Single-center, retrospective study on changes in pain-relieving therapy after bone metastasis detection by bone scintigraphy in prostate cancer patients

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Whole-body bone scintigraphy (WB-BS) is used for detecting and monitoring metastatic spread of prostate cancer (PCa) and to investigate bone pain episodes. To investigate the impact of a positive WB-BS on pain-relieving medicine prescription in PCa patients, a single-center, retrospective cohort study with PCa patients classified as positive for bone metastases (BM) by WB-BS was conducted. Demographic, clinical, and ambulatory pain-relieving medicine prescription data were evaluated. Pain-relieving medicines were categorized according to the WHO 'Analgesic Ladder'. Regimens adopted before and after WB-BS were compared. Differences were considered significant at p<0.05. A total of 180 PCa patients were diagnosed with BM, 64.4% of whom were ≥65 years of age. Thirty-three patients were prescribed analgesics only after WB-BS, mostly including NSAIDs and weak opioids. Pain-relieving prescription changed after WB-BS in patients with prescriptions before and after WB-BS, with a reduction in NSAIDs and adjuvants and an increase in weak and strong opioids. In addition, 40% of patients with WHO analgesic step 1 drugs and 21.7% of patients with WHO step 2 drugs before WB-BS changed to other WHO steps after WB-BS. Pain-relieving prescriptions changed after a positive WB-BS, providing evidence that it could contribute to clinical management of painful metastatic PCa patients.

Keywords: Bone scan. Pain-relieving medicine. Prostate cancer. Bone metastases. Opioid.

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men in Brazil, with approximately 130,000 new cases projected for 2020–2021 (INCA, 2019). The majority of PCa patients are diagnosed in the early stages, and about 30% of them may experience disease progression. Furthermore, at initial diagnosis, 4% of patients have metastatic PCa, and patients who relapse after primary hormonal therapy usually develop castration-resistant PCa (Yaldo et al., 2016).

Bone metastases (BM) are a common complication of prostate cancer, occurring in 70% of men with advanced PCa and 90% of men with castration-resistant PCa. BM may cause severe pain and skeletal-related events, resulting in high morbidity and mortality (Levren et al., 2011; Pignot et al., 2018).

Whole-body bone scintigraphy (WB-BS) with Tc-99m methylene diphosphonate (99mTc-MDP) is used for detecting and monitoring metastatic spread of the cancer to the skeleton, with 95% sensitivity and moderate specificity (Levren et al., 2011; Marquez-Lopez et al., 2015). In PCa, WB-BS is the recommended investigation in newly diagnosed patients, in patients with recurrent disease, and in patients receiving a treatment response evaluation, but it is also commonly motivated by bone pain episodes, as skeletal metastases are the most common reason for cancer-related pain (Levren et al., 2011; Zacho et al., 2017).

As pain episodes are associated with BM in PCa patients, treatment is performed according to the three-step 'Analgesic Ladder' published by the World Health

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Organization (WHO) (WHO, 1996). For mild pain (Step 1), non-opioid analgesics such as NSAIDs are recommended with addition of adjuvant drugs if there is a neuropathic component. For moderate pain (Step 2), weak opioid analgesics are added. For patients with moderate to severe pain (Step 3), strong opioid analgesics are recommended together with non-opioid analgesics and adjuvant drugs if there is a neuropathic component (Muralidharan, Smith, 2013).

Although WB-BS is applied to investigate bone pain episodes, no studies have assessed its contribution to cancer pain management in an ambulatory routine. In addition, according to the report from the Center for Disease Control and Prevention (CDC), more than 70 000 drug overdose deaths occurred in the United States in 2017 and approximately two thirds (47,600) involved an opioid (Wilson et al., 2020). In this study, we investigated pain treatment patterns and the impact of a positive bone scan in pain-relieving medication prescription in PCa patients. The results are relevant for presenting the practice of safe use of opioids in the treatment of chronic cancer pain.

MATERIAL AND METHODS

Study design and inclusion criteria

This was a retrospective cohort study performed in the Nuclear Medicine Department of the Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil. The inclusion criteria were (1) referral as part of a routine clinical bone scintigraphy from January 2016 to December 2017, (2) diagnosis of prostate cancer, and (3) age ≥18 years. Patients who had a WB-BS but were not routinely assisted at the institute were excluded.

Data collection

Patients' data were retrieved from hospital electronic records. Firstly, PCa patients were analyzed to determine the final diagnosis of bone metastasis according to combination of the results of the WB-BS, additional imaging, and clinical follow-up. All bone scans were routinely analyzed by physicians with experience in nuclear medicine. Patients were classified as having BM if the initial WB-BS was classified as malignant or if additional magnetic resonance imaging (MRI) or computed tomography (CT) proved metastasis in cases of equivocal findings on WB-BS. For patients with two or more WB-BS during the referred period, the last bone scan was considered.

For PCa patients classified as positive for BM, socio-demographic and clinical data were collected, such as date of cancer diagnosis, age, number of metastases (single or multiple), and date of death (if applicable). In addition, ambulatory pain-relieving medicine prescriptions performed within 90 days before to 90 days after WB-BS were evaluated. An ambulatory prescription is valid for a period of 90 days in the institution, after which a new prescription is necessary to obtain medications from the institution's pharmacy. Thus, pain relief medications were classified as AINEs, adjuvants, weak opioids, and strong opioids, and the patient's pain treatment was categorized according to the WHO 'Analgesic Ladder'. Regimens adopted before and after WB-BS were compared.

Approvals

The protocol was approved by the local Human Ethics Committee of INCA (n. 1.699.846), and all methods were performed in accordance with Brazilian and international clinical research guidelines and regulations.

Statistical analysis

A descriptive analysis was performed by means of absolute and relative frequencies. The prescription frequencies before and after WB-BS were compared using the chi-square test. Results were considered statistically significant at $p<0.05$. All analyses were performed using the SPSS statistical package (SPSS version, 23.0, Inc. – Chicago, IL-USA).

RESULTS

A total of 4736 WB-BS were analyzed, and 1245 (26.2%) were given a positive diagnosis for bone

metastases in the study period (January 1, 2016 to December 31, 2017), of these, 180 (14.4%) were patients with prostate cancer (Table I). Most patients were older than 65 years at diagnosis (64.4%), and multiple bone metastases were more common than single metastases (86.7% vs. 13.3%). Seven patients (3.9%) died less than 90 days after WB-BS.

TABLE I - Characteristics of prostate cancer patients with bone metastases diagnosed by whole-body bone scintigraphy at INCA in 2016 and 2017 (*n* = 180)

Characteristic	*n* (%)
Age	
<65 years	64 (35.6)
≥65 years	116 (64.4)
Frequency of bone metastases	
Single	24 (13.3)
Multiple	156 (86.7)
Death	
≤90 days	7 (3.9)
>90 days	23 (12.8)
Time between hospital registration and WB-BS	
≤90 days	37 (20.6)
>90 days	143 (79.4)

Ambulatory pain-relieving medicine prescriptions performed within 90 days before to 90 days after WB-BS were evaluated. Sixty-seven patients (37.2%) had no prescriptions at any of the analyzed time points. Patients with analgesic prescriptions were divided into three groups: (a) Patients with prescriptions before WB-BS, prescribed up to 90 days before WB-BS and with no analgesic prescriptions within a period of 90 days after WB-BS; (b) Patients with prescriptions after WB-BS, with only an analgesic prescription within a period of up to 90 days after WB-BS and; (c) patients with analgesic prescriptions up to 90 days before and after WB-BS. According to the WHO Analgesic Ladder, prescriptions were classified as step 1, when they included only NSAIDs (dipyrone, acetaminophen, tenoxicam, or diclofenac) or adjuvants (gabapentin, amitriptyline, pregabalin, or venlafaxine); step 2, when they included a weak opioid (tramadol or codeine); and step 3, when they included a strong opioid (morphine, fentanyl, methadone, and oxycodone). NSAIDs and adjuvants could be combined in steps 2 and 3.

The distribution of analgesic prescriptions in groups a, b, and c is presented in table II. Percentages above 100% represent concomitant use of different analgesic classes. Six patients (3.3%) were prescribed analgesics only before WB-BS (a); none of them were prescribed strong opioids. A total of 33 patients (18.3%) were prescribed an analgesic only after WB-BS (b), with most prescriptions including NSAIDs, adjuvants, and weak opioids and 6.1% including strong opioids. A total of 74 patients (41.1%) were prescribed analgesics before and after WB-BS (c). This group was subdivided and analyzed individually before and after WB-BS and both, in order to detect changes in analgesic prescription. Sixty-two (83.8%), 17 (22.9%), and 21 (28.4%) patients were prescribed at least an NSAID and adjuvant (step 1 on WHO Analgesic Ladder), a weak opioid (step 2), and a strong opioid (step 3) before and after WB-BS, respectively. Moreover, a reduction in NSAID and adjuvant and an increase in weak and strong opioid prescription from 90 days before WB-BS to 90 days after bone scan was observed in this group.

TABLE II - Analgesic medication prescribed for prostate cancer patients with bone metastases for ambulatory pain relief 90 days prior or after WB-BS, according to the WHO 'Analgesic Ladder' ($n =113$)

Patient Group	a	b	c			p value
Characteristic	Prescriptions before WB-BS ($n = 6$) n (%)	Prescriptions after WB-BS ($n = 33$) n (%)	Prescriptions before and after WB-BS ($n = 74$) n (%)			p value
			before	after	before and after	
NSAIDs and adjuvants	4 (66.6)	26 (78.7)	4 (5.4)	0 (0.0)	62 (83.8)	<0.0001
Weak opioid	4 (66.6)	13 (39.4)	6 (8.1)	7 (9.4)	17 (22.9)	<0.0001
Strong opioid	0 (0.0)	2 (6.1)	0 (0.0)	8 (10.8)	21 (28.4)	0.034

Considering patients who were prescribed analgesics before and after WB-BS (c, n = 74), 23.3% in WHO analgesic step 1 before WB-BS changed to step 2 and 16.7% changed to step 3 after WB-BS. Of those who were on step 2 before WB-BS, 13.0% changed to step 3 and 8.7% returned to step 1. Moreover, all the patients who were already using medications from the third step before WB-BS remained on the third step (p<0.0001; Table III).

Regarding analgesic prescription classification and the frequency of bone metastases, there was no statistically significant difference in analgesic prescription type between patients with single and multiple metastases (p=0.103; Table IV).

TABLE III - Change in analgesic prescription step according to the WHO Analgesic Ladder for patients with prescriptions before and after WB-BS (group c, $n = 74$)

Step before WB-BS	Step after WB-BS n (%)			p value
	1	2	3	
1	18 (60.0)	7 (23.3)	5 (16.7)	
2	2 (8.7)	18 (78.3)	3 (13.0)	<0.0001
3	0 (0.0)	0 (0.0)	21 (100)	

TABLE IV - Frequency of bone metastasis diagnosed by whole-body bone scintigraphy in prostate cancer patients at INCA in 2016 and 2017, according to patients' analgesic prescriptions (n = 180)

Patient Group		a	b	c	
Frequency of bone metastases	Without prescription ($n = 67$) n (%)	Prescriptions before WB-BS (a) ($n = 6$) n (%)	Prescriptions after WB-BS (b) ($n = 33$) n (%)	Prescriptions before plus after WB-BS (c) ($n = 74$) n (%)	p value
Single	14 (20.9)	1 (16.7)	4 (12.1)	5 (6.8)	0.103
Multiple	53 (79.1)	5 (83.3)	29 (87.9)	69 (93.2)	

DISCUSSION

The present research assessed pain medicinal management in prostate cancer patients after a positive WB-BS in a cancer reference hospital in Brazil from January 2016 to December 2017. A total of 180 patients were included, and 64.4% were older than 65 years. Considering that prostate cancer incidence and mortality increase after age 50, advancing age is a well-established risk factor for prostate cancer (INCA, 2019).

Thirty-seven patients were probably diagnosed with bone metastases during staging, as the time between WB-BS and hospital registration was less than 90 days. Detection of bone metastases at the time of diagnosis directly influences treatment choice, as well as patient prognosis, BS being recommended for the investigation of BM (Zacho et al., 2017). Moreover, although prostate-specific antigen (PSA) testing has led to an increase in the rate of control of PCa, reducing the incidence of bone metastases at diagnosis, advanced or metastatic disease is still reported in up to 22% of newly diagnosed patients (Briganti et al., 2010).

Sixty-seven patients (37.2%) had no analgesic prescription at any of the analyzed time points, probably due to WB-BS for cancer staging or restaging, without associated pain. Thirty-three patients (18.3%) did not have an analgesic prescription before WB-BS but received one after WB-BS (group b), probably due to a positive result for bone metastasis being correlated with previous pain. Most of the patients in this group had a prescription of WHO step 1 analgesic ladder (NSAIDs and adjuvants) drugs or a weak opioid prescription, suggesting mild or moderate pain. Although only 6.1% (n = 2) had a strong opioid prescription, this is a significant finding as it appeared in prescriptions only after WB-BS, which may have contributed to the association of patient pain with bone metastases and to the determination of pain-relieving therapy, as demonstrated earlier (Meohas et al., 2005).

Levren et al. (2011) retrospectively evaluated the relationship between pain and bone metastases in prostate cancer patients and showed that 47% of them reported pain at the time of BS. Also, they highlighted that it is important to consider clinical information about pain when reviewing bone scintigraphy, because when metastases are present, they are usually located in the same region of pain.

Analysis of analgesic prescriptions in patients who had prescriptions before and after WB-BS (group c) showed that this group was more likely to use drugs from WHO analgesic ladder step 3, when compared with groups a and b ($p<0.03$). The pattern of pain-relieving medication prescription changed after WB-BS, with a reduction in NSAID and adjuvant and an increase in weak and strong opioid prescription from 90 days before WB-BS to 90 days after bone scan. In addition, 40% of patients with WHO analgesic step 1 drug and 21.7% of patients WHO step 2 drug prescription before WB-BS changed to other WHO steps after WB-BS. All patients already using drugs from the third step before WB-BS remained on this step after WB-BS ($p<0.0001$). One of the characteristics of metastatic bone pain is that it is not only intolerable and severe but also progressive in many patients. As bone remodeling progresses, spontaneous and severe pain may occur and seriously impairs quality of life when dyskinesia or bone fracture is present (Mantyh, 2014). In addition, complications from neuropathic pain constantly occur in the case of metastasis to the vertebrae and in the case of multiple metastases patients may develop hypercalcemia (Hara, 2008).

Patients who had prescriptions only before WB-BS did not use analgesics of WHO analgesic ladder step 3, suggesting pain of mild or moderate intensity, which could be non-cancer pain or cancer pain further managed by non-pharmacological means. Some patients may have a single site of pain and other areas of asymptomatic bone metastasis, while others may have multifocal pain, which could fluctuate between one region and another (Raphael et al., 2010).

The results of this study are a portrait of the pain management experience after a positive WB-BS in metastatic prostate cancer patients of a reference institution in cancer treatment in Brazil. Its strength lies primarily in sample size, the inclusion of patients diagnosed and treated in the same institution, and the use of additional images to confirm bone metastases. Limitations of this study include its retrospective nature and lack of data on patient pain levels and localization at

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prescription time and other comorbidities which could cause pain.

Analgesic prescription for pain management changed after a positive whole-body bone scintigraphy, providing evidence that bone scintigraphy could also contribute to clinical cancer pain management in metastatic prostate cancer patients.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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