codein				
No	Ref	0.744	Ref	0.985
Yes	0.88 (0.408-1.896)		1.007 (0.456-2.224)	

HR, hazard ratio; NR, not reached; OS, Overall survival; PFS, progression-free survival; Ref, reference; SCC, squamous cell carcinoma.

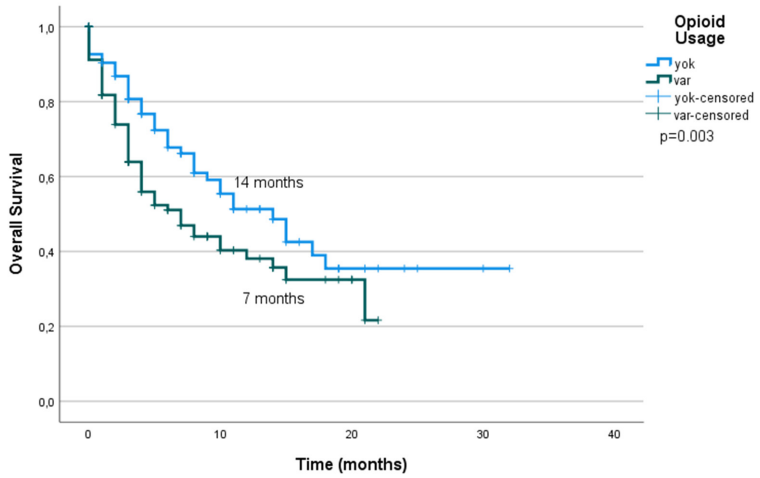

Figure 3. OS according to opioid analgesic usage.

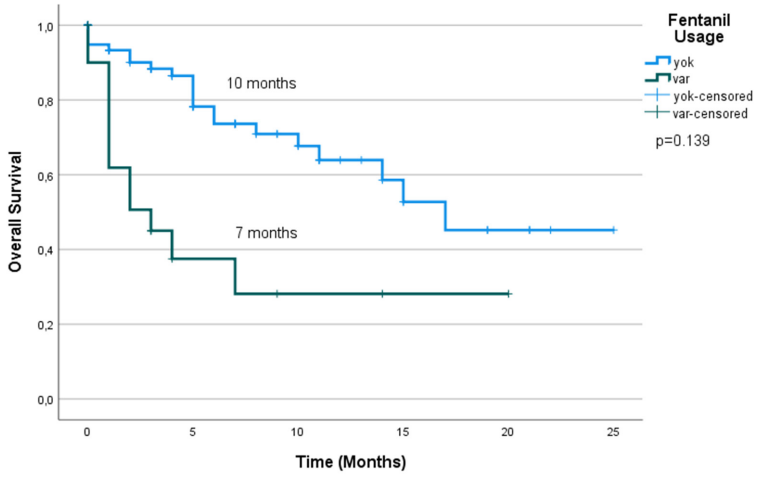

Figure 4. OS in the fentanyl-using group with bone metastases.

Multivariate analyses: The OS rates between the adenocarcinoma and (SCC groups showed no significant difference [HR (95% CI) = 1.606 (0.928-2.777), (P = 0.090)]. However, patients with bone metastases exhibited significantly poorer OS compared to those without bone metastases [HR (95% CI) = 1.810 (1.064-3.079) (P = 0.029)].

The OS rates showed no statistically significant variations among different patient groups. Patients who used OA and those who did not had comparable OS rates [HR (95% CI) = 0.798 (0.096-6.618), (P = 0.835)]. Similarly, no substantial difference in OS was observed between patients who used tramadol and those who did not [HR (95% CI) = 1.402 (0.691-2.846), (P = 0.35)]. The OS rates for patients who used fentanyl were also not significantly different from those who did not use it [HR (95% CI) = 0.675 (0.359-1.270), (P = 0.223)]. **Table 4** presents the findings from the multivariate analysis of OS.

The multivariate analysis of patients without bone metastases revealed no statistically significant difference in OS between those treated with tramadol and those not receiving tramadol [HR (95% CI) = 2.577 (0.547-12.134), (P = 0.231)]. Similarly, no significant OS difference was observed between patients who used fentanyl and those who did not [HR (95% CI) = 3.009 (0.756-11.98), (P = 0.118)].

A multivariate analysis of patients with bone metastases revealed no significant difference in OS between the OA-free group and OA receiving group [HR (95% CI) = 0.551 (0.052-5.823), (P = 0.62)]. Similarly, no substantial OS difference was observed between patients treated with tramadol receiving group and tramadol-free group [HR (95% CI) = 1.622 (0.68-3.86), (P = 0.275)]. However, fentanyl-free group demonstrated significantly better OS compared to fentanyl receiving group [HR (95% CI) = 0.38 (0.169-1.854), (P = 0.019-V presents the multivariate OS results based on the presence or absence of bone metastasis.

Discussion

With the increasing importance of ICI therapy in oncology, studies to improve the response in patients receiving ICI and to select the group that will benefit best are continuing rapidly, and DDI are becoming an important issue. An increasing number of studies have suggested that OAs may have potential negative conse-

quences on the survival of cancer patients. However, the effect of OA type on survival in patients receiving ICIs is not yet fully understood.

Our findings revealed a remarkable association between OA treatment and decreased PFS and OS in NSCLC patients treated with nivolumab. This suggests that the use of fentanyl in the group with bone metastases and tramadol in the group without bone metastases may adversely affect the survival outcomes when combined with nivolumab.

In a study of patients with metastatic NSCLC receiving pembrolizumab, antibiotic use was associated with poor survival outcomes [14]. In a study by Güven et al., a high rate of polypharmacy was found in patients aged 75 years and older who received ICI, and OA was found to be one of the most frequently interacting drugs [24]. The OA-ICI interaction is of interest because of the role of OAs in tumor growth and progression and the frequent drug interactions of ICIs.

In a study conducted in NSCLC cell culture, OAs were found that OAs may increase tumor differentiation and metastasis by increasing apoptosis and EGFR activation, and suppressing angiogenesis [8]. OAs may also alter the intestinal microbiota, cytokine production, and T cell activity, thereby reducing the therapeutic efficacy of ICIs [21].

Hong et al. evaluated the effect of ICI and concomitant drug use on the survival of 8870 patients with NSCLC and other cancers. The number of patients with NSCLC was 7128 (80%), the number of patients receiving Nivolumab was 2355 (26.6%), and the number of patients with OA was 4703 (53.0%). Patients with OA had worse survival than those without OA [25]. The effect of OA in patients receiving nivolumab was not evaluated separately and OA types were not included. In a meta-analysis of 2690 patients receiving ICI, patients with OA had worse OS than those without OA. In a subgroup analysis, in the NSCLC group, those with OA had shorter OS than those without OA [26]. In a study by Taniguchi et al., 298 patients with NSCLC receiving nivolumab were included; 38 OA users and 38 OA non-users were matched after propensity score matching. The median OS in the OA group was lower than that in the non-OA group [27]. In a meta-analysis of 1174 NSCLC patients treated with ICI by Guo et al., the use of OA was associated with worse PFS and OS in NSCLC patients treated with ICI [28]. In our study, the median PFS and OS were better in patients OA-free group than in patients OA receiving. However, this difference did not remain significant in the multivariate analysis. The lack of statistical significance is related to the limited sample size.

In our study, patients without bone metastases had better PFS than those with. The group with bone metastases had worse OS than the group without bone metastases which is consistent with the literature. In a meta-analysis of NSCLC patients receiving ICI, bone metastases were associated with worse OS [29]. In a study by Boticelli et al. in a heterogeneous cancer group of 196 patients using ICI, patients with bone metastases had the worst prognosis [30].

When we look at the types of OA, in a study of 635 patients with heterogeneous cancer population receiving ICI, morphine use was found to be poor prognostic in all 3 subgroups in univariate analysis [31]. In a study of 734 patients receiving palliative radiotherapy for bone metastases, morphine led to shorter survival [32].

Since there were only eight patients using morphine in our study, PFS and OS were not significant. However, in the group with bone metastases, the OS of the patients who did not use fentanyl was significant. To our knowledge, this is the first study in which fentanyl use was found to be a poor prognostic predictor of OS in patients with NSCLC receiving ICI. Negative prognostic effect of fentanyl on patient survival Due to the increase in near-death pain, prospective studies with a large number of patients are needed.

Although the poor prognostic effect of bone metastasis is known, when the effect of OA type on survival in the group without bone metastasis was analyzed, patients who used tramadol had worse PFS than patients who did not. Based on our review, no relevant studies appear to exist in the current literature. We suggest exercising caution when choosing OA patients for the non-chemotherapy Met group who have a comparatively more favorable prognosis.

Our study has limitations, primarily due to its retrospective nature. Additionally, the study's sample size was inadequate to draw robust conclusions. At the same time, the wide confidence intervals in our study reduce the reliability of the results. Hydromorphone and oxycodone could not be accessed in our country because of drug restrictions. None of the patients received ICI in the 1st step. The fact the patients used several OAs simultaneously was a confounding factor in our study. Whether OA treatment is used more frequently in the group with poor prognosis or whether OA leads to poor prognosis, is difficult to establish a causality principle because additional markers indicating tumor burden, such as PDL-1, tuor mutational burden, are not accessible due to cost.

This study shows that caution should be exercised in the combination of OAs with ICI, that specific opioid types may produce different clinical outcomes, and that we should approach the use of OAs more carefully in clinical practice. These findings contribute to the literature and have an impact on clinical decision-making. This study sheds light on new questions about the role of OA in cancer treatment.

Conclusion

In conclusion, OA use was associated with poor PFS and OS. Fentanyl use led to worse OS in the group with bone metastases, whereas tramadol use led to worse PFS in the group without bone metastases. The prognostic impact of OA may differ according to the site of metastasis; therefore, prospective studies that include the type of OA are needed.

Disclosure of conflict of interest

None.

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