Support Care Cancer
DOI 10.1007/s00520-015-2951-y

REVIEW ARTICLE

Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group

Sebastiano Mercadante[1,6] · Paolo Marchetti[2] · Arturo Cuomo[3] · Massimo Mammucari[4] · Augusto Caraceni[5] · on behalf of the IOPS MS study Group

Received: 19 May 2015 / Accepted: 14 September 2015

Abstract Controversies exist about the definition and epidemiology of breakthrough cancer pain (BTcP), the pharmacological treatment options, drug dosing, and how to select the medications for BTcP among the new fentanyl products. Existing data were critically evaluated to provide recommendations by an expert group. An algorithm to diagnose BTcP should be used followed by a careful assessment. Fentanyl products provide efficacy and rapidity of action to counteract the temporal pattern of BTcP. The doses of opioids used for background pain should guide the choice of the doses of fentanyl products. The choice of fentanyl products should be based on individual clinical conditions.

Keywords Breakthrough pain · Opioids · Fentanyl · Morphine

✉ Sebastiano Mercadante
terapiadeldolore@lamaddalenanet.it

[1] Anesthesia and Intensive Care & Pain Relief and Supportive Care, La Maddalena, Italy

[2] Molecular and Clinical Medicine Medical Oncology, La sapienza University of Rome, Rome, Italy

[3] Abdominal Medical Oncology, National Cancer Institute Pascale, Naples, Italy

[4] Primary Care Unit, ASL RME, Rome, Italy

[5] Palliative Care, Pain Therapy and Rehabilitation, National Cancer Institute, Milan, Italy

[6] Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via San Lorenzo 312, 90146 Palermo, Italy

Introduction

Breakthrough cancer pain (BTcP) has been described more than 20 years ago and has been recognized as an important clinical problem in its own right requiring independent assessment and targeted treatment [1]. BTcP affects a large number of cancer patients and causes deterioration of the quality of life [2]. As a consequence, more attention has been paid to this issue in last years.

On 15th March 2010, the Italian government approved a new law (n.38), with the intent to improve pain assessment and treatment, imposing physicians and nurses to register the characteristics of pain in any patient's chart. According to these new indications from the Minister of Health, a group of experts started a program to organize a national observatory for exploring these activities. In particular, the experts focused on BTcP to provide information regarding this phenomenon developing an Italian Oncologic Pain Survey (IOPS). In a first survey of a large sample of cancer patients recruited in different settings, BTcP has been found to represent a clinically relevant condition with a negative impact on the patient's quality of life. A number of factors were associated with the BTcP, including the course of disease and the setting of care [3]. This information may help stratifying patients or predicting the risk of development of BTcP with specific characteristics. These results prompted a new survey with the intent to assess more than 4000 patients that is expected to be concluded in 1 year. The aim of this paper is to provide updated recommendations on BTcP and its treatment on behalf of the IOPS expert group, after careful examination and critical appraisal of literature.

Published online: 05 October 2015

Methods

An expert group met to provide these recommendations. The most relevant issues regarding BTcP were selected by the experts, and literature reviewed accordingly. As the aim of this review was not an evidence-based approach, which often does not provide useful information to translate in clinical practice, the literature was selected to explore some clinical questions and a critical analysis was performed to outline practical recommendations. This approach was performed to evidence some bias on data interpretation reported in literature, which did not often reflect clinical practice. These issues were identified by the principal investigator (SM) and proposed to the other experts for an initial consensus. The participants of expert group were selected on the basis of their research activity in the field of BTcP. A draft was then prepared by one author (SM) who analyzed the most recent literature and provided an expert opinion. Documentation was circulated among the experts to provide an advice and to reach a final agreement.

Thus, available scientific data were evaluated by a critical interpretation of existing data to provide practical recommendations by the

Results

Five relevant and controversial areas requiring clarification were identified by the expert group. They included the definition and epidemiology of BTcP for an appropriate diagnosis, how to assess this phenomenon, the pharmacological treatment options, drug dosing of new fentanyl preparations, and how to select the medications for BTcP.

Discussion

Definition and epidemiology

BTcP has been variably reported in literature, ranging in 40–80 % of cancer patients with pain, depending on the setting and the definition used to identify it [1–6]. The pioneer definition suggests that "BTcP is a transitory increase in pain to greater than moderate intensity which occurs on baseline pain of moderate intensity or less" [1]. This sentence sounds ambiguous, as pain intensity should be severe (on a numerical scale 7/10), but the baseline pain could be moderate (on a numerical scale 4–6/10). From a clinical point of view, this gray area of moderate pain is commonly considered as needing a better analgesia. It has been reported that such range of pain intensity significantly interferes with daily activity and that mild pain should be considered at least ≤4/10 on a numerical pain scale [7, 8]. Thus, the differences between the intensity of BTcP could be minimal (1–2 points on a numerical scale). This approach has been largely used in patients' selection in most studies of BTcP. In some epidemiological studies, there was no operational definition a priori, even though patients could have their pain uncontrolled or were not receiving opioids [9, 10]. For example, background pain intensity was severe-maximal in more than half of patients, and differently from what has been observed by others [9, 11], surprisingly, the intensity of baseline pain was higher in patients without BTcP. In other studies, most patients had uncontrolled background pain, were receiving nonopioid analgesics or weak opioids, or were unsatisfied with their pain control [11, 12].

Subsequently, other definitions were proposed, such as "a transient exacerbation of pain that occurs irrespective of basal analgesia"[13], "episodes of pain occurring on an unrealistic pain-free background" [14], or "any transient flare of pain subjectively distinguishable from an otherwise more or less stable background pain" [15].

The original definition was then refined as follows: "BTcP is a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy" [1], in which a second variable was introduced and regarded the use of stable doses of opioids able to maintain baseline pain control. This definition also formed the basis for a further refinement: ".. despite relatively stable and adequately controlled baseline pain," [16–18], presumably by giving around the clock opioid administration.

Recent larger studies provided a better characterization of BTcP, by using a specific algorithm for diagnosis (Fig. 1). An observational European study of 1000 patients with BTcP reported that BTcP episodes were about three/day. Incident-predictable and spontaneous-unpredictable BTcP had similar percentages with a median duration of 60 min, which was shorter in incident-predictable BTcP. Activity was strongly triggering BTcP [19]. In a large Italian study of 1412 patients, most patients reported two to three BTcP episodes/day, and 80 % patients reported that the BTcP had a significant negative impact in everyday life. The majority of patients reported a fast onset of BTcP, which was predictable in about half of patients, while BTcP with a gradual onset was less predictable [3].

It is difficult to have a clear idea on a complex phenomenon such as BTcP without a prospective evaluation and an optimized analgesic approach. For these reasons, it is likely that BTcP should be more correctly defined as an episode of severe intensity in patients receiving an adequate treatment with opioids able to provide at least mild analgesia [3, 19].

This has been confirmed by a recent study of patients who asked for a BTcP medication when they had a pain intensity of ≥7 on a numerical scale 0–10 and were satisfied with a pain intensity of ≤4/10 after receiving a BTcP medication, suggesting that these cutoff points could help selecting patients in studies of BTcP, avoiding to include patients with intermediate situations which often lend misinterpretation of data reported

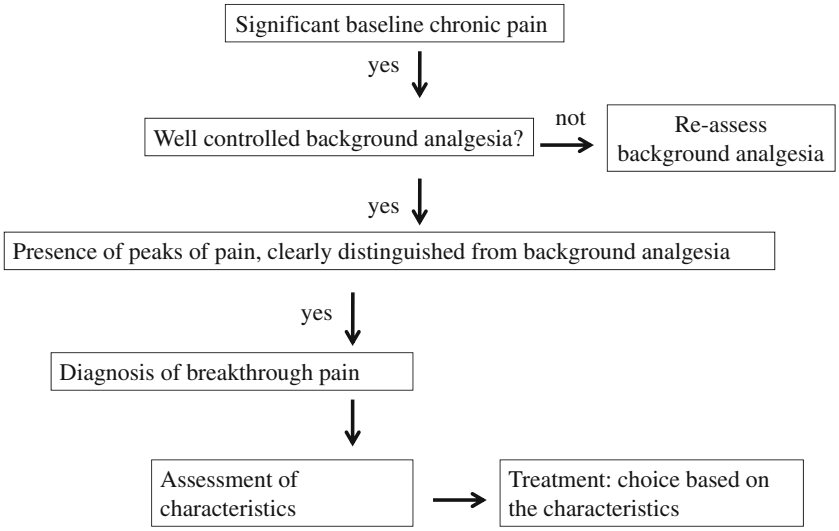

Fig. 1 Algorithm for diagnosis, assessment, and treatment of BTcP

in the literature [7]. Of interest, despite reducing the level of background pain intensity by increasing opioid doses, the number of patients presenting BTcP did not decrease, but a lower number of episodes and a lower intensity of BTcP were obtained, thus improving the general outcome. According to this information, the phenomenon of BTcP should be expected in about 70 % of patients, despite receiving effective regular opioids in doses of ≥60 mg/day of oral morphine equivalents for background analgesia [8]. In contrast, optimization of background analgesia in patients with BTcP with visceral abdominal mechanism may produce greater benefits, as the prevalence of BTcP may be halved. This is probably due to the exclusion of the bone-related incident pain component [20]. The clinical setting and the stage of disease may also influence the prevalence of BTcP. For example, patients with a poor performance status receiving palliative care are less likely to present BTcP [3]. This finding has been explained by the reduced physical activity, minimizing the incident component of pain induced by movement due to bone metastases. Another reason could rely on a more intensive pain management in the palliative care setting [5, 6]

Considering that all fentanyl products for BTcP are indicated only in patients tolerant to at least 60 mg of oral morphine equivalents, this limit could be utilized for a further screening of patients with BTcP. At the moment, there is no information about BTcP in patients receiving low doses of strong opioids (less than 60 mg/day of oral morphine equivalents) or opioids for mild-moderate pain (Table 1).

Recommendation Regrettably, many epidemiological and clinical studies included inappropriate and confounding definitions of BTcP. Indeed, BTcP should be defined as a relevant change in pain intensity of severe intensity in patients who receive an effective treatment with opioids, presumably in doses of at least 60 mg of oral morphine equivalents, able to provide acceptable analgesia with a mild pain intensity for most hours of the day.

According to this definition, we expect that about 70 % of cancer patients with pain, managed with effective dose of oral morphine equivalents for their background pain, may manifest an exacerbation of pain of severe intensity [8]. Apart from predictable-incident pain due to movement, two to three episodes per day should make the background opioid doses to be acceptable when providing a basal analgesia with mild pain.

Assessment

According to the definition provided above, a specific assessment should be performed to provide further information for an individualized treatment. Several tools to assess patients' experience of BTcP have been proposed, but only a minority has been partially validated [21].

A BTcP questionnaire comprised specific questions to assess BTcP. Delphi national and international panels followed by patient pre-testing on the clarity and feasibility of completing the instrument provided some indications about the screening of BTcP, grouping the principal items which are commonly used in the clinical setting [22].

Key issues included the relationship to baseline pain, the last time in which BTcP was experienced, frequency, intensity of pain at peak, location, quality, time from onset to peak intensity, duration, causes, predictability, general relief, relief from BTcP medication, satisfaction with BTcP medication, onset of pain relief, and satisfaction with onset of pain relief. Other items completed by professionals included etiology of BTcP and inferred pathophysiology of BTcP. More recently, a new assessment tool for BTcP has been developed and validated. This instrument provided information on how BTcP, efficacy, and toxicity of BTcP medications may interfere with

Table 1 Characteristics of opioids used for BTcP

	Dosing	Analgesic Onset	Availability (%)
Oral morphine	1/6[a]	30–45′	30
Oral oxycodone	1/6[a]	30–45′	40–50
OTFC	200–1600	15–30′	50
FBT	100–800	15′	65
SLF	100–800	10′	70
FBSF	100–800	15′	65
INFS	50–200	5–10′	80–90
FPNS	100–400	5–10	70

OTFC oral transmucosal fentanyl cytrate, *FBT* fentanyl buccal tablet, *SLF* sublingual fentanyl, *FBSF* fentanyl buccal soluble film, *INFS* intranasal fentanyl spray, *FPNS* fentanyl pectyn nasal spray

[a] Percentage of daily doses

daily life. Reliability and validity of the tool tested on a group of patients was reasonably good [23].

The relationship with background analgesia has been variably explored. It has been found that patients with BTcP had more intense and more frequent background pain than patients without BTcP [1, 4], supporting the idea that a further optimization of background analgesia may result in a reduction of BTcP phenomenon [24]. Recently, it has been shown that, despite optimization of analgesic therapy and reduction of background pain intensity, the number of patients with BTcP did not change significantly. While the phenomenon cannot be abolished, this approach may reduce the number of episodes/day, duration, and severity of BTcP with consequent benefits for patients [8].

The number of episodes considered to be acceptable has been invariably reported as being one to four episodes per day, supposing that for a 1-h duration, a drug could be given to cover this short period, while the remaining daily hours are covered by background analgesics. However, this concept cannot be extended to BTcP induced by movement associated to bone metastases. The presence of incident bone pain due to movement represents a unique category of BTcP, as pain is induced by activity and the number of episodes is difficult to account, as the patient will try to avoid painful maneuvers. In some circumstances, every movement induces pain of variable duration, depending on the will of patients or stopping the activity. As a consequence, it is quite obvious that more attention should be paid on optimization of background opioid analgesia, to allow a better ability to move [24]. Opioid doses should be balanced with a realistic expectation and an individual compromise between physical activity and adverse effects should be followed. Paradoxically, very advanced cancer with a poor performance status or bedridden patients will develop BTcP less frequently [3, 5], probably due to a lesser ability to move. An appropriate balance between physical activity and background analgesics, an appropriate information, and a therapeutic compromise should guide the management of BTcP.

Recommendation There is a need of careful evaluation of the characteristics of BTcP by existing tools, of the level of background analgesia, and of analgesic regimens for both background and BTcP. Even the characteristics and the temporal pattern of incident pain should be assessed in individuals as a guide for a possible anticipatory treatment

Pharmacological treatment

Several papers about the treatment of BTcP have been published in the last years, including controlled double-blind randomized trials of the efficacy of medications for BTcP. Traditionally, oral morphine has been offered for years as BTcP medication in doses of 1/6 of the daily dose [25]. NICE guidelines suggest to offer immediate-release oral morphine for the first-line rescue medication of BTcP and do not offer fast-acting fentanyl as first-line rescue medication (www.nice.org.uk/cg140). While oral opioids have been the mainstay approach for patients who are receiving around the clock opioid regimen, the onset and duration of action of oral opioids may not be suitable for treating many BTcP events [26]. This is confirmed by the analysis of existing literature [27]. A mixed-treatment analysis suggested that fentanyl formulations were more efficacious treatment options than oral morphine [28]. Recently developed guidelines support this approach and recommend treating BTcP using rapid or short-acting opioids with pharmacodynamics that mirror the rapid onset and short duration of the presenting pain [9]. An updated Cochrane review reported on the utility of seven different transmucosal fentanyl formulations in comparison with oral opioids. Oral and nasal transmucosal fentanyl formulations were an effective treatment for BTcP. When compared with placebo or oral morphine, participants gave lower pain intensity and higher pain relief scores for transmucosal fentanyl formulations at all time points. Global assessment scores also favored transmucosal fentanyl preparations [29]. In a Canadian survey, patients stated that the most important features of a new treatment for BTcP were the ability to relieve pain completely and quickly. Patients expressed willingness to try transmucosal products (80 %) or nasal products (59 %) [30].

Recommendation Accumulated evidence shows that transmucosal fentanyl formulations provide a more effective and rapid analgesia in comparison with oral morphine. There are still some possible indications for oral opioids that include a slow-onset BTcP or a preemptive administration of oral opioids about 30 min before a predictable BTcP triggered by known events. As mentioned before, some patients require a very strict individualization of the treatment in consideration of the onset and predictability of an event of BTcP.

Dosing

While of oral opioids, there is a general consensus on using a percentage of the daily dose for BTcP, approximately 1/6th [27], the choice of the dose of the fentanyl preparation for BTcP to be prescribed as needed remains controversial. Almost all comparative studies of fentanyl preparations supported that doses should be titrated starting with the lowest available strength. This statement has been quoted by evidence "B" by an expert group in the UK [31]. However, these randomized trials have never specifically examined this issue, and the information gathered is just consequential to the study design aimed to demonstrate superiority of fentanyl over placebo, oral morphine, or other oral opioids. Titration phases were open and not controlled, exactly like other open studies assessing the efficacy and the safety of opioids given in doses proportional to the opioid basal regimen, even in aged population [32, 33]. Thus, data were not so solid to produce a recommendation of level B. When original data were available, a simulation of a calculation of opioid doses used for background analgesia and those achieved after individual titration showed mean values of proportional doses of fentanyl very close to those found after titration [34].

On the other hand, the reasons for these findings are not clearly explained, considering that the presence of tolerance should suggest a dose proportional to those used for background analgesia. Some data need accurate interpretation. For example, in successful patients treated with oral transmucosal fentanyl citrate (OTFC) the regular rescue dose was a moderate predictor of the effective OTFC dose. A relationship between the OTFC dose and the fixed scheduled opioid had been already found, and regular rescue dose was a moderate predictor of the effective OTFC dose [33, 34]. Of interest, despite a large interindividual variability in patients' dose requirements, observations from data pooled from the same trials of OTFC showed a statistically significant relationship between the BTcP and around the clock opioid dose, also considering that the protocol was not aimed to demonstrate that [22]. In a real clinical scenario, patients receiving a mean oral morphine dose of 132 mg, required 800 μg of OTFC [35], suggesting that titration process may provide even higher doses that those expected by using proportional doses to basal opioid regimen.

Finally, dose titration may make the practical use of transmucosal fentanyl difficult in the daily activity, particularly at home or in outpatients. The use of different pieces or spray of fentanyl preparations for treating each episode may be time consuming exceeding the spontaneous duration for BTcP which can spontaneously subside, as evidenced by successful placebo-treated patients [33, 34]. Most patients may be reluctant to try the dose and avoid to use these drugs, preferring, at the end, traditional oral dosing of morphine [36].

Indeed, the need to titrate has never been determined on the basis of a comparison between titration strategy and proportional strategy. To scientifically affirm the need of titration, a randomized trial should compare groups titrated versus groups nontitrated [32]. For instance, fentanyl products, given in doses proportional to the basal opioid regimen in large number of patients, even at home or fragile patients and at high doses, have been found to be quite effective and, above all, safe, avoiding to titrate the dose, which is considered unpleasant for patients, reducing their compliance with the treatment [34–40]. These experiences suggested that opioids given as needed could be safety used at proportional doses, regardless of the modality of administration, because of the protective role of the level of tolerance to opioids given for background analgesia. Of interest, the only existing controlled study confirmed that proportional doses of fentanyl buccal tablet (FBT) are more effective than doses achieved after titration, while tolerability is similar [41].

Recommendation It is likely that patients receiving high doses of opioids as basal analgesic regimen will not be candidates for titration with minimal initial doses of fentanyl, as they are opioid tolerant, and the process would be time consuming and not appreciated by patients. Thus, a reliable compromise between the different opinions could be to start skipping some steps of titration in highly tolerant patients, until more information will be available to settle the question. Future studies in large sample of patients with the different fentanyl products should make clear this controversial issue.

How to selects fentanyl products

The choice of fentanyl products is still matter of controversies. It is clear that the molecule is always the same, so that the differences regard the clinical application of the different delivery systems. These products have different pharmacokinetic profiles and availability which may make the difference in individual clinical situations.

Few comparison studies have been published. The efficacy of intranasal fentanyl spray (INFS) was compared with that of OTFC in an open-label, crossover trial. Time to onset of meaningful pain relief was 11 min with INFS versus 16 min with OTFC. The pain intensity difference was significantly greater for INFS than OTFC from 5 min post-dosing. A significant proportion of patients achieved a pain intensity reduction at 5′ and 10′. Higher sums of pain intensity differences from 0 to 15 min and from 0 to 60 min were achieved with INFS and more patients preferred INFS than OTFC. No serious adverse effects were attributed to study medications [39].

More recently, a comparison of nasal product was performed, based on different availability of fentanyl pectin nasal spray (FPNS) (about 60–65 %) and INFS (about 80–90 %). However, the minimal commercially available strength of

FPNS is 100 μg, which is the double of that of INFS, that is, 50 μg. Indeed, these dosages have been similarly suggested to start the treatment in patients tolerant to 60 mg of oral morphine equivalents, as they would be equivalents. Despite this premise, INFS and FPNS were similarly effective and well-tolerated treatments for BTcP management. Both delivery systems, in doses proportional to the basal opioid regimen, provided significant analgesia within 5–10 min, achieving a mean decrease in pain intensity of more than 50 % 20 min after administration, without producing relevant adverse effects. The similar onset of action of FPNS could seem to be unexpected, given the characteristics of the products. Despite FPNS generates lower C-max for its formulation, modulating fentanyl absorption, the dose given in this study was approximately the double in respect to INFS, as for the minimal available strengths, commonly employed as starting doses in titration studies, which are 100 and 50 μg, respectively. Of interest, the similar analgesic trend was observed at the different dose levels which were given proportional to the basal opioid regimen [42]. Thus, it is likely that patients may benefit from similar but not identical amounts of fentanyl. The presence of a certain level of tolerance may explain this finding, also in respect to the occurrence of adverse effects. In patients responsive to opioids, an opioid dose proportional to the basal opioid regimen has a predictable therapeutic window which provides efficacy with limited toxicity

Data regarding some practical aspects of administering BTcP medications have been rarely examined. Fentanyl buccal tablet (FBT), sublingual fentanyl (SLF), and INFS given as placebo have been assessed in addition to their usual rescue analgesic used for BTcP. For accessibility, the usual rescue analgesic was rated mildly easy and significantly better than FBT and INFS, but not SLF. For easy administration, the usual rescue analgesic and SLF were similar, and SLF was rated better than FBT and INFS. SLF was also rated the best for palatability and overall impression. However, it was unclear what was the usual rescue analgesic and only three fentanyl products were evaluated in the form of placebo [43].

Practical considerations have to be meaningfully suggested, although they have never been considered in studies. The assessment of oral and nasal mucosal surfaces is mandatory. In patients with oral problems, for example, due to mucositis, dry mouth, or infection, oral transmucosal products may be of concern, and nasal products should be preferred. On the other hand patients with rhinitis or nasal lesions are not candidate for nasal administration.

In a recent report assessing the acceptability of rapid-onset opioids for BTcP in advanced cancer patients, all fentanyl products were well accepted, with OFTC being significantly considered to be more problematic for modality of administration and late pain relief, in comparison with other products. Thus, the second generation of fentanyl delivery systems seems to have more favorable characteristics for some practical issues [44]. OTFC, formulated as self-administration of a solid drug matrix on a handle, requires patient discipline and focus, which may limit compliance, particularly in patients with weakness, a common symptom in advanced stage of disease. On the other hand, experience with OTFC suggests that the use of this product can be discontinued when sufficient analgesia is produced as the unit is easily removed from the mouth with the handle. Such flexibility is not available with administration of the other ROOs [27]. This off-label use has never been assessed in a scientific way. Furthermore, this approach requires skilled patients and cannot be proposed in old or severely ill patients.

Regardless of the individual indication found after careful assessment of the clinical condition, it is of paramount importance to consider patients' and relatives' education to maximize the effects of the fentanyl products. Another relevant aspect is the patient's experience and compliance. A balance between the individual indications and the patients' will, preference, and ability to use the product is fundamental to find an acceptable compromise and to plan an appropriate prescription which will be correctly followed by patients and relatives.

Recommendation The various different fentanyl products should be chosen according to different clinical and practical conditions considering their indications, ability to use the delivery system, and mucosal conditions due to oncological-radiotherapy treatment that may impede a good absorption. The periodical assessment of the clinical conditions capable of interfering with the bioavailability of the drugs and their effectiveness is useful for providing the continuous efficacy of fentanyl delivery systems.

Conclusion

The expert group recommends to follow a clear algorithm to diagnose BTcP, taking into account the several factors which can influence BTcP. A careful assessment should provide the correct information to individualize the treatment. Fentanyl products, regardless of the cost, are the mainstay of the pharmacological treatment of BTcP, although oral opioids could be useful in some specific circumstances. The dose of fentanyl products to be administered should take into account the level of opioid tolerance of patients. Finally, given the paucity of comparison studies among fentanyl delivery systems, the choice should be based on individual considerations according to the onset of BTcP, a careful examination of local mucosal areas, and evaluation of patients' preferences and experience.

Conflict of interest IOPS activity is sponsored by an unrestricted grant of Molteni Pharmaceutical, Italy.

The authors had full control of all primary data and agree to allow the journal to review their data if requested.

Appendix

The IOPS MS Study Group

Mediati Rocco Domenico[6], Caruselli Amanda[1],Costanzi Andrea[2], Russo Gennaro[3], Bracchi Paola[4], Dodaro Lucia[5], Contu Viviana[8], Fora Gianluca[8], Veronese Barbara[10], Alu Massimiliano[11], Chiurazzi Bruno[12], Sgarlata Massimiliano[13], Kasa Alma[14], Donelli Emanuela[15], Silvestro Stefania[15], Romano Carmela[17], Ghidoni Silvia[18], Palermo Loredana[19], Pisanu Giovanni Maria [20], Imperatori Luca[21], Diacciati Sara[22], Samolsky Dekel Boaz[23], Bruno Emanuela[24], Saulle Serena[25], Bonotto Marta[26], De santis Stefano[27], Tammaro Dario[28], Ginocchi Laura[29], Zampieri Mari[31], Fioroni Iacopo[32], Gallo Gloria[33], Saber Benhaz[33].

Dauri Mario[7], Airoldi Mario[8], Azzarello Giuseppe[9], Bandera Mauro[10], Blasi Livio[11], Carteni Giacomo[12], Costanzo Veruska[13], Degiovanni Daniela[14], Fusco Flavio[15], Guardamagna Vittorio[16], Iaffaioli Vincenzo[17], Lazzari Marzia[7], Liguori Simeone[18], Lorusso Vito[19], Mameli Sergio [20], Mattioli Rodolfo[21], Mazzei Teresita[22], Melotti Rita Maria[23], Menardo Valentino[24], Miotti Danilo[25], Moroso Stefano[26], Natoli Silvia[7], Orsetti Remo[27], Papa Alfonso[28], Ricci Sergio[29], Sabato Alessandro Fabrizio[7], Scelzi Elvira[30], Sofia Michele[31], Tonini Giuseppe[32], Valle Alessandro[33]

6 Pain Relief, Palliative Care, Oncology Department, Careggi Hospital, Florence Primary Care Unit, ASL RME, Rome,

7 Emergency care, Critical care Medicine, pain Medicine and Anesthesiologydepartement, Tor Vergata University of Rome

8 2nd Medical Oncology Division, Cittàdella Salute e dellaScienza Hospital of Turin, Turin

9 Dip SpecialitàMediche, UOCOncologiaedEmatologiaOncologica; ASL 13 Mirano, Venezia, Italia

10 Ospedaliera Papa Giovanni XXIII - Unit of Paliative Care and Pain Therapy, Bergamo, Italy

11 Medical Oncology Unit, ARNAS Civico, Palermo

12 Medical Oncology, A.O.R.N A. Cardarelli, Naples

13 Palliative Care Unit, SAMO ONLUS, Catania

14 Palliative Care Unit, Ospedale S. Spirito, CasaleMonferrato, Italy

15 SSD Cure Palliative Dipartimento Cure PrimarieedAttivitàDistrettuali ASL3 Genovese

16 UnitàOperativa di Cire Palliative e Terapia del dolore - IRCCS IstitutoEuropeo di Oncologia (IEO) - Milano, Italia

17 Abdominal Medical Oncology, National Cancer Institute, IRCCS Foundation Pascale, Naples

18 Ospedaliera Papa Giovanni XXIII - Unit of Palliative Care and Pain Therapy, Bergamo, Italy

19 Medical Oncology Unit, National Cancer Research Centre "Giovanni Paolo II", Bari

20 Pain Therapy Unit, “A. Businco” Hospital, ASL 8, Cagliari, Italy

21 S. Croce Hospital, Medical Oncology Unit, Fano - Pesaro, Italy

22 Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Florence

23 Department of Medicine and Surgery Sciences, University of Bologna, Bologna

24 StrutturaSempliceAlgologia, A.O. S. Croce e Carle, Cuneo, Italy

25 Salvatore Maugeri, Foundation IRCCS, Pavia, Italy

26 Medical Oncology, University Hospital S. Maria dellaMisericordia, Udine, Italy

27 Pain Medicine Unit, S. Camillo-Forlanini Hospital, Rome

28 Pain Relief, A.O. Dei Colli, Monaldi Hospital, Naples

29 Division of Medical Oncology, Department of Oncology, S. Chiara University Hospital, Pisa

30 U.O OncologiaMedica, P.O. Castelfranco Veneto- Treviso, Italy

31 U.O.C. Cure Palliative, Hospice e Medicina del Dolore. P.O di GarbagnateM.se, Milano

32 Department of Medical Oncology, Campus Bio-Medico University of Rome

33 Cure Palliative, Fondazione FARO, Torino

References

1. Portenoy RK, Hagen NA (1990) Breakthrough pain: definition, prevalence and characteristics. Pain 41:273–281
2. Portenoy RK et al (1999) Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 81:129–134
3. Mercadante S et al (2015) Italian Oncologic Pain Survey (IOPS): a multi-centre Italian study of breakthrough pain performed in different settings. Clin J Pain 31:214–221
4. Caraceni A et al (2004) Working Group of an IASP Task Force on Cancer Pain. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. Palliat Med 18: 177–183
5. Mercadante S et al (2009) Breakthrough pain advanced cancer patients : a longitudinal study. Support Care Cancer 38:554–560
6. Mercadante S et al (2010) Breakthrough pain in oncology : a longitudinal study. J Pain Symptom Manag 40:183–190
7. Mercadante S et al (2013) Meaningful cut-off pain intensity for breakthrough pain changes in advanced cancer patients. Curr Med Res Opin 29:93–97
8. Mercadante S et al (2013) Relationship between background cancer pain, breakthrough pain, and analgesic treatment: a preliminary study for a better interpretation of epidemiological and clinical studies. Curr Med Res Opin 29:667–671
9. Caraceni A et al (2012) Episodic (breakthrough) pain prevalence in a population of cancer pain patients. Comparison of clinical diagnoses with the QUDEI—Italian questionnaire for intense episodic pain. J Pain Symptom Manag 43:833–841
10. Greco MT et al (2011) Epidemiology and pattern of care of breakthrough cancer pain in a longitudinal sample of cancer patients.

Results from the Cancer Pain Outcome Research Study Group. Clin J Pain 27:9–18
11. Gómez-Batiste X et al (2002) Breakthrough cancer pain: prevalence and characteristics in patients in Catalonia, Spain. J Pain Symptom Manag 24:45–52
12. Zeppetella G et al (2000) Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manag 20:87–92
13. Svendsen KB et al (2005) Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. Eur J Pain 9:195–206
14. Swanwick M (2001) The prevalence of episodic pain in cancer: a survey of hospice patients on admission. Palliat Med 15:9–18
15. Petzke F, Radbruch L, Zech D, Loick G, Grond S et al (1999) Temporal presentation of chronic cancer pain: transitory pains on admission to a multidisciplinary pain clinic. J Pain Symptom Manag 17:391–401
16. Davies A et al (2011) Multi-centre European study of breakthrough cancer pain: pain characteristics and patient perceptions of current and potential management strategies. Eur J Pain 15:756–763
17. Bennett D et al (2005) Consensus panel recommendations for the assessment and management of breakthrough pain. Part 2—management. Pharm Ther 30:354–361
18. Hagen NA et al (2008) The Alberta Breakthrough pain assessment tool for cancer patients. A validation study using a Delphi process and patient think-alounr interview. J Pain Symptom Manag 35:136–152
19. Davies A et al (2013) Breakthrough cancer pain: an observational study of 1000 European oncology patients. J Pain Symptom Manag 46:619–628
20. Mercadante S et al (2014) Breakthrough pain in patients with abdominal cancer pain. Clin J Pain 30:510–514
21. Haugen D et al (2010) Assessment and classification of cancer breakthrough pain: a systematic literature review. Pain 149:476–482
22. Hagen NA et al (2007) A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. J Palliat Med 10:47–55
23. Webber K et al (2014) Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. J Pain Symptom Manag 48:619
24. Mercadante S et al (2004) Optimization of opioid therapy for preventing incident pain associated with bone metastases. J Pain Symptom Manag 28:505–510
25. Hanks GW et al (2001) Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 84:587–593
26. Zeppetella G (2013) Evidence-based treatment of cancer-related breakthrough pain with opioids. J Natl Compr Cancer Netw 11: S37–S43
27. Mercadante S (2012) Pharmacotherapy for breakthrough cancer pain. Drugs 72:181–190
28. Jandhyala R et al (2013) Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. J Pain Symptom Manag 46:573–580
29. Zeppetella G, Davies AN (2013) Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev 10:CD004311. doi:10.1002/14651858.CD004311.pub3
30. Bedard G et al (2013) A survey of Canadian cancer patients' perspectives on the characteristics and treatment of breakthrough pain. Support Care Cancer 21:2557–2563
31. Davies AN et al (2009) The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain 13:331–338
32. Mercadante S (2009) Breakthrough pain: on the road again. Eur J Pain 13:329–430
33. Mercadante S (2011) The use of rapid onset opioids for breakthrough cancer pain: the challenge of its dosing. Crit Rev Oncol Hematol 80:460–465
34. Mercadante S (2011) Rapid onset opioids for breakthrough pain: titrating or not titrating, this is the question. Eur J Pain (Suppl. 2): 443-448
35. Zeppetella GB (2008) Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. J Pain Symptom Manag 35:563–567
36. Webber K et al (2011) Breakthrough pain: a qualitative study involving patients with advanced cancer. Support Care Cancer 19: 2041–2046
37. Mercadante S et al (2013) The use of sublingual fentanyl for breakthrough pain by using doses proportional to opioid basal regimen. Curr Med Res Opin 29:1527–1532
38. Mercadante S et al (2013) The use of fentanyl buccal tablets for breakthrough pain by using doses proportional to opioid basal regimen in a home care setting. Support Care Cancer 21:2335–2339
39. Mercadante S et al (2007) Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. Br J Cancer 96:1828–1833
40. Mercadante S (2006) Fentanyl buccal tablet in breakthrough pain in opioid-tolerant patients with cancer. Drugs 66:2394–2395
41. Mercadante S et al (2012) Dosing fentanyl buccal tablet for breakthrough cancer pain: dose titration versus proportional doses. Curr Med Res Opin 28:963–968
42. England R et al (2011) How practical are transmucosal fentanyl products for breakthrough cancer pain? A survey of user opinion. BMJ Support Palliat Care 1:349–351
43. Mercadante S et al (2014) Intranasal fentanyl versus fentanyl pectin nasal spray for the management of breakthrough cancer pain in doses proportional to basal opioid regimen. J Pain 15:602–607
44. Mercadante S et al (2014) Patients' acceptability of different fentanyl products for breakthrough cancer pain. Clin Oncol 26:806