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BREAKTHROUGH PAIN IN ADULTS WITH CANCER

Multidisciplinary cases collection

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1 Breakthrough cancer pain: the oncologist's perspective

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ABSTRACT
The binomial quantity of life and quality of life (QoL) is the reference for all decisions in oncology. In terms of QoL, the presence of pain is very common in the continuum of cancer but often neglected by patients, who assume its inevitability, and by doctors, who privilege the overall survival. Breakthrough cancer pain (BTcP) is very frequent, interferes profoundly with daily activities and causes high levels of emotional distress.
We present a clinical case of a patient with rapidly evolving poorly differentiated carcinoma, with probably pulmonary origin, and metastasized to the brachial muscle region of the right arm. Even with radiotherapy and chemotherapy the patient's performance status decreased and control of his pain acquired primary importance. This was accomplished with a long-acting transdermal fentanyl patch for his severe background pain and sublingual fentanyl tablets for his BTcP.

INTRODUCTION

When a medical oncologist faces a new patient, he has three main goals: to increase overall survival, to improve quality of life (QoL), and, if possible, to keep the cost reasonable to the patient and society. He also knows that therapies improving survival can augment QoL, and that increasing QoL he can prolong the survival of his patients. But, frequently the oncologist focuses his action on survival and puts well-being, like pain, in second place. Often, the patient also links his cancer to the presence of pain and feels he is obliged to suffer. Because of that, both doctor and patients frequently neglect pain, do not give it proper attention and undertreat this symptom which has an important impact on the patient's daily life and diminishes his ability to tolerate cancer treatments, thereby worsening his prognosis.

Pain can occur at any time during the continuum of cancer disease, being more prevalent with more advanced illness. It is estimated to be around 50% at the time of diagnosis and in early phases, increasing to 74% at advanced stages.[1] A meta-analysis of 52 studies calculated a prevalence of 33% in cancer survivors after curative treatment.[2]

Breakthrough cancer pain (BTcP) is usually defined as a "transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relatively stable and adequately controlled background pain".[3] Typically, it reaches its maximum severity within 5 minutes from the start and persists up to 30-60 minutes.[4] Like the background cancer pain, BTcP causes an increased emotional distress, with anxiety and depression reported in almost 65% of subjects, strongly interfering with daily activities in 81% of patients. This emphasizes the need for adequate BTcP control mainly with fast-acting transmucosal drugs, like sublingual fentanyl tablets.[5]

We present a clinical case demonstrating that more than quantity of life, what patients frequently need is QoL, especially regarding pain, and that to control it sublingual fentanyl tablets are a good option.

CASE REPORT

A 64-year-old male presented for the first time to our consultation on 13th November 2017 to evaluate his clinical conditions to start a systemic treatment for a poorly differentiated carcinoma with sarcomatoid areas, probably originated on the lung, and metastasized to the brachial muscle region of the right arm (Figs. 1 and 2). He was an ex-smoker (±30 pack-year) and had a history of dyslipidaemia for more than 20 years. The disease history had begun

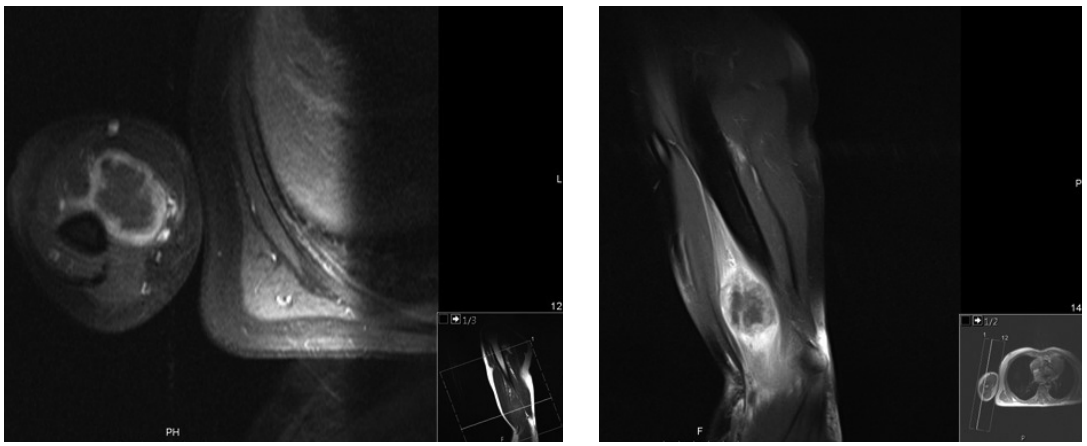

Figure 1. MRI of the right arm showing the cancer mass.

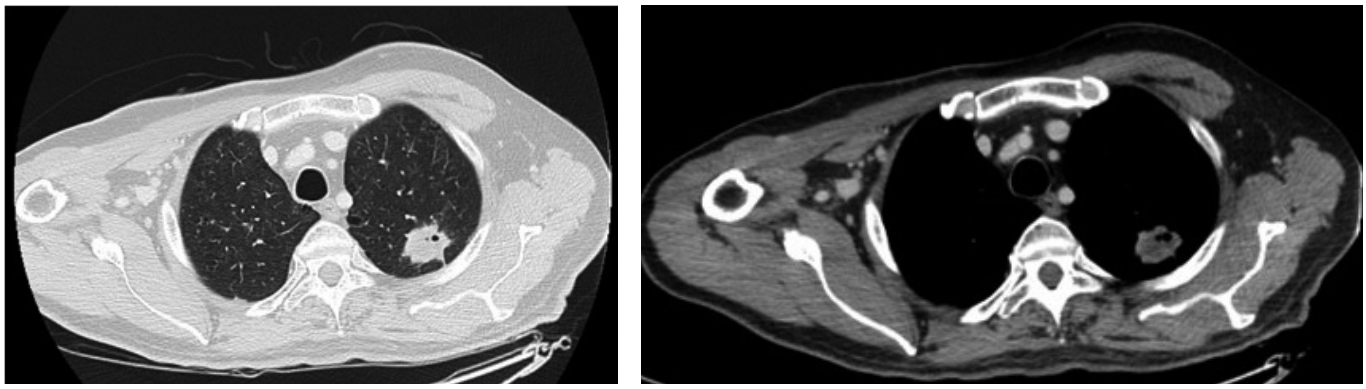

Figure 2. Thoracic CT scan showing a mass 3 cm in diameter at the superior lobe of the left lung.

a month earlier when he noticed a fast-growing tumefaction on the right arm accompanied by rapidly increasing pain. The physical examination showed a petrous tumefaction nearly 12 cm in diameter on the distal right arm, that strongly limited elbow mobility, and with severe uncontrolled pain (numerical rating scales [NRSs], score of 8) medicated with tramadol 200 mg bid, and clonixin 600 mg 8/8 h. Discussed by our multidisciplinary board, the clinical case strongly suggested that it was a primary lung cancer, although without mutations on EGFR, ALK ROS1 or BRAF but with a KRAS mutation. The patient began a pain control scheme with a transdermal patch of fentanyl, 50 µg/72 hours, and was submitted to palliative radiotherapy to the muscle metastasis, 30 Gy in 10 fractions, in December 2017. After this treatment, the mass diminished to 8 cm in diameter, the patient gained some mobility, but the pain remained intense (NRS 6), with more than six episodes per day of BTcP (NRS 9), especially with certain movements. We increased the dose of the fentanyl transdermal patch to 100 µg/72 hours, and introduced sublingual fentanyl tablets (133 µg, as required). After 3 days, the patient perceived a significant background pain reduction (NSR 4) but he needed to increase the sublingual fentanyl tablets to 267 µg, achieving with that dose a good control of his BTcP, and with no side-effects related to the analgesic scheme instituted. The patient and his pain maintained the assessments every 2-3 days until stabilization of pain. He started a chemotherapy protocol with carboplatin and paclitaxel and had 3 cycles from December 2017 to February 2018. He developed pneumoperitoneum being submitted to a laparotomy on 19th February 2018, that confirmed the existence of peritoneal carcinomatosis (Fig. 3). The patient died on 14th March 2018, 4 months after the diagnosis.

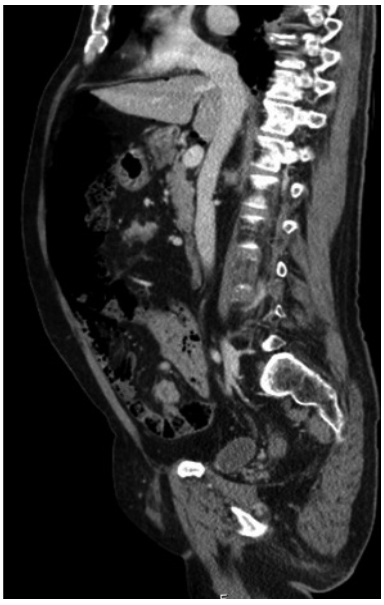

Figure 3. Abdominopelvic CT scan showing the pneumoperitoneum.

DISCUSSION

For a great number of cancer patients the oncologic multidisciplinary team cannot offer an extended quantity of life. For these patients the main goal will be the preservation and, when possible, the increment of their quality of life (QoL). And this will, in large part, rely on pain control, since it is one of the most important factors contributing to the deterioration of QoL, especially BTcP.

This clinical case demonstrates most of these aspects, particularly important in a rapidly evolving cancer case, with few treatment options and in which pain control was a major concern. It is crucial to screen routinely for pain, assess its characteristics and mechanism (location, medical treatments, number of episodes, onset, position, quality, radiation, severity and triggers), assess personalized pain goals and formulate personalized pain treatment plans (analgesia based on pain mechanism, individual preference and treatment history; psychological distress counselling and pastoral care for spiritual distress; chemical education and close monitoring). It is also mandatory to perform regular pain assessment (duration of follow-up, medication side-effects, adherence and aberrant behaviours).[6] For moderate to intense pain, transdermal long-acting fentanyl could be a good choice, and for BTcP sublingual fentanyl tablets are an excellent choice for its rapid onset of action, level of pain control, easy to balance between the dose prescribed and patient needs, and safety profile.

CONCLUSIONS

- In oncology, cancer patients and doctors should balance between quantity of life and QoL.
- Pain is an important and frequent symptom in cancer patients, that substantially affects QoL, but it is often neglected.
- BTcP is very frequent, strongly interfering with daily activities and causing increased emotional distress.
- We cannot extend the lives of most cancer patients, and QoL becomes the most important parameter, where achieving pain control is of extreme importance.
- For background moderate to intense pain, transdermal long-acting fentanyl could be a good choice, while sublingual fentanyl tablets are an excellent choice for BTcP.

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2 Involvement of a patient in the decision-making process in breakthrough cancer pain treatment

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ABSTRACT
In this case, we describe a patient with breast cancer and bone metastases who suffered strong incidental pain induced by movement. Short-acting morphine used at the beginning appeared poorly tolerated. Good pain management has been successfully achieved using sublingual fentanyl citrate tablets. One of the most important success factors was the involvement of the patient in the decision-making process.

INTRODUCTION

Persistent pain is one of the most frequent symptoms in cancer patients. It occurs in 64% of end-stage cancer patients but is particularly common in oesophageal, pancreatic or breast cancers, in which it exceeds 90%.[1]
Such a high occurrence means pain should be treated as an inherent consequence of a neoplastic disease, that is why it is commonly called cancer pain.
Pain lasting at least 12 hours a day is called background pain. It usually requires around the clock (ATC) administration of analgesic medication. According to the WHO cancer pain relief rules, the choice of an analgesic should depend on the pain intensity. Mild pain needs non-opioid drugs such as ibuprofen or acetaminophen, while strong pain (NRS 7-10) requires strong opioids, like morphine, oxycodone, hydromorphone, fentanyl, buprenorphine, tapentadol, or methadone. Moderate pain may be treated both by weak opioids, like tramadol, or by small dosages of first-choice strong opioids (morphine, oxycodone, or hydromorphone).[2]
Cancer pain rarely has invariable intensity. In most cases, its dynamics change, with periods of significant exacerbation. This transient exacerbation of quite well-managed cancer pain treated with ATC opioids is called episodic or breakthrough cancer pain (BTcP).[3] The aetiology of BTcP in approximately 40% of cases is unknown and this type of BTcP is called idiopathic pain. A known incident causes the remaining cases, and so they are called incidental pain. Usually, these are movement-induced incidents. However, some of them are predictable. A cough, spontaneous movements, hiccup, deep breath, etc. cannot be predicted, and although the cause is known, the resulting pain cannot be prevented. That is why it is not the aetiology, but the unpredictability of pain exacerbation that is the determinant of the right choice of rescue medication.

CASE REPORT

A 46-year-old patient with stage 4 breast cancer (*carcinoma ductale infiltrans NST C3, ER 100%, PR 5%, HER 2 negative*) and multiple metastases to the bones presented to the palliative care outpatient unit. She was a mother caring for two children. Her husband had limited possibilities to take care of the family due to excessive working hours. The woman knew the bad news about her health and prognosis, but she did not want the support of a psychologist. Over the three years of the disease, she underwent left-side palliative mastectomy, chemotherapy (adriamycin + cyclophosphamide - 9 cycles, and doxorubicin) resulting in partial remission, and hormonotherapy (tamoxifen). In spite of the treatment, progression was observed and paclitaxel was initiated.
Scintigraphy revealed multiple metastases to the back sections of left ribs VII and XI, the lateral sections of right ribs V, VI, VIII and IX, and vertebrae Th9 and L4-L5, without pathological bone fractures. No metastatic changes were found in CT examination of the chest and USG of the abdomen. The woman received radiotherapy on the area

of Th-L spine (20 Gy in 5 fractions). The main cause of suffering was strong pain present in two locations: the first in the lumbar spine area radiating to the left hip joint and the left thigh. Its intensity was NRS 7 on the first visit, with exacerbations provoked by movement. The second location was painful left ribs with a pain intensity of NRS 3 in spite of taking oxycodone controlled release tablets 20 mg per day.
The patient complained of moderate fatigue and severe constipation. The frequency of bowel movements was once a week, despite regular herbal laxatives and lactulose use. No major deviations from the normal state were found on physical examination.
Pain treatment was modified on the first visit. Oxycodone was replaced with oxycodone/naloxone controlled release tablets at doubled dose (40+20 mg a day; 20+10 mg oxycodone+naloxone tablets b.i.d.) due to uncontrolled pain and opioid-induced constipation. Pregabalin 75 mg b.i.d. and morphine 10 mg immediate release tablets p.r.n. were added. Seven days after her hospital visit, the patient reported complete relief of rib pain and the decrease of pain intensity in the lumbar area down to NRS 2-3. However, strong pain exacerbations lasting 30-60 minutes persisted while moving. Incidental unpredictable pain was diagnosed. The patient did not accept morphine, as it interfered with her daily activity. She seldom could predict the incidental pain and take the morphine tablet in advance of it, so the effect of rescue medication would appear too late. The side-effect of morphine was troublesome somnolence that was unacceptable for the patient, as she continued taking care of her children in spite of the advanced disease. On the second visit, the basic treatment remained unchanged, and the rescue morphine immediate-release tablets were replaced with fentanyl citrate for the incidental pain. Four forms are available on the market (two intranasal, one sublingual and one sub-buccal) and their modes of application were presented to the patient who chose sublingual tablets. The dose of 133 µg turned out to be sufficient.

DISCUSSION

If an episode of BTcP can be predicted, the patient ought to be given immediate-release formulations of opioids with short half-lives, preemptively in the 20-30 minutes preceding the provoking manoeuvre.[2] All of the episodes are transient, although significant augmentation and fast onset characterize most of them. Two-thirds last less than 30 minutes (Fig. 1).[4] Usually, they do not exceed 3-4 per day and are more frequent in inpatient hospices.[5] Breakthrough cancer pain not only substantially impedes pain treatment, but it also decreases health-related quality of life and increases the cost of treatment.[6]
In this case, we would like to emphasize the need for personalization of the breakthrough cancer pain management. The right choice of a rescue medication requires consideration of multiple factors (Fig. 2): the number and length of the episodes, their predictability and relation to the known incidents, ease and route of administration, accessibility (including price) of the medication, the patient's awareness, and his/her preferences.[7] The patient not only was instructed in the possible treatment alternatives but was also included in the decision-making process. She chose sublingual tablets, as so many patients do, as it is perceived as one of the most natural and easiest routes of administration. By involving the patient in the decision-making process, we attained her better compliance and, hence, pain relief.

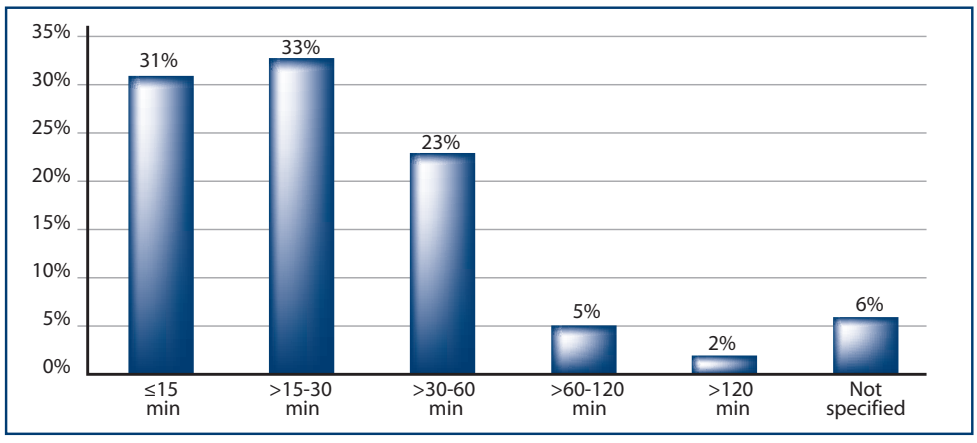

Figure 1. Duration of breakthrough pain episodes.[4]

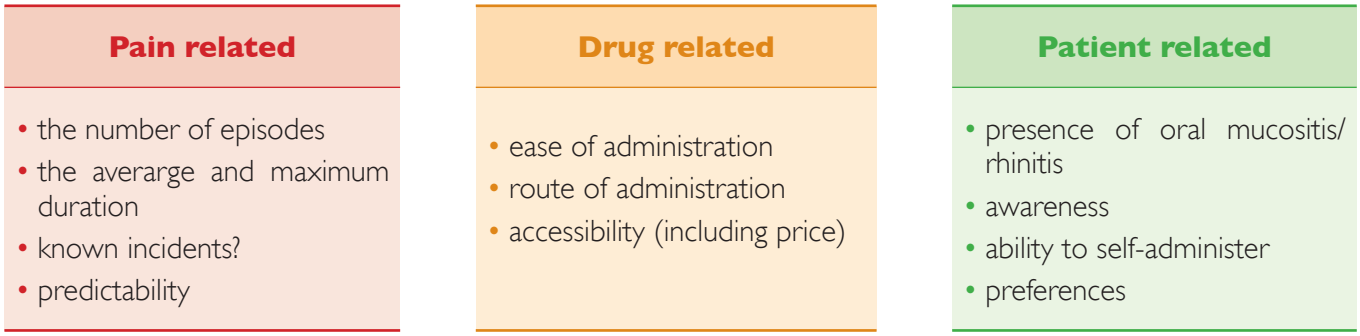

Figure 2. The factors influencing the right choice of a rescue medication.

We assumed that if the daily frequency of the pain exacerbations exceeds 3, we would rather increase the ATC opioids instead of multiple doses of fast-acting fentanyl. It is reported that two-thirds of BTcP episodes last up to half an hour, with 87% not exceeding one hour. This was the case in this patient. She suffered movement-induced incidental pain. She could not predict most of the exacerbations, although the incidents were volitional. Fentanyl citrate appeared the best solution. Administered at the beginning of the painful episode, it reveals its analgesic effect within 6 minutes, which lasts around one hour. Rarely the patient was able to predict the painful incident and take the rescue pill in advance, 20 minutes before.[8] The route and ease of administration were important to the patient, as she continued regular daily activities and wanted to keep the procedures private.

Oral forms of fentanyl citrate require a minimal amount of sputum. Xerostomia occurs in 78-82% of end-stage cancer patients, and mainly results from the anti-cholinergic effect of opioids and other drugs, and the disease itself. When using oral forms of fentanyl, it is advised to moisten the mucosa before their administration.[9] Oral mucositis does not affect absorption of fentanyl significantly and has no meaningful clinical effect, that is why there is no need to modify the doses in case of local oral inflammation.[10,11]

All forms of transmucosal fentanyl citrate are easy to administer. It is worth considering a patient's preferences of the route of administration. The patient should be assisted in the first use of these forms, to verify if she/he can open the package and prepare the right dose without problems or mistakes. The oral forms of fentanyl require postponing eating and drinking for several minutes, which is not a problem. Usually during the BTcP episode patients stop any physical activity, including eating and drinking.

In this case, the painful episodes lasted 30 to 60 minutes. Morphine was effective in longer-lasting episodes, as it reveals its analgesic effect 30 minutes after administration. The reason for changing it to fentanyl citrate was increased somnolence that affected the patient's daily activity. Fentanyl appeared very well tolerated and improved the patient's quality of life.

The layer structure of sublingual fentanyl citrate tablets ensures rapid dissociation and absorption of the active substance before swallowing. Alkalization to pH 7.3-8.4 makes fentanyl citrate's absorption quick. Most of the medicine passes directly to the well-vascularized sublingual area and directly to the central circulation, omitting the liver. This explains its very quick onset of action.

An important issue with all transmucosal fentanyl citrate forms is the setting of the rescue dose. The drug should be initiated from the lowest recommended doses, which in this patient was 133 µg, and increased gradually in the case of insufficiency of a dose. During disease progression, doses of analgesics are increased in many cases and are usually explained by the worsening clinical situation, rather than the phenomenon of tolerance. In the time of observation after the second visit, the patient did not require any further dose modifications of opioids.

In summary, the involvement of the patient in the decision-making process helps set optimal ATC and rescue medications, which improves pain management and increases the patient's health-related quality of life. The choice of the right form of a rescue drug should be based on the actual clinical situation, but it should also include the patient's preferences and the physician's experience.

CONCLUSIONS

- The aetiology of breakthrough cancer pain in approximately 40% of cases is unknown.
- That is why it is not the aetiology, but the unpredictability of pain exacerbation that is the determinant of the right choice of rescue medication.
- In this patient, sublingual fentanyl citrate tablets appeared the best solution; administered at the beginning of the painful episode, revealing its analgesic effect, which lasted around one hour, within 6 minutes.
- Fentanyl appeared very well tolerated and improved the patient's quality of life.

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3 Bone pain in patients with prostate carcinoma refractory to castration: review of the therapeutic arsenal

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ABSTRACT
Bone pain secondary to bone metastasis is one of the complications with the greatest impact on the quality of life of cancer patients. This type of metastasis is especially frequent in patients affected by prostate cancer, where a wide therapeutic arsenal has been developed including analgesic drugs, biphosphonates and monoclonal antibodies targeting bone resorption mechanisms, radiotherapy and radioactive isotopes. We present the clinical case of a 77-year-old man diagnosed with prostate carcinoma refractory to castration who needed different treatments for bone pain during his disease.

INTRODUCTION

Bone pain induced by cancer (CIBP) is the most common symptom produced by bone metastases, and is linked to a significant deterioration of patients' quality of life (QoL).[1] Management of CIBP represents a challenge for physicians, patients and their care-givers, since achieving pain control and preserving QoL may be as important for patients as cancer control itself. Approximately three quarters of patients with cancer present pain during their evolution,[2] and this ratio is even higher in patients with bone metastases.[3] CIBP can have different intensity (mild, intermediate or severe) and temporal characteristics: continuous or irruptive.

We present a case report of a patient diagnosed with advanced prostate carcinoma refractory to castration (CPRC) with bone metastases and pain as the main symptom of the disease. Our main aim was to review the efficacy of treatments for CIBP.

CASE REPORT

A 77-year-old man without a major medical history was initially diagnosed in January 2006 with prostate adenocarcinoma T1N0M0, and treated with brachytherapy. He remained free of disease until February 2010, when raised serum levels of PSA were detected (PSA 16 ng/dl), and pelvic bone metastases were confirmed in a bone scan.

The patient was initially treated with androgen deprivation therapy (ADT) with PSA normalization until April 2011, when he presented a biochemical relapse (PSA 8 ng/dl) that was followed during further months by slow progress until August 2011 (PSA 27.5 mg/dl). Once the disease became refractory to castration treatment, he started first-line chemotherapy with intravenous docetaxel 75 mg/m^2 every 21 days, associated with intravenous zoledronic acid 4 mg every 21 days. After 6 cycles, treatment with docetaxel was interrupted due to radiological progression with the appearance of new bone metastases, and pelvic bone pain (Fig. 1).

In November 2011, he started second-line treatment with oral abiraterone acetate 1000 mg/day, with rapid improvement of bone pain. After 12 cycles treatment was stopped due to radiological and symptomatic disease progression, with severe hip pain that made

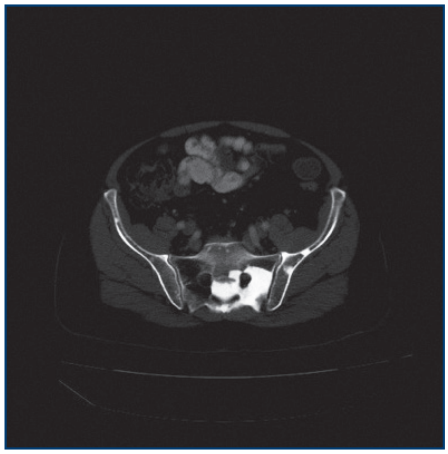

Figure 1. Pelvic metastases as radiological progression after first-line treatment with docetaxel (November 2011).

walking difficult. He started analgesic treatment with major opioids for basal pain (transdermal fentanyl 25 µg/h), and submucosal fentanyl for acute pain episodes (irruptive pain) and due to mobilization (incidental pain), with a need for 3-4 doses per day. The patients was referred to the Radiotherapy Department, and after receiving external radiotherapy with palliative doses (35 Gy) he was able to progressively diminish opioid doses until complete suspension.

In December 2012, the patient initiated third-line treatment with Radium-223 that had to be stopped due to poor tolerance, regarding asthenia and diffuse arthralgias that disappeared with non-steroidal anti-inflammatory drugs and treatment interruption. In March 2013 he started fourth-line treatment with intravenous cabazitaxel 20 mg/m^2 every 21 days, with a radiological and biochemical response. After completing ten cycles (December 2013), he stopped cytotoxic treatment, and started a close follow-up until December 2014 when he presented worsening of bone pain associated with radiological progression in a bone scan (Fig. 2). The patient needed to reintroduce both transdermal fentanyl for basal pain scaling the dose up to 75 µg/h, and fast-acting sublingual fentanyl for irruptive episodes (133 µg) to achieve symptomatic control. He reinitiated cabazitaxel at the same dose for eight additional cycles and has been able to reduce the dose of painkillers to 25 µg/h for transdermal fentanyl.

In September 2015, the patient suffered clinical and radiological progression, he started fifth-line treatment with oral cyclophosphamide 50 mg per day, with a progressive improvement in pain control (no need for opioids), partial remission in bone scan (Fig. 3) and reduction in PSA serum levels (basal PSA in September 2015: 279 ng/dl, nadir PSA in June 2017: 10.2 ng/dl).

In October 2017, treatment was stopped after biochemical and radiological progression, and the patient needed to reintroduce analgesia with the same drugs mentioned above, and progressively increase doses. During the following months the patient experienced a rapid deterioration of his Performance Status, and active treatment was dismissed.

In March 2018, the patient suffered intense and diffuse bone pain refractory to pharmacological analgesia. We opted for palliative treatment with samarium-153, and he received a single dose on 15th April 2018, with excellent tolerance and improvement in pain control. Currently, he has recovered his ability for daily basic activities.

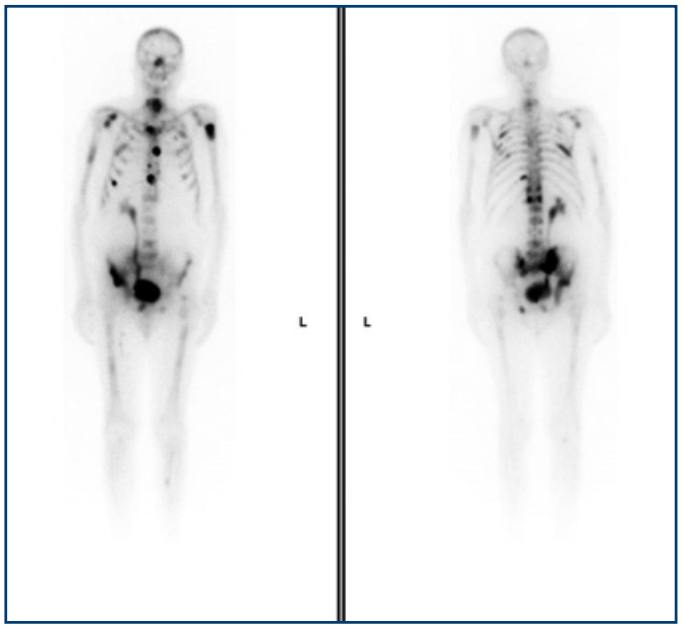

Figure 2. Bone gammagraphy showing diffuse bone metastases (December 2014).

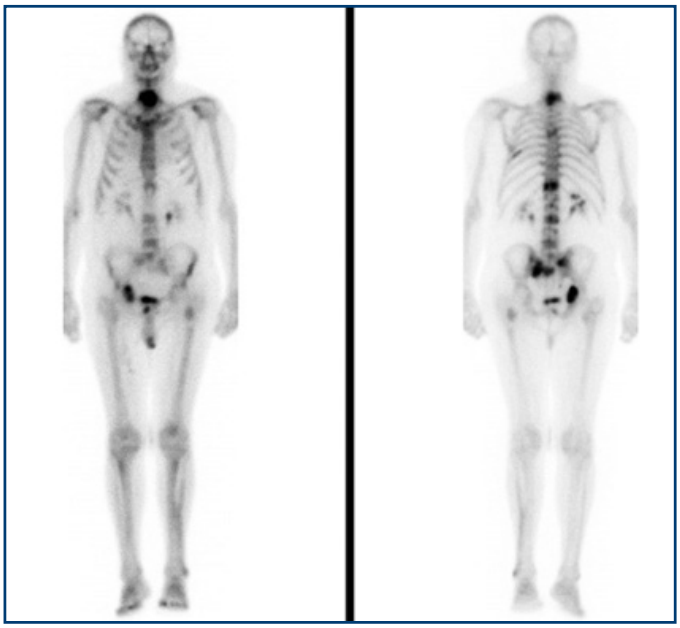

Figure 3. Bone scan after treatment with oral cyclophosphamide (September 2015).

DISCUSSION

Identifying causal factors and understanding the severity and origin of CIBP is essential for correct management and the choice of the best therapeutic approach for each patient.[4] The treatment arsenal includes analgesic drugs, such as non-steroidal anti-inflammatories and opioids,[5,6] external radiotherapy,[7] bisphosphonate and anti-receptor activator of nuclear factor-B ligand (RANKL) antibody treatments that decrease bone resorption,[8,9] and radioactive isotopes, such as radium-223 or samarium-153,[10] can also reduce the onset of pain. However, even with these well-accepted clinical treatment modalities, half of patients with CIBP do not achieve controlled pain status,[11] which gives an idea of the magnitude of this health problem, and the challenge it represents for physicians in charge of these patients. We present the clinical case of a patient exemplifying the complexity of the treatment of CPRC. During his evolution, the patient received a wide variety of treatments with the dual objective of controlling the disease and prolonging his survival, as well as controlling his symptoms and maintaining his quality of life. The use of analgesic treatments has been modified over the years depending on the needs of the patient, and adapted at all times to the intensity of pain, which was fundamentally conditioned by the anti-tumour efficacy of the anti-neoplastic drugs he received.

CONCLUSIONS

- Half of patients with bone pain induced by cancer do not achieve acceptably controlled pain status.
- Achieving pain control and preserving quality of life may be as important for patients as cancer control itself.
- The use of analgesic treatments has to be modified over the time depending on the needs of the patient, and adapted to the intensity of pain.

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4 Breakthrough pain management with oral transmucosal fentanyl citrate in a patient with sarcoma

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ABSTRACT
Breakthrough cancer pain (BTcP) is characterized by a transient exacerbation of pain in patients already receiving adequate analgesia with opioids. During recent years, an improvement has been observed in the management of BTcP by a therapeutic approach based on the principle of rescue dosing, which has been widely accepted. More specifically, the addition of short-acting opioids on an as-needed basis in conjunction with the use of long-acting opioids (e.g. transdermal fentanyl patches) has shown significant clinical benefit. We report the case of a 71-year-old patient who presented with a metastatic neoplasm of mesenchymal origin from Schwann cells (malignant peripheral nerve cell tumour). During the last months of her life, due to disease progression (multiple metastatic bone lesions), she described several episodes of BTcP, although she never stopped using long-term acting fentanyl patches. BTcP was successfully managed with titrated doses of oral transmucosal fentanyl citrate which seems effective with a good safety profile. The purpose of introducing this case report is to demonstrate the basic principles of BTcP management, with a special focus on oral transmucosal fentanyl citrate formulations.

INTRODUCTION

Pain in cancer patients is a complex symptom that affects various aspects of life such as daily activity, physical functioning, psychological status and social life. The prevalence of pain among cancer patients is very high. Almost all patients with malignant disease will experience one or recurrent episodes of acute pain. Moreover, chronic pain is experienced by 30-50% of patients under antineoplastic therapy and 75-90% of patients with advanced disease.[1,2]

The choice of analgesics is mainly based on the World Health Organization (WHO) analgesic ladder which categorizes pain in 3 levels according to its intensity. For mild pain the preferred analgesics are non-opioids such as acetaminophen, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). In case of mild to moderate pain the introduction of milder opioids such as codeine or tramadol in combination with non-opioids such as NSAIDs is required. Finally, moderate and severe pain are managed by stronger opioid derivatives such as morphine and fentanyl with or without the aid of non-steroidal anti-inflammatory drugs or paracetamol.

As mentioned above, opioids are the cornerstone of analgesia management. They are subdivided according to their action in mu receptors as pure agonists, pure antagonists and mixed agonists/antagonists and according to their duration of action as long and short acting (Table 1). Morphine is the prototype opioid drug. It is considered the standard for comparison and is used mainly for moderate or severe cancer pain.[3]

A widely used opioid is fentanyl, which is highly lipophilic and administered via parenteral route or formulations developed for transdermal or oral transmucosal administration. The transdermal formulation is used for chronic pain management and it is widely popular among many patients due to its mode of administration and infrequent dosing (transdermal patch changed every 2-3 days). It is also preferred because of its advantage over oral release morphine in terms of its side-effects profile.[4,5] Another advantage of fentanyl over morphine is the safe administration in patients with renal insufficiency due to the lack of active metabolites excreted by the kidneys. Of particular interest are also drugs with combined mechanisms of action, such as tramadol.

The main characteristic that differentiates tramadol from other opiate derivatives is its mechanism of action,

Drug name	Approximate equivalent doses	Serum half life	Duration of effect
Morphine (mu agonist, oral)	30 mg	2-3 hours	3-6 hours
Oxycodone (mu agonist, oral)	20 mg	2-3 hours	3-6 hours
Fentanyl (mu agonist, parenteral)	0.1 mg/(100 μg)	7-12 hours	0.5-1 hours (IV) 1-2 hours (SC)
Morphine (mu agonist, parenteral)	10 mg IV/SQ	2-3 hours	3-4 hours
Tramadol (mu agonist/monoamine reuptake blockade, oral)	300 mg	6 hours	4-6 hours

Table 1. Commonly used, oral and parenteral pure mu opioid agonists and with mixed mechanism of action formulations for chronic cancer pain.

which is based both on mu receptor binding, serotonin and norepinephrine reuptake blockade. Tramadol is widely used for the management of moderate and severe pain.[6]

Another formulation which has gained popularity in recent years is transmucosal fentanyl which is used mainly for the management of breakthrough pain (BTcP).

BTcP defines episodes of pain of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia.[7] Given its high prevalence among cancer patients, BTcP has been managed by a therapeutic approach based on the principle of rescue dosing and has been widely accepted. This approach is based on the administration of a short-acting opioid on an as-needed basis for BTcP in conjunction with the administration of long acting opioids (e.g. transdermal fentanyl patches). The following case report describes the benefit from the use of transmucosal fentanyl preparations for the management of BTcP.

CASE REPORT

A 71-year-old female patient presented to an internal medicine clinic suffering from multifocal bone pain. CT scans demonstrated the presence of multiple osteolytic lesions and pulmonary nodules. The biopsy showed a metastatic neoplasm of mesenchymal origin from Schwann cells (malignant peripheral nerve cell tumour). Immunohistochemistry (IHC) showed positivity for vimentin and S-100 protein, but no expression for CD99, desmin, SMA, AE1/AE3, CK8/18, synaptophysin, CD56,TTF-1, CD34 or c-kit.

At first, due to bone pain the patient underwent irradiation of vertebrae (L4, L5, S1) and the pelvis. After the completion of radiotherapy, she started first-line chemotherapy with liposomal doxorubicin. Although there was some pain relief initially with paracetamol and NSAIDs, she soon needed opioid derivatives in order to relieve the pain. More specifically, fentanyl transdermal patches (25 μg/h) were administered with concurrent use of paracetamol and codeine (500 + 30 mg tab) thrice daily.

Six months later, although her clinical condition was initially improved with the administration of first-line chemotherapy (liposomal doxorubicin), she started complaining of increased fatigue, low grade fever and weight loss. Imaging studies demonstrated disease progression with multiple pulmonary nodules increased in number and size and new bone lesions (Figs. 1 and 2). Bone scintigraphy, in particular, revealed new bone lesions in the head of the humeral bone and upper third of left tibia. Although she was irradiated in the above-mentioned areas and never stopped the use of opioids, she started complaining of pain deterioration in intensity

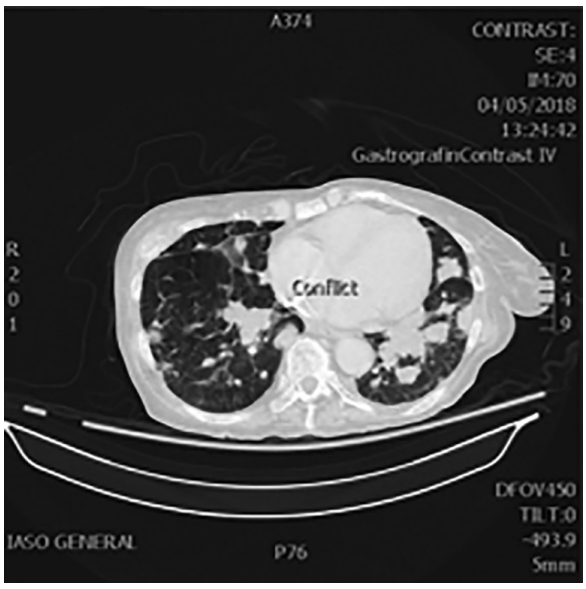

Figure 1. Multiple pulmonary nodules due to disease progression.

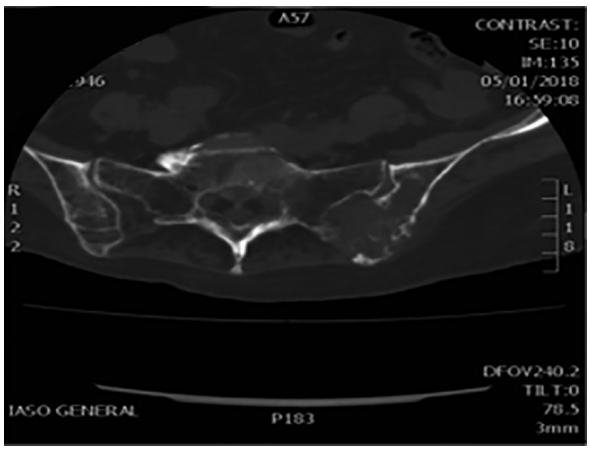

Figure 2. Multiple bone lesions in the pelvis.

and duration. She described at least 5-6 episodes of BTcP and although the dosage of fentanyl patches was gradually increased (from 25 μg/h to 75 μg/h) in order to decrease the number of episodes, the onset of administration of oral transmucosal fentanyl citrate was necessary. The initial dosage of 133 μg sublingually during BTcP episodes was initially successful. At the same time, the patient started second-line treatment with pazopanib 800 mg daily.

The patient never responded to pazopanib treatment and her health was rapidly deteriorating. She had more episodes of BTcP in shorter intervals worse in intensity and duration. That is why titration of sublingual fentanyl citrate was necessary. More specifically, the dosage was increased at the beginning to 267 μg in order to relieve 4 episodes of BTcP, later to 400 μg and finally to 533 μg 4 times daily. The patient died 2 months after the diagnosis of disease progression, but pain management, especially with the administration of transmucosal fentanyl citrate for BTcP, had a significant positive impact on her quality of life.

DISCUSSION

BTcP is characterized by a transient exacerbation of pain in patients already receiving adequate analgesia with opioids.[8] Adequate management of BTcP is essential for the quality of life of cancer patients, given its high prevalence. One of the most important factors for successful management of BTcP is its assessment. It is important for healthcare providers to ask all the necessary questions in order to evaluate the intensity and duration of BTcP episodes since that type of pain is characterized by heterogeneity.[9] Not sufficiently controlled BTcP leads patients to experience more pain-related hospitalizations and physician office visits;[10] an American survey indicated that people without adequately controlled BTcP had a significantly higher rate of hospitalization than those without BTcP (36.9% vs 22.5%) and dramatically higher estimated annual costs of healthcare ($ 1.7 million compared with $ 192000).[11]

According to the Board of Directors of the European Association for Palliative Care (EAPC), episodes of BTcP should be treated with immediate release oral opioids or with buccal or intranasal fentanyl preparations. In some cases, these fentanyl preparations are preferable due to their more rapid onset of action and duration of effect.[12] The most widely used fentanyl preparations for BTcP are oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), sublingual fentanyl (SLF), fentanyl buccal soluble film (FBSF), intra-nasal fentanyl spray (INFS), fentanyl pectin nasal spray (FPNS) having an onset of action ranging from 5-15 minutes and good tolerability (Table 2).[13] Accumulated evidence indicates that oral transmucosal fentanyl formulations act faster and are more effective in rapid pain management than oral morphine.

Fentanyl transmucosal preparations	Onset of analgesia	Dose range	Duration of effect
Oral transmucosal fentanyl citrate (OTFC)	15 minutes	200 μg-1600 μg	2-3 hours
Fentanyl buccal tablet (FBT)	10-15 minutes	100 μg-800 μg	4 hours
Sublingual fentanyl (SLF)	5 minutes	100 μg-800 μg	2 hours
Sublingual fentanyl citrate	6 minutes	133 μg-800 μg	1 hour
Intra-nasal fentanyl spray (INFS)	5 minutes	50 μg-200 μg	2-4 hours
Fentanyl pectin nasal spray (FPNS)	5 minutes	100 μg-800 μg	1 hour

Table 2. Most widely used oral mucosal fentanyl preparations for breakthrough cancer pain management.

The patient used a sublingual formulation of fentanyl citrate, recently available in Greece, which was developed for the treatment of BTcP. The sublingual tablet consists of different layers coated on a neutral core. The fentanyl citrate layer is surrounded by an alkalinizing layer that increases the solubility of fentanyl and provides optimal oromucosal conditions for rapid dissolution and absorption.

The efficacy and safety profile of this formulation was demonstrated in a study performed by Novotna et al.[14] It was a randomized placebo-controlled study with crossover, which included patients with a confirmed diagnosis of cancer, experiencing 1-4 episodes of BTcP per day with a life expectancy of at least 2 months. The primary end point was the sum of pain intensity differences at 30 minutes. The results were encouraging since this new form of oral transmucosal fentanyl citrate provided significant improvement in pain intensity compared to placebo as early as 6 minutes post administration with an effect lasting over 60 minutes. Moreover, the safety profile was typical of opioid administration, since most common adverse events were vomiting, nausea, diarrhoea, dry mouth and somnolence (range 2.2-5.5%).[14]

To conclude, this case study showed the effectiveness of oral fentanyl citrate in this sarcoma patient. This type of fentanyl citrate provides to be easy to use and has a rapid onset of action.

CONCLUSIONS

- In breakthrough pain, the addition of short-acting opioids on an as-needed basis in conjunction with the use of long-acting opioids has shown significant clinical benefit.
- Accumulated evidence indicates that oral transmucosal fentanyl formulations act faster and are more effective in rapid pain management than oral morphine.
- In this case report, the patient used a sublingual formulation of fentanyl citrate, which provided rapid dissolution and absorption.
- This type of fentanyl citrate provides to be easy to use and has a rapid onset of action.

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5 Pain management during the treatment of oropharynx tumours

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ABSTRACT
A 66-year-old patient was diagnosed with unresectable squamous cell carcinoma of the oropharynx with bilateral lymph node involvement. She was treated with induction chemotherapy (QT), followed by concomitant QT plus external beam radiotherapy (ERT). Before starting treatment the patient already presented a VAS 4 pain, which during the ERT and QT increased until a VAS 7 was reached in addition to associated breakthrough pain. Medication with opioids in patches and a sublingual formulation was calibrated to achieve a good control of the pain.

INTRODUCTION

Tumours of the head and neck are placed in the fifth position among the malignant tumours and are the eighth cause of death from cancer.[1,2] A third of the patients only present in the initial stage, whereas the majority of them have advanced disease at diagnosis.[3] Surgery and radiotherapy are the first option in the early stages, whereas the addition of chemotherapy and targeted therapy increases survival in advanced disease with a consequent increase in secondary comorbidity in the treatments that this involves.[4,5] Among them it is important to emphasize the pain these patients will present during their disease and treatment. The prevalence of oncologic breakthrough pain differs according to studies and the study population. But, according to the last systematic review published in 2014, it is 59%.[6] Breakthrough pain is intense, transitory and spontaneous in spite of a suitable control of the basic pain. Therefore, the drug that we use to control it must also be powerful, with a fast onset of action and with a limited duration so as not to generate undesirable adverse effects. In addition, it would be desirable for it to be simple to administer. A suitable diagnosis and treatment of the pain will be essential to improve the prognosis and quality of life in these patients.

CASE REPORT

A 66-year-old woman presented the following personal background: arterial hypertension, chronic bronchitis and ex-smoker of 20 cigarettes/day. She had no family or personal oncological history of interest.

In November 2017 the patient referred odinophagia and the emergence of bilateral cervical adenopathy. To relieve the pain she took paracetamol 1 gram 2-3 times a day. Physical exploration disclosed an ulcerated lesion in the oropharynx in the right tonsil, with fibrin remains, also affecting the ipsilateral pillar. On the neck, she presented solid laterocervical adenopathies, the largest on the left measuring approximately 2.5 to 3 cm in the IIA area.

Results of pathological tests and other investigations

CT of neck-thorax (22.11.2017)

- Ulcerated mass of 3 cm located in the right palatal tonsil with wall extension to the ipsilateral pharyngeal and tonsillar pillar; infiltration of intrinsic muscles by the lingual root was observed contacting the lingual extrinsic muscles.
- Bilateral metastatic adenopathies of up to 3 cm maximum diameter with internal necrosis located in bilateral ganglion stations IIA and III (Fig. 1).

Biopsies (15.11.2017)

- Right tonsil: invasive carcinoma with predominant areas of basaloid aspect associated with zones of focal keratotic differentiation and invasive fusocellular areas.

Treatment plan

Facing a case of a 66-year-old woman with squamous cell carcinoma of the oropharynx (right tonsil) with voluminous bilateral cervical ganglions (N2c), the case was evaluated by the Committee of head and neck tumours and radical treatment with QT induction with cisplatin, followed by QT/ERT with cetuximab was prescribed.

Pain assessment: Tools and results

We were faced with a patient who already presented basal pain produced by her tumour, but in addition we knew that this pain would be increased by the treatment and that she would present episodes of breakthrough pain.
In agreement with the algorithm published by Davies, the first step is to ensure a good control of the basal pain. If, in spite of this, transitory exacerbations of pain appear we can speak of breakthrough pain.
Multiple analogous, verbal, numerical and visual scales already exist to quantify and monitor pain. However, the analogical visual scale (VAS) is extended to clinical use, in which 0 is pain absence and 10 is the worst imaginable pain. Before initiating treatment, the patient presented VAS 4. After the beginning of radiotherapy to 22 Gy (Fig. 2), the patient presented odynophagia grade 1 (VAS 5) that evolved with the oncologic treatment associated with oral mucositis grade 2 with an increase in pain to VAS 7. We administered tramadol 50 mg every 6-8 hours. After three days, there was no improvement, so we changed to fentanyl patches of 25 µg associating oral fentanyl citrate 133 µg as a rescue medication for the episodes of breakthrough pain. With this treatment the patient presented a temporary improvement, but after the following cycle of associated QT/ERT she developed a mucositis and dermatitis grade 2 that forced us to increase the patches up to 50 µg with rescue medication of 267µg. In this way we were able to control basal and breakthrough pain (VAS 2), maintaining the oral ingestion and without interruption of treatment.

Current outcome

One month after the end of treatment (Fig. 3), the patient presents moderate xerostomia and slight dysphagia. She only needs sublingual fentanyl citrate as rescue medication prior to the main meals. The patient is pending evaluation of CT response.

DISCUSSION

Oncologic breakthrough pain has a high incidence in advanced cancer. In particular, in this group of tumours almost 100% of patients will present breakthrough pain at some point in their disease. The treatment of this pathology is multidisciplinary, including in many cases surgery, chemotherapy and radiotherapy, with all the side-effects and comorbidities involved. In particular, as we have seen in this clinical case, basal and breakthrough pain are prominent. Opioid drugs have been demonstrated to control basic pain in the majority of cases. In breakthrough pain, the objective is fast-acting short-lasting pain control. For this reason, fentanyl citrate is the drug of choice both for its rapid onset of action (within 15 minutes) and its short period of action. In addition, this sublingual tablet is a good option in these patients. The patient began the control of pain with drugs on

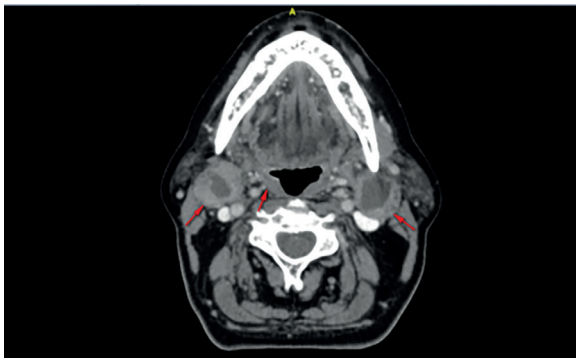

Figure 1. CT diagnosis.

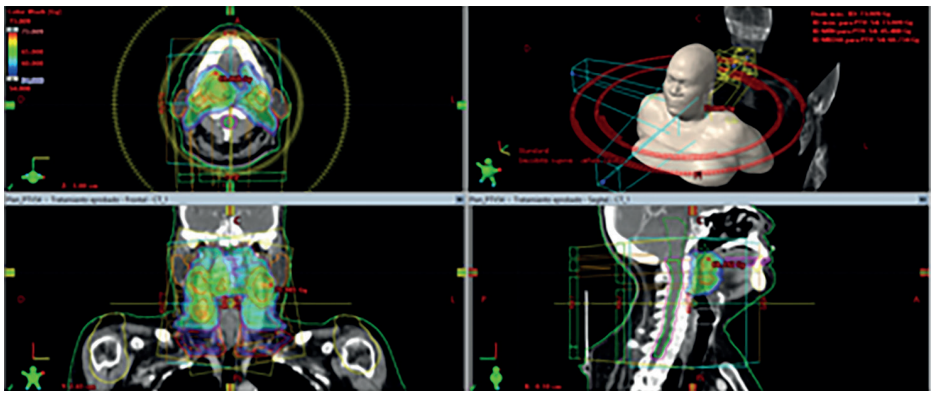

Figure 2. Radiotherapy planning.

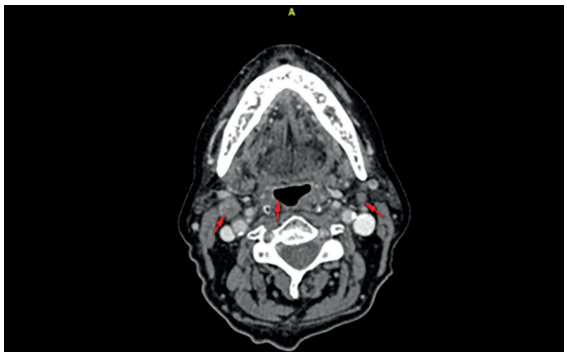

Figure 3. CT after treatment.

the first step of the WHO ladder,[7] but after two weeks of treatment these were already insufficient. We know that the pain was produced as much by her tumour as by the mucositis caused by the treatment. With the experience gained from clinical practice we know that these patients require third step analgesia, and thus we directly administered fentanyl patches plus fentanyl citrate as rescue medication for the episodes of exacerbation. The patient's swallowing capacity was altered, which is why the sublingual administration was a good option.

CONCLUSIONS

- Oncologic patients have a high probability of suffering breakthrough pain during their disease.
- The different therapeutic modalities against the tumour, surgery, chemotherapy, radiotherapy or systemic treatments, can negatively impact on the patient's pain.
- A good control of the basal and breakthrough pain presupposes fewer treatment interruptions, which offer prognostic benefits.
- Fentanyl rescue medication is a fundamental tool for the control of breakthrough pain in these patients and thus to improve their quality of life.

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