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Breakthrough pain in patients with multiple myeloma: a secondary analysis of IOPS MS study

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Abstract. – OBJECTIVE: The aim of this study was to characterize breakthrough pain (BTcP) in patients with multiple myeloma (MM).

PATIENTS AND METHODS: This was a secondary analysis of a large multicenter study of patients with BTcP. Background pain intensity and opioid doses were recorded. The BTcP characteristics, including the number of BTcP episodes, intensity, onset, duration, predictability, and interference with daily activities were recorded. Opioids prescribed for BTcP, time to achieve a meaningful pain relief after taking a medication, adverse effects, and patients' satisfaction were assessed.

RESULTS: Fifty-four patients with MM were examined. In comparison with other tumors, in patients with MM BTcP was more predictable (p=0.04), with the predominant trigger being the physical activity (p<0.001). Other BTcP characteristics, pattern of opioids used for background pain and BTcP, satisfaction and adverse effects did not differ.

CONCLUSIONS: Patients with MM have their own peculiarities. Given the peculiar involvement of the skeleton, BTcP was highly predictable and triggered by movement.

Key Words:
Multiple myeloma, Cancer pain, Breakthrough pain, Opioids, Palliative care.

Introduction

Multiple myeloma (MM) is the second most common hematological tumor representing 1.8% of all new cancer cases and is the 14th cause of cancer death in the US[1]. The improvements in therapeutic options for MM, together with supportive care, have significantly increased the percentage of patients with long survival[2]. Bone lesions are one of the most common complications of MM[3]. Up to 90% of patients complain of bone pain. In about 33% of patients, MM is diagnosed after a bone fracture, leading to severe pain and increased morbidity and mortality[4,5].

Other than a persistent background pain experienced for most hours of the day, patients may experience episodes characterized by the rapid increase of pain with a short onset and duration. This phenomenon is known as breakthrough pain (BTcP) and is defined as a transitory peak in pain intensity, that occurs spontaneously or is induced by a specific trigger in patients having stable and well controlled background pain for most hours of day[6]. The typical temporal pattern of BTcP interferes with the quality of life[7]. Data regarding the characteristics of BTcP in patients with MM, that has the peculiar characteristic to be a bone disease, are lacking. The primary outcome of this study was to characterize BTcP in patients with MM in comparison with other primary tumors. The secondary outcome was to evaluate background pain and BTcP management, as well as patients' satisfaction with medications used for BTcP and side effects induced by BTcP medication.

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Patients and Methods

This was a secondary analysis of a previous observational, prospective, multicenter study, the IOPS-MS Study (Italian Oncologic Pain multiSetting Multicentric Survey)[8]. The research was carried out in accordance with the conditions of the Declaration of Helsinki, recommendations guiding physicians in biomedical research involving human subjects, and was approved by the independent Ethic Committee of Fondazione PTV Policlinico Tor Vergata Hospital of the University of Rome "Tor Vergata" (identifiers: Ethical Approval Letter No. 21/13 dated 20 Feb 2013). Written informed consent was obtained from each patient.

Patients were screened in different settings including outpatient, inpatient, or day-hospital and were visited in palliative care, oncology, radiotherapy, and pain therapy settings. From the original study, patients with a primary diagnosis of MM were selected.

Inclusion criteria were age ≥18 years, a primary diagnosis of MM, well-controlled background pain (pain intensity ≤ 4 on a 0-10 numerical scale), a diagnosis of BTcP, defined according to a pre-defined algorithm[8]. Exclusion criteria were unstable background pain, peaks of low pain intensity, and poor compliance.

Age, gender, and Karnofsky level were recorded. Average pain intensity (on a numerical scale 0-10), and opioids and doses used for background pain [expressed as oral morphine equivalents (OME)][9], were recorded, as well as the use of adjuvants.

The characteristics of BTcP, including number of episodes, intensity, predictability, onset (≤ 10 min or > 10 min), duration of untreated episodes, interference with daily activities (nothing, a little bit, much, very much) were assessed. Analgesics used for BTcP and the time to achieve a meaningful pain relief after taking the BTcP medication, and patients' satisfaction with BTcP treatment (very satisfied, satisfied, not satisfied, and neither satisfied nor dissatisfied) were recorded. Adverse effects to be attributed to medications used for BTcP were also collected.

Statistical Analysis

Descriptive statistics for patients' characteristics, basal pain and BTP have been reported providing mean values and frequencies stratified by MM occurrence. Comparisons between patients with and without MM were performed using the Chi-square, Fisher's exact or two-sample independent *t*-test, as appropriate. The statistical software SAS v. 9.4 (available at: https://www.sas.com/it_it/home.html?utm_source=google&utm_medium=cpc&utm_campaign=brand-global&utm_content=GMS-88251&gclid=EAIaIQobChMI-36HLr6e9_AIVVbvVCh1PqAhZEAAYASAAEgJGUfD_BwE) was used and *p*-values <0.05 were considered statistically significant.

Results

Fifty-four patients with MM were selected from the 4,016 patients recruited in the original study (1.3%). The mean age was 69.9 (SD 10.4) years, and 25 patients (46.3%) were males. The mean Karnofsky was 53.5 (SD 17.4). Pain mechanisms were mixed, nociceptive, and neuropathic in 34 (63.0%), 17 (31.5%), and 3 (5.5%) patients, respectively. No differences with other primary tumors (p=0.84) were found.

Fifty-three (98.1%) and 29 (53.7%) patients were receiving opioid drugs for background pain and for BTcP, respectively. The mean pain intensity of background pain was 3.11 (SD 1.14), which was in line with that found in other tumors (1.98, SD 1.07, p=0.41). The mean OME was 127.8 (SD 173.2) mg/day, which was relatively higher than that reported in patients with other tumors (95.8, SD 108.8) mg/day, although it did not attain significance (p=0.18).

BTcP Characteristics

The mean number of BTcP episodes was 2.7/day (SD 1.9, range 1-8). No statistical difference in comparison with other primary tumors was found (2.4/day, SD 1.4, p=0.21).

The mean intensity of BTcP was 7.61 (SD 1.38). No statistical difference with other tumors (7.51 SD 1.27, p=0.61) was found. The mean duration of an untreated episodes was 44 (SD 35) minutes. No statistical differences with other types of tumors were found (p=0.93).

BTcP was predictable in 24 patients (44.4%), a proportion that was statistical higher than that reported in patients with other tumors (30.3%, p=0.04). The main trigger of predictable BTcP was the movement (44.4%). Procedures, and other causes were the other triggers (5.6% and 3.7%, respectively). In comparison with other tumors, patients with MM were more likely to have predictable BTcP with movement (44.4% *vs.* 20.2%, p<0.001), while there were no differences in other triggers such as procedures (5.6% *vs.* 3.0%,

p=0.23) or other causes (3.7% *vs.* 3.3%, p=0.70).

BTcP onset was short (≤ 10 minutes) in 39 patients (72.2%), while 15 patients (27.8%) reported a slower onset of BTcP. No differences with other tumors were found (p=0.71). The mean time to achieve a meaningful pain relief after taking a BTcP medication was 13.5 (SD 6.6) minutes. This was significantly shorter than in patients with other types of tumors (16.6, SD 14.1 minutes, p=0.02).

BTcP interference with daily activity was found to be mild, much, and very much in 4 (7.4%%), 33 (61.1%%), and 17 (31.5%) patients, respectively. There was no difference in comparison with other tumors, 13.8%, 57.5%%, and 28.5%, respectively (p=0.57).

Analgesics Used for Background Pain

Drugs administered for background pain are reported in Table I. There was no difference in the prescription of anti-inflammatory drugs between patients with and without MM (5.6% *vs.* 9.1%, p=0.48), as well in the use of paracetamol (p=0.41), as well as opioids (all p>0.05).

Forty-one patients (75.9%) were receiving adjuvant drugs, including benzodiazepines (n. 2, 3.7%), anticonvulsants (n. 19, 35.2%), antidepressants (n. 6, 11.1%), antiemetics (n. 5, 9,3%), laxatives (n. 18, 33.3%), and corticosteroids (n. 21, 38.9%).

In comparison with other tumors, patients with MM were more frequently prescribed laxatives (33.3% *vs.* 16.4%, p=0.002), while no differences in the use of anticonvulsants (35.2% *vs.* 30.6%, p=0.146), antidepressants (11.1 *vs.* 9.4%, p=0.64), corticosteroids (38.9% *vs.* 37.4% p=0.89), antiemetics (9.3% *vs.* 9.0% p=0.81), and benzodiazepines (3.7% *vs.* 10.7%, p=0.12) were found.

Analgesics Used for BTcP

Opioids used for BTcP in patients with and without MM are reported in Table II.

No difference in BTcP medications between patients with and without MM was found (all p>0.05).

Adverse Effects

Adverse effects to be attributed to BTcP medications were found in just one patient (1.9%). No differences with other tumors (1.3%) were found (p=0.51). No adverse effects of severe intensity were reported.

Satisfaction

Most patients with MM were satisfied or very satisfied with BTcP medication, 29 (58.0%) and 9 (18.0%), respectively. No differences with other primary tumors were found (62.0% satisfied and 8.9% very satisfied, p=0.10).

Table I. Opioids used for background pain in patients with and without MM.

Drugs	n (%) in patients with MM	n (%) in patients without MM	*p*-value
Non steroidal anti-inflammatory drugs	3 (5.6%)	349 (8.8%)	0.62
COX2	0 (0.0%)	16 (0.4%)	0.99
Paracetamol	15 (27.8%)	898 (22.7%)	0.41
Hydromorfone	4 (7.4%)	124 (3.1%)	0.09
Morphine SR	4 (7.4%)	145 (3.7%)	0.14
Oxycodone SR	6 (11.1%)	485 (12.2%)	0.99
Codeine+paracetamol	2 (3.7%)	220 (5.6%)	0.77
Oxycodone+paracetamol	4 (7.4%)	175 (4.4%)	0.30
Oxycodone+naloxone	16 (29.6%)	1,136 (28.7%)	0.88
Tapentadol	3 (5.6%)	192 (4.8%)	0.75
Tramadol+paracetamol	1 (1.9%)	8 (0.2%)	0.11
Tramadol	2 (3.7%)	161 (4.1%)	0.99
Morphine IR	1 (1.9%)	184 (4.6%)	0.52
Morphine IV	1 (1.9%)	103 (2.6%)	0.99
Morphine SC	0 (0.0%)	89 (2.2%)	0.63
Methadone	0 (0.0%)	43 (1.1%)	0.99
Others	2 (3.7%)	67 (1.7%)	0.24
Fentanyl TD	16 (29.6%)	1,086 (27.4%)	0.76
Buprenorphine TDs	1 (1.9%)	120 (3.0%)	0.99

SR: slow release, IR: immediate release, IV: intravenous, SC: subcutaneous, TD: transdermal.

Table II. Opioids used for BTcP in patients with and without MM.

Drugs	n (%) in patients with MM	n (%) in patients without MM	*p*-value
Oral Transmucosal Fentanyl Citrate (OTFC)	1 (1.9%)	129 (3.3%)	0.99
Fentanyl Buccal Tablet (FBT)	6 (11.1%)	429 (10.8%)	0.83
Fentanyl Buccal Sublingual Tablet (FBST)	7 (13.0%)	563 (14.2%)	0.99
Fentanyl Pectin Nasal Spray (FPNS)	8 (14.8%)	799 (20.2%)	0.39
Intranasal Fentanyl Spray (INFS)	0 (0.0%)	40 (1.0%)	0.99
Morphine IR	9 (16.7%)	554 (14.0%)	0.55
Morphine SC	1 (1.9%)	164 (4.1%)	0.73
Morphine IV	1 (1.9%)	128 (3.2%)	0.99
Others	11 (20.4%)	806 (20.3%)	0.99

IR: immediate release, IV: intravenous, SC: subcutaneous.

Discussion

This is the first paper reporting data regarding the characteristics of BTcP in MM patients. The sample was gathered from a large study assessing the characteristics of BTcP in general population of patients with cancer[8].

In this subgroup of patients BTcP was found to be more predictable, with predominant trigger being physical activity, in comparison with the general population of patients with cancer. Moreover, time to meaningful pain relief was shorter. Indeed, the other characteristics, including number of episodes, intensity, duration, onset, and interference with daily activity did not differ. Background pain and opioid doses were similar to those reported in general cancer population, as well the pattern of drugs used for BTcP, adverse effects, and level of satisfaction with BTcP medications. This reflects the typical clinical features of patients with a bone disease.

Most pain syndromes experienced by patients with MM are due bone disease. Painful osteolysis, especially occurring in lumbar spines, may be observed in these patients. In addition, MM may induce other potentially painful complications, such as the physical deconditioning syndrome, characterized by muscle atrophy and physical debilitation. Patients with skeletal involvement suffer from a localized and sometimes irradiated continuous pain at rest, sometimes complicated by neuropathic symptoms and by movement-related incidental pain.

Metastatic cancer-induced bone pain has a unique and complex pathophysiology characterized by nociceptive and neuropathic components[10]. The nociceptive component is determined by the release of algogenic substances by tumor and stromal cells, the release of acids by bone-destroying osteoclasts, as well as mechanical destabilization or fracture of the bone. Indeed, the neuropathic component is induced by tumor cell growth which damages the distal ends of nerve fibers normally innervating the bone and by triggering a pathological sprouting of both sensory and sympathetic nerve fibers. All these mechanisms induce peripheral and central sensitization[11]. Thus, the bone has a lower pain threshold, for which normally a non-painful stimulus such as movement, drives an exacerbation of pain which lasts variably, also depending on the bone site and duration of activity.

The occurrence of incident pain was recorded in 38% of patients with advanced hematological malignancies with a higher rate in MM patients, in which this pain feature was recorded in 85% of patients[12]. Comparative data regarding BTcP characteristics in patients with MM are lacking. There is only a descriptive follow-up study[13] on three patients with MM experiencing BTcP from vertebral fracture, who were treated with Fentanyl Pectin Nasal Spray (FPNS) successfully.

From a clinical perspective, treating patients with a primary or metastatic bone disease is challenging. Pain at rest is commonly controllable with analgesic drugs used for background pain, while pain on movement may be severe enough to limit physical activity. This predictable event is difficult to manage. An increase in the dose of the opioid prescribed for background pain may produce a better analgesia, thus improving physical activity or reducing the number of BTcP episodes induced by movement. The attempt to optimize background analgesia, however, may result in the development of adverse effects[14]. Accordingly, an individual compromise between the level of quality of life, number of BTcP episodes to eventually treat, and occur-

rence of adverse effects, is necessary. This may explain the shorter time to achievement of meaningful pain relief, which may result from a combination of the effect of the drugs and stopping activity. The management of these variables requires a high level of expertise and adequate training of patients[15].

Some of these episodes could be preceded by analgesics given prior to starting an expected painful activity, giving immediate-release oral morphine 30 minutes before, or a rapid onset fentanyl formulation 5-10 min before, according to the analgesic onset of these drugs. When an episode of high intensity occurs for whatever reason, the achievement of a rapid analgesia is necessary. Indeed, patients may spontaneously stop their activity as a reaction to the high pain intensity resulting in a spontaneously subset of pain[16].

Limitations

There are some study limitations, due to the secondary analysis of an original trial in patients who were diagnosed with BTcP. Thus, information about the prevalence of BTcP in patients with MM remains unknown. Unfortunately, very limited data exist in literature. The analgesic treatment was based on the local policy of participating centers having a large experience in the management of background pain and BTcP. Thus, this data should reflect the real world, providing a picture of the characteristics of BTcP in MM patients and of drugs prescribed for either background pain or BTcP.

Conclusions

Patients with MM have their own peculiarities, including a predictable incident pain due to movement. Future studies should be performed to analyze the prevalence of BTcP in patients with MM, as well as the optimal management strategy for their individual pattern of BTcP.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The research was carried out in accordance with the conditions of the Declaration of Helsinki, recommendations guiding physicians in biomedical research involving human subjects, and was approved by the independent Ethic Committee of Fondazione PTV Policlinico Tor Vergata Hospital of the University of Rome "Tor Vergata" (identifiers: Ethical Approval Letter No. 21/13, dated 20 Feb 2013).

Informed Consent

Written informed consent was obtained from each patient.

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Availability of Data and Materials

The datasets generated during/and or analyzed during the current study are available from the corresponding author upon request.

Authors' Contributions

All authors contributed to the planning, conduction and final revision of the manuscript. SM wrote the manuscript.

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