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The role of tapentadol in cancer pain pharmacotherapy in patients with metastatic malignant disease

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Abstract. – OBJECTIVE: The aim of this study was to establish the effects of prolonged formulation of tapentadol in combination with palliative radiotherapy on bone metastatic changes in oncology patients with primary breast cancer and proven bone metastases.

PATIENTS AND METHODS: The research was conducted as a prospective study at the Clinic for Oncology, University Clinical Center Nis, Nis, Serbia, during a three-month interval of monitoring the patients. The first group comprised 30 patients with mentioned malignancy for which tapentadol was prescribed, and they underwent palliative radiotherapy for bone metastatic changes. The second group comprised 30 patients with the same disease treated only with pain relief radiotherapy to metastatic changes. All the patients were interviewed using the Pain Detect questionnaire.

RESULTS: Significantly more patients from the first group had severe pain in comparison to patients from the control group (χ^2=16.596; p<0.001) at the second measurement and also at the third measurement (χ^2=15.357; p<0.001). At the third measurement, pain with a neuropathic component was significantly more present in patients from the control group (χ^2=8.541; p=0.014). There was a significant pain reduction in both groups – Tapentadol group (χ^2=59.513; p<0.001) and control group (χ^2=60.000; p<0.001) – and also a significant reduction of neuropathic pain component: Tapentadol group (χ^2=56.267; p<0.001) and control group (χ^2=60,000; p<0.001). There was a statistically significant positive correlation between tapentadol dose and pain intensity according to the numerical pain scale at all three measurements.

CONCLUSIONS: Tapentadol prolonged-release formulation is an effective pharmacotherapy solution, along with palliative radiotherapy, for pain relief in patients with skeletal metastatic breast cancer. Palliative radiotherapy in these patients does not provide adequate neuropathic pain component relief.

Key Words:
Tapentadol, Pain, Cancer, Pharmacotherapy.

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Introduction

According to GLOBOCAN, there were about 10 million recorded cancer deaths in oncology patients in 2020. The most commonly diagnosed cancer worldwide was female breast cancer, with an estimated 2.26 million cases in the same year[1]. This malignity is a significant factor in the total mortality rate[2]. The skeletal system is the most common site of metastatic breast cancer, which significantly affects the survival rate in these patients. Complications of such an advanced disease primarily include painful metastatic changes, spinal cord compression, pathological fractures, and hypercalcemia of malignancy[3]. The presence of metastatic changes on the body's skeleton disrupts the normal balance between osteoclasts and osteoblasts, resulting in bone destruction, the highest pain intensity, pathological fractures, and further progression of the disease itself.

The therapy for breast cancer carcinoma nowadays is combined multimodality treatment (surgical treatment, radiation treatment, chemotherapy, hormone therapy, biologically targeted therapy, immunotherapy, and supportive therapy) for underlying disease complications. Tumors 0-IIA stage are operable, so their initial treatment is in the scope of surgery that may combined with neoadjuvant chemotherapy, depending on the size and histopathological characteristics of the tumor. Stages IIB and III stand for local or locoregional advanced disease, so initial treatment is performed using a systemic form of treatment [chemotherapy +/- targeted (biologic) or hormonal therapy], followed by surgical treatment within locoregional treatment, then adjuvant therapy (radiotherapy, chemotherapy, hormonal therapy, and biological therapy). Grade IV is metastatic cancer treated with systemic therapy in combination with opioid pharmacotherapy and palliative radiotherapy[4-6].

Cancer pain may be acute and chronic. Acute pain can be associated with diagnostic or therapeutic procedures, or it may be caused by the tumor itself or accompanied pathology. Chronic cancer pain involves primarily bone pain and soft tissue pain, pain in tumor-invaded organs, and paraneoplastic pain syndrome[7].

Tapentadol (3-dimethylamino-1-ethyl-2-methyl-propyl-phenolhydrochloride) is a new opioid analgesic. It has a dual mechanism of action. Apart from acting as the classic μ opioid-receptor agonist, it also inhibits noradrenaline reuptake, thus enabling two synergic mechanisms of action in one molecule, resulting in the reduction of ascending pain signals, and enhancing the descending inhibition of pain, adequately relieving both nociceptive and neuropathic pain component[8]. Tapentadol has good pharmacological profile with weak interaction and addiction potential, and low risk of tolerance development. It is not a pro-drug, so its efficacy does not depend on metabolic activation. Metabolism of tapentadol does not produce active metabolites, so there is no risk of potential toxicity due to their accumulation. It has been proved that tapentadol should be given to oncology patients over a longer period of time at high doses to get an adequate pharmacotherapeutic response. Tapantadol is a drug of choice for neuropathic cancer pain that is refractory to standard first-line opioids therapy with classic μ opioid agonists[9].

Safety and efficacy of tapentadol in vulnerable populations, such as the elderly, has been confirmed in Aurilio's study that showed prolonged formulation of tapentadol, if treated adequately, is a proper pharmacotherapy option for the management of musculoskeletal pain in opioid naive patients in this fragile group[10].

Prolonged tapentadol formulation is an adequate pharmacotherapy option both for neuropathic component relief, as primarily described in patients with osteoarthritis, and in those with low back pain, as well as in some painful conditions associated with neuropathic pain component within the mixed pain syndrome[11].

Symptomatic treatment in oncology patients with bone metastases, apart from analgesics application, inevitably includes palliative radiotherapy of bone metastases, besides systemic chemotherapy and immune and hormonal therapy for the treatment of the disease itself. Osteolytic bone metastases, such as breast cancer metastatic changes, are commonly accompanied by pain, pathological fractures, and hypercalcemia[12]. Radiotherapy achieves pain relief to a certain degree in 60% of patients with bone metastases[13]. The therapeutic response to painful skeletal sites can be expected within 4 weeks after radiotherapy. The efficacy of palliative radiotherapy is higher in patients with moderate pain than in patients with severe pain. Prolonged radiation (20Gy in 5 fractions or 30Gy in 10 fractions) showed a better therapeutic response in patients with painful bone metastatic changes, while short-term radiation of 8Gy in one fraction is commonly applied in these painless changes or in patients with short survival prognosis[14].

Pain Detect Questionnaire

Asking the patient to answer the questions and to rate their pain enables physicians to determine whether the pain is nociceptive or neuropathic, which is crucial for guiding the clinician in prescribing appropriate pharmacotherapy modalities. Patient's score of 1-12 means that their pain has a neuropathic component <15%, so that is mostly based on the nociceptive component. The patient's score of 13-18 is defined as the possible presence of a neuropathic component, and the clinician has to use other tools to assess the patient's pain. If the patient's score is 19-38, it is clear that the pain has a predominant neuropathic component[15].

The aim of this study was to establish the effects of applied opioid pharmacotherapy by prolonged formulation of tapentadol, a strong opioid analgesic, in combination with palliative radiotherapy to bone metastatic changes in oncology patients with primary breast cancer and proven bone metastases before and after palliative radiotherapy to bone metastases.

Patients and Methods

The study was conducted as a prospective study at the Clinic for Oncology, University Clinical Center Nis, Nis, Serbia during a three-month interval of monitoring the patients. The Ethical Board of the University Clinical Center Nis approved this study with decision No. 4665/6. Before being included in the study, all patients signed an informed consent form. The form explained the study design and informed patients that they could leave the study at any time without any negative impact on their future treatment.

Patients

Patients enrolled in the study were classified into two groups. The first group comprised 30 patients with primary breast cancer and proved painful bone metastases for which opioid analgesic was prescribed, and they underwent palliative radiotherapy for bone metastatic changes. The second was the control group comprised 30 patients with primary breast cancer and proved painful bone metastases treated only with palliative pain relief radiotherapy to metastatic changes.

This study included only the patients with an established diagnosis of primary breast cancer with proven metastatic disease in terms of the presence of bone metastases proved by the skeletal scintigraphy method. The patients included in the study are those who experience pain with a numerical pain scale rating of greater than 4 out of 10, according to their own subjective estimation. All the patients from the first group before palliative radiotherapy to painful metastatic bone sites, received opioid analgesic pharmacotherapy in an adequate drug dose regimen, depending on pain intensity on the numerical pain scale (NPS) and data about whether or not they were on opioid pharmacotherapy by some other opioid analgesic and at what dose regimen by using equianalgesic dosing charts. As for opioid analgesics, a prolonged formulation of tapentadol, a strong opioid analgesic, was introduced along with a quick-acting peroral formulation of morphine sulfate the patients were taking to treat breakthrough pain if needed, up to max four times a day. The fast-acting formulation of morphine sulfate is the gold standard for breakthrough pain therapy in chronic cancer pain. That is why it was used as a fast-acting formulation for rapid pain relief in the patients in this study. In accordance with European recommendations, if necessary, the patients were given 1/6 of the equivalent analgesic daily dose of long-acting tapentadol that these patients are currently taking. Thus, in accordance with the daily dose of a long-acting opioid, oral morphine sulfate was given as needed when the pain broke out in a dose of 1/6 of the daily dose of tapentadol. Based on that, each patient always received the same dose of morin as needed, which is 1/6 of their daily dose of tapentadol, which was equianalgesically converted into oral morphine. If the patients needed to take more than 4 doses of morphine during the day, this was an indication for increasing the dosage regimen of long-acting tapentadol analgesia. Patients from the second group were only on radiotherapy pain relief to bone metastatic changes and pain intensity monitoring.

All the patients were interviewed using the Pain Detect questionnaire. Pain is a symptom of a disease that cannot be measured by any objective measure, and there is also no specific marker that can be monitored without referring to the intensity of the pain. The only officially recognized quantitative parameter as a measure of pain intensity is pain scales. In this study, the Pain Detect questionnaire (which has been used so far in the world literature as a quantitative measure for assessing the intensity of pain and the share of the neuropathic pain component in the patient's total pain) was used. We chose to use this tool to assess the neuropathic component of pain in oncology patients who experience mixed pain.

This is in addition to the classic visual-analog pain scale or NPS, which can only measure the nociceptive component of pain. We believe that using this tool will provide a more comprehensive understanding of the patient's pain experience.

There were three-time points of patients' evaluation regarding their pain, scoring, and correction of pain relief treatment as follows: first – before radiotherapy initiation, when opioid pharmacotherapy was introduced to patients from the first group using long-acting tapentadol in relation to pain intensity according to the NPS and in relation to previously receiving some other opioid analgesic and its dose; second – a month after radiotherapy to metastatic changes; and third - two months after completion of radiotherapy.

Statistical Analysis

The statistical calculations were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Qualitative data are expressed as frequencies and percentages, while quantitative data are presented as mean±standard deviations. The Chi-square test and Fisher test were used for the comparison of frequencies. Mann-Whitney test was used for comparisons of abnormally distributed numerical data while Friedman test was used for repeated measures. Pearson and Spearma's rank correlation was used to determine the relationship between variables. Statistical significance was accepted for $p<0.05$.

Results

Table I shows the distribution of patients according to pain intensity categories on the numerical pain scale (NPS) –mild, moderate, or severe pain – at three monitoring time intervals (initial introduction of therapy, a months after palliative radiotherapy, and two months later, that is three months after completion of radiotherapy).

Initial measurement showed no significant differences in the mean value of pain between the groups ($Z=1.191$; $p=0.234$). There was no significance in pain intensity (moderate and severe pain) ($\chi^2=0.480$; $p=0.488$).

At the second point of pain intensity reevaluation, it was determined that the mean value of the numerical pain scale (NPS) was significantly higher in patients receiving tapentadol ($Z=3.245$; $p=0.001$). A significantly higher number of patients in the experimental group reported severe pain compared to the control group ($\chi^2=16.596$; $p<0.001$), so opioid pharmacotherapy was continued using adjusted dosage regimen of tapentadol prolonged formulation.

At the third point of pain reevaluation in patients, mean value of NPS was statistically significantly higher in patients receiving tapentadol ($Z=4.142$; $p<0.001$). Statistically significantly greater number of patients from the control group had mild pain in comparison to patients from tapentadol group who had moderate pain ($\chi^2=15.357$; $p<0.001$), so further correction of dosage regimen of this opioid was carried on.

Table II shows the distribution according to categories (nociceptive pain, no neuropathic pain component, pain with neuropathic component) at all three time interval of patients' monitoring by using Pain Detect scores.

At first measurement there was no significant difference in mean values of Pain Detect questionnaire between studied group ($Z=0.619$; $p=0.536$). All the patients from both groups had pain with neuropathic component ($p=1.000$).

At second measurement, the mean value of Pain Detect questionnaire was not significantly different between the patients of the studied groups

Table I. Distribution of patients by categories of pain intensity at all time points of follow-up.

Measurement time	Tapentadol group	Control group	p*
NPS1			
Moderate pain	4 (13.3)	6 (20.0)	
Strong pain	26 (86.7)	4 (80.0)	**0.488**
NPS2			
Moderate pain	17 (56.7)	30 (100.0)	
Strong pain	13 (43.3)	0 (0.0)	**<0.001**
NPS3			
Mild pain	9 (30.0)	24 (80.0)	
Moderate pain	20 (66.7)	6 (20.0)	
Strong pain	1 (3.3)	0 (0.0)	**<0.001**

*Chi-square test.

Table II. Distribution of patients by categories of Pain Detect scores.

	Tapentadol group	Control group	*p*
Pain Detect score 1			
No established neuropathic pain	1 (3.3)	0 (0.0)	
Pain with a neuropathic component	29 (96.7)	30 (100.0)	1.000[1]
Pain Detect score 2			
Nociceptive pain	3 (10.0)	2 (6.7)	
No established neuropathic pain	7 (23.3)	4 (13.3)	
Pain with a neuropathic component	20 (66.7)	24 (80.0)	0.501[2]
Pain Detect score 3			
Nociceptive pain	16 (53.3)	13 (43.3)	
No established neuropathic pain	12 (40.0)	6 (20.0)	
Pain with a neuropathic component	2 (6.7)	11 (36.7)	**0.014**[2]

[1]Fisher's test, [2]Chi-square test.

Table III. Pain values according to the numerical pain scale (NPS) and Pain Detect score values at all test moments in both examined groups of patients.

	Tapentadol group	*p**	Control group	*p**
NPS1	7.67±1.03		7.40±0.93	
NPS2	6.07±1.29		5.03±0.72	
NPS3	4.23±1.25	**<0.001**	2.93±0.69	**<0.001**
Pain Detect score 1	28.47±4.88		23.13±4.99	
Pain Detect score 2	19.77±5.14		21.23±4.95	
Pain Detect score 3	12.57±4.23	**<0.001**	14.40±5.59	**<0.001**

*Friedman Test.

(Z=1.279; p=0.201). Distribution of patients according to pain categories showed no statistically significant difference (χ^2=1.382; p=0.501).

Mean values of Pain Detect questionnaire at third measurement were not significantly different between the groups (Z=1.254; p=0.210). Pain with neuropathic component was significantly more present in patients from the control group (χ^2=8.541; p=0.014).

Table III shows a comparison of NPS values for three measurements separately for Tapentadol group patients and control group patients. In both groups, there was a significant pain reduction according to the numerical pain scale: tapentadol group (χ^2=59.513; p<0.001) and control group (χ^2=60.000; p<0.001). This table shows a comparison of the values of the Pain Detect score for three measurements separately for the patients from the tapentadol group and separately for the patients from the control group. In both groups, there was a significant reduction of the pain neuropathic component: tapentadol group (χ^2=56.267; p<0.001) and control group (χ^2=60,000; p<0.001).

There was a statistically significant positive correlation between tapentadol dose and pain intensity according to NPS at all three measurements:

Table IV. Correlation of tapentadol dose and pain intensity according to numerical pain scale (NPS) at all times of measurement.

Tapentadol dose		NPS1	NPS2	NPS3
First measurement	ρ	0.464		
	p	**0.010**		
Second measurement	ρ		0.750	
	p		**<0.001**	
Third measurement	ρ			0.443
	p			**0.014**

ρ-Spearman rank correlation.

first measurement (ρ=0.464; p=0.010), after a month (ρ=0.750; p<0.001), and after three months (ρ=0.443; p=0.014), as shown on Table IV and on Figures 1, 2 and 3.

Discussion

Pain management in painful bone metastases means not only pain relief but also improvements in quality of life for these patients at a proper level, as well as reduction of skeletal morbidity in terms of potential pathologic fractures, spinal

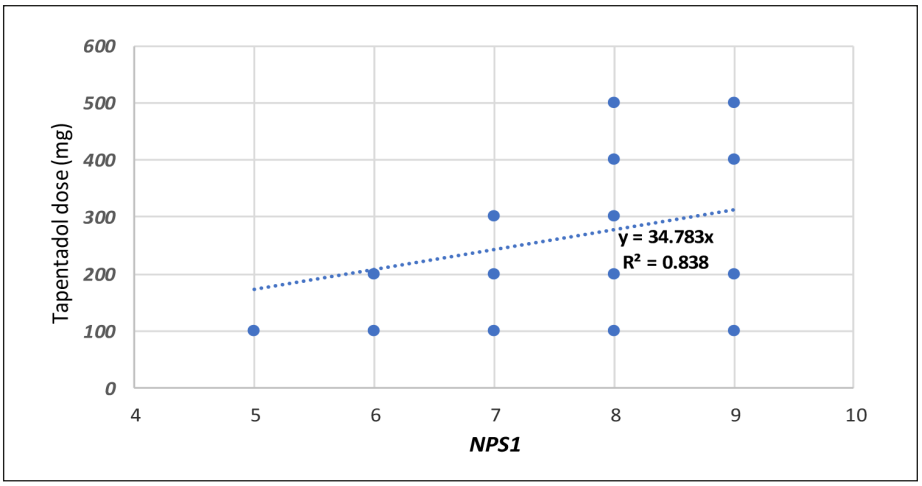

Figure 1. Correlation of tapentadol dose and pain intensity according to numerical pain scale (NPS) at the first time of assessment.

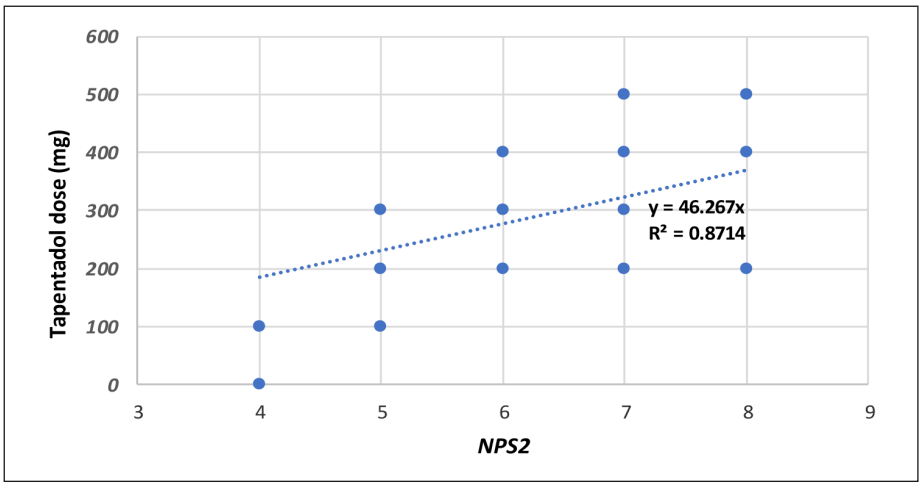

Figure 2. Correlation of tapentadol dose and pain intensity according to numerical pain scale (NPS) at the second time of assessment.

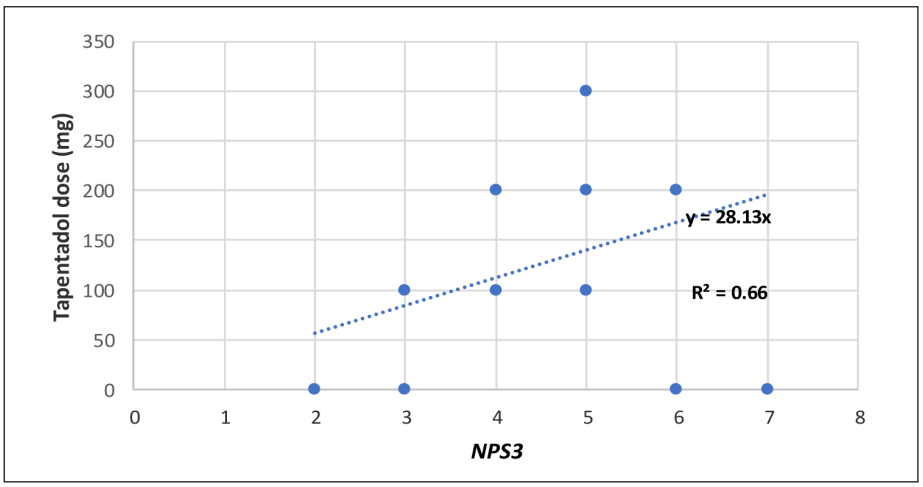

Figure 3. Correlation of tapentadol dose and pain intensity according to numerical pain scale (NPS) at the third time of assessment.

cord compression, and other problems. Accordingly, the treatment of these painful changes primarily includes systemic analgesia and palliative radiotherapy to these changes, along with the application of other co-analgesics[16].

Table I shows the distribution of patients by categories of pain intensity at all time points of follow-up. At the second time point of pain intensity reevaluation, the mean value according to NPS was significantly higher in patients who received tapentadol, and a significantly greater number of patients from this group had severe pain grade in comparison to the controls, which really is an indication for strong opioid administration[17]. At the third point of measurement, tapentadol pharmacotherapy continued in the first patient group with a dosage correction regimen (since their pain is no longer severe but moderate), while patients from the control group had mild pain, so they were not prescribed opioid pharmacotherapy.

Pain Detect questionnaire is a validated and standardized questionnaire for the screening and assessment of neuropathic pain component[18]. This study reached the result that this category of oncology patients in both studied groups has pain with a neuropathic component based on the initial score obtained by the Pain Detect questionnaire. The results of this study (Table II) show that at the third time point of pain reevaluation, the neuropathic pain component is significantly more present in the patients from the control than in those on tapentadol pharmacotherapy. This shows that this drug not only acts on the nociceptive pain component but also on the neuropathic pain component, and thus, it could be a drug of choice for this kind of pain in the studied population, as previously described[19].

This study obtained results in terms of a significant decrease in pain intensity according to NPS in both studied groups ($p<0.001$). Also, in both groups, there was a statistically significant ($p<0.001$) reduction in the neuropathic pain component in comparison to Pain Detect test values, as shown in Table III.

This study recorded a statistically significant positive correlation between tapentadol daily dose and pain intensity according to NPS at all three measurements: first measurement ($p=0.010$), second measurement ($p<0.001$), and third measurement ($p=0.014$), as presented in Table IV, Figures 1, 2 and 3. A positive correlation was expected since a clinician, at each point of the patient's pain reevaluation obtained by the patient, decides on further correction of the tapentadol dosage regimen.

Apart from the aforementioned information on tapentadol and the fact that it is differentiated from classic opioid analgesics, Italian authors[20] concluded that its classic mechanism of opioid receptor agonism results in analgesia in acute painful conditions, while in chronic painful conditions analgesia and pain relief are achieved by noradrenaline reuptake inhibition. Among all the safety aspects, the most important one is the fact that tapentadol absolutely does not induce electrocardiographic changes and no prolongation of the QT interval. Also, it significantly reduces serotonin syndrome induction, and it takes a longer period of time to potentially develop analgesic tolerance. According to this, tapentadol is a novel and an adequate pharmacological solution primarily for chronic mixed pain relief, the pain with both nociceptive and neuropathic components, thus reducing the need for adjuvant co-analgesics and potential polypharmacy, as well as all side effects of potential drug interactions that could happen.

Before this study, the same Italian authors[21] had conducted a study proving that a tapentadol dosage regimen of 350-450 mg/day is an adequate pharmacological solution for the management of moderate to severe cancer pain in previously "opioid naïve" oncology patients, proving it to be an effective analgesic and a well-tolerated one regarding its potential side effects.

Another study conducted in Italy[22] evaluated tapentadol as a potent opioid analgesic drug and its use in oncology patients. The study found that tapentadol significantly reduces the incidence of gastrointestinal side effects such as nausea, vomiting, and constipation. The conclusion of the study was that tapentadol is indicated for use at the third analgesic ladder for severe pain in oncology patients, and further studies are needed to establish its efficacy correlation in palliative pain relief in these patients.

Quality of life is of great importance in all categories of patients, including oncology ones, and the benefits of tapentadol prolonged release and maintenance of quality of life in geriatric patients who are on this pharmacotherapy in terms of its favorable effects on their psychophysical and cognitive functions, assessment of anxiety and depression, have been proven in the TaPE study[23].

A study by German authors[24] showed that predictors for the treatment response of tapentadol for mixed pain in the lumbosacral spine could be adequately reached by using the Pain Detect questionnaire as an appropriate tool. Baron et al[25] compared the analgesic effectiveness of tapentadol extended-release formulation with prolonged

fixed combination of oxycodone/naloxone in the pharmacotherapy of mixed pain in the lumbosacral spine, and one of the diagnostic tools was also Pain Detect score. The efficacy of tapentadol prolonged release was superior to oxycodone/naloxone prolonged release fixed combination in terms of adequate mixed pain relief and more favorable gastrointestinal tolerability. The Pain Detect test was of course used for patients in this study as a diagnostic tool[25]. In this indication area, the efficacy and tolerability of tapentadol prolonged release has also been proven during rehabilitation treatment in patients who underwent laminectomy[26].

A recent study[27] confirmed that the Pain Detect questionnaire score adequately correlates with pain intensity in chronic pain patients. They concluded that most chronic pain patients have neuropathic pain in addition to a nociceptive pain component. This diagnostic tool is an appropriate instrument for follow-up and continuous re-evaluation of patients undergoing chronic mixed pain pharmacotherapy.

Conclusions

Tapentadol prolonged release formulation is an adequate pharmacotherapy solution along with palliative radiotherapy for pain relief in skeletal metastatic breast cancer patients. Palliative radiotherapy in these patients does not provide adequate neuropathic pain component relief, but this effect is achieved with synergistic effects of opioid analgesic tapentadol in patients who are already on radiotherapy treatment.

Tapentadol is an opioid analgesic effective in moderate to strong mixed cancer pain relief in these patients, with minimal adverse effects of this drug and adequate nociceptive and neuropathic pain component relief; the use of adjuvant co-analgesic can be minimized, and polypharmacy can be avoided in these patients. Tapentadol dosage is positively correlated with pain intensity on the numeric pain scale; an increase in pain intensity requires an increase in the daily dosage regimen of this drug. This study confirmed the place of tapentadol as a strong opioid analgesic in pain therapy for this category of oncology patients.

Pain Detect questionnaire is an efficient diagnostic tool for the assessment of neuropathic components in this type of pain and further follow-up of patients on treatment. Pain Detect questionnaire was used as a globally recognized tool for the mixed type of pain that these patients have, which contributed to improving the quality of this research.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All participants provided informed consent for participation in the study.

Ethics Approval

This study involving human participants was conducted in accordance with the amended Declaration of Helsinki. The Ethical Board of the University Clinical Center Nis approved this study by decision No. 4665/6.

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Authors' Contributions

DK, ALP, RZ – designed study protocol, writing the manuscript; IP, AC, IC, MTM, MR, VDJ, IB – collecting patients date during study; GNR, BM, HJ, HT – searching of world literature and discussion of the obtained results with the results of previous research; MAA, DM – statistical data analysis. All the authors approved the final version of the article to be published.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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