

Evaluation of Patients with Solid and Hematological Malignancies Referred to the Pain Department in an Oncology Branch Hospital

Bir Onkoloji Dal Hastanesinde Ağrı Bölümüne Danışılan Solid ve Hematolojik Maligniteli Hastaların Değerlendirilmesi

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ABSTRACT

Objective: It is aimed to investigate pain and pain-associated clinical factors in patients with solid and hematological cancers referred to the pain department.

Methods: The study included patients referred to the pain department due to cancer pain. The demographic and clinical features, type of pain, visual analog scale (VAS) scores, and 6-month survival data were evaluated.

Results: The median VAS score of the patients was 7.0. The VAS score did not significantly differ between solid and hematological malignancies ($p=0.149$). The World Health Organization analgesic ladder was 2 or 3 for almost 90% of the patients. The ratio of patients in the WHO-analgesic ladder-1 was higher in hematologic malignancies ($p=0.012$). The median number of analgesics was similar between the solid and hematological malignancies ($p=0.556$). The VAS scores were weakly correlated with 6-month mortality in the solid cancer group ($Rho=.322$, $p<0.01$). In the hematological cancer group, a moderate positive correlation was found between the cancer stage and the VAS score ($Rho=.625$, $p<0.01$). In the solid tumor group, VAS scores were higher in the mixed pain group than in the nociceptive pain group ($p=0.013$). In hematologic malignancies, VAS scores were higher in patients with mixed pain than in patients with only neuropathic pain or only nociceptive pain.

Conclusion: Pain management in cancer should include evaluation of cancer treatments that may cause pain, consideration of non-opioid agents, and evaluation for the presence of neuropathic pain.

Keywords: Cancer pain, neuralgia, nociceptive pain

ÖZ

Amaç: Ağrı bölümüne yönlendirilen solid ve hematolojik kanserli hastalarda ağrı ve ağrı ile ilişkili klinik faktörlerin araştırılması amaçlanmıştır.

Yöntem: Çalışmaya kanser ağrısı nedeniyle ağrı bölümüne yönlendirilen hastalar dahil edildi. Demografik ve klinik özellikler, ağrı tipi, görsel analog skala (VAS) skorları ve 6 aylık sağkalım verileri değerlendirildi.

Bulgular: Hastaların medyan VAS skoru 7,0 idi. Solid ve hematolojik maligniteler arasında VAS skoru anlamlı farklılık göstermemiştir ($p=0,149$). Hastaların yaklaşık %90'ında Dünya Sağlık Örgütü analjezik basamakları 2 veya 3 idi. Hematolojik malignitelerde WHO analjezik merdiven-1'deki hastaların oranı daha yüksekti ($p=0,012$). Kullanılan medyan analjezik sayısı solid ve hematolojik maligniteler arasında benzerdi ($p=0,556$). Solid kanser grubunda VAS skorları 6 aylık mortalite ile zayıf korelasyon göstermiştir ($Rho=.322$, $p<0,01$). Hematolojik kanser grubunda, kanser evresi ile VAS skoru arasında orta derecede pozitif korelasyon bulunmuştur ($Rho=.625$, $p<0,01$). Solid tümör grubunda, VAS skorları karışık ağrı grubunda nosiseptif ağrı grubuna göre daha yüksekti. ($p=0,013$). Hematolojik malignitelerde, VAS skorları karışık ağrısı olan hastalarda sadece nöropatik ağrısı veya sadece nosiseptif ağrısı olan hastalara göre daha yüksekti.

Sonuç: Kanser ağrısında ağrı yönetimi, ağrıya neden olabilecek kanser tedavilerinin değerlendirilmesini, opioid olmayan ajanların dikkate alınmasını ve nöropatik ağrı varlığının değerlendirilmesini içermelidir.

Anahtar sözcükler: Kanser ağrısı, nevralji, nosiseptif ağrı

INTRODUCTION

More than half of all patients with cancer have moderate-to-severe intensity pain, often in multiple sites and with various etiologies and causative mechanisms (1). Studies

have shown that the prevalence of cancer-related pain ranges from 14–100% (2). A total of 53% of patients experience pain at all stages of the disease, and 33% continue to experience pain even post-treatment (3). Cancer pain is caused by medi-

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ators from cancer cells and immune system cells that affect nociceptors (4). Another type of pain experienced by patients with cancer is visceral pain. Direct irritation of the tumor, stretching of the organ, contraction, necrosis, ischemia, and inflammation can cause visceral pain. It is a blunt pain carried via C fibers. Neuropathic pain is another type of pain seen in patients with cancer resulting from nervous system involvement. Lastly, there is treatment-related pain in those who receive chemotherapy-radiotherapy or surgery. Although cancer pain is divided into groups such as neuropathic and somatic, it is usually mixed. It has been shown that 60% of cancer-related pain may have combined characteristics. So, it should always be kept in mind that somatic and neuropathic pain treatments should be considered together (5).

The psychological and social consequences of cancer pain, in addition to its physical manifestations, affect the quality of life in patients with cancer. Therefore, management of psychological and social effects during the treatment is essential. Initial assessment and re-evaluation are of great importance in managing cancer pain. It is crucial to monitor treatment efficiency or inadequacy and recognize the pain of different localizations and characters as the disease progresses. Pharmacologic approaches, physical methods, neurolytic blocks, cognitive and behavioral approaches, intraspinal analgesics, and co-analgesics can be used in treatment. There are many approaches to improving a patient's quality of life when treating cancer pain. The most effective treatment approach should be multi-disciplinary, involving the patient, family, and healthcare professionals, considering the location, severity, nature, type of cancer, and psychosocial status. There are many studies and publications on cancer pain; however, few studies evaluated the data of an oncological branch center comparing solid and hematological cancers (6-8).

In this study, we aimed to obtain an overview and clinical experience of a population of patients with cancer-related pain referred to the pain management department and identify clinical factors associated with the type of pain and pain severity.

MATERIAL and METHODS

Selection and Description of the Cases

Ethical committee approval was obtained for the study. The study included patients referred to our hospital's Department of Pain Medicine for managing cancer pain between 01/10/2023 and 31/12/2023. Patients with incomplete demographic and clinical data and visual analog scale (VAS) scores in the hospital database were excluded from the study. The demographic and clinical features such as age, gender, type of cancer, primary organ of cancer, cancer treatments,

presence of metastasis, kind of pain, the WHO (World Health Organization) analgesic ladder, analgesics, side effects of analgesics, VAS scores, performed invasive treatments for pain relief, and 6-month survival data were recorded. The Douleur Neuropathique 4 Questionnaire (DN4) was used to determine the presence of neuropathic pain. The DN4 questionnaire was developed to assess neuropathic pain; the Turkish reliability and validity study was performed (9,10).

Data were analyzed using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Armonk, NY). The normality of the numerical data distribution was examined using the Shapiro-Wilk normality test. Continuous variables with normal distribution were presented as standard deviation, those without normal distribution were presented as median and interquartile range (IQR; 25th-75th percentile), and qualitative data were expressed as frequency and percentage. Numerical variables with parametric or nonparametric distribution between the two groups were compared using independent samples t-tests and Mann-Whitney U tests. For comparisons of more than two groups in terms of numeric parameters, the Kruskal-Wallis test was used. The categorical data were compared using the chi-squares test, according to the frequency of expected counts, and the Fischer exact, Pearson chi-square and Yate's continuity correction test were applied. The Spearman correlation analysis was used to investigate the possible variables correlated with the VAS scores. The confidence interval was 95%, and the accepted margin of error was 5%. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The study included 120 patients. The median age was 61 years; 48.3% of them were female and 51.7% were males. Ninety-nine (82.5%) patients had a solid malignancy, and 21 (17.5%) had a hematological malignancy. The female/male ratio was similar in the solid and hematological cancer groups ($p=0.473$). Inpatient consultations were more frequent than out-patient consultations, and the type of consultation was not significantly different between the solid and hematological cancer groups ($p=0.229$). Nearly half of the patients had a systemic disease (Table I).

Clinical features of the patients related to cancer are presented in Table II. Nearly 4/5 of the patients had solid malignancy. The most common cancers were gastrointestinal tumors, hematological malignancies, and breast tumors, respectively. The median duration after diagnosis was 12 months, and it was similar between solid and hematological cancers ($p=0.793$). Almost 90% of the patients had stage 3-4 disease, and 70% had metastatic disease primarily to bone, lung, and liver. No significant differences in the cancer stage were found between the solid and hematological cancers ($p=0.112$). The

Table I: Age, Gender, Type of Consultations, and Systemic Diseases of the Patients (N=120)

			Median (IQR) or n (%)	p
Age	Solid tumors		62.0 (16.0)	0.175
	Hematological malignancies		58.0 (27.0)	
Gender	Solid tumors	Female	46 (46.5)	0.473
		Male	53 (53.5)	
	Hematological malignancies	Female	12 (57.1)	
		Male	9 (42.9)	
Type of consultation	Solid tumors	Out-patient	41 (41.4)	0.229
		Inpatient	58 (58.6)	
	Hematological malignancies	Out-patient	12 (57.1)	
		Inpatient	9 (42.9)	
Systemic disease	Total		58 (48.3)	NA
	HT		34 (28.3)	
	DM		17 (14.2)	
	CAD		5 (4.2)	
	CHF		2 (1.6)	
	AF		3 (2.5)	
	COPD		5 (4.2)	
	CRD		5 (4.2)	
	CVD		2 (1.6)	
	Others		20 (16.7)	
Number of systemic diseases	1		26 (21.7)	NA
	2		18 (15.0)	
	3		9 (7.5)	
	≥4		5 (4.2)	

NA: Not compared between the groups because of the low number of cases in the columns, **IQR:** Interquartile range, **HT:** Hypertension, **DM:** Diabetes mellitus, **CAD:** Coronary arterial disease, **CHF:** Congestive heart failure, **AF:** Atrial fibrillation, **COPD:** Chronic obstructive pulmonary disease, **CRD:** Chronic renal disease, **CVD:** Cerebrovascular disease.

6-month mortality ratio after consultation with the algology department was 55.8%. The mortality ratio was similar in patients with solid and hematological cancers ($p=0.229$).

The pain characteristics of the patients are shown in Table III. The median VAS score is 7.0. The VAS scores did not differ between those with solid and hematological cancers ($p=0.149$). Nearly 90% of the patients have nociceptive pain, and 1/4 of them have neuropathic pain. The type and cause of pain were similar in those with solid and hematological cancers ($p=0.756$, $p=0.556$). The most common pain sites were the abdominopelvic region and the chest or thoracic spine. The median number of analgesics taken weekly was 2 for solid and hematological malignancies without a significant difference ($p=0.551$). The most commonly used opioid analgesics were tramadol and morphine. The WHO analgesic ladder was 2 or 3 for almost 90% of the patients. The ratio of patients in WHO Analgesic Ladder-1 was higher in those with hematological cancers than those with solid tumors ($p=0.012$); therefore,

the ratio of WHO Ladder 2 and 3 was similar in both groups. The side-effect frequency is 10.8%, and the most commonly encountered side-effect was nausea-vomiting. Invasive pain management was performed in 10 (0.3%) patients.

No correlation was found between the VAS score and age, gender, time of diagnosis, presence of metastases, cancer stage, history of surgery, chemotherapy (CT), radiotherapy (RT), immunotherapy, or hormone therapy in patients with solid tumors. Therefore, a weak correlation was found between the VAS and 6-month mortality ($Rho=.322$, $p<0.01$) (Figure 1). In the group with hematological cancer, a weak negative correlation was found between age and the VAS score ($Rho=-.459$, $p=.037$), a moderate positive correlation was found between cancer stage and the VAS score ($Rho=.625$, $p<0.01$) (Figure 2 and 3). No correlation was found between the VAS score and gender, duration of diagnosis, history of CT, RT, immunotherapy, or bone marrow transplantation, and 6-month mortality ($p>0.05$). When patients were categorized

by pain type into nociceptive, neuropathic, and mixed pain, a significant difference was found between these three groups in patients with solid malignancies ($p=0.046$); the VAS score was lower in the nociceptive pain group than in the mixed pain group ($p=0.013$), but no difference was found in other pairwise comparisons ($p>0.05$). In patients with hematologic malignancies, there was a significant difference between these three pain groups ($p=0.031$), and the VAS scores were

higher in patients with mixed-type pain than in patients with only neuropathic pain ($p=0.035$) and only nociceptive pain ($p=0.026$). When patients were grouped according to the cause of pain (local tumor invasion or compression, metastasis, and local tumor invasion or compression and metastasis together), there was no significant difference in the VAS scores regarding the cause of pain in patients with solid malignancies ($p>0.05$).

Table II: Clinical Features of the Cancer Patients

	Median (IQR) or n (%)
Type of malignancy	Solid tumors 99 (82.5)
	Hematologic malignancies 21 (17.5)
Primer organ	Lung 11 (9.2)
	Breast 15 (12.5)
	Gastrointestinal system 34 (28.3)
	Gynecological system 10 (8.3)
	Genitourinary system 13 (10.8)
	Endocrine system 11 (0.8)
	Hematologic malignancy 21 (17.5)
	Two or more system malignancies 5 (4.2)
	Other organ/system tumors 10 (8.3)
Duration of cancer (months)	Solid tumors 12.0 (39.0)
	Hematologic malignancies 16.0 (31.0)
Stage of cancer	1 2 (1.7)
	2 8 (6.7)
	3 29 (24.2)
	4 81 (67.5)
	All 84 (70.0)
Metastasis	Brain 50 (41.7)
	Bone 27 (22.5)
	Lung 31 (25.8)
	Liver 6 (5.0)
Cancer treatment	Surgery 62 (51.7)
	Chemotherapy 87 (72.5)
	Radiotherapy 35 (29.2)
	Immunotherapy 28 (23.3)
	Hormone therapy 12 (10.0)
Bone marrow transplantation	4 (3.3)
Mortality in 6-months	All patients 67 (55.8)
	Solid tumors 58 (58.6)
	Hematologic malignancies 9 (42.9)

IQR: Interquartile range.

Table III: Characteristics of Pain of the Patients with Solid Tumors and Hematological Malignancies

		All patients	Solid tumors (n=99)	Hematological malignancies (n=21)	p
VAS score (0-10) (median: IQR)		7.0 (1.0)	8.0 (1.0)	7.0 (2.0)	0.149
Type of pain, n (%)	Nociceptive	93 (77.5)	78 (78.8)	15 (71.4)	0.756
	Neuropathic	5 (4.2)	4 (4.1)	1 (4.8)	
	Nociceptive and neuropathic	22 (18.3)	17 (17.2)	5 (23.8)	
Cause of pain, n (%)	Local tumor invasion or compression	68 (56.7)	54 (54.5)	14 (66.7)	0.565
	Metastasis	18 (15.0)	16 (16.2)	2 (9.5)	
	Local tumor invasion or compression together with metastasis	34 (28.3)	29 (29.3)	5 (23.8)	
Pain localization, n (%)	Head, neck, or cervical region	12 (10.0)	11 (11.1)	1 (4.8)	NA
	Chest or thoracic spine	19 (15.8)	14 (14.1)	5 (23.8)	
	Lumbosacral	3 (2.5)	2 (2.0)	1 (4.8)	
	Abdominopelvic	32 (26.7)	28 (28.3)	4 (19.0)	
	Upper extremity	3 (2.5)	3 (3.0)	0 (0.0)	
	Lower extremity	4 (3.3)	3 (3.0)	2 (9.5)	
	Two or more anatomic regions	47 (39.2)	39 (38.8)	8 (38.1)	
Analgesic treatment, n (%)	Paracetamol (po)	20 (16.7)	18 (18.2)	2 (9.5)	NA
	NSAID (po)	26 (21.7)	20 (20.2)	6 (28.6)	
	Tramadol (po)	70 (58.3)	62 (62.6)	8 (38.1)	
	Codein (po)	3 (2.5)	2 (2.0)	1 (4.8)	
	Oxycodone (po)	10 (8.3)	7 (7.1)	3 (14.3)	
	Morphine (po)	35 (29.2)	30 (30.3)	5 (23.8)	
	Fentanyl (tts)	23 (19.2)	21 (21.2)	2 (9.5)	
	Gabapentinoid (po)	23 (19.2)	18 (18.2)	5 (23.8)	
Number of analgesics, n (%)	1	56 (46.7)	46 (46.5)	10 (47.6)	NA
	2	52 (43.3)	41 (41.4)	11 (52.4)	
	3	11 (9.2)	11 (11.1)	-	
	≥4	1 (0.8)	1 (1.0)	-	
Median analgesic number (IQR)		2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	0.551
WHO analgesic ladder, n (%)	1	13 (10.8)	7 (7.1)	6 (28.6)	0.012
	2	54 (45.0)	48 (48.5)	6 (28.6)	
	3	53 (44.2)	44 (44.4)	9 (42.9)	
Side effects of analgesics (need to change treatment), n (%)	Nausea-vomiting	6 (5.0)	6 (6.1)	-	
	Constipation	3 (2.5)	3 (3.0)	-	
	Dizziness-sedation	5 (5.1)	4 (4.1)	1 (4.8)	
	Opioid-induced hyperalgesia	1 (0.8)	1 (1.0)	-	
	Other	1 (0.8)	1 (1.0)	-	
Side effects of analgesics (need to treatment change), n (%)	Paracetamol (po)	-	-	--	
	NSAID (po)	--	-	-	
	Tramadol (po)	5 (4.2)	5 (5.1)	-	
	Codein (po)	-	--	-	
	Oxycodone (po)	1 (0.8)	-	1 (4.8)	
	Morphine (po)	5 (4.2)	5 (5.1)	-	
	Fentanyl (tts)	2 (1.7)	2 (2.0)	-	

Table III: Cont.

	All patients	Solid tumors (n=99)	Hematological malignancies (n=21)	p-value
Invasive pain management, n (%)	Celiac neurolysis	2 (1.7)	2 (2.0)	NA
	Splanhic neurolysis	3 (2.5)	3 (3.0)	
	Peripheral nerve block	2 (1.7)	2 (2.0)	
	Erector spine plane block	1 (0.8)	-	
	Stellate ganglion block	1 (0.8)	1 (4.8)	
	Other	1 (0.8)	1 (4.8)	

NA: Not compared between the groups because of the low number of cases in the columns; IQR: Interquartile range, VAS: Visual analog scale, NSAID: Non-steroidal anti-inflammatory drug, WHO: World Health Organization.

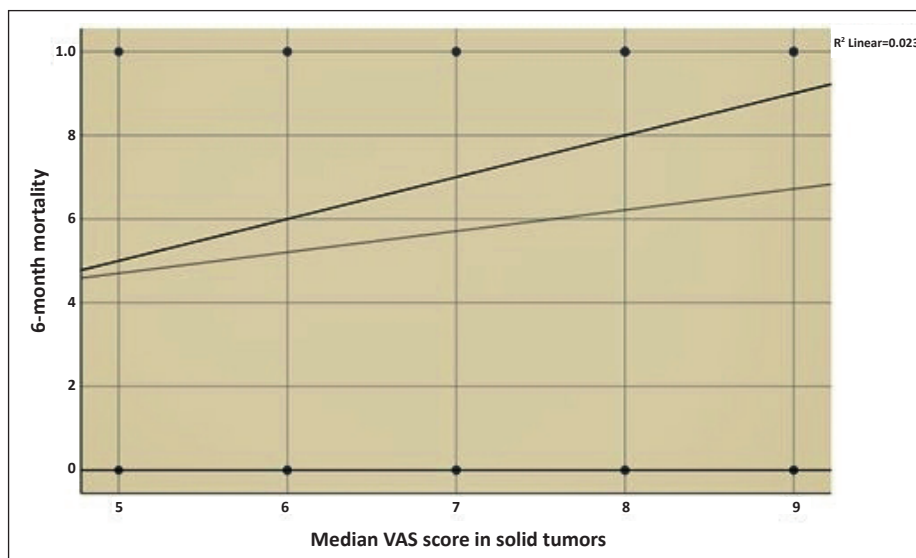


Figure 1. The simple scatterplot of mortality and VAS score for solid tumors.

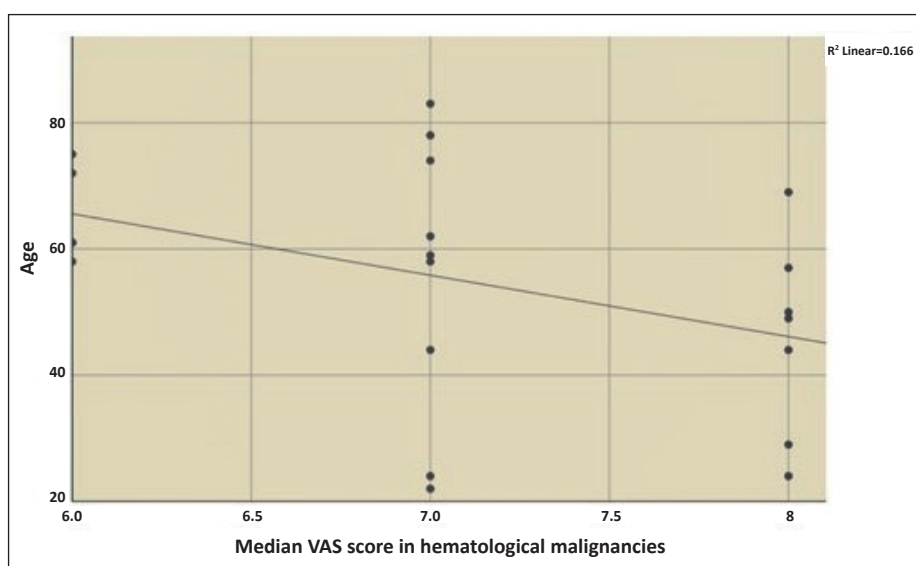


Figure 2. The simple scatterplot of age and VAS score for hematological malignancies.

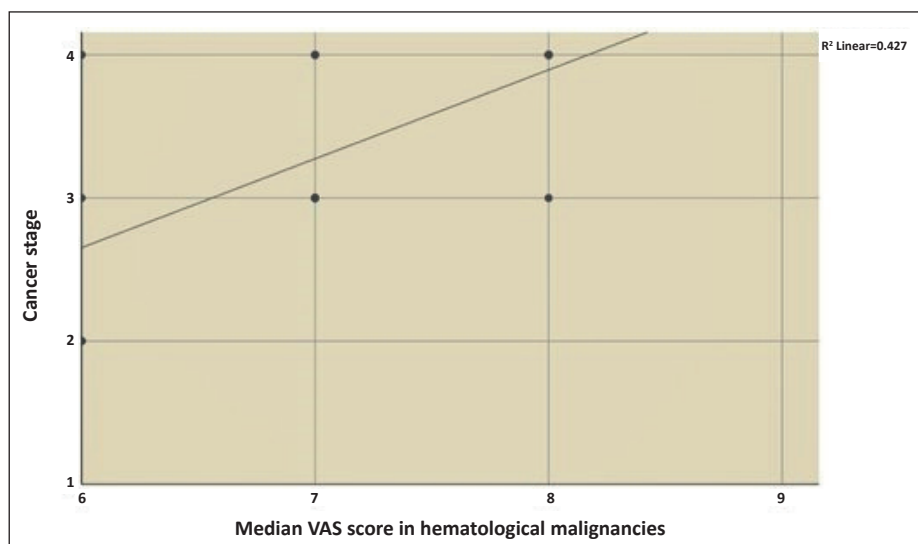


Figure 3. The simple scatterplot for cancer stage and VAS score for hematological malignancies.

DISCUSSION

Despite the advances in cancer treatment, the increase in the incidence of cancer, the complex etiology of cancer pain, and the limited number of analgesic agents used in the treatment cancer pain is still a significant cause of morbidity. Pain is the most common symptom that causes patients with cancer to visit the emergency department, and more than one third of patients diagnosed with cancer experience inadequately treated pain (11). A systematic review reported that the prevalence of pain remains high (44.6%), especially in patients with advanced, metastatic, and terminal cancers (12). According to the WHO ladder, the step was 2 or 3 for most patients. No correlation was found between the cancer stage and the VAS scores for solid malignancies. This may be because most patients had stage 3-4 diseases. Therefore, the 6-month mortality was correlated with pain severity in patients with solid cancer, indicating that patients with terminal diseases had severe pain. Therefore, the VAS score was associated with the stage of cancer in the hematological cancer group, similar to the literature (13).

In this study, pure neuropathic, mixed, and pure nociceptive pain prevalence was 4.2%, 18.3%, and 77.5%, respectively. In a meta-analysis conducted in 2012, these prevalences were reported as 19%, 20%, and 59% (14). Our study's low pure neuropathic pain may be sourced from developing new therapeutic agents likely to cause fewer side effects and neuropathy.

More than half of the patients were taking more than two analgesics. The second non-opioid agent in most patients was acetaminophen and nonsteroidal anti-inflammatory drugs. These agents were helpful to lower opioid doses and decrease pain considerably, especially in patients with bone

metastases and sometimes in visceral pain, although most patients had advanced cancer.

The frequency of side effects requiring treatment change was 10.8%, similar to that in the literature. In a Cochrane review, it was reported that 10-20% of patients under opioids needed to change treatment (15). In this study, the most common side effects requiring an opioid switch were nausea and vomiting, constipation, and sedation. Opioid-induced hyperalgesia (OIH), an interrelated phenomenon that contributes to pain worsening during opioid administration, was seen in only one patient under morphine treatment (16). A Canadian review reported suspected OIH prevalence as 0.01% per patient per physician practice year for chronic pain (17). The management of OIH includes the addition of N-methyl-D-aspartate antagonists to opioid shift or lowering the dose; in our patient, opioid rotation to fentanyl from morphine was used (18).

There are many invasive pain modalities to manage cancer pain, including sympathetic neurolytic blocks, vertebroplasty, kyphoplasty, osteoplasties, peripheral nerve blocks, implantable devices as epidural or intrathecal therapy, as well as peripheral and spinal cord stimulation and cordotomy for refractory interventional cancer pain. Epidural or intrathecal therapies and surgical modalities such as osteoplasties and vertebroplasty-kyphoplasty were not included in the patients for whom invasive pain management was applied. Apart from these procedures, the frequency of patients for whom invasive pain management was performed is 8.3%. However, we could not evaluate the effect of these pain procedures on pain severity and decrease in opioid consumption.

The limitations of the study are that the frequency and effect of alternative therapies such as massage, acupuncture,

and herbal medicines were not evaluated, breakthrough pain could not be assessed, drug doses were not recorded, and the effectiveness of interventional pain treatments could not be assessed due to the retrospective nature of the study and lack of data.

CONCLUSION

Pain management in cancer should include evaluation of the effect of not only the disease but also treatment methods and agents used in cancer treatment, consideration of non-opioid agents in treatment management, and assessment for the presence of neuropathic pain.

AUTHOR CONTRIBUTIONS

Conception or design of the work: HG

Data collection: HG

Data analysis and interpretation: HG

Drafting the article: HG

Critical revision of the article: HG

The author (HG) reviewed the results and approved the final version of the manuscript.

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