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Breakthrough pain in patients with head & neck cancer. A secondary analysis of IOPS MS study

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ABSTRACT

Aim: To characterize breakthrough pain (BTcP) in patients with Head and neck (H&N) cancer.
Methods: This was a secondary analysis of multicenter study of BTcP. Background pain intensity and opioid dose were recorded. The number of BTcP episodes, their intensity, predictability, onset, duration and interference with daily activities were collected. Opioids used for BTcP, and the mean time to meaningful pain relief after taking medication, were assessed. The presence of mucositis was also assessed.
Results: 205 patients with H&N cancer were examined. The mean number of BTcP episodes was 2.8/day, which was higher than in general population. The mean intensity of BTcP was 7.4. BTcP was more predictable in H&N cancer than in other tumors. The main trigger of predictable BTcP was the ingestion of food (76.5%). BTcP onset was fast in 148 patients (72.2%). The mean time to meaningful pain relief after taking a BTcP medication was 15.3 min and BTcP interference with daily activity was relevant in most patients (89.2%). Transdermal drugs and nasal fentanyl preparations were more frequently used for background pain and BTcP, respectively. A consistent number of patients with H&N cancer (38.5%) exhibited different levels of oral mucositis.
Conclusion: BTcP in patients with H&N cancer is characterized by a larger number of episodes/day and the predictability, particularly with ingestion of food. The use of drugs for background analgesia and BTcP were conditioned by the possible interference with swallowing or local mucosal damage.

Introduction

More than half million of new cases of head and neck (H&N) cancer are diagnosed worldwide each year, possibly due to rising alcohol and tobacco consumption and increased sun exposure, as well as human papilloma virus [1]. Patients with H&N cancer frequently experience pain, even long after the completion of treatment. The prevalence of pain among this population has been estimated at 70%, which is higher than what has been observed in other types of cancer [2]. Pain experienced one year after diagnosis has been found to be predictive of poor quality of life, disability [3] and shorter survival [4], particularly in the advanced stage of disease [5]. Of interest, orofacial pain onset has been also reported to predict transition to H&N cancer [6].

Pain may arise for a variety of mechanisms, including direct invasion of bone, cancer infiltration of nerve roots, regional metastases, infection, ulceration, and inflammation [7]. Moreover, pain related to surgery or chemotherapy, and radiation-induced mucositis or radiation-induced brachial plexopathies often account for treatment-related pain [8,9]. The aggressive erosive nature and the rich sensory innervation of the large area of H&N, render it one of most painful tumors [7,10–12], with consequent implications for patients in terms of quality of life, nutrition, as well as treatment outcomes. Studies have reported that pain is associated with pre-treatment pain score, less education, neck dissection, feeding tube, dry mouth, depression, analgesic consumption, less physical activity, and poor quality of sleep [7,10–15]. Thus, patients with H&N cancer having these risk factors may require more aggressive pain management [1]. Of interest, although higher doses of opioids are needed than those reported in other cancers, pain was considered acceptable and most patients were classified as partially responsive, underlining that an appropriate management may provide an adequate pain relief [13–15]. Cancer pain management in this population is challenging and often sub-optimal. Undertreatment may occur for different reasons, mainly related to poor screening or assessment of pain, inadequate knowledge and prescription of analgesia, and poor opioid adverse-effect management [16]. In the long-term, H&N cancer pain impacts adversely on quality of life, and pain is persisting

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in survivors the substantial pain persisting beyond 5 years in one in six survivors [4].

Breakthrough pain (BTcP) may further complicate the clinical picture. This phenomenon has been defined as a transitory peak in pain intensity, that occurs spontaneously or in relation to a specific trigger, in patients with stable and well controlled background cancer pain [17]. The temporal pattern of this kind of pain interferes with quality of life [18]. Cancer patients experience peaks of pain intensity with different characteristics in terms of predictability, onset, and duration [19,20]. Indeed, data regarding BTcP in H&N cancer patients are lacking.

The aim of this study was to characterize BTcP and its interference in patients with H&N cancer. The secondary outcome was to analyze patients' satisfaction and drugs used for BTcP, as well adverse effects associated with BTcP medication.

Methods

This was a secondary analysis of a large, national, multicenter study of BTcP that involved 32 centers [21]. The local ethical committees approved the protocol at each center, and written informed consent was obtained from each patient. Patients were seen as outpatient, inpatient, or day-hospital, and were recruited in palliative care, oncology, radiotherapy, and pain therapy settings. Thirty-two centers participated in the study and represented all the regions of Italy.

Inclusion criteria were: age ≥18 years, a diagnosis of cancer, stable and well-controlled background pain (pain intensity ≤4 on a 0–10 numerical scale), the presence of BTcP episodes clearly distinguished from background pain, with moderate-severe intensity, according to a pre-defined algorithm [18]. Exclusion criteria were: a condition of an unstable or uncontrolled background pain (> 4/10); peaks of low pain intensity (< 5/10), and poor collaboration. From the original study, patients with H&N were selected.

Age, gender, visit setting, cancer characteristics, extent of the disease (loco regional or metastatic), type of ongoing anticancer treatments, and Karnofsky status were recorded.

Average pain intensity in the last 24 h (on a numerical scale 0–10), and opioids used for background pain and their doses, expressed as oral morphine equivalents (OME) [22], as well as other analgesic drugs, were recorded.

The number of episodes, their intensity (on a numerical scale 0–10), predictability and precipitating factors, onset (≤10 min or > 10 min), duration of an untreated episode, interference with daily activities (on a scale from 0 to 3, none and very much, respectively), were collected. Opioid drugs and doses used for BTcP, and the mean time to meaningful pain relief after taking medication, were assessed. Adverse effects to be attributed to these medications were also recorded. The presence of mucositis was assessed, grading oral lesions according to World Health Organization (WHO) criteria [23].

Statistics

Descriptive statistics for patients' characteristics, Background pain and BTcP have been provided in terms of mean values and frequencies according with H&N cancer occurrence. Comparability of groups, affected or not affected by H&N cancer, have been checked performing a multivariate Hotelling T2 test, setting a first type error at 5%, followed by pairwise comparisons with Bonferroni's correction for familywise error. Gender and age have been tested for confounding. A logistic regression provided different probabilities of H&N cancer occurrence conditioning on gender. In the following analysis confounding has been controlled by stratification. χ^2 tests have been used to assess the statistical association between H&N cancer and Breakthrough pain characteristics. Continuous variables pair-wise comparisons have been performed using *t*-tests, coping with the lack of homoscedasticity between groups by the Satterthwaite correction. The statistical analysis has been carried out using the statistical software STATA (StataCorp, College Station, Texas, version 14).

Table 1
Characteristics of patients with H&N cancer and other primary tumors.

		n. 205 with H&N	n. 3811 with other tumors	P
Age (yrs, mean SD)		61.9 (10.80)	64.7 (12.30)	0.0001
Gender (F/M)		53 (25.8%)/ 152 (74.1%)	1761 (46.2%)/ 2050 (53.8%)	0.0001
Karnofsky (mean SD)		68.5 (18.31)	61.4 (12.68)	
Disease	Loco-regional	113 (55.1%)	623 (16.3%)	
	Metastatic	92 (44.9%)	3188 (83.6%)	
Anticancer treatment	Disease-oriented	173 (86.1%)	2857 (77.6%)	
	Palliative Care	28 (13.9%)	826 (22.4%)	
Place of Visit	Outpatients	71 (34.6%)	1307 (34.3%)	
	Day hospital	50 (24.4%)	412 (10.8%)	
	Home care	13 (6.3%)	564 (14.8%)	
	Hospice	8 (3.9%)	93 (2.4%)	
	Hospital inpatient	63 (30.7%)	1435 (37.6%)	
Setting	Palliative care	24 (11.7%)	696 (18.2%)	
	Oncology	114 (55.6%)	1973 (51.8%)	
	Pain therapy	61 (29.8%)	1123 (29.5%)	
	Radiotherapy	6 (2.3%)	19 (0.5%)	
Xerostomia Y/N		52 (25.4%)/ 153 (74.6%)	537 (14.1%)/ 3274 (85.9%)	
Mucositis	G0	126 (61.5)	3320 (87.1%)	0.0001
	G1	29 (14.1%)	350 (9.1%)	
	G2	26 (12.7%)	101 (2.6%)	
	G3	19 (9.3%)	34 (0.9%)	
	G4	5 (2.4%)	6 (0.2%)	
Mean background pain intensity at T0		3.0 (SD 1.9), range 0–10	3.0 (SD 1.8), range 0–10	0.909

Results

From 4016 patients recruited in the original study, 205 patients (5.1%) had H&N cancer. The characteristics of this group of patients are described in Table 1. In comparison with the general population of advanced cancer patients, H&N cancer patients were predominantly younger (P = 0.0001), males (P = 0.0001), and had a higher level of mucositis (P = 0.0001). Pain mechanism was mixed, nociceptive, and neuropathic in 128 (62.5%), 61 (29.8%), and 16 (7.8%) patients, respectively.

In comparison with patients with other primary diagnoses recorded in the original study, no significant differences were found in pain mechanism (p = 0.968), background pain intensity (p = 0.932), the use of nonsteroidal anti-inflammatory drugs and paracetamol (p = 0.962 and p = 0.101, respectively) (see below).

Background pain

The mean pain intensity of background pain was 3.0 (SD 1.9). No differences with other tumors were found (p = 0.909). One-hundred-ninety-eight (96.1%) and 141 (68.8%) patients were receiving opioids for background pain and BTcP, respectively. The mean OME was 95.5 mg/day. No differences with other tumors were found (p = 0.612).

Breakthrough pain

The mean number of BTcP episodes was 2.8/day (SD 1.42, range 1–10); 93 patients (45.4%) had 1–2 episodes/day, 92 patients (44.9%) had 3–4 episodes/day, and 20 patients (9.8%) had ≥5 episodes/day. A statistical difference in comparison with other primary tumors was found (p = 0.000).

The mean intensity of BTcP was 7.4 (SD 1.34, range 5–10). No

differences with other tumors were found (p = 0.471). The mean duration of untreated episodes was 36.1 min (SD = 30.4). No statistical differences with other types of tumors were found (p = 0.097).

BTcP was predictable in 85 patients, and was more frequent in H&N cancer than in other tumors (41.5% vs 29.9%, p = 0.000). The main trigger of predictable BTcP was the ingestion of food (76.5%). The other triggers were movement, procedures, cough, and other causes (10.6%, 1.2%, 1.2%, and 10.6%, respectively). In comparison with other tumors, patients with H&N cancer were more likely to have predictable BTcP with ingestion of food (76.5% vs 12.2%) than with other triggers, such as movement, procedures, and cough (10.6% vs 67.8%, 1.2% vs 6.3%, and 1.2 vs 3.5% respectively) (p = 0.0001).

BTcP onset was fast (≤10 min) in 148 patients (72.2%), while 57 patients (27.8%) experienced a slower onset of BTcP. No differences with other tumors were found (p = 0.303)

The mean time to meaningful pain relief after taking a BTcP medication was 15.3 min (SD = 10.04). No statistical differences with other types of tumor were found (p = 0.376).

BTcP interference with daily activity was mild, much, and very much in 22 (10.8%), 124 (60.8%), and 58 (28.4%) patients, respectively. No differences were found in interference with daily activities in comparison with other tumors (p = 0.507).

Analgesics used for background pain

Drugs administered for background pain included: anti-inflammatory drugs (ketorolac, dicloreum, and ibuprofen) (n. 25, 12.2%), paracetamol (n. 77, 37.6%); weak opioids (tramadol, codeine) (n. 15, 7.6%); oral morphine (n. 20, 9.8%), oral hydromorphone (n. 2, 1.0%), oxycodone (n. 27, 13.2%); oxycodone/naloxone (n. 42, 20.5%), tapentadol (n. 8, 3.9%), parenteral morphine (n. 11, 4.4%), methadone (n. 4, 1.9%) transdermal fentanyl (n. 72, 35.1%), transdermal buprenorphine (n. 12, 5.8%). One-hundred-forty-two patients (70.3%) were receiving adjuvant drugs, including benzodiazepines (n. 22, 10.7%), anticonvulsants (n. 71, 34.6%), antidepressants (n. 18, 8.8%), antiemetics (n. 15, 7.3%), laxatives (n. 27, 13.3%), and corticosteroids (n. 77, 37.6%). Women with H&N cancer were more frequently prescribed adjuvants (82.7% vs 68.6%, p = 0.030). In particular, corticosteroids were more frequently used (54.7% vs 36.3%, p = 0.006).

Opioids used for background pain in patients with and without H&N cancer are reported in Table 2. Oxycodone/naloxone was less frequently prescribed (20.5% vs 29.1%, p = 0.008). No differences in the use of methadone were found (p = 0.209), unless for women who were more frequently receiving methadone (5.7% vs 1.2%, p = 0.007). Transdermal fentanyl was also more frequently used (35.1% vs 27.0%, p = 0.011), the difference being more relevant in women (49.1% vs 28.4%, p = 0.001). Transdermal buprenorphine was more frequently used (5.8% vs 2.9%, p = 0.015), but such a difference was more evident in males (5.9% vs 2.4%, p = 0.009). No differences in OME were found (p = 0.498).

Table 2
Opioids used for background pain in patients with and without H&N cancer (some of them also in combination).

	n (%) with H&N cancer	n (%) without H&N cancer	p
Oral morphine	20 (10.1%)	309 (8.3%)	0.402
Oral hydromorphone	2 (1.0%)	126 (3.4%)	0.064
Oxycodone	27 (13.6%)	637 (17.1%)	0.183
Oxycodone/naloxone	42 (21.2%)	1110 (29.8%)	0.008
Tapentadol	8 (4.0%)	187 (5.0%)	0.515
Parenteral morphine	11 (5.5%)	182 (4.9%)	0.297
Methadone	4 (2.0%)	39 (1.0%)	0.209
Transdermal fentanyl	72 (36.4%)	1030 (27.6%)	0.011
Transdermal buprenorphine	12 (6.0%)	109 (2.9%)	0.015

Table 3
Opioids used for BTcP in patients with and without H&N cancer.

	n (%) H&N cancer	n (%) no H&N cancer	p
Oral transmucosal fentanyl citrate	5 (2.4%)	125 (3.3%)	0.507
fentanyl buccal tablet	19 (9.3%)	416 (10.9%)	0.460
sublingual fentanyl tablets	14 (6.8%)	556 (14.6%)	0.002
Fentanyl pectin nasal spray	56 (27.3%)	751 (19.7%)	0.008
Intranasal fentanyl	5 (2.4%)	35 (0.9%)	0.033
Oral morphine	31 (15.1%)	532 (13.9%)	0.641
Parenteral morphine	15 (7.3%)	278 (7.3%)	0.990

Analgesics used for BTcP

Opioids used for BTcP in patients with and without H&N cancer are reported in Table 3.

Nasal fentanyl preparations were more frequently used in patients H&N cancer, while sublingual fentanyl (SLF) was less frequently used (Table 3).

Level of mucositis and adverse effects

A consistent number of patients with H&N cancer (38.5%) exhibited different levels of oral mucositis. Of them, 29 patients had oral aching/erythema (grade 1), 26 had oral erythema/ulcer/solid diet tolerated (grade 2), and 19 patients had oral ulcers/only liquid diet tolerated (grade 3). In 5 patients oral feeding was impossible (grade 4). Only 12.9% of patients with other primary diagnoses manifested oral mucositis. The difference was highly significant (p = 0.0001). Also the severity of oral mucositis was significantly higher in patients with H&N cancer compared with patients with other primary tumors (grade 1, 14.1% vs 9.18%; grade 2, 12.7% vs 2.65%; grade 3 9.3% vs 0.9%; and grade 4, 2.4% vs 0.2%) (p = 0.0001).

Adverse effects

Adverse effects attributable to BTcP medications were found in 4 patients (2.8%), No differences with other tumors were found (3.7%, p = 0.551). No adverse effects of severe intensity were reported (3 of mild intensity, 1 of moderate intensity)

Discussion

The findings of this study provided relevant information regarding background pain and a phenomenon, BTcP, that has never been described in patients with H&N cancer. First, in comparison with the general population affected by other primary tumors, H&N cancer patients exhibited more episodes of BTcP, which were more predictable, particularly with the ingestion of food. This finding can be explained by the local characteristics of H&N cancer, which also suggest a more intensive treatment of background pain [1]. Pain is a significant morbidity characterized by multifactorial mechanisms in patients with H&N cancer, also resulting from the treatments directed against the tumor. Pain should be managed with multiple medications in a multimodal approach [24]. Of interest, corticosteroids were more frequently given in patients with H&N cancer. Transdermal drugs, particularly fentanyl, were more frequently prescribed in H&N cancer patients. Transdermal fentanyl may be an important option, thanks to the modality of administration, the good safety, and tolerability profile to control baseline pain, although head-to-head studies of fentanyl versus other strong opioids are lacking [25]. In the only existing comparative study of patients with H&N cancer having a neuropathic component, methadone appeared more effective than transdermal fentanyl [26]. The use of methadone, which appeared more frequently prescribed in women,

may have a potential in neuropathic pain conditions, but in this study there is no apparent explanation for this finding, considering that this substance is really rarely prescribed in this country [27].

Secondly, a large number of patients had oral mucositis of severe intensity. This finding corresponds to the clinical condition of patients who received many treatments with high local toxicity potential, including surgery, chemotherapy, and radiotherapy. The presence of high levels of mucositis could have influenced the choice of drugs for both background pain (transdermal preparations) and above all BTcP, with nasal fentanyl preparations being more frequently prescribed. This choice could be explained by the difficulties in giving oral medications for background pain and oral transmucosal fentanyl preparations for BTcP. In fact, patients with H&N cancer are likely to have a serious mucosal damage making local absorption unpredictable. There are no existing studies regarding BTcP in patients with H&N cancer for comparison.

There are some study limitations, due to the secondary analysis of an original trial in patients who were selected for the presence of BTcP. Thus, we do not have information about the prevalence of this phenomenon in patients with H&N cancer. Moreover, no specific treatment was given, as treatment was based on local policy. However, data were collected from centers with experienced personnel for the management of background pain and BTcP. Indeed, this data reflects the real world, giving a picture of the characteristics of such patients, as well as the most common analgesic treatments employed for this kind of patients either for background pain or BTcP. The sample was sufficiently numbered to provide preliminary but solid data. The descriptors for the study population refer only to “H&N cancer”, which is a broad term that refers to an anatomically complex region of the body afflicted with a wide variety of histologies and stages of cancer. Additional information regarding anatomic subsite (oropharynx, parotid gland, larynx, etc), histology (squamous cell, salivary, thyroid, etc), and stages (I, II, III, IV) would enhance the external generalizability of these findings. A better characterization in terms of anticancer intervention could provide more specific data. Thus, a specific study with a larger sample of patients may provide further information about factors influencing background and BTcP presentation.

In conclusion, BTcP in patients with H&N cancer has its own peculiarities, including a larger number of episodes/day and the predictability, particularly with ingestion of food. Transdermal preparations and nasal fentanyl preparations were more likely to be prescribed for background pain and BTcP, respectively, possibly to avoid interference with swallowing or local mucosal damage. Future studies should be performed to analyze the prevalence of BTcP in this population as well as the optimal management strategy for H&N cancer pain and BTcP.

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Declaration of Competing Interest

No conflict of interest to be declared.

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Data availability

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.06.006.

References

[1] Shuman AG, Terrell JE, Light E, et al. Predictors of pain among patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2012;138:1147–54.
[2] Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
[3] Taylor JC, Terrell JE, Ronis DL, et al. Disability in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2004;130:764–9.
[4] Funk GF, Karnell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. Arch Otolaryngol Head Neck Surg 2012;138:123–33.
[5] Osthus AA, Aarstad AK, Olofsson J, Aarstad HJ. Head and neck specific Health Related Quality of Life scores predict subsequent survival in successfully treated head and neck cancer patients: a prospective cohort study. Oral Oncol 2011;47:974–9.
[6] Lam DK, Schmidt BL. Orofacial pain onset predicts transition to head and neck cancer. Pain 2011;152:1206–9.
[7] Talmi YP, Waller A, Bercovici M, et al. Pain experienced by patients with terminal head and neck carcinoma. Cancer 1997;80:1117–23.
[8] Epstein JB, Wilkie DJ, Fischer DJ, et al. Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. Head Neck Oncol 2009;1:26.
[9] Chen AM, Hall WH, Li J, et al. Brachial plexus-associated neuropathy after high-dose radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012;84:165–9.
[10] Chua KS, Reddy SK, Lee MC, et al. Pain and loss of function in head and neck cancer survivors. J Pain Symptom Manage 1999;18:193–202.
[11] Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain 1999;82:263–74.
[12] Van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, et al. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. Pain 2007;132:312–20.
[13] Mercadante S. Opioid responsiveness in patients with advanced head and neck cancer. Support Care Cancer 1998;6:482–5.
[14] Mercadante S, Casuccio A, Pumo S, Fulfaro F. Opioid responsiveness-primary diagnosis relationship in advanced cancer patients followed at home. J Pain Symptom Manage 2000;20:27–34.
[15] Trotter PB, Norton LA, Loo AS, et al. Pharmacological and other interventions for head and neck cancer pain: a systematic review. J Oral Maxillofac Res 2013;3(4):e1.
[16] Greco MT, Roberto A, Corli O, et al. Quality of can- cer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014;32:4149–54.
[17] Mercadante S, Portenoy RK. Breakthrough cancer pain: twenty-five years of study. Pain 2016;157:2657–63.
[18] Portenoy RK, Bruns D, Shoemaker B, Shoemaker SA. Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 2: impact on function, mood, and quality of life. J Opioid Manag 2010;6:109–16.
[19] Mercadante S. Treating breakthrough pain in oncology. Expert Rev Anticancer Ther 2018;18:445–9.
[20] Davies A, Buchanan A, Zeppetella G, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manage 2013;46:619–28.
[21] Mercadante S, Marchetti P, Cuomo A, et al. Factors influencing the clinical presentation of breakthrough pain in cancer patients. Cancers (Basel) 2018;10(6).
[22] Mercadante S, Ferrera P, Villari P, et al. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009;37:632–41.
[23] http://www.icssc.org/documents/resources/aemanual2003appendicesfebruary_06_2003%20final.pdf.
[24] Ing JW. Head and neck cancer pain. Otolaryngol Clin North Am 2017;50:793–806.
[25] Giusti R, Bossi P, Mazzotta M, et al. The use of fentanyl in pain management in head and neck cancer patients: a narrative review. Br J Pain 2018;12:155–62.
[26] Haumann J, Geurts JW, van Kuijk SM, et al. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. Eur J Cancer 2016;65:121–9.
[27] Mercadante S, Valle A, Agnelotti C, Caruselli A. The poor use of methadone in Italian hospices. Support Care Cancer 2013;21:2225–8.