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IMPACT OF PROCEDURAL PAIN IN RADIOTHERAPY TREATMENT

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Abstract – *Objective:* *80% of patients with advanced cancer suffer from chronic pain and 40-80% of these suffer from breakthrough cancer pain (BTcP). In this setting, palliative radiotherapy (RT) plays an important role in cancer pain management. On the other hand, the so called procedural pain (PP), due to the positioning during RT, could compromise patients' quality of life and the therapeutic procedure itself.*

Patients and Methods: *From April to June 2014, 130 patients (66% treated with curative purposes, 34% for palliative purposes) were enrolled for a daily survey about the pain perception and relative analgesic therapy.*

Results: *99.2% of patients completed treatment. PP was referred in 18% of patients during CT-simulations (CTS), and in the 18.5% at the first session of RT. The reduction of incidence of procedural pain was accompanied by a reduced intensity of pain: from mean NRS 9 at CTS time to mean NRS 5 at last session. Analgesic therapy was modified especially in the initial phases of radiation treatment; at final evaluation, 59% of patients received pain therapy at fixed times (21% opioid) and 25% at request (18% using ROOs).*

Conclusions: *Management of cancer related pain during RT plays a fundamental role in palliation for metastatic patients. Radiation oncologist has to correctly assess cancer pain, first of all the procedural one, in order to improve patients' compliance to treatment and quality of life.*

KEYWORDS: *Procedural pain, Radiotherapy, Bone metastases.*

INTRODUCTION

Pain is one of the main symptoms in oncologic patients. Cancer pain is related to compression or irritation phenomena, which involves neighboring tissues and organs affected by cancer. Also, it is dependent on cancer development, especially in bone metastases, and in some cases it results from therapeutic procedures[1]. "Procedural pain" (PP) is related to diagnostic or therapeutic procedures, being generally predictable[2]. Patients undergoing radiation treatments can experience predictable pain with a worse compliance to treatment, and mucosal damage following radiation therapy can

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itself lead to pain. Depending on anatomical districts, radio-induced damages can involve oral cavity and gastrointestinal structures, causing stomatitis, esophagitis, gastritis, enteritis, proctitis, or cystitis, vaginitis, proctitis and rectal tenesmus[3]. Pain, due to oral disease, could prevent patients from speaking, eating, drinking or swallowing, leading to a worse quality of life and reducing compliance to RT and its efficacy[4,5]. In our experience, PP is associated with:

- lying on treatment table for a sustained time during radiotherapy session or radiation TC simulation;
- wearing of the customized immobilization mask for patients with head and neck cancer;
- mucositis and xerostomia during concomitant radio-chemotherapy for head and neck cancers, causing odynophagia[5,6];
- proctitis.

Mucositis is a process that involves the endothelial and connective tissue of the submucosa[3] and xerostomia is the subjective complaint of dry mouth, that usually reflects a decreased presence of saliva[7,8]. Radiotherapy causes xerostomia by indirect damage of epithelial and connective tissue elements of the gland including blood vessels and nerves, or by direct damage to salivary glands, affecting saliva production and secretion[9,10]. In order to overcome this kind of pain, it should be selected analgesic drugs mimicking kinetics of the same pain (rapid onset and high degrees of pain intensity). Recent guidelines recommend short-acting opioids and rapid-acting fentanyl – Rapid Onset Opioids – ROOs –, and several studies confirm that fentanyl-based medications are more effective than oral morphine[1,11-14]. PP management with transmucosal oral fentanyl could be affected by the presence of mucositis and xerostomia[15]. This experience would evaluate patients treated subsequently in our Radiotherapy Department for three consecutive months, to assess the PP, its management, and its impact on the delivery of radiation treatment, compliance and patients' quality of life.

PATIENTS AND METHODS

From April to June 2014, after the Ethics Committee approval of our Institution, we conducted a prospective observational study in collaboration with the Department of Anesthesia and Pain Management. Assessed characteristics were site of radiation treatment, purpose of treatment, basal pain and pain flares intensity. Characteristics of pain were reported using a 11 points numeric rate scale (NRS), where 0 means absence of pain and 10 means the worst tolerable pain. The percentage of patients who completed the course of radiotherapy, the presence of background pain and procedural pain in different time of the treatment, and the presence of alteration of oral mucosa, were evaluated. The data were processed during four key moments: CT-simulation (CTS), first, second and last day of treatment with radiotherapy. For patients with bone or visceral metastases, we assessed values even for intermediate sessions (fraction number 10, 11, 17 and 30).

STATISTICAL ANALYSIS

After qualities check on the database, all variables were evaluated, and for each of them, descriptive statistics were performed: mean, median, standard deviation, minimum and maximum values for continuous variables, absolute and relative frequencies for categorical variables. Descriptive analyses were conducted for the total population, and subgroups of patients were categorized by gender, type of patient, oncological disease, metastases, pain control levels (NRS), presence/absence of BTcP and presence/absence of oral cavity alterations in various sessions of radiotherapy. The prescriptive schemes were also evaluated for basic pain and for BTcP in relation to above-mentioned features. Data were processed using SPSS® (IBM, Armonk, NY, USA), version 10.0.

RESULTS

One-hundred-thirty subsequent patients have been enrolled, 60.8% (N=79) are female, 39.2% (N=51) are male. Table 1 shows patients characteristics: most represented site of treatment was breast, with or without supraclavicular region, followed by bone localizations. The purpose of radiation treatment was palliative in 34%, and in 22% bone metastases treatment was planned (Table 1). 99.2% of patients completed the radiotherapy treatment: one patient prematurely stopped RT for gastrointestinal toxicity. At CTS, 35% had a basal pain (median NRS 6), while 16% had BTcP. Procedural pain incidence was 18% at CTS, 19% at first session, 5% at the second session, and 4% at the last session (Figure 1). 59% of patients was in analgesic treatment for background pain, 21% was with opioids and 25% assumed rescue doses (18% with fentanyl ROOs). Procedural pain relief was reported according to decrease of the intensity from mean NRS 9 at CT-simulation, to mean NRS 5 at last session (Figure 2). Analgesic therapy was modified especially in the initial phases of radiation treatment, 10% in CTS, 1.5% at the first session, 4.8% at the second

TABLE 1. Patients' characteristics and site of radiation treatment.

Patients' characteristics	
Primary tumour	***%***
Breast/SVC	37
Gastrointestinal	9
Gynecological	3
Head/Neck	4
Bone	22
Brain	5
Sarcoma/Lymphoma	4
Prostate	11
Lung/Mediastinum	5
Purpose of treatment	***%***
Curative	66
Palliative	34
Site of palliation	***%***
Gastrointestinal	2
Head/Neck	1
Bone	22
Brain	5
Sarcoma/Lymphoma	2
Lung/Mediastinum	2

session, none at the time of the last session. In order to control procedural pain in these patients, fentanyl ROOs (18%) were prescribed in these percentage, according to different needs and characteristics of the patients: Fentanyl Pectin Nasal Spray (FPNS) 67%, Fentanyl Buccal Sublingual Tablet (FBST) 9%, Fentanyl Buccal Tablet (FBT) 5%, Morphine Immediate Release (IRM) 4%. For a rapid control of pain symptoms, the formulation with pectin was the most rapid in pain relief: 4.6 minutes to reach procedural pain relief, while it was 7.4 in Fentanyl Buccal Tablet FBT, 10.33 in

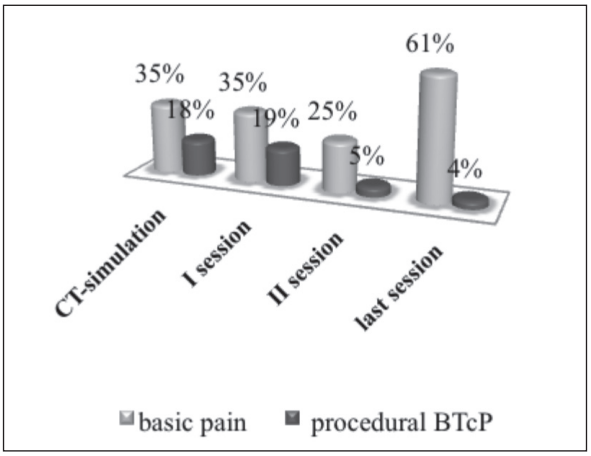

Fig. 1. Percentage of basal pain and procedural pain at CT-simulation, I session, II session, last session of radiotherapy.

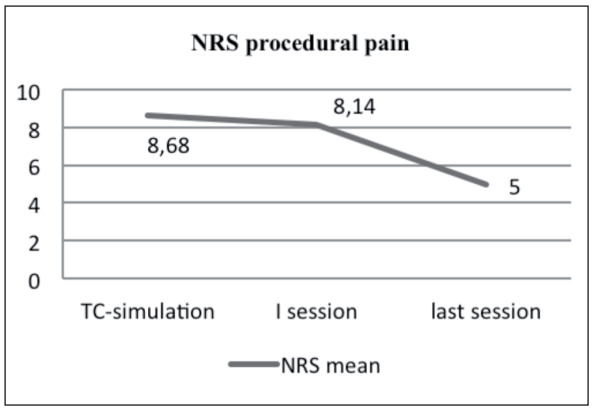

Fig. 2. Pain intensity of procedural pain in CT-simulation, first session, last session.

Fentanyl Buccal Sublingual Tablet FBST, 9 in Morphine Immediate Release IRM. 39.2% (n=51) of patients evaluated were affected by metastatic cancer, the 72.5% of them had basal pain. RT for metastatic patients was scheduled in sessions ranging from 1 to 10 fractions, for breast and prostate curative treatment erased up to 30 sessions. 39.2% of metastatic patients had not predictable BTcP and 60.8% had predictable one. In the first 10 sessions, background pain had higher intensity in patients with mixed pain than patients with nociceptive pain. Between sessions from 11 to 30, nociceptive pain (71.4%), with greater NRS, became prevalent (Table 2, Table 3). Alterations of oral mucosa were found in the 17% of patients (Table 4) with a more relevant prevalence of xerostomia.

TABLE 2. Background Pain (BP) characteristics in the I, X, XI, XVII, XXX RT sessions.

RT session (patients treated)	*Background pain (BP) % (no.)*	*Type of BP (%)*	
		Nociceptive	*Mixte*
I (51)	70.6 (36)	33.3	61.1
X (18)	55.6 (10)	40	60
XI (9)	66.7 (6)	50	50
XVII (8)	87.5 (7)	71.4	28.6
XXX (1)	100 (1)	100	0

TABLE 3. Background Pain (BP) Intensity in the I, X, XI, XVII, XXX RT sessions.

RT Session (patients treated, no.)	*NRS in Nociceptive BP NRS Media (± SD)*	*NRS in Mixed BP NRS Media (± SD)*
I (51)	5.33 (2,02)	6.00 (2.37)
X (18)	2.75 (1.26)	4.71 (1.72)
XI (9)	2,67 (2.89)	2.67 (1,53)
XVII (8)	2.40 (2.07)	1.50 (0.71)
XXX (1)	4	_

TABLE 4. Percentage of oral mucosa disorders.

Orale cavity alterations	*%*
Xerostomia	52%
Mucositis	35%
Candidiasis	13%

DISCUSSION

Cancer pain can be categorized into nociceptive (somatic or visceral) and neuropathic pain: the first one involves the direct activation of nociceptors, in the second case there is a strong involvement of nervous structures, disproportionate to the size of the lesion. Pain during radiation therapy (RT) has both nociceptive and neuropathic qualities[16]. This experience shows that the longer is the treatment, the more prevalent is the nociceptive component. This is probably due to an increased inflammatory component given by the RT. Actually, guidelines recommend that persistent cancer pain should be managed with a round-the-clock treatment, often with a stable dosage of opioids. Despite analgesics medications, many patients can experience acute episodes of severe pain, known as breakthrough cancer pain (BTcP), that may arise either unpredictably or predictably, often triggered by movement, exercise, or other activities[17-19]. BTcP discloses distinguishing temporal patterns, such as time of onset and duration, being associated with a significant negative impact on both quality of life (including activities of daily living, sleep, social relationships and mood) and medical outcome[20], with an incidence between 40 and 80% in cancer patients[21-24]. Predictable BTcP may be particularly associated with the radiotherapy process, such as for wounds or sores, or prolonged immobilization during the procedures of radiotherapy treatment. The background pain in patients undergoing RT may be absent or moderate at rest but increased by physical efforts, certain movements or changes of position. Predictable pain could be treated with a short-acting opioid, provided that it is administered up to an hour before the event, which is often impracticable. By contrast, a rapid-acting fentanyl with a fast onset of action should be preferred, being administered few minutes before pain onset[25]. Our observation shows that nasal formulation with pectin gives an immediate resolution of pain, confirming what supported in previous study[26], on the opposite of oral transmucosal formulation that showed a longer resolution of pain probably influenced by patients' oral conditions. In this experience, a share of patients has oral disorders, but the major one was xerostomia – perception of dry mouth – as confirmed by literature in radiated patients[27]. Many randomized trials have shown the equivalence in terms of resolution of different fractionation schemes symptomatology (30 Gy in 10 fractions, 20 Gy in 5 fractions, and a single fraction of 8 Gy), although longer treatments have the advantage of a lower incidence of reprocessing on the same site[28-32]. Also, the choice of the fractionation scheme affects patient compliance[33,34]. Then, there could be the need for an interruption of the treatment session, or even the planned treatment cycle[29]. Procedural pain can negatively impact the radiation treatment, not only for execution but for carrying out the scheduled program, so it is desirable to have a correct patient management and an appropriate and effective use of available opioids drugs[35,36]. A Cochrane review states the utility of seven different transmucosal fentanyl formulations, compared to oral formulations. Transmucosal administration, both nasal and oral, are effective in the BTcP control[37,38]. In clinical practice, short-acting opioids before and during radiotherapy allow a considerable number of patients with BTcP to complete the schedule of radiation treatment[33]. Our experience demonstrates that Fentanyl Pectin Nasal Sprays give a more rapid control of pain during radiation treatment.

CONCLUSIONS

The management of procedural pain with the use of ROO-based medications could be an effective therapeutic option for the radiation oncologist, allowing a better compliance to the treatment. The integrity of oral and nasal mucosa, as well as patients preferences and experiences, should lead to an appropriate choice of analgesic drugs formulation.

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Conflict of Interests:
There are no financial competing interests to declare.

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