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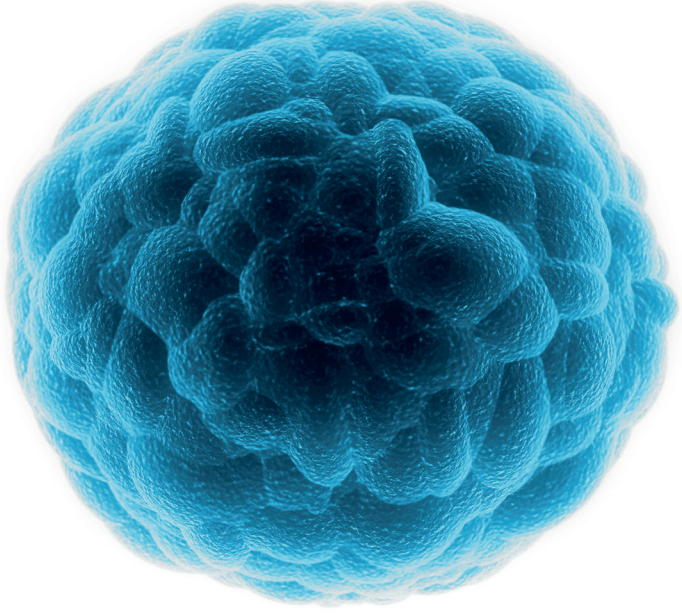

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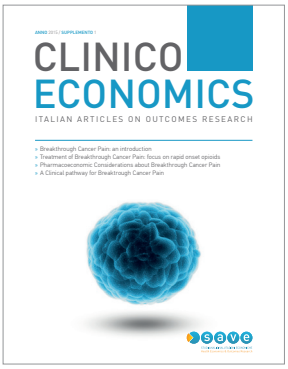

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Indice

CLINICO ECONOMICS

Breakthrough Cancer Pain: an introduction

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ABSTRACT

Il dolore rappresenta il sintomo più frequente associato al cancro ed è uno dei più temuti. Il dolore da cancro è caratterizzato principalmente da due componenti: il dolore di fondo o persistente, descritto come dolore che dura per 12 o più ore al giorno, e gli episodi di dolore significativo e grave, chiamato "breakthrough cancer pain" (BTcP). La definizione più accettata di BTcP è "esacerbazione transitoria del dolore che avviene sia spontaneamente sia in seguito a prevedibili o imprevedibili fattori scatenanti, a fronte di un dolore di base adeguatamente controllato da un trattamento ATC (around the clock)". I tassi di prevalenza riportati variano ampiamente, dal 33% fino al 95% dei pazienti a seconda della definizione di BTCP, i metodi utilizzati per valutare BTcP, e le popolazioni studiate. BTcP possiede diverse caratteristiche: a inizio veloce: inferiore o uguale a 3 minuti. Iops 2015 mostra che una percentuale di pazienti ha riportato un tempo di inizio pari a 10 minuti grave in intensità: Numerical Rating Scale (NRS) ≥ 6. In generale autolimitante con una durata media di 30 minuti. BTcP è di solito diviso in due sottotipi: dolore ideopatico e dolore spontaneo. La diagnostica e la gestione del dolore da cancro dovrebbero sempre iniziare con un' accurata raccolta delle informazioni riguardanti la storia del paziente e una visita medica. Recentemente è stato rivisto da Taylor un algoritmo diagnostico step by step usando dati da precedenti studi.

BTcP ha gravi conseguenze su tutti i pazienti, provoca un' importante sofferenza, sveglia i pazienti durante la notte, influenza negativamente la loro capacità di eseguire attività di routine e la loro disponibilità a partecipare alle attività. E' stato inoltre dimostrato che BTcP aumenta significativamente il tasso di ricovero in ospedale. Il Breakthrough cancer pain deve essere valutato e trattato in particolare con farmaci che abbiano una rapida insorgenza e breve durata d'azione, in modo che il loro effetto analgesico corrisponda con le dinamiche di un tipico episodio di BTcP.

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INTRODUCTION

Pain represents the most frequent symptom associated with cancer and one of the most dreaded (Cleeland, 1984). The prevalence of pain increases with disease progression, with rates of 30-40% during early disease, rising to 70-90% in advanced disease (Schrijvers D 2007; Mercadante et al, 2015). Pain is second only to incurability among the factors people fear most about the diagnosis of cancer (Ashles et al, 1983).

Increasing evidence shows that survival in oncologic patients is linked to symptom control (Temel et al 2010), including pain management as one of the most decisive determinants of the quality of life (NCCN, 2014).

Cancer pain is mainly characterized by two components: background or persistent pain, described as pain lasting for 12 or more hours per day (WHO, 1996) and episodes of significant and severe pain that 'breaks through' the around-the-clock analgesia, termed "breakthrough cancer pain" (BTcP).

DEFINITION OF CANCER BREAKTHROUGH PAIN

The definition "breakthrough pain" was popularized by Portenoy and Hagen, who were the first to describe it as an entity distinct from background chronic pain (Portenoy et al, 1990).

The most accepted definition of BTcP is *"a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relative stable and adequately controlled background pain"* (Davies et al, 2009).

Some authors in the past included in BTcP also the pain that consistently occurs just before the scheduled dose of around-the-clock (ATC) analgesia, so called 'end of dose pain', which results from an inadequate ATC analgesic dose or the fact that the interval between administrations is too long (Payne, 2007). End-of-dose cancer pain should not be considered breakthrough pain though, as it does not fit the above definition, because background pain is not controlled with the optimum dose of ATC medication (Zeppetella et al, 2013). This type of pain is best managed by addressing the frequency or dose of the ATC basal analgesic rather than by adding a BTcP medication.

Background pain flares and intermittent pain (without background pain) cannot be considered BTcP either, since pain episodes occurring without basal pain or with poorly controlled basal pain cannot be taken to represent breakthrough cancer pain (Taylor et al, 2013).

These differences in the use of the breakthrough pain nomenclature may lead clinicians to errors in classification and could have complicated the systematization of clinical results (Margarit et al, 2012).

The presence of breakthrough pain is associated with relatively worse psychological and functional outcomes (Portenoy et al, 1999), and a less positive response to opioid therapy (Mercadante et al, 1992).

PREVALENCE

Breakthrough pain is common in patients with cancer. The reported prevalence rates vary widely, from 33% up to 95% of patients (Margarit et al, 2012) depending on the definition of BTCP, the methods used to assess BTCP, and the populations studied. Large differences in the diagnosis of breakthrough pain by clinicians of different countries have been found, suggesting that this entity is diagnosed differently in various countries (Mercadante et al, 2002).

Furthermore, studies have shown that the characteristics of BTCP vary between subjects and also within subjects in quality and intensity of the pain (Davies et al, 2011).

PATHOPHYSIOLOGY AND CLINICAL CHARACTERISTICS

It has been estimated that breakthrough cancer pain is a direct consequence of the mass effect of the neoplasm in 70-80 % of all cases, the result of anti-cancer

treatment in 10-20 % of patients and in less than 10 % the pain is not related to either the malignant disease or its treatment (Margarit et al, 2012).

The background ATC medication dose does not predict the severity of BTcP episodes (Portenoy et al, 1999; Taylor, 2013): a patient with a high level of basal pain and associated high-basal analgesic dose could have BTcP episodes of mild intensity. On the other hand a patient with a low-level background pain, and a corresponding low dose of ATC analgesic dose, could experience high-intensity breakthrough pain episodes requiring high doses of BTcP medications.

BTcP has several characteristics:

» Rapid onset: inferior or equal to 3 minutes (Portenoy et al, 1990). Lops study 2015 shows that a proportion of patients reported an onset time of 10 minutes.

» Severe in intensity: Numerical Rating Scale (NRS) ≥ 6 (Hwang et al 2003).

» Generally self-limiting with a mean duration of 30 minutes (Zeppetella et al, 2011).

The number of daily episodes is variable, and although there is no exact number of episodes there are usually 3 to 6; but in most situations a number of episodes greater than 4 is considered indicative of uncontrolled baseline pain, forcing the revision of the around-the-clock medication (Margarit et al, 2012; Taylor et al, 2013).

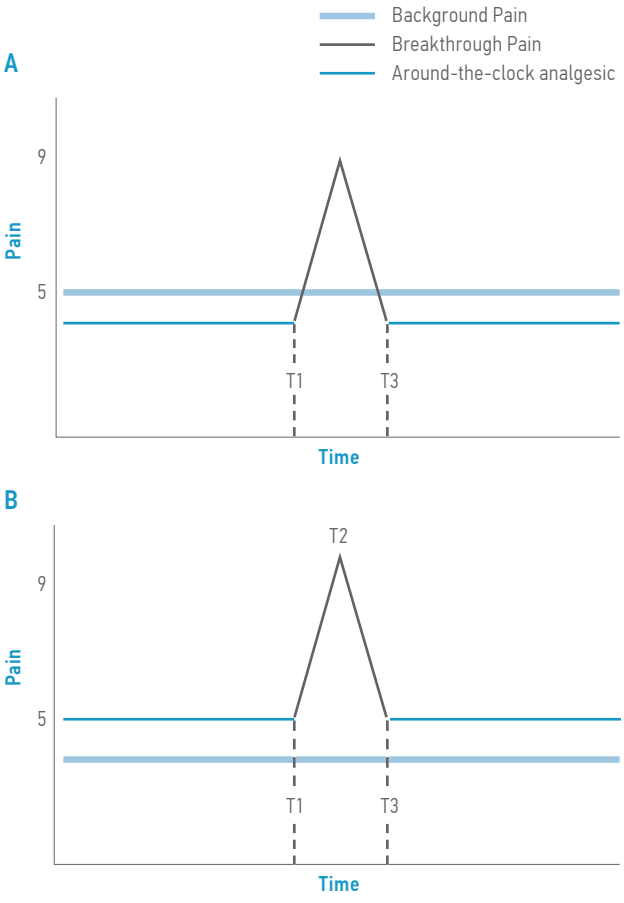
BTcP is usually divided into two subtypes:

» Incident pain, precipitated by factors such as movement, walking, coughing, sitting and standing. In some cases, the causes are predictable and can be anticipated, although, occasionally, pain can be precipitated by factors such as flatulence and bladder spasm that are unpredictable.

» Spontaneous pain, that occurs in the absence of a relationship to specific activities and lacks a definite trigger (Zeppetella et al, 2013).

Breakthrough cancer pain is not a single entity, but a spectrum of various entities. In fact BTcP may be related to several causes (mass-related, treatment-related,

FIGURE 1
Depiction of a cancer breakthrough pain episode (from Taylor et al, 2013). A Cancer breakthrough pain with stable background pain, controlled by opioid therapy. The patient's pain is under stable, adequate control (background pain is ≤4 out of 10 on the NRS) since the background pain line is below the around-the-clock analgesic line. At T1, the patient experiences a sudden, rapid increase in pain that "breaks through" the around-the-clock analgesic; this breakthrough cancer pain episode peaks at 9 out of 10 on the NRS at T2; T3 represents how long the breakthrough pain lasts. Note that an analgesic line above the basal pain line does not mean that the basal pain has been reduced to zero but rather that the background pain is adequately controlled (≤4 out of 10 on NRS). B, Cancer background pain flare, without adequate control. The patient's pain is not under adequate control since the around-the-clock analgesic line is below the patient's background pain line. At T1, the patient experiences a sudden, rapid increase of pain, which peaks at 9 out of 10 on the NRS (T2) and last until T3. This is known as a background pain flare. NRS = Numerical Rating Scale.



concomitant illness), and also the pathophysiology can be different, as BTcP may have a nociceptive or neuropathic origin (Davies et al, 2009).

» Nociceptive pain can further be divided into somatic pain and visceral pain. Pain described as sharp, well localized, throbbing, and pressure-like is likely to be somatic nociceptive pain. It is often determined from bone metastasis. Visceral nociceptive pain is often described as more diffuse, aching, and cramping.

» Neuropathic pain results fromdisfunction or injury of the peripheral or central nervous system. It might be described as burning, sharp, or shooting. (NCCN, 2014)

DIAGNOSIS

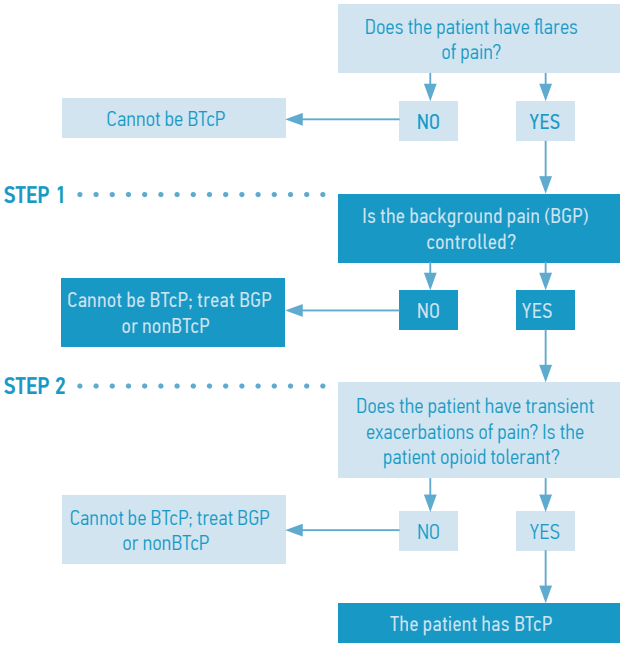
The diagnostic process and the assessment of cancer pain should always begin with careful history taking and a thorough physical examination. During every contact with the patient the physician should pursue the education of the patient and caregivers in order to establish a common language to discuss the patient's pain and avoid misunderstandings (Taylor, 2013).

A step-by-step diagnostic algorithm was recently reviewed by Taylor (Taylor, 2013) using data from previous studies (Mercadante, 2011; Davies et al, 2009) and is presented in the picture below.

Step 1: after it has been ascertained that the cancer patient has flares of pain, the physician must verify the background pain is well controlled by the ATC medication, in which case the patient will report a pain score of 0-4 on the Numerical Rating Scale (NRS) (Davies et al, 2009). As mentioned above, if flares of pain are more frequent than 4 times a day, the ATC therapeutic regimen should be reviewed.

Step 2: once the ATC medication has been optimally adjusted, then it must be assessed if the patient is "opioid tolerant" as defined by the US Food and Drug Administration (FDA) as a state when the patient has been on an ATC opioid regimen equivalent to at least 60 mg of oral

FIGURE 2
Diagnostic algorithm for Breakthrough Cancer Pain. Modified from Taylor, 2013. Data from Mercadante, 2011 and Davies et al, 2009. Description in the text.BTcP breakthrough cancer pain; BGP background pain.



morphine daily, at least 25 µg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone daily or an equianalgesic dose of another opioid daily for 1 week or longer. This is the requirement patients generally must meet in order to be prescribed rapid-onset-opioids (ROO) for their BTcP (Davies et al, 2009).

Notwithstanding the simplicity of the diagnosis, a survey conducted by the American Pain Foundation found that 52% of all patients who complain to their physician of pain are told that breakthrough pain is a normal side effect of cancer or its treatment (American Pain Foundation, 2010).

ASSESSMENT

A recent review of the global literature on breakthrough cancer showed how there are many assessment tools for BTcP but none has been independently clinically validated nor is widely used in clinical practice (Haugen et al, 2010). These deficiencies present a major challenge

to the conduct of high quality research as well as to clinical practice.

Ideally BTcP assessment (Taylor, 2013; Haugen et al, 2010) should include:

- the number of BTcP episodes;
- the relationship between BTcP and the background pain (the same or different);
- the intensity of the BTcP episodes;
- the temporal factors of BTcP; including its frequency, onset, duration, and relationship to fixed analgesic dose;
- where BTcP episodes are occurring in the body;
- the quality of the BTcP (eg, burning, aching, lancinating, throbbing);
- any potential treatment-related factors, including exacerbating and relieving factors, such as precipitating events and predictability, response to treatment (time-to-meaningful relief), and treatment satisfaction;
- whether the BTcP interferes with activities of daily living and quality of life.

CONSEQUENCES

Breakthrough cancer pain causes heavy consequences on all patients who experience it. A recent survey from the American Pain Foundation showed that BTcP causes significant suffering (in 82% of all patients), wakens patients at night (73%), and influences negatively their capacity to perform routine tasks (76%) and their disposition to participate in activities (83%). (American Pain Foundation, 2011).

It was also showed that BTcP significantly increases the hospital admission rate in cancer patients who suffer from it compared with patients without such pain (36,9% versus 22,5% respectively) (Fortner et al, 2002; American Pain Foundation, 2011). An association has also been determined between the presence of breakthrough cancer pain and a decline in patient survival (Scharpf et al, 2009).

CONCLUSIONS

Breakthrough cancer pain is a complex and heterogeneous condition defined as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relative stable and adequately controlled background pain. It is very common in patients with cancer pain, and has an undeniable impact upon both patient and caregivers' quality of life. Breakthrough cancer pain must be assessed and treated specifically with medications that can grant a rapid onset and a short duration of action, in order to match their analgesic effect with the dynamics of a typical BTP episode.

REFERENCES

- Ahles TA, Blanchard EB, Ruckdeschel JC. The multidimensional nature of cancer-related pain. Pain. 1983 Nov;17(3):277-88
- American Pain Foundation. Breakthrough cancer pain: mending the break in the continuum of care. J Pain Palliat Care Pharmacother. 2011;25(3):252-64
- Cleeland CS. The impact of pain on the patient with cancer. Cancer 1984 Dec 1;54(11 Suppl):2635-41
- Davies A, Zeppetella G, Andersen S, Damkier A, Vejlgaard T, Nauck F, Radbruch L, Sjolund KF, Stenberg M, Buchanan A. Multi-centre European study of breakthrough cancer pain: pain characteristics and patient perceptions of current and potential management strategies. Eur J Pain. 2011 Aug;15(7):756-63
- Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Med-

icine of Great Britain and Ireland. Eur J Pain. 2009 Apr;13(4):331-8

» Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain. 2002 Feb;3(1):38-44

» Haugen DF, Hjermstad MJ, Hagen N, Caraceni A, Kaasa S; European Palliative Care Research Collaborative (EPCRC). Assessment and classification of cancer breakthrough pain: a systematic literature review. Pain. 2010 Jun;149(3):476-82

» Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. Pain. 2003 Jan;101(1-2):55-64

» Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, Cruz JJ, Galvez R, Mañas A, Zaragozá F. Breakthrough cancer pain - still a challenge. J Pain Res. 2012;5:559-66

» Mercadante S, Lazzari M, Reale C, Cuomo A, Fusco F, Marchetti P, Mediati RD, Chiurazzi B, Ciuffedra L, Caraceni A, Iaffaioli V, Luzzani M, Micheletto G, Papa A, Raffaeli W, Valle A, Caruso M, Di Costanzo F, Pinato G, Nardi F, Barni S, Natoli S, Mammucari M, Sabato AF, Dauri M; IOPS Study Group. Italian Oncological Pain Survey (IOPS): A Multicentre Italian Study of Breakthrough Pain Performed in Different Settings. Clin J Pain. 2015 Mar;31(3):214-21

» Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, Ripamonti C, De Conno F; Steering Committee of the European Association for Palliative Care (EAPC) Research Network. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer. 2002 Feb 1;94(3):832-9

» Mercadante S. Managing breakthrough pain. Curr Pain Headache Rep. 2011 Aug;15(4):244-9

» Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007 Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007 Jan-Feb;-8Suppl 1:S3-7

» Portenoy RK, Hagen NA. Breakthrough pain: Definition, prevalence and characteristics. Pain 1990 Jun;41(3):273-81

» Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990 Feb;79(2-3):303-12

» Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, Frigerio V, Ingham J, Loseth DB, Nordbrock E, Rhiner M. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain. 1999 Feb;79(2-3):303-12

» Scharpf J, Karnell LH, Christensen AJ, Funk GF. The role of pain in head and neck cancer recurrence and survivorship. Arch Otolaryngol Head Neck Surg. 2009 Aug;135(8):789-94

» Schrijvers D. Pain control in cancer: recent findings and trends. Ann Oncol 2007 Jul;18Suppl 9:ix37-42

» Taylor DR: Managing Cancer Breakthrough Pain. 1st ed. London: Springer Healthcare; 2013

» Temel JS, Greer JA, Muzikansky A, et al Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010 Aug 19;363(8):733-42

» World Health Organization. Cancer pain relief second edition with a guide to opioid availability. whqlibdoc.who.int/publications/9241544821.pdf. Published 1996. Accessed February 20, 2015

» Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev. 2013 Oct 21;10:CD004311

» American Pain Foundation, news release, Jan. 28, 2010

» NCCN Guidelines v. 2.2014 Adult Cancer Pain http://www.nccn.org/professionals/physician_gls/f_guidelines.asp Accessed February 20, 2015

Treatment of Breakthrough Cancer Pain: focus on rapid onset opioids.

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ABSTRACT

Il dolore oncologico (BTcP) è una esacerbazione transitoria di dolore che si verifica sia spontaneamente, o in relazione ad un trigger prevedibile o imprevedibile specifico, nonostante il dolore di fondo sia relativamente stabile e adeguatamente controllato. Il trattamento dei BTcP richiede la comprensione delle sue caratteristiche e una diagnosi quanto più precisa possibile delle tendenze temporali e le modalità della sua comparsa. Per promuovere questo processo è fondamentale la responsabilizzazione dei pazienti e dei caregiver. Il processo di empowerment è appositamente pensato con lo scopo di aumentare la capacità degli individui di valutare e trattare il dolore permanente e BTcP nella vita di tutti i giorni. Le recenti linee guida sul dolore episodico intenso in pazienti con cancro suggeriscono che i farmaci ideali sarebbero da pensare su misura per ogni singolo episodio di BTcP, con la farmacodinamica dovrebbero ricalcare le caratteristiche del dolore da trattare: con esordio rapido e breve durata. Nonostante oggi gli oppioidi a rapida insorgenza (Roos) restano l'unico trattamento accreditato per BTcP, in questo studio viene presentato un breve riassunto degli agenti terapeutici comunemente utilizzati per il suo trattamento: non oppiacei, oppioidi deboli, forti oppiacei a rilascio immediato, oppioidi parenterali, oppioidi rapida insorgenza (ROOS). Per quanto riguarda i ROOs è stato in questa sede approfondito il Fentanyl nelle sue diverse formulazioni, sono stati analizzati vantaggi e svantaggi delle varie forme presenti in commercio. BTcP è una condizione comune, spesso sottostimata a causa di fattori correlati ai pazienti e medici. E' stato tradizionalmente gestito con i farmaci orali a normale rilascio e con breve durata d'azione, utilizzando sempre lo stesso oppioide per il trattamento del dolore di base e BTcP. Tuttavia, i profili farmacocinetici e la farmacodinamica degli oppioidi orali non rispecchiano fedelmente le caratteristiche del BTcP, potenzialmente con conseguente trattamento inadeguato e effetti collaterali problematici. Negli ultimi due decenni sono stati sviluppati nuovi

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oppiacei a rapida insorgenza a base di Fentanyl, con accumulo prove della loro elevata efficacia, sicurezza e tollerabilità. Anche se molti studi in BTcP hanno dimostrato la loro superiorità rispetto agli oppioidi orali, gli oppioidi a esordio rapido sono ancora notevolmente sottoutilizzati. Dal momento che il dolore da cancro comprende anche dimensioni fisiche e psicosociali, così il complemento di approcci non farmacologici (cognitivi, fisici e riabilitativi) si è dimostrato estremamente utile ai fini di una migliore terapia medica.

Un numero sempre maggiore di evidenze negli ultimi anni suggerisce che l'integrazione di un approccio multimodale al dolore da cancro può avere un impatto significativo nel fornire sollievo dal dolore.

INTRODUCTION

Breakthrough cancer pain (BTcP) is 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 (Davies et al, 2009). BTcP is an heterogeneous condition, with wide inter and intra-individual variations (Vellucci, 2015). Thus the prevalence of BTcP ranges from 33% up to 95% of cancer patients, with increasing prevalence in more advanced stages of disease (Margarit et al, 2012).

BTcP is generally characterized by a typical temporal pattern which includes a rapid outbreak (a few minutes) from a state of well-controlled background pain, and a short duration, in most cases not exceeding 30-90 minutes. BTcP is associated with a significant negative impact on quality of life, including activities of daily living, sleep and social relationships the prevalence of depression and anxiety (Portenoy et al, 1999; American Pain Foundation, 2011) and the rate of recurrent hospital admission (Fortner et al, 2002).

From an economic perspective BTcP weighs significantly on the patient and the caregiver. A deficient management of BTcP raises the costs of care for the institutions and increases the risk of undue demands on healthcare resources (Abernethy et al, 2008). BtcP also represents a social cost in terms of productivity. If that was not enough, the BTcP determines an increased risk of dissatisfaction with opioids treatment and exposes the physician to the problems of a therapeutic failure. In Italy a recent study showed that one-third of patients suffering from breakthrough cancer pain did not receive any kind of rescue therapy, even with 3 or more episodes per day. Another third received a World Health Organization level-one drugs, and morphine was more frequently administered than oral transmucosal fentanyl (Greco et al, 2011). A similar trend has been confirmed in a recent European survey, with only 19.1% of patients receiving a transmucosal fentanyl formulation licensed for the management of BTcP. Growing evidence is thus showing how BTcP in European and North American cancer patients is currently not optimally managed (Bedard et al, 2015).

EMPOWERMENT OF PATIENTS WITH BTcP

The treatment of BTcP requires understanding of its features and a diagnosis as accurate as possible of the time trends and the manner of its occurrence. The diagnostic process can be a real challenge, nevertheless Portenoy and other authors have suggested diagnostic criteria for breakthrough pain. When patients have a normal mental status, the diagnosis of BTP usually make one's way through the patient pain self-report. Multiple sources can provoke BTcP and physicians must ask specific questions while investigating recent episodes of pain, to obtain details regarding the possible etiology, severity, source and pattern (Abrahm, 2005). To promote this process is crucial the empowerment of patients and caregiver.

The process of empowerment is specifically meant to increase the ability of the individuals to assess and treat baseline pain and BTcP in every-day life (Vellucci, 2015).

The process of empowerment, trough deep information, recognizes multiple purposes:

1. Understand the importance of BTcP and how to share clinical information about it
2. Learn about the different types of pain, with a special focus on BTcP
3. Understand the terms used to describe different types of pain
4. Know and to have a multidimensional pain day-book for the detection of pain
5. Understand the basics of pain therapy and BTcP

Certainly this behavioral model needs to be personalized to individual demandings.

BREAKTHROUGH CANCER PAIN PHARMACOLOGIC THERAPY

Comprehension of what "breakthrough cancer pain" truly represents is an obvious requirement for an appropriate treatment: for example end-of-dose cancer pain, which is not to be considered breakthrough pain (Davies et al, 2009) is best managed by addressing the frequency or dose of the ATC basal analgesic rather than by adding a rescue medication (Taylor, 2013). In 2002 BTcP was the focus of a semantic debate, motivating a major consensus meeting of the expert working group of the European Association for Palliative Care (Mercadante et al, 2002). The finding of the meeting was the introduction of the term "episodic" or "transient", both more straightforward than "breakthrough", which has not a literary translation in several languages. However, today the term " breakthrough pain" has gradually been adopted and remains the only one to be used in the medical literature. In many cases though, BTcP is referred to as "episodic pain" or in Italian as "dolore episodico intenso", that can increase the gap with the less experienced clinicians and introduce a further semantic complication in an already complex contest.

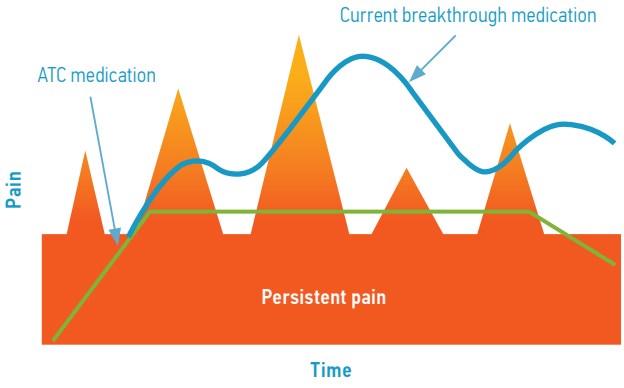
The diagnosis of breakthrough cancer pain and its subsequent treatment require that the background or chronic pain is well controlled by the around-the-clock (ATC) analgesia. Adequately controlled pain will correspond for most patients to a pain score on the 0-10 Numerical Rating Scale (NRS) of 0 to 4 (Taylor, 2013).

The European Association for Palliative Care (EAPC) strongly recommended that ATC opioid therapy must be properly titrated before potent rescue opioid analgesics are to be considered (Caraceni et al, 2012).

One study of metastatic cancer patients with BTcP demonstrated that increasing the basal analgesic beyond the dose required to manage the chronic pain could reduce the intensity of incident pain to acceptable level. Nonetheless it was observed that the escalation of the ATC medication to control both the background and the breakthrough pain could result in an unacceptable rate of side effects (Mercadante et al, 2004) and can cause considerable frustration in the patient and the caregiver.

The recent guidelines on breakthrough pain in patients with cancer recommend that the ideal rescue medications would be tailored to single episode of BTcP, with pharmacodynamics mirroring those of the pain being treated: with quick onset and short duration (Caraceni et al, 2013).

FIGURE 1
Difficulties with around-the-clock medication and breakthrough cancer pain. The ATC (green line) medication controls the persistent/background pain (red rectangle). The flares of BTcP (red peaks) break through the ATC medication. The oral opioids (white line) effectpeaks after the flare of cBTP subsides. This mismatch between the temporal profile of the BTcP flare and the BTcP medication can lead to excessive sedation when the peak effect of the opioid is not opposed by pain. Adapted from Taylor, 2013 and Bennett et al, 2005



Despite today rapid-onset opioids (ROOs) remain the only treatment credited for BTcP, below is presented a brief summary of the therapeutic agents commonly used for its treatment.

NON-OPIOIDS

The rationale for adding a non-opioid to an opioid is to add a drug with a different mechanism of action with the aim of improving pain control and/or reducing opioid requirements and minimizing opioid side effects (Vardy et al, 2014).

Despite the widespread use of non-steroidal anti-inflammatory agents or acetaminophen in cancer pain management, there is a paucity of data concerning specifically the management of BTcP (Mercadante et al, 2012) and limited evidence for adding either agent to an opioid. Studies have not been conducted to determine which type of breakthrough cancer pain can be alleviated by NSAIDs or acetaminophen in concomitant therapy, although anecdotally it is suggested that they are more effective for pain associated with inflammation (Vardy et al, 2014). The use of these drugs in the therapy of BTcP introduces many unknown factors. First of all the Onset Time effect, most times longer than that of BTcP, making NSAIDs more suitable for ATC use. Moreover considering the high incidence of adverse effects with continuous utilization of NSAIDs they should not be considered first line therapy in BTcP (Bhala et al, 2013)

WEAK OPIOIDS

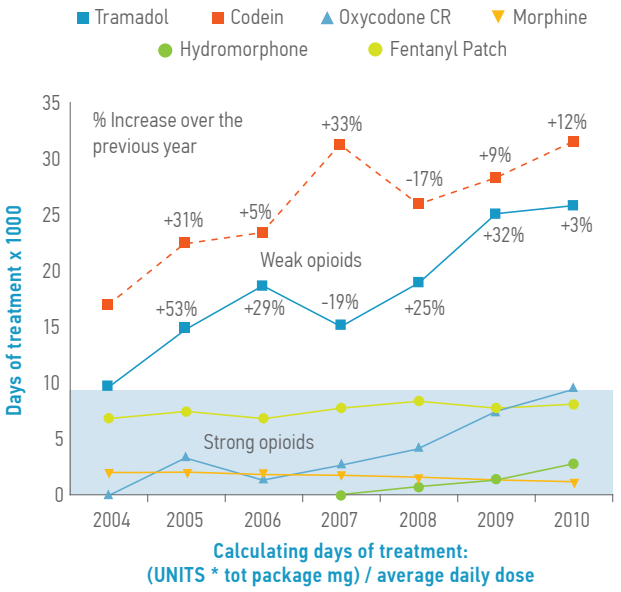
For the management of moderate cancer pain, the clinical relevance of the recommendations of WHO analgesic ladder step 2 to use so-called weak opioids is increasingly being debated (Schug et al, 2015; Maltoni et al, 2005). Data from the medical service requirements of IMS Health indicated that the use of weak opioids in Italy from 2004 to 2010 shows a trend of significant growth (Vellucci et al, 2012).

Moreover, in patients experiencing BTcP the pharmacokinetic and pharmacodynamic profiles of oral weak opioids may not be well suited to match the attributes of the pain episodes, as highlighted in the following section on immediate release strong opioids (Taylor, 2013; Caraceni et al, 2013).

IMMEDIATE RELEASE STRONG OPIOIDS

Until a few years ago, immediate-release oral opioids like morphine, oxycodone and hydromorphone were the only drugs available for the treatment of BTcP (Hanks et al, 2001). Recent EAPC guidelines recognize

FIGURE 2
Use of strong and weak opioids from 2004 to 2010 in Italy. Data from the Medical Service Requirements of IMS Health, http://www.imshealth.com/portal/site/ims Adapted from Vellucci R 2012



no important differences in the efficacy of morphine, oxycodone and hydromorphone given by the oral route, recommending them as first line therapy in moderate or severe chronic cancer pain (Caraceni et al, 2012).

Pharmacokinetic studies have suggested a poor correlation of the analgesic effect of oral opioids with the dynamics of a typical BTcP episode. Orally administered morphine, oxycodone and hydromorphone undergo extensive first pass effect, are hydrophilic in nature and achieve maximum plasma concentration at 30-90 minutes (Zeppetella, 2009; Bennett et al, 2005).

A study on 50 oncologic patients pointed out that the average duration of breakthrough pain episodes was 35 minutes and the average time to meaningful pain relief following oral opioids was 30-40 minutes, highlighting the suboptimal pharmacokinetics and pharmacodynamics of this class of medications (Zeppetella, 2008).

Accumulating evidence suggest that oral immediate release (IR) opioids may be inferior to the new rapid-onset opioids (ROOs) formulations for relief of BTcP: a double blind study of 93 patients experiencing BTcP demon-

strated that pain intensity scores at 15, 30, 45 and 60 minutes were significantly higher with oral morphine than with oral transmucosal fentanyl citrate (OTFC) (Coluzzi et al, 2001). A recent trial comparing oral oxycodone with fentanyl buccal tablet (FBT) showed that pain intensity differences at 15, 30 and 60 minutes were more favourable with FBT than with oral oxycodone (Ashburn et al, 2011).

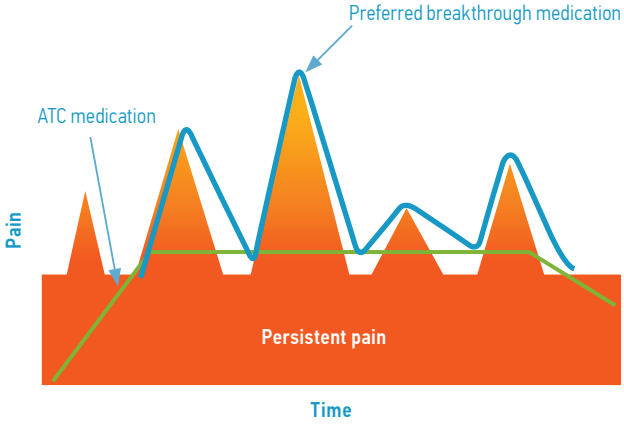
Traditionally oral morphine was the drug most used for the BTcP, but this immediate-release formulation is characterized by the onset of the analgesic effect in about 20-30 minutes and a peaking just after 60-90minutes (Bailey et al, 2006), with a prolonged duration of about 3-6 hours (Bailey et al, 2006). These features do not appear to be adequate for most episodes of BTcP, making oral morphine not superior to placebo for the first 45 minutes after administration (Zeppetella, 2013). The oral IR opioids are not the optimal rescue medication for vast majority part of BTcP episodes and may play a role in the management of that episodes lasting for more than 60 min in pre-emptive treatment of volitional incident pain or procedural pain (Davies et al, 2009). However, the use of IR formulations in these subgroup of episodes of BTcP requires a significant forethought: take a dose of medication at least thirty minutes before of the triggering event for the BTcP. (Davies et al, 2008)

PARENTERAL OPIOIDS

Intravenous morphine is an effective method to provide fast pain relief in cancer patient due to the complete bioavailability of the drug and the rapid onset of action. The obvious inconvenience is the need of a port system or an intravenous line, which may not be present in outpatients, and trained personnel. The use of intravenous morphine in BTcP episodes was evaluated in patients receiving oral morphine (Mercadante, 2004) and was found to be effective, to be well tolerated, and to be safe. Other authors have reported on the use of intravenous morphine to treat breakthrough pain episodes in patients receiving continuous infusions of morphine (i.e. intravenous patient-controlled analgesia) (Wagner et al, 1989; Swanson et al, 1989).

In a comparative study of 25 patients, intravenous morphine was more effective than oral trasmucosal fentanyl citrate 15 minutes after administration, while no differences were found at 30 minutes. (Mercadante et al, 2007). Although this route can be used in community settings, and the technique can be taught to patients and their caregivers, in everyday practice, this route is generally restricted to inpatient settings. Intravenous administration has low acceptability rate when the pain is mild to moderate in intensity (38% acceptability), but is more accepted when the pain is severe in intensity (83% acceptability) (Walker et al, 2003).

FIGURE 3
A model of ideal breakthrough cancer pain medication. This figure illustrates how the ideal BTcP medication would perfectly match the time course of the BTcP episode. This pharmacokinetic and pharmacodynamic?pattern of action is most closely mimicked by rapid onset opioids. Adapted from Taylor, 2013 and Bennett et al, 2005

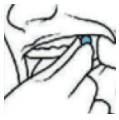
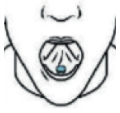


RAPID ONSET OPIOIDS (ROOS)

FENTANYL

Transmucosal administration of lipophilic opioids has gained a growing popularity in recent years due to the rapid effect, clinically observable 5–15 minutes after drug administration, and the non-invasive form.

FIGURE 4
Properties and characteristics of the rapid onset opioids currently available. Adapted from Stanley, 2014

Formulation	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Nasal Solution	FENTANYL CITRATE Oral Solution
Route of Administration						
	Buccal Lozenge	Buccal Tablet	Buccal Film	Sublingual Tablet	Intranasal Spray	Sublingual Spray
Bioavailability	50%	65%	71%	54%	Est 60%	76%

Currently, all the rapid-onset opioids approved for treating cancer breakthrough pain (BcTP) in the United States and the European Union are fentanyl-based (Taylor, 2013).

Fentanyl is a synthetic mu-receptor agonist opioid. Its onset of action and its peak plasma concentration are dependent on the dosage used and the method of delivery: after intravenous injection analgesia may occur after 1 to 5 minutes. Buccal transmucosal delivery systems produce analgesia in 10-15 minutes and sublingual and intranasal sprays in 5-10 minutes (Stanley, 2014). Fentanyl achieves equilibrium across the blood–brain barrier in approximately 6 minutes, and the rapid onset of the ROOs is primarily due to their lipid solubility and rapid absorption across mucosal membranes and subsequent rapid crossing of the blood–brain barrier (Scott et al, 1985).

Fentanyl's estimated duration of action is 2-4 hours, although the unpredictability of BTcP episodes makes determining the duration of effect of an analgesic challenging in this setting (Taylor, 2013). Like other opioids fentanyl is extensively metabolized in the liver by the cytochrome P450 isoenzyme system (CYP3A4), and as a result, potential drug interactions may occur when fentanyl is given concurrently with other drugs that affect CPY3A4 activity (Kurella et al, 2003).

Fentanyl, like the other mu-receptor stimulating opioids, may cause adverse effects such as fatigue, sedation, nausea, vomiting, dizziness, respiratory depression (leading to apnea in higher doses), bradycardia (secondary to a central vagal stimulating action), and unconsciousness/anesthesia in higher doses irrespective of the mode of administration (Stanley, 2014). It is reported that fentanyl causes less constipation and pruritus compared to morphine (Mayes et al, 2006).

Notwithstanding the widely accepted properties of ROOs in breakthrough cancer pain treatment, a recent survey of 1000 European and 94 Canadian patients experiencing BTcP reported fentanyl-based ROO administration in less than 20% of the responders. The authors also claimed for the need for deeper patient education about BTcP, as only half of the patients reported taking their BTcP medications when they needed them (Bedard et al, 2015).Nowadays Fentanyl is the only rapid-onset analgesic suitable and approved for BTCP treatment.

Fentanyl formulations are only indicated for the management of BTP in patients with cancer, taking at least 60 mg/day oral morphine or an equianalgesic dose of another oral opioid. Notwithstanding these indication, the off-label use of fentanyl preparations is common. A study observed that in the period of april through June 2005 of 95 patients who received a prescription for OTFC, 84, about 90 %, was off-label (Prime Therapeutics, 2007).

Post-marketing surveillance has provided information on the real-life use of fentanyl ROOs outside the clinical trial setting. In 2014 a post-marketing surveillance study of fentanyl buccal tablets was conducted in primary care setting in England, using the non-interventional observational cohort technique of Modified

Prescription-Event Monitoring (M-PEM) (Osborne et al, 2011). Five hundred and fifty one patients received a fentanyl buccal tablets prescription from General Practitioners in England, of which 168 or about 30,5%, were reputed off-label prescriptions. Off-label FBT was prescribed for the treatment of pain and chronic non cancer pain, in one minor patient and 5.6% of patients had no prescribed treatment with opioids ATC. Furthermore 13 patients were using CYP3A4 inhibitors during treatment with FBT, and one patient reported to be concomitantly using an IMAO inhibitor (which can precipitate severe and unpredictable potentiation of opioid analgesics). Also in different patients, FBT prescriptions were reported at doses that exceeded the maximum daily dose licensed. Fortunately there were no events or suspected ADRs reported, however the authors state that it was impossible to draw any definitive conclusion on safety and efficacy of FBT from this limited piece of information.

Formerly two randomized trials have examined the use of FBT in chronic non-cancer pain, and found that it was more efficacious than both placebo and oxycodone and generally well tolerated (Farrar et al, 2010; Ashburn et al, 2011). FBT was examined in other two randomized, double-blind, placebo-controlled Trial to treat patients with chronic low back pain and chronic neuropathic pain (Portenoy et al, 2007; Simpson et al, 2007). FBT was found to be well tolerated and efficacious in both of these patient populations (Portenoy et al, 2007; Simpson et al, 2007). An extreme caution is advised before prescribing ROOs for an off-label indication.

TITRATION

Currently, all ROOs include titration instructions in their package inserts that recommend starting all patients on the lowest dose of the drug and proceeding with a stepwise upward titration (Taylor, 2013). The goal of titration for each patient should be to achieve adequate analgesia with minimal adverse effects. A controversial issue is whether a patient should be started with a ROO dose proportional to the ATC dose, because there is only limited data about the correlation between the BTcP medication dose and the total daily analgesic dose.

In consequence of the rapid action of ROOs, titration can be accomplished quickly, usually within 24-72 hours. Thorough communication with the patient during ROOs titration is especially recommended, as it can avoid the patient from becoming disheartened and the risk of too frequent dosing (Taylor, 2013).

While it appears safer to initiate treatment at the lowest dose, clinical experience suggests that highly opioid-tolerant patients may require higher BTcP medication levels than patients on low doses of opioids (Mercadante et al, 2011). Some authors support a beginning ROO dose of 10% of total daily analgesic dose (Rhiner et al, 2010; Doulton, 2014). A recent randomized clinical trial demonstrated how there is no advantage in terms of pain control or adverse effect with upward titration of fentanyl buccal tablet compared to administering doses proportional to basal opioid regimen. A proportional approach, being simpler than titration, may raise compliance rates for the patients and result in a more widespread use of ROOs from physicians (Mercadante et al, 2012). On the other side, recommendations have been issued that the dose of ROOs to be given for an episode for BTcP should be determined by individual titration (Davies et al, 2008).

Perhaps "in medio stat virtus", and this issue could be relevant to non-specialists, as in clinical practice the pain specialist can rapidly titrate starting with relatively higher doses of opioids in highly-tolerant patients, skipping some steps of dose titration (Mercadante, 2011). The profound variability in responsiveness to opioids may perhaps encourage non-specialists to titrate ROOs starting with a low dose, providing availability of assays for rapid identification of effective dose.

RAPID ONSET OPIOIDS (ROOS)

The first ROO commercialized for BTcP was oral transmucosal fentanyl citrate (OTFC), a fentanyl-impregnated lozenge, available in six dosage strengths (200, 400, 600, 800, 1200 and 1600 mcg). This formulation was designed to exploit the high permeability of oral muco-

sa, 20 times that of the skin, and the rich vascularity of approximately 200 cm2. Absolute availability is about 50%, and in most patients time to analgesic onset is 15 minutes (Aronoff et al, 2005).

Four early studies have shown the effectiveness of OTFC in the management of BTcP (Mercadante, 2012). One study compared OTFC with oral morphine, as discussed above (Coluzzi et al, 2001). Pain control at all time points between 15 and 60 minutes was significantly more favorable with OTFC, with a comparable rate of adverse effects.

Long-term studies have showed how OTFC is well tolerated in patients who achieve an effective dose, with no discontinuation of the drug due to adverse effects (Hanks et al, 2004; Payne et al, 2001). Good tolerability was evident even in a controlled study involving highly tolerant patients, where OTFC was administered at starting doses of 1600 Mcg (Mercadante et al, 2007).

Since the approval of OTFC, several other formulations have been developed for this indication (fig.5). Fentanyl buccal tablet (FBT) is formulated to enhance fentanyl absorption across the buccal mucosa using an enhanced effervescent absorption technology (Blick et al 2006) and to correct some limits of the OTFC formulation. The mean time to analgesic onset is 15 minutes. The median time to maximum serum concentration is shorter for FBT (47 minutes) than OTFC (91 minutes) (Freye et al, 2008). Dose adjustment for oral mucositis may not be required (Darwish et al, 2007). FBT dissolved within 30 minutes in 14 of 16 patients with or without oral mucositis, and tmax and Cmax were comparable in both groups. Patients with oral mucositis did not report exacerbations of their oral symptoms during the study (Darwish et al, 2007).

Application-site reactions are mostly self-limiting and resulted in treatment discontinuation in only 2% of patients (Taylor, 2013).

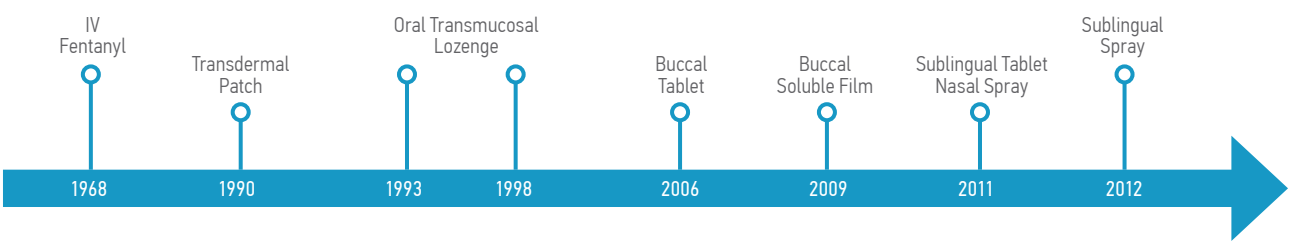
The FBT dissolution time or "dwell time" in the mouth does not influence the rate and extent of fentanyl absorption through the oral mucosa (Darwish, 2007).

Compared with placebo, FBT shows a significant abatement in summed PIDs over 60 minutes (SPID60) and PID at 10 minutes, significant improvement in analgesia at 10 minutes and substantial clinically relevant decrease in pain intensity at 5 and 15 minutes, respectively.

FBT employment also resulted in lower rates of rescue medication use and significantly greater medication performance assessment scores (Portenoy et al, 2007; Simpson et al, 2007; Slatkin et al, 2007; Farrar et al, 2010).

A recent comparative study of oral immediate-release oxycodone and FBT found out that FBT provided relief of BTcP more rapidly than oxycodone (Ashburn et al, 2011). Systemic exposure following buccal and sublingual FBT placement appears to be bioequivalent and generally well tolerated (Darwish et al, 2008). FBT is therefore a reasonable alternative for opioid tolerant patients requiring treatment for BTcP. FBT efficacy is comparable if inserted in the sublingual or buccal position, offering a wide possibility of titration thanks to the possibility to place different pills simultaneously.

FIGURE 5
Rapid onset opioids: year of market entry. Adapted from Stanley, 2014



After FBT a sublingual formulation of fentanyl (SLF) was developed. The quickness of action of SLF is similar to that of the FBT (Mercadante et al, 2014). This formulation consists of a small tablet made of a mix of active drug particles and water-soluble carrier particles coated with a muco-adhesive agent (Chwieduk et al, 2010). Application-site abnormalities, inflammation of the mucosa (stomatitys), have rarely been reported (Rauck et al, 2009).

In a randomized, crossover study of 27 adults with BTcP, patients received placebo and SLF 100, 200 or 400 mg for one BTP episode without a preliminary titration phase to find dose with best efficacy (Lennernas et al, 2010). SLF 400 mg was associated with the greatest improvements in PID when compared with placebo and the other doses assessed.

A multicentre, randomized, placebo-controlled, phase III study assessed the efficacy of SLF from 100 to 800 mcg in 66 patients with BTcP (Rauck et al, 2009). After administration of SLF, the mean SPID30 was greater than with placebo (49.5 vs 36.6; p = 0.0004). Pain relief and amelioration of PID were also greater with SLF compared with placebo at 10 minutes and remain significant in all the 60 minutes assessment period.

These two studies showed how sublingual fentanyl has a fast effect and is well tolerated up to 12 months, with high levels of patient satisfaction (Lennernas et al, 2010; Rauck et al, 2009)

The most recently developed modality of delivery of fentanyl is the intranasal route. This delivery system is thought to take advantage of the 150-180 cm2 surface of the thin and highly vascularized nasal mucosa. It has proved particularly useful for administering lipophilic opioids to improve the bioavailability and avoid first pass liver metabolism (Vyas et al, 2005). The nasal route may present some advantages, especially in patients with mucosal damages or salivary dysfunction (Mercadante et al, 2014). Two formulations of intranasal fentanyl (INFS) have been developed: an aqueous solution and a pectin-based drug delivery system in the form of a gel (Watts et al, 2009). Intranasal Fentanyl is available in doses of 50, 100 and 200 mg/spray. The pharmacokinetics of INFS 50–200 mg were assessed in a population of patients affected by BTcP; median tmax values were between 12 and 15 minutes and the plasma concentration increased in a dose dependent manner and were comparable to studies conducted in healthy volunteers. (Kaasa et al, 2010). In a study conducted in patients who underwent oral surgery, the bioavailability of INFS was 89% (Foster et al, 2008). The efficacy of INFS has been assessed in a double-blind, randomized, placebo-controlled, crossover study to treat BTcP patients. Pooled mean PID scores at 10, 20, 40 and 60 minutes, compared with placebo, were significantly higher for all INFS doses (PID10 scores 1.10 vs 2.36, p<0.001). The mean global impression of treatment for INFS was 1.88 versus 0.95 for placebo (p<0.001) and 75.4% of patients stated that they judged the efficacy of treatment as good/very good/excellent for INFS compared with 30.9% for placebo (Kress et al, 2009).

An open-label, crossover trial compared the efficacy of INFS with OTFC, time to onset of pain relief was 11 minutes for INFS and 16 minutes with OTFC. Pain intensity was reduced to a significantly lower level with INFS at 5, 15 and 60 minutes compared to OTFC. The only adverse effect was nausea, occurring in less than 5% of the patients (Mercadante et al, 2009).

The other nasal formulation for the treatment of BTcP is Fentanyl pectin nasal spray (FPNS). This formulation aims to prolong the contact of fentanyl and the nasal mucosa and modify the pharmacokinetic profile compared with the INFS. The pharmacokinetics of FPNS and OTFC have been compared in a open-label, single-dose, crossover study of opioid-naive healthy subjects (Fisher et al, 2010).

FPNS offer a dose independent t_{max} that was less than with OTFC: 15–21 minutes versus 90 minutes (p<0.01). The FPNS's C_{max} rise in a dose proportional manner for 100 mcg, 352 pg/mL and 800 mcg and was significantly higher for FPNS versus OTFC (p<0.001). FPNS has been compared with oral morphine immediate release in a double-blind, crossover study of patients with BTcP (Davies et al, 2011).

FPNS use resulted in good improvement in pain intensity (≥2-point reduction on a 0-10 numeric scale) for a higher number of FPNS treated BTP episodes. At 30 minutes, the differences between FPNS and morphine sulphate in terms of analgesic effects began to diminish (Davies et al, 2011).

FPNS obtained an improvement ≥2 points in absolute pain in a randomized study versus placebo in subjects affected by BTcP, within 10 minutes, in 33% of episodes treated ($p < 0.05$). Furthermore a at 10 minutes clinically pain reduction of 33% was observed in episodes treted with FPNS versus 24% of placebo ($p < 0.01$).

In a 16-week multicenter open-label trial comprising 356 patients with BTcP, there was no need of an additional rescue medication in 94 percent of FPNS-treated episodes. Furthermore an increase from the initial dose of FPNS was unnecessary in more than 90 percent of patients (Portenoy et al, 2010).

One of the most recently developed formulation is the new sublingual fentanyl, three-layer, citrate tablet (FE tablet). The absolute bioavailability of the FE tablet lozenge has been reported to be approximately 70%. Data obtained in vitro and in vivo suggest a dwell time of 30 minutes to reach an exposure similar to OTFC. Efficacy was tested in a prospective, multicentre, randomised, double-blind, crossover study, which compared the FE tablet to placebo in 73 opioid-treated patients (from 91 enrolled) affected by BTcP. Mean SPID at 30 minutes after dosing was significantly greater for the FE tablet than placebo (75.0 versus 52.5; $p<0.0001$). Patients treated for BTcP episodes with placebo required 38.4 % rescue medication versus 17.5% of episodes treated with the FE tablet ($p<0.0001$). In the study 40 adverse events were recorded (8.8 % of the patients) that were judged to be related to the treatment. There were no reports of respiratory depression, circulatory depression, hypotension or shock. Adverse events were mostly of mild or moderate severity, peculiar of opioid treatment, including somnolence (2.2 %), diarrhoea (3.3 %), nausea (4.4 %) and vomiting (5.5 %) (Novotna et al, 2014).

CONCLUSIONS

Breakthrough cancer pain is a common condition, often undertreated. It has traditionally been managed with short-acting oral normal-release medications, using consistently the same opioid for the treatment of baseline and BTcP. However, the pharmacokinetic and pharmacodynamics profiles of oral opioids do not mirror closely the characteristics of BTcP, potentially resulting in inadequate treatment and problematic adverse effects. In the last two decades were developed new fentanyl-based rapid onset opioids, with accumulating evidence of their high efficacy, safety and tolerability. Although many studies in BTcP have proven their superiority over oral opioids, rapid onset opioids are still greatly underused.

Since cancer pain also encompasses physical and psychosocial dimensions, the adjunct of non-pharmacological approaches (cognitive, physical and rehabilitative) to the best medical therapy has proven highly beneficial. Growing evidence in recent years suggests that the integration of a multimodal approach to cancer pain may have a significant impact in providing pain relief.

REFERENCES

» Abernethy AP, Wheeler JL, Fortner BV. A health economic model of breakthrough pain. Am J Manag Care. 2008 May;14(5 Suppl 1):S129-40

» Abrahm JL. Assessing the patient in pain. In: Abrahm JL, ed. A Physician's Guide to Pain and Symptom Management in Cancer Patients, 2nd edition. Baltimore, MD: Johns Hopkins University Press; 2005: 107-47

» American Pain Foundation, news release, Jan. 28, 2010

» Aronoff GA, Brennan MJ, Pritchard DD, et al. Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. Pain Med 2005; 6: 305-14

» Ashburn M, Slevin K, Messina J, et al. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. AnesthAnalg 2011; 112: 693-702

» Ashburn M, Slevin K, Messina J, et al. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. AnesthAnalg 2011; 112: 693-702

» Bedard G, Davies A, McDonald R, Hawley P, Buchanan A, Popovic M, Wong E, Chow E. Breakthrough cancer pain: a comparison of surveys with European and Canadian patients. Support Care Cancer. 2015 Mar;23(3):791-6

» Bennett D, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessmentand management of breakthrough pain: Part 2 Management. Pharmacy and Therapeutics. 2005;30:354-361

» Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382:769–79

» Blick S, Wagstaff AJ: Fentanyl buccal tablets in breakthrough pain in opioid-tolerant patients with cancer. Drugs 66:2387-2393, 2006

» Caraceni A, Davies A, Poulain P, Cortés-Funes H, Panchal SJ, Fanelli G. Guidelines for the management of breakthrough pain in patients with cancer. J NatlComprCancNetw. 2013 Mar;11Suppl 1:S29-36

» Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D, Zeppetella G; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012 Feb;13(2):e58-68

» Chwieduk C, McKeage K: Fentanyl sublingual in breakthrough pain in opioid-tolerant adults with cancer. Drugs 70:2281-2288, 2010

» Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain. 2001 Mar;91(1-2):123-30

» Darwish M, Kirby M, Jiang JG, Tracewell W, Robertson P Jr. Bioequivalence following buccal and sublingual placement of fentanyl buccal tablet 400 microg in healthy subjects. Clin Drug Investig. 2008;28(1):1-7

» Darwish M, Kirby M, Robertson P, Tracewell W, Jiang JG. Absorption of fentanyl from fentanyl buccal tablet in cancer patients with or without oral mucositis: a pilot study. Clin Drug Investig. 2007;27:605-611

» Davies A, Sitte T, Elsner F, et al. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain. J Pain Symptom Manage 2011; 41 (2): 358-66

» Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. 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. 2009 Apr;13(4):331-8

» Doulton B. Pharmacologic management of adult breakthrough cancer pain. Can Fam Physician. 2014 Dec;60(12):1111-4

» Farrar JT, Messina J, Xie F, Portenoy RK. A novel 12-week study, with three randomized, double-blind placebo-controlled periods to evaluate fentanyl buccal tablets for the relief of breakthrough pain in opioid-tolerant patients with noncancer-related chronic

pain. Pain Med. 2010 Sep;11(9):1313-27

» Fisher A, Watling M, Smith A, et al. Pharmacokineticsand relative bioavailability of fentanyl pectin nasal spray 100- 800mg in healthy volunteers. Int J ClinPharmacolTher 2010; 48 (12): 860-7

» Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain. 2002 Feb;3(1):38-44

» Foster D, Upton R, Christrup L, et al. Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. Ann Pharmacother 2008; 42 (10): 1380-7

» Freye E. A new transmucosal drug delivery system for patients with breakthrough cancer pain: the fentanyl effervescent buccal tablet. J Pain Res. 2008;2:13-20

» Gallagher R, Hawley P, Yeomans W. A survey of cancer pain management knowledge and attitudes of British Columbian physicians. Pain Res Manag. 2004 Winter;9(4):188-94

» Hanks GW, Conno F, Cherny N, et al., Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001; 84: 587-93

» Hanks GW, Nugent M, Higgs CM, et al. Oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer: an open, multicentre, dose-titration and long-term study. Palliat Med 2004; 18: 698-704

» Kaasa S, Moksnes K, Nolte T, et al. Pharmacokinetics of INFS in patients with cancer and breakthrough pain. J Opioid Manag 2010; 6 (1): 17-26

» Kress HG, Oronska A, Kaczmarek Z, et al. Efficacy and tolerability of INFS 50 to 200 mg for break- through-pain in patients with cancer: a phase III, multi- national, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-labelextension treatment period. ClinTher 2009; 31 (6): 1177-91

» Kurella M, Bennett WM, Chertow GM: Analgesia in patients with ESRD: A review of available evidence. Am J Kidney Dis. 2003;42:217-228

» Lennernas B, Frank-Lissbrant I, Lennernas H, et al. Sub-lingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain: results from a randomized phase II study. Palliat Med 2010; 24: 286-93

» Maltoni M, Scarpi E, Modonesi C, et al. A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. Support Care Cancer 2005;13(11):888-94

» Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, Cruz JJ, Galvez R, Mañas A, Zaragozá F. Breakthrough cancer pain - still a challenge. J Pain Res. 2012;5:559-66

» Mayes S, Ferrone M: Fentanyl HCL patient-controlled iontophoretic transdermal system for pain: Pharmacology. Ann Pharmacother. 2006;40:2178-2186

» Mercadante S, Ferrera P, Adile C, Casuccio A. Fentanyl buccal tablets for breakthrough pain in highly tolerant cancer patients: preliminary data on the proportionality between breakthrough pain dose and background dose. J Pain Symptom Manage. 2011;42:464-469

» Mercadante S, Porzio G, Gebbia V. New opioids. J ClinOncol. 2014 Jun 1;32(16):1671-6

» Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, Ripamonti C, De Conno F; Steering Committee of the European Association for Palliative Care (EAPC) Research Network. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer. 2002 Feb 1;94(3):832-9.

» Mercadante S, Radbruck L, Davies A, et al. A comparison of INFS with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain:

an open-label, randomized, crossover trial. Curr Med Res Opin 2009; 25: 2805-15

» Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. Br J Cancer. 2007 Jun 18;96(12):1828-33

» Mercadante S, villari P, Ferrera P, Casuccio A. optimization of opioid therapy for preventing incident pain associated with bone metastases. J Pain Symptom Manage. 2004;28:505-51

» Mercadante S. Pharmacotherapy for breakthrough cancer pain. Drugs. 2012 Jan 22;72(2):181-90

» Mercadante S. Rapid onset opioids for breakthrough pain: Titrating or not titrating, this is the question! European Journal of Pain Supplements Volume 5, Issue S2, pages 443–447, November 2011

» Novotna S, Valentova K, Fricova J, Richterova E, Harabisova S, Bullier F,Trinquet F; ETHYFYL Study Group. A randomized, placebo-controlled study of a new sublingual formulation of fentanyl citrate (fentanyl ethypharm) for breakthrough pain in opioid-treated patients with cancer. Clin Ther. 2

» Osborne V, Layton D, Fogg C, Al-Shukri M, Shakir SA. Utilization of fentanyl buccal tablets in England: exploring off-label use reported in a cohort study. Eur J Pain. 2014 Apr;18(4):506-12

» Pasternak GW. Opioids and their receptors: Are we there yet? Neuropharmacology. 2014 Jan;76Pt B:198-203

» Payne R, Coluzzi P, Hart L, et al. Long-term safety of transmucosal fentanyl citrate for breakthrough cancer pain. J Pain Symptom Manage 2001; 22: 575-83

» Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. J ClinOncol. 2014 Jun 1;32(16):1662-70

» Portenoy RK, Messina J, Xie F, et al. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid- treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin 2007; 23 (1): 223-33

» Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, Frigerio V, Ingham J, Loseth DB, Nordbrock E, Rhiner M. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain. 1999 Feb;79(2-3):303-12

» Portenoy RK, Raffaeli W, Torres LM, et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioidtolerant patients. J Opioid Manag 2010; 6 (5): 319-28

» Portenoy RK, Taylor D, Messina J, et al. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 2006; 22 (9): 805-11

» Prime Therapeutics. Study finds 90 percent of Actiq® "lollipop" prescriptions are off-label, 16-1-2007 [online]. Available from URL: http://www.primetherapeutics.com/pdf/Actiq.pdf (Accessed 2015 April 30)

» Rauck R, Reynolds L, Geach J, et al: Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: A randomized, double-blind, placebo-controlled study. Curr Med Res Opin 28:859-870, 2012

» Rauck R, Tark M, Reyes E, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 2009; 25: 2877-85

» Rhiner MI, von Gunten CF. Cancer breakthrough pain in the presence of cancer-related chronic pain: fact versus perceptions of health-care providers and patients. J Support Oncol. 2010 Nov-Dec;8(6):232-8

» Schug SA, Chandrasena C. Pain management of the cancer patient. Expert OpinPharmacother. 2015 Jan;16(1):5-15

» Scott JC, PonganisKv, Stanski DR. EEG quantification of narcotic effect: The comparative pharmaco-

dynamics of fentanyl and alfentanil. Anesthesiology. 1985;62:234-241

» Simpson DM, Messina J, Xie F, et al. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2007; 29 (4): 588-601

» Slatkin NE, Xie F, Messina J, et al. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol 2007; 5 (7): 327-34

» Stanley TH. The fentanyl story. J Pain. 2014 Dec;15(12):1215-26

» Swanson G, Smith J, Bulich R, New P, Shiffman R. Patient-controlled analgesia for chronic cancer pain in the ambulatory setting: a report of 117 patients. J ClinOncol. 1989 Dec;7(12):1903-8

» Taylor DR: Managing Cancer Breakthrough Pain. 1st ed. London: Springer Healthcare; 2013

» Temel JS, Greer JA, Muzikansky A, et al Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010 Aug 19;363(8):733-42

» Vardy J, Agar M. Nonopioid drugs in the treatment of cancer pain. J ClinOncol. 2014 Jun 1;32(16):1677-90

» Vellucci R, Breakthrough Cancer Pain. Eur J Oncol; Vol. 20, Suppl n. 1, pp. 11-12, 2015

» Vellucci R. Heterogeneity of chronic pain. Clin Drug Investig. 2012 Feb 22;32Suppl 1:3-10

» Vyas TK, Shahiwala A, Marathe S, Misra A. Intranasal drug delivery for brain targeting. Curr Drug Deliv. 2005 Apr;2(2):165-75

» Wagner JC, Souders GD, Coffman LK, Horvath JL. Management of chronic cancer pain using a computerized ambulatory patient-controlled analgesia pump. HospPharm. 1989 Aug;24(8):639-40, 642-4

» Watts P, Smith A: PecSys: In situ gelling system for optimised nasal drug delivery. Expert Opin Drug Deliv 6:543-552, 2009

» WHO. Cancer pain relief, 2nd ed. Geneva: World Health Organization, 1996

» Zeppetella G. Dynamics of breakthrough pain vs pharmacokinetics of oral morphine: implications for management. Eur J Cancer Care 2009; 18: 331-7

» Zeppetella G. Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. J Pain Symptom Manage. 2008 May;35(5):563-7

Pharmacoeconomic Considerations about Breakthrough Cancer Pain

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ABSTRACT

BTcP è associato ad una serie di complicazioni fisiche, psicologiche/emozionali e sociali problematiche che a loro volta sono non solo una fonte rilevante di morbilità supplementare in questi pazienti, ma sono anche responsabili di importanti implicazioni economiche, non solo per il paziente.

È stata effettuata una revisione sistematica della letteratura sulla banca dati elettronica PubMed da dicembre 2014 a febbraio 2015. Le parole chiave usate comprendono "dolore episodico intenso cancro" e "costo-efficacia" o "economia" o "farmacoeconomica," e termini MeSH inclusi sono "dolore episodico intenso" e "neoplasie", o "economia" o "analisi costi-benefici". Non è stata posta alcuna restrizione per quanto riguarda la lingua o il tipo di studio. Un totale di venti articoli sono stati identificati tramite PubMed. Tra i 10 studi inclusi, sono prensenti due progetti di miglioramento della qualità, due studi di indagine, tre modelli analitico- decisionali, una revisione della letteratura, due studi incentrati sulle farmacoeconomia di oppioidi rapida insorgenza e uno che si focalizza sul contesto economico della salute.

Abbiamo analizzato 10 articoli concentrandoci sul peso economico del dolore oncologico episodico intenso. BTcP è un problema che si verifica frequentemente ed è associato ad un aumento delle spese mediche: i costi sanitari diretti, costi indiretti, e costi intangibili. Di essi fanno parte i costi di un aumento delle prescrizioni, più visite legate al dolore da professionisti del settore sanitario, e più ricoveri, nonché i costi relativi alla cura dei bambini, i metodi di rilievo di dolore alternativi, la psicoterapia, la perdita di guadagno, lo stress e la tensione sui membri della famiglia. Nel caso di BTcP, i costi sanitari diretti possono comprendere le spese ospedaliere, costi di analgesici e altri farmaci, radioterapia, chirurgia; costi non sanitari diretti potrebbero includere il costo dei trasporti

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per raggiungere l'ospedale, il parcheggio durante una visita clinica, pedaggi autostradali, alloggio durante la notte per la famiglia o gli operatori sanitari, e pasti per coloro che accompagnano il paziente in ospedale. Per BTcP, i costi intangibili comprendono il dolore del paziente, la sofferenza, la depressione, l'ansia, perdita del sonno, e la stanchezza, così come il disagio della famiglia e/o del caregiver.

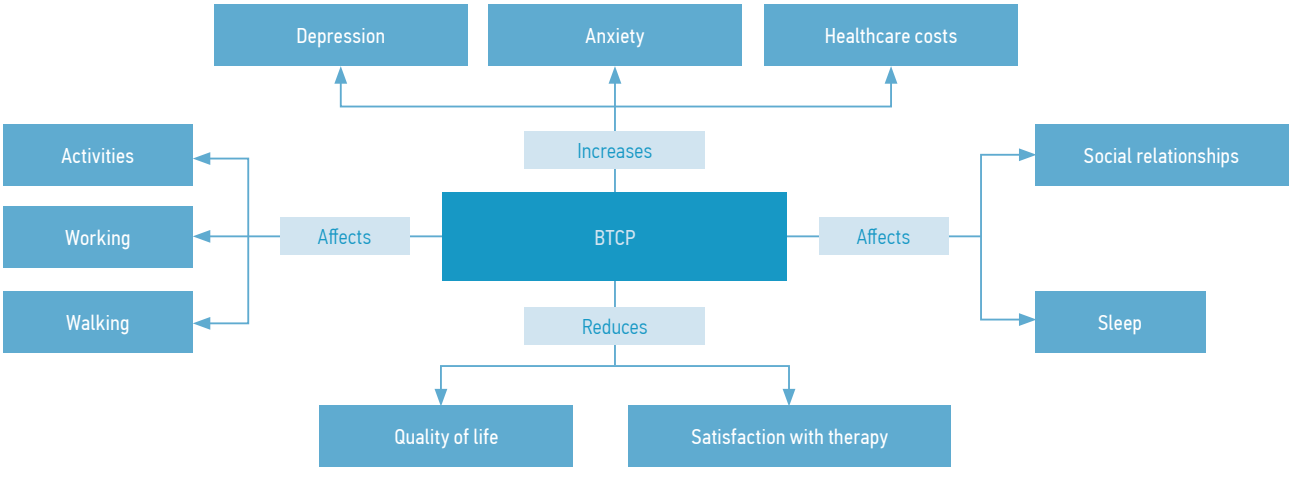
Sono necessari ulteriori studi e modelli di costo per valutare la qualità della vita e il miglioramento del rapporto costo-efficacia dei trattamenti analgesici per il BTcP. Per delineare la gamma completa di fattori che, presi insieme, descrivono l'impatto del BTcP sui pazienti, provider e la società, sarebbe interessante sviluppare un modello economico di salute globale al fine di migliorare il processo decisionale clinico, ottimizzare i risultati, e migliorare la soddisfazione riguardante i processi di cura in tutti i soggetti interessati. Nel caso di HTA nel dolore oncologico, valutazioni etiche risultano essere molto importanti al fine di una corretta gestione del paziente.

Among other things, breakthrough cancer pain (BtcP) episodes negatively influence the patients' daily life from a psychological and social point of view. Most patients with BTcP show levels of stress, fear and frustration which are determined by BTcP representing a constant reminder to their disease and its worsening and being associated with a loss of independence. BTcP episodes have indeed both a physical and psychological impact on patients, one reason being that pain occurrence is often linked to exercise. Consequently, patients limit exercise to minimize the BTcP episode, independence and quality of life in these patients are therefore seriously impaired. Moreover, the BTcP unpredictability has important psychological consequences which affect the patients' personal perception of themselves and their disease, triggering a vicious circle of anxiety and prostration.

As already mentioned, BTcP is associated with a number of problematic physical, psychological/emotional and social complications which themselves are not only a relevant source of additional morbidity in these patients, but are also responsible for significant economic implications, not only for the patient and their relatives, but also for the healthcare system and society (Vellucci, 2015). Patients with BTCP are more likely to incur higher direct costs (e.g., costs for medical visits, analgesic prescription charges) and indirect costs (e.g., transportation costs, over the-counter medicine charges) than patients without BTcP. Furthermore, patients with BTcP may require additional healthcare resources through an increase in emergency and medical visits and hospital admissions, with longer hospital stays, than patients who are not experiencing BTcP (Abernethy, 2003; Fortner, 2003). These studies utilized either patient-reported direct and indirect costs or hospital records to determine the number of health care encounters, and all studies used a fixed price for each encounter to calculate the direct cancer-related costs. In all studies, the cost for BTcP was not set apart from other cancer care or comorbidities and this differentiation still represents a difficult methodological problem. However, future studies would benefit from using actual health care claims data to more accurately represent direct costs related to BTP, instead of using literature-defined costs per encounter. The estimation of the patient's responsibility for direct charges would also provide a unique perspective to pain-related costs at the patient level, which could be used in shared decision-making

FIGURE 1

Figure shows that the experience of pain has individual features that are unique to each patient. It is influenced by the patient's past experiences in confronting this symptom, and by the physical, psychical, social, spiritual, and economic situation in which each person faces his or her disease. It is therefore necessary to avoid underestimating the economic and human impact of the poor or inadequate treatment of pain on patients and in their families. Reproduced from Zeppetella, 2011.



between the patient and clinician when treating BTcP. Studies comparing the cost for pain-related pharmacotherapy are also warranted, since increased expenditure of around-the-clock and BTcP medications may be offset by a reduction in expensive hospitalizations, procedures, and emergency department visits, and could further justify the use of the more expensive rapid-onset opioids, as demonstrated with general strategies to improve pain management.

METHODS

We performed a systematic literature search of PubMed electronic database through December 2014 and February 2015. The key words included "breakthrough cancer pain" and "cost effectiveness" or "economics" or "pharmacoeconomic," and MeSH terms included "breakthrough pain" and "neoplasms", or "economics" or "cost-benefit analysis" (search strategy example is: ("cost-benefit analysis" [MeSH Terms] OR ("cost-benefit" [All Fields] AND "analysis" [All Fields]) OR "cost-benefit analysis" [All Fields] OR ("cost" [All Fields] AND "effectiveness" [All Fields]) OR "cost effectiveness" [All Fields]) AND (breakthrough [All Fields] AND ("neoplasms" [MeSH Terms] OR "neoplasms" [All Fields] OR "cancer" [All Fields]) AND ("breakthrough pain" [MeSH Terms] OR "pain" [All Fields]).

There were no language or study design restrictions. A

TABLE 1
The table summarizes the main features of the studies, which are later described in more details.

Authors	Year	Type of analysis	Model	Time horizon	Country	Efficacy data
Grant M, Ferrell BR, Rivera LM, Lee J.	1995	Quality improvement project	-	1989 -1990 / 1992 -1993	USA	Hospitalization costs
Fortner BV, Okon TA, Portenoy RK.	2002	Survey study	-	1997-1998	USA	Direct medical costs
Fortner BV, Demarco G, Irving G, et al	2003	Survey study	-	April 1998 - January 1999	USA	Direct medical costs; Indirect medical costs; Predictors of costs
Fortner BV, Okon TA, Ashley J, et al.	2003	Quality improvement project	-	August 1997- October 1998	USA	Direct medical costs, Indirect medical costs, Global Qol
Abernethy AP, Samsa GP, Matchar DB	2003	Cost effectiveness analysis	Decision Analitic Model	1 month	USA	Direct costs
Abernethy AP, Wheeler JL, Fortner BV,	2008	Health economic framework	-		USA	Direct medical costs, indirect medical costs, Intangible costs
Vissers DC, Lenre M, Tolley K et al	2011	Cost effectiveness analysis	Decision Analitic Model	1 year	Sweden	Direct costs
Ruggeri M, Oradei M, Turrizzani A, Cicchetti A.	2013	Cost effectiveness analysis	Markov model		Italy	Cost of therapy
Kuan-Ling Kuo, Surasak Saokaew, and David D. Stenehjem.	2013	Literature review	-	August 2012		
Josep Darbà, Lisette Kaskens, Rainel sánchez-de la Rosa.	2014	Budget impact analysis	BIM	2012 - 2015	Spain	Drug costs, medical resource utilization, unit costs, annual mean cost per patient

total of twenty articles were identified via PubMed; after the exclusion of irrelevant articles not pertaining to the pharmacoeconomic aspects of the treatment of breakthrough cancer pain, 7 potentially relevant articles were retrieved for more detailed evaluation.

A manual search of the references cited from the identified articles was also performed. Three other pertinent articles were identified. Among the 10 included studies, there were two quality improvement projects, two survey studies, three decision-analytic models, one literature review, two studies focusing on the pharmacoeconomics of rapid-onset opioids and one health economic framework.

RESULTS

We analyzed 10 articles focusing on the economic burden of breakthrough cancer pain.

The first author reporting on the economic impact of unrelieved cancer pain was Grant in 1995. In this study, he assessed the benefit of implementing a variety of general strategies to improve pain management and decrease unscheduled readmissions for uncontrolled cancer pain at a National Cancer Institute, called cancer center. The general strategies implemented included increased nurse education to encourage their active role in pain management, making pain management a focus in the institution, and creating a supportive care

Cost efficacy indicators	Results	Statistical Significance
	LOS= 12 days= $ 5,097,960 (4066 admission). Reduction of hospitalization costs: $ 2,719,245	
-	BTcP patient= more hospitalization, longer LOS. > emergency department. > office. c/p/y= $ 12,000 BTcP $2,400 non BTcP	p<0.02. p<0,08. p<0,01. p<0,04 (pain related hospitalization). p< 0,01 (physician office visit)
-	DIRECT COSTS: Hospitalization patient/month: $631,48; medical visit $89,58; analgesic medication $81,76; INDIRECT COST: extrahouse hold assitance patient/month: $24,70	predictor of direct costs of BTcP: BTcP p<0,01; high pain intensity p<0,01; lower houshold income p<0,01; younger patient p<0,05. indirect costs: BTcP: p<0,04; p<0,01.
-	Cost of a day: $ 1,550. cost month/patient pre implementation: $5,070 vs $1,442 post implementation.	p<0,02. Reduction in pain related hospitalization p< 0,04. Reduction in emergency department p<0,001.
ICER	GBC: $579; OBC: $465; UC: $315. ICER: GBC with OBC : $452; OBC with UC $601; GBC with UC $527.	
-	-	
QALY	90% of costs: acquisition drugs; 81% hospital stay. INFS> OTFC: avoid 25% of addiotional BTcP, saved 174€, gained 0,046 QALY. INFS> FBPT: avoid 24% of additional BTcP, gained 0,043 QALY. INFS is cost effective.	
ICER QALY QoL	treatment with Fentanyl: 8893€ ; 0,63 QALY. Treatment with morphine: 6431 €; 0,29 QALY. ICER: 10,140 €/QALY. BTcP TREATED WITH FENTANYL is cost effective. QOL: 0,001 morphine; 0,46 with Fentanyl	
-	Average annual budget saving with Fentanyl : 2.6 milion €. 0,5% decrease of total costs. 29€ reduction of average patient cost.	

service. The study compared hospital readmission rates for uncontrolled cancer pain prior to the implementation of these broad strategies (1989–1990) with the post-implementation readmission rate (1992–1993). A total of 4066 admissions (including readmissions) occurred during the post-implementation period compared with 5772 total pre-implementation admissions. The pre-implementation readmissions for uncontrolled pain were 255 (4%), with an average length of hospitalization of 12 days. Based on the average length of stay and $1,666.00 per day as the average daily cost of hospitalization for pain management, the total cost for readmission for pain management during this time period was $5,097,960.00 for 4066 admissions. During the post-implementation period, however, the average length of stay for uncontrolled pain was 11.8 days and a reduction in readmissions (n = 121; 3%) was observed. The total cost for pain management was therefore reduced to $2,378,715.00 during the study period compared with the pre-implementation group, using the same cost per day. This study did not provide the method or source of cost estimations. The authors concluded that the general strategies implemented to improve pain management and the associated readmission rate resulted in a $2,719,245.00 reduction in hospitalization costs, which easily justified the pain management strategies and resources implemented during the time period. This study did not specifically assess BTcP, but demonstrates the significant economic impact of unrelieved cancer pain and how general pain management strategies can improve patient care while reducing health care utilization and, subsequently, costs.

Fortner et al in 2002 conducted a telephone survey study to investigate the relationship between BTcP and direct medical costs. Participants were identified through a consumer survey from 1997–1998 in which responders indicated that an immediate family member had cancer. The survey was stopped after 1000 adult patients actively being treated for cancer completed the survey. Survey respondents were asked about the occurrence of BTP and pain-related medical visits (hospitalizations, office visits, and emergency department visits). The frequency of medical encounters and the duration of hospitalization were used to generate cost estimates based on literature-defined cost per encounter or cost per day of hospitalization. The estimated yearly cost data were normalized by the Blom's method, since it was positively skewed due to most patients reporting no costs in each categories. Comparisons were made between patients reporting BTcP and those who did not. Overall, 53% of respondents experienced cancer related pain, with 25% receiving around-the-clock pain medication; 64% (n = 160) reported BTcP and 36% (n = 89) did not. The mean age of patients reporting BTcP was 2 years younger than patients not reporting BTcP. Patients with BTcP reported more frequent hospitalizations with longer lengths of stay ($P < .02$) and an increased number of emergency department ($P < .08$) and office ($P < .01$) visits compared with those without BTP. Resultantly, the total costs for patients with BTcP were increased with respect of non-BTcP patients and the estimated total annual cost per patient per year was $12,000.00 for BTcP patients compared with $2,400.00 for non-BTcP patients, which is statistical significant both for pain-related hospitalizations ($P < .04$) and for physician office visits ($P < .01$) after controlling for their scheduled analgesics. The greatest expense for both BTcP and non-BTcP patients was hospitalization (90% and 88%, respectively), followed by physician office visits and emergency department visits. This study was limited by its nonrandomized design, which may have resulted in a selection bias. Other limitations include a recall bias that may affect the true number of pain-related medical visits recalled, and lastly, the cost estimates used for health care encounters were based on average costs reported in the literature for general medical encounters, whereas pain-related encounters may cost more than non-pain-related encounters.

A subsequent study by Fortner et al in 2003 was designed to describe not only the direct cancer-related pain costs but also the indirect costs and the potential predictors of these costs. The study surveyed 144 patients from four private oncology practices in California, Colorado, Tennessee, and Washington. Patients

included were older than 18 years, they camplained pain from cancer or its treatment, and were able to complete questionnaires. Interviewers were trained pain-management nurses. A Brief Pain Inventory survey was utilized to measure pain severity and patients were asked to describe pain-related costs in the 3 months leading up to the survey. The cost estimation is the same as Fortner et al (2002) based on the literature, and the cost of analgesic medications was determined based on the average wholesale price in the 1999 Drug Topics Red Book. Direct costs were defined based on patient-reported pain-related hospitalizations, emergency department visits, and physician office visits over a 3-month period. Prescription or nonprescription pain medications were also included as direct costs. Indirect costs included transportation-related expenses, childcare expenses, household assistance, complementary medicine expenses, over-the-counter medications, educational materials, and psychotherapy counseling. The mean age of this cohort was 54 years. The cohort was predominantly Caucasian (85%), female (75%), and had breast cancer (40%). BTcP occurred in 23% of patients. Overall, direct medical expenses accounted for 93% of the total costs. The greatest mean cost was associated with hospitalizations ($631.48 per patient per month), followed by medical visits ($89.58 per patient per month) and analgesic medications ($81.76 per patient per month). Despite the cost of hospitalization, only a minority (7.9%) of patients reported being hospitalized. The greatest indirect cost associated with cancer-related pain was extra household assistance ($24.70 per patient per month). Overall, the mean direct and indirect pain-related cost as reported by these cancer patients was approximately $900 per month or $10,000 per year projected per patient, assuming costs would be incurred proportionally over the year. This study also assessed predictors of direct pain-related costs and found that breakthrough pain (P <.01), higher pain intensity (P <.01), lower household income (P <.01), and younger patients (P <.05) incurred significantly higher costs. As for predictors of indirect pain-related costs: breakthrough pain (P =.04) and higher pain intensity (P <.01) incurred significantly higher costs. The limitations of this study include failure to incorporate lost productivity in the indirect costs, including only outpatient cancer patients, and failure to quantify the cost of BTcP.

In 2003, Fortner and colleagues (Fortner et al, 2003) implemented a multisite quality-improvement project aimed at improving the pain management and lives of outpatient cancer patients reporting pain. The study also assessed the economic impact of the quality-improvement project. The study recruited nonrandom independent cohorts cancer pain patients pre- and post-implementation of the quality-improvement project. The quality-improvement project focused on nurse education, pain assessment and management prompts, and documentation tools. The authors surveyed patients for self-reported measures of pain intensity, pain interferences, quality of life, satisfaction with pain treatment, attitudes toward pain, and pain-related medication costs. Both direct and indirect costs related to pain in the 3 months leading up the survey were assessed, as previously described. Pre- and post-implementation patient characteristics were similar with regards to demographics and cancer types. However, the authors did not control for or assess comorbidities or cancer staging differences in the patient populations. The results demonstrate that during the study period and across multiple institutions, recent pain severity and interference in daily life was reduced, and patients were less concerned with becoming addicted to pain medications. Post-implementation patients also had significantly lower mean direct medical costs ($5070/month/patient pre-implementation vs. $1442/month/patient post-implementation; P <.02) and, as previously demonstrated, these differences were driven by reduced pain-related hospitalizations (14% of patients pre-implementation vs. 4% post implementation; P<.04) and emergency department visits (22% of patients pre-implementation vs. 3% post-implementation; P <.01). No differences in indirect costs were observed with the implementation of the quality improvement project. Similar to Grant et al, this study demonstrates that general pain improvement strategies can improve patient satisfaction in pain

control and daily activities while significantly reducing the pain-related costs associated with health care encounters, in particular hospitalizations.

Abernethy et al in 2003 performed a cost-effectiveness analysis using a decision-analytic model comparing three different literature-defined strategies for cancer pain management. The first part of the model was constructed to estimate the prevalence of cancer and cancer-related pain in the general population based on the National-Cancer-Institute-published US cancer counts and the prevalence of cancer-related pain was inferred from literature review. The second part of the model assessed the efficacy and cost of cancer pain management by means of guideline-based care (GBC), oncology-based care (OBC), or usual care (UC) in a baseline population of 100,000 individuals demographically similar to the US population. Guideline based care assumed patients were treated according to the Agency for Healthcare Research and Quality clinical practice guidelines published in 1994. Oncology-based care was similar to guideline-based care with the exception that long- and short-acting opioids and nonopioid analgesics were prescribed less frequently. Overall this strategy was considered 25% less effective than GBC in the treatment of cancer-related pain. Usual care was based on care provided by non-pain or non-oncology specialists, which was described as suboptimal and was considered 25% less effective than OBC. The efficacy of the different cancer pain management strategies was determined by means of literature review. Intervention costs were derived from direct medical costs, including pharmaceutical costs (medications for pain and treatment of adverse events) and non-pharmaceutical costs (anesthesiology or surgical procedures, etc.). Direct medical encounters and direct non-medical, indirect, and intangible costs were not included in the model. Results were modeled over 1 month using a payer perspective. Of the 100,000 modeled individuals, approximately 0.51% (n = 508) were determined to have cancer and 0.20% (n = 205) suffered from cancer pain. Effective pain management was achieved in 80%, 55%, and 30% of cancer pain patients in the GBC, OBC, and UC groups, respectively. The cost of each strategy per month per cancer pain patient was $579, $466, and $315, respectively. The incremental cost-effectiveness ratio per additional patient relieved of cancer pain was of $452 when comparing GBC with OBC, $601 when comparing OBC with UC, and $527 when comparing GBC with UC. The authors concluded that guideline-based cancer pain management is a cost-effective strategy leading to more patients relieved of pain with a modest increase in cost. Limitations of the studyis the inclusion of only direct costs associated with pain interventions, since costs of untreated pain (hospitalization, lost wages, etc.) are a significant driver in the economics of cancer-related pain, as described by Grant et al. and Fortner et al. Secondly, the probabilities used in the model may be considered out of date and as such did not include rapid-onset opioids, many input parameters were assumed, and the model did not specifically address BTcP. However, a recent prospective, observational study of over 3000 outpatient medical oncology patients demonstrated that 33% of patients reporting pain were receiving inadequate analgesic prescriptions, which closely approximates the 45% of patients not achieving adequate pain relief by oncology-based care in the model. Overall, this model demonstrates that cancer-related pain is undertreated and the cost to improve care is relatively minimal; however, the utilization and cost of rapid-onset opioids may alter the model results.

Abernethy et al in 2008 described a health economic framework to assess BTcP management on an individual and population level. The proposed health economic framework overlays three perspectives: patient, provider, and society; three cost domains: direct, indirect, and intangible; and three end points: costs, outcomes, and benefits. Benefits attributable to effective BTcP management included cost savings, symptom improvement, positive qualitative outcomes, and any improvement in intangible factors. The authors concluded that application of this framework would assist clinicians in decision-making for patients with BTcP and provide a framework for health economic analysis

for BTcP management at the population level to assist institutional and payer decision-making in maximizing benefits while reducing costs and the negative effects of BTcP.

In 2011, Visser et al. conducted a study in Sweden from the payer perspective. They developed a decision-analytic model to estimate the cost-effectiveness of rapid-onset opioids for the treatment of BTP, including INFS, OTFC, and FBT. Efficacy data were derived from a mixed treatment comparison meta-analysis of six randomized controlled trials. Costs for general practitioner visits, specialized home care, and hospital stays were based on the study by Fortner et al (2002). Swedish pharmacy selling prices in 2008 were used for drug acquisition costs. The utilities were generated by time trade-off methods, and the time horizon in the model was 1 year. It was assumed that patients with BTcP would not have additional productivity loss or other non-medical opportunity costs, and the indirect medical costs were more likely to be attributable to cancer rather than BTcP. The results demonstrate that overall costs associated with the treatment of BTcP with INFS, OTFC, or FBT were mostly attributable to the purchase of drugs (90%). In comparison, the majority (81%) of total costs in the placebo arm was attributable to hospital stays. In the base case analysis, INFS dominates OTFC. Compared with OTFC, INFS avoided an additional 25% of BTP, saved €174, and gained 0.046 quality adjusted life years (QALYs). Compared with FBT, INFS avoided an additional 24% of BTP, and gained 0.043 QALYs. The authors concluded that, based on the probabilistic sensitivity analysis, there is a 99% probability that INFS is the most cost-effective intervention. The limitations of this study include the 1-year time horizon, which may inadequately assess the utility measures that were assessed over a 10-year period. The data for resource use of BTP were based on the telephone survey by Fortner et al, 2002, which as discussed earlier may contain selection, information, and recall bias and did not specifically address rapid-onset opioids. The Swedish perspective of the model would also need to be adapted to be applicable to the US payer perspective. Inclusion of other rapid-onset opioids such as FBSF, SLF, and FSS would also provide additional insight in the comparative effectiveness of the entire class of rapid-onset opioids. This model also compared INFS, OTFC, and FBT with placebo; since many consider immediate release morphine as the gold standard of treatment in clinical practice, including morphine in the model may impact on the results. Including an oral opioid as the base case in a decision-analytic model would necessitate including only trials studying a rapid-onset opioid against an oral opioid. Furthermore, few studies (Coluzzi et al, 2001; Fallon et al, 2011) have been conducted comparing a rapid-onset opioid with morphine and these studies have shown a slight statistical advantage of the rapid-onset opioids (OTFC and FPNS) in pain relief relative to immediate-release morphine, with debatable clinical benefit and at the expense of an increased incidence of treatment-related side effects. Lastly, safety was not included in this model, since it was primarily assumed that no differences in adverse events would be observed because the active ingredient was the same (fentanyl); however, to fully measure the net benefit of a rapid-onset opioid, inclusion of safety would be preferable.

Kuan-Ling Kuo et al in 2013 summarized the available pharmacoeconomic studies of BTcP in the context of the availability of several formulations of rapid-onset opioids administered by various routes, which are significantly more expensive than oral opioids. A systematic literature search of PubMed and Tufts registry through August 2012 was conducted using key words including "breakthrough cancer pain" and "cost effectiveness." The analyzed studies demonstrate BTcP causes significant financial burden to patients and society through increased hospitalization and health care utilization. Only one study comparing placebo with INFS, oral transmucosal fentanyl citrate, and oral transmucosal fentanyl buccal tablet has demonstrated the cost-effectiveness of these rapid-onset opioids for the treatment of BTcP. Overall the authors found there is a lack of pharmacoeconomic studies for BTcP management with rapid-onset opioids. Further studies are warranted to assess the net benefit of rapid-onset opioids to oral opi-

oids to assist decision-making by patients, clinicians, and payers.

Ruggeri et al in 2013 performed a cost effectiveness analysis, whose aim is to estimate the cost per Quality Adjusted Life Year (QALYs) of fentanyl nasal spray (FNS, aqueous solution of fentanyl citrate) FNS compared to the use of morphine. They carried out the analysis by constructing a Markov model that simulates the natural history of a hypothetical cohort of 100 advanced cancer patients: the patients in the case arm of the study are treated with FNS), and those in the control arm with morphine. Consistently with the FNS FNS treatment indications, the hypothesis was that patients would have a minimum of 1 to a maximum of 4 episodes of BTcP per day, and that administration of FNSFNS might cause side effects which influence both cost and quality of life (QoL). Based on the literature data, the authors populated their model considering the probability of the daily frequency of episodes of BTcP and the associated probability of side effects reported in the literature. Quality of life weights were used to differentiate the health status associated to BTcP depending on whether FNSFNS or placebo was used. Probabilistic sensitivity analysis was conducted to assess the variability of results associated to the variation of costs, side-effect episodes, daily BTcP episodes, and BTcP prevalence. The results of their analysis show that the treatment of BTcP with FNSFNS costs 8,893 euros with an outcome of 0.63 QALYs, whilst the treatment with morphine costs 6,431 euros for a QALY of 0.29. These data generate an ICER of 10,140 euros/QALY. Overall, the Cost Effectiveness Acceptability Curve shows that the treatment of BTcP with FNS would have an 86% probability of costing less than 30,000 euros/QALY. The results clearly show that FNS administration is a good and sustainable investment in health, despite the collateral effects and the short life expectancy of advanced cancer patients.

Ruggeri et al also report the hospitalizations, days of hospital stay, visits and emergency visits considered by Fortner et al. which were used to estimate the costs to the Italian national health service perspective. Hospitalizations were attributed a cost of euro 700.00, by referring to the oncology DRG (Diagnosis Related Groups) tariffs and the mean cost of a day of hospitalization reported by the Italian Ministry of Health. The mean cost of emergency access was estimated at 125.00 euros, and the cost of a medical consultation at 20.66 euros as reported by the Italian tariff for outpatient services.

Darba et al in 2014 assessed the economic impact of fentanyl buccal tablets for the management of breakthrough cancer pain (BTcP) in Spain. They developed a 4-year budget impact model for the 2012–2015 period for patients with BTcP, from the perspective of the Spanish National Health System. BTcP products included in this model were rapid-onset opioids containing fentanyl (buccal, sublingual, or nasal transmucosal). Prevalence data on cancer, BTcP, opioid use, and number of BTcP episodes were obtained from the literature. Input data on health care resources associated with opioid use and opioid-induced side effects were obtained by consulting experts in oncology from different Spanish hospitals. Resources used included drugs, medical and emergency visits, other non-pharmacologic treatments, and treatment of opioid-induced side effects. Unit costs were obtained from the literature, and a 3% discount rate was applied to costs. Based on the unit costs for drugs and health care resources, the annual BTcP treatment costs per patient associated with each fentanyl product were determined to estimate the overall budget impact based on the total treatment population and the percentage of drug utilization associated with each product. One-way sensitivity analyses were conducted to test the robustness of the model. Patients treated with oral opioids for BTcP were estimated at 23,291 in 2012, with an increase to 23,413 in 2015. The average annual budget savings, with an increase of fentanyl buccal tablets, fentanyl sublingual tablets, and INFS, and a decrease in oral transmucosal fentanyl citrate, was estimated at €2.6 million, which represents a 0.5% decrease in the total costs of BTcP over the next 4 years. Results of the sensitivity analysis showed that the model was most sensitive to drug cost per day for the fentanyl buccal tablet. A 50% decrease in the daily cost of the fentanyl buccal tablet resulted in the largest

overall decrease in budget impact: €5.4 million. The increase in use of the fentanyl buccal tablet leads to overall savings in the budget impact for the Spanish National Health System. Although the economic impact of treatment for BTcP was shown to increase over 4 years due to population growth, the average annual cost per patient was reduced by €29 with increased use of the fentanyl buccal tablet.

DISCUSSION

BTP is a frequently occurring problem associated with increased medical costs. It is possible that incremental costs associated with BTP treatments may be justified by improvement in the quality of life or reduction of more expensive pain related events, such as hospitalizations. Additional studies and cost models are needed to evaluate quality-of-life improvements and the cost-effectiveness of more systematic analgesic treatments for BTcP.

The costs taken into account regarding BTcP are: direct medical costs, indirect costs, intangible cost. This includes increased prescription costs, more breakthrough-pain-related visits to healthcare professionals, and more hospitalizations, as well as costs relating to child care, alternative pain relief methods, psychotherapy, loss of earnings, and stress and strain on family members (Davis, 2011; Abernethy, 2008). In the case of BTcP, direct medical costs might include hospital charges, cost of analgesics and other medications, radiotherapy, surgery, and clinician time; direct non-medical costs might include the cost of gas to drive to the clinic, parking during a clinic visit, highway tolls, overnight lodging for family or caregivers, and meals for these individuals while attending to the patient in the hospital. Direct medical costs can be obtained from institutional and clinical accounting systems; however, diagnostic and clinical variables that link the expense to episodes of BTcP are nonexistent, making direct accounting for BTcP much more problematic than it first appears. Direct non-medical costs can be calculated once the types of costs are enumerated and the corresponding direct medical event is linked to the BTcP episode (Abernethy, 2008). Indirect costs become more difficult to identify in full and, likewise, to compute. Indirect costs for BTP might encompass, for example, lost income as a result of time taken off work for a BTP episode, a spouse's or caregiver's lost income because of time off work, or the expense of extra household help. These costs carry a monetary price tag but are not directly related to the health issue at hand. Many indirect costs can be documented only through the direct report of patients; obtaining this information is becoming more feasible with recent advances in data collection. Specifically, novel information technology allows for the gathering of information directly from patients regarding how they value various costs and outcomes. Patient-reported values can now be integrated into the analysis to create a more comprehensive model of costs and benefits, one that can guide clinicians in their decision-making with a truer depiction of the impact of possible treatment paths. (Abernethy, 2008). Intangible costs, which by their nature elude quantifying, have typically been omitted from many pharmacoeconomic studies. For BTcP, intangible costs include the patient's pain, suffering, depression, anxiety, loss of sleep, and fatigue, as well as the family's and/or caregiver's distress. Recent developments in clinical/research methodology enable capture of these intangibles in ways not previously possible. New technologies such as the e/Tableta wireless notebook and penstyle personal computer have been validated as methods for collecting research quality, patient-reported outcomes; these data can include scores for intangible costs such as depression, fatigue, anxiety, and QOL (Abernethy, 2008).

From the patient/caregiver perspective, BTcP exacts a well-documented toll on QOL and incurs personal expense. For providers and institutions, treatment of unmanaged BTcP substantially raises the costs of care and places undue demands on healthcare resources. On the societal level, BTcP hampers productivity and its costs strain an already overburdened payer system. By delineating the full array of factors that, taken together, describe the impact of BTcP on patients, providers, and society, a comprehensive health economic model will improve clinical decision making, optimize outcomes,

and enhance satisfaction with the processes of care across all stakeholder levels. Extension of this model to population-level analyses will help to improve institutional and societal/payer decision-making, thereby minimizing the negative effects of BTcP while maximizing potential benefits and offsets of good BTcP management.

Access to an adequate pain therapy is one of the objectives of Law 38 of 15 March, 2010, which caused Italy to stand out for its sensitivity and attention to the patient's rights. The so-called "Law 38 on pain" is indeed the first regulatory system in Europe recognizing that pain has an influence on the patient's quality of life and a disabling potential that need to be contained by recognizing and protecting the patients' basic rights. The assessment of the economic aspects of pain treatments, together with the issues pertaining to the quality of life, is an element that cannot be set aside in redefining the current and future setting of cancer pain therapy. As concerns HTA in the management of breakthrough cancer pain, i.e. severe pain appearing in cancer patients who are already treated for basic pain, ethical issues take on special relevance in the evaluation. Indeed, the equitable implications of introducing a therapy against severe breakthrough pain involve social justice concerns that cannot be pushed to the background of our political economic evaluations. For a cancer patient suffering from severe breakthrough pain, the correct treatment of this symptom implies accessing a higher quality of life, which is even more valuable when, as is often unfortunately the case, this very life is limited in time by the disease that causes pain in the first place. In the case of HTA in breakthrough cancer pain, ethical evaluations appear to be the most important assessment focus among the considered ones.

REFERENCES

» Abernethy AP, Samsa GP, Matchar DB. A clinical decision and economic analysis model of cancer pain management. Am J Manag Care. 2003;9:651–664.

» Abernethy AP, Wheeler JL, Fortner BV, A health economic model of breakthrough pain, Am J Manag Care, 2008;14:S129–40.

» Darbà J , Kaskens L, Sánchez-de la Rosa R. Budget impact analysis of the fentanyl buccal tablet for treatment of breakthrough cancer pain. ClinicoEconomics and Outcomes Research 2014:6 1–9

» Fortner BV, Demarco G, Irving G, et al. Description and predictors of direct and indirect costs of pain reported by cancer patients. J Pain Symptom Manag. 2003;25:9-18.

» Fortner BV, Okon TA, Ashley J, et al. The Zero Acceptance of Pain (ZAP)TM Quality Improvement Project: evaluation of pain severity, pain interference, global quality of life, and pain-related costs. J Pain SymptomManage. 2003;25:334–343.

» Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain. 2002 Feb;3(1):38-44

» Grant M, Ferrell BR, Rivera LM, Lee J. Unscheduled readmissions for uncontrolled symptoms. A health care challenge for nurses. NursClin North Am. 1995;30:673–682.

» Kuan-Ling Kuo, SurasakSaokaew, and David D. Stenehjem. The Pharmacoeconomics of Breakthrough Cancer Pain. Journal of Pain & Palliative Care Pharmacotherapy. 2013;27:167–175.

» Ruggeri et al. Cost Effectiveness Analysis of Instanyl for the Treatment of Breakthrough Cancer Pain (BtcP) J Palliative Care Med 2013, 3:2

» Vissers DC, Lenre M, Tolley K, Jakobsson J, Sendersky V, Jansen JP. An economic evaluation of short-acting opioids for treatment of breakthrough pain in patients with cancer. Value Health 2011; 14:274–8.

A Clinical pathway for Breaktrough Cancer Pain

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ABSTRACT

Insieme con le linee guida, i percorsi sanitari o percorsi assistenziali diagnostico terapeutici (PDTA, Percorsi Diagnostico Terapeutici Assistenziali) sono strumenti di gestione clinica che permettono di definire gli standard di assistenza sanitaria e di verificare l'appropriatezza dell'assistenza fornita. I PDTA sono costituiti da processi singoli che possono essere semplici o complessi, a seconda della quantità di risorse umane e strutturali coinvolti. Possono anche essere definiti come strumenti di gestione clinici volti a fornire ai pazienti misure efficaci attraverso una sequenza logica di azioni entro un periodo di tempo ottimale. Attualmente ci sono alcuni fattori di inappropriatezza nel trattamento del BTcP in Italia; primo fra tutti il mancato riconoscimento clinico di questa entità di dolore, a causa di un' insufficiente modalità di rilevazione e monitoraggio quotidiano del dolore, anche se questo è un obbligo previsto all'art. 7 della legge 38/2010 (legge italiana n. 38 del 2010). Risulta necessaria una strategia integrata che comprenda la disponibilità di un trattamento specifico per il cancro nelle diverse forme farmaceutiche, adeguato uso di analgesici, attento controllo del dolore basale, e l'indicazione adeguata alle procedure interventistiche sul dolore. In questo lavoro abbiamo analizzato la prospettiva del paziente, della famiglia e care giver, il setting di cura, gli attori medici coinvolti, in particolare: il medico di medicina generale, specialista oncologo/radioterapista, terapeuta del dolore, il team delle cure palliative, l'Assistenza Domiciliare Integrata (ADI) e i care giver/associazioni di volontariato. In una situazione complessa come quella dovuta al BTcP in particolare, la possibilità di prendere globalmente in carica il paziente e, se necessario, tutta la famiglia, è un modo per migliorare l'assistenza e l'efficacia della terapia. Tale obiettivo è meglio perseguito attraverso un percorso di cura diagnostico terapeutico (PTDA). Il PDTA per il dolore da cancro è uno strumento di gestione utile per sostenere il medico che ha in cura il paziente. La condivisione di un percorso diagnostico e terapeutico non comporta la perdita di indipendenza e flessibilità, ma risulta essere uno strumento che supporta gli operatori nello svolgimento delle loro funzioni, con un costante adeguamento agli standard internazionali.

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INTRODUCTION

Together with guidelines, healthcare pathways or diagnostic and therapeutic care pathways (PDTA, Percorsi Diagnostico Terapeutici Assistenziali) are clinical management tools allowing to define healthcare standards and ascertain the appropriateness of the provided assistance. Healthcare pathways are made up by single processes which can be simple or complex, depending on the quantity of human and structural resources involved. They can also be defined as clinical management tools aimed at providing patients with effective measures through a logical sequence of actions within an optimal time period.

Healthcare pathways are typically developed for patients with frequent and costly diagnoses, associated with high health risks. Their purpose is to better use resources, improve the quality of care, and reduce delays in providing effective treatments. Their key principles are: focus on patients, multi-professional integration, practice based on EBM, and continuous quality improvement. Finally, the healthcare pathway allows to put guideline recommendations in a context, as regards a disease or clinical problem, within a specific setting, taking into account the available resources and local circumstances.

On a more general level, healthcare pathways allow to focus healthcare professionals' attention on citizens care requirement and on the "fulfilled" satisfaction of this demand. It is also possible to better coordinate and integrate professionals and services to adequately respond to the demand of assistance, to identify the necessary resources, to obtain specific and effective results and to measure and quantify the actual service, increasing the transparency of the healthcare pathway itself. Moreover, the implemented pathways in a healthcare service/body/region can be assessed in the light of the available human, technological, and economic resources.

Other advantages linked with the adoption of healthcare pathways include increased satisfaction and better communication among the care team members, and the possibility to change the organizational culture by promoting cooperation and a multidisciplinary approach. The need to prolong and modulate treatments during long term therapies, with possible switch between various drug classes, presents the physician with emerging pharmacoeconomic themes, especially regarding the used drug cost-effectiveness ratio and the available resources. All this makes it necessary to structure a diagnostic and therapeutic care pathway (PDTA, Percorsi Diagnostico Terapeutici Assistenziali) as a guiding tool for professionals in their fields of competence in diagnosis and treatment, and also as a useful tool of management to reach health objectives (Conferenza stato regioni 2014).

THE ITALIAN CONTEXT

Law no. 38 was approved in Italy on 15 March 2010, giving a permanent status to some resources and facilities already provided for in the following laws:

- Law no. 12 of 8 February, 2001, concerning "Norme per agevolare l'impiego dei farmaci analgesic oppiacei nella terapia del dolore" (Regulations to facilitate the use of opioid analgesic drugs in pain therapy)
- DM (ministerial decree) of 24 May, 2001, "Approvazione del ricettario per la prescrizionedeifarmaci di cui all'allegato III bis introdotto dalla legge 8 febbraio 2001, n. 12" (Approval of prescription pad for prescribing drugs as of Annex III bis introduced by law no.12 of 8 February, 2001)
- DM (ministerial decree) of 3 August, 2001 "Approvazione del registro di carico e scarico" (Approval of charge and discharge book)
- DM (ministerial decree) of 4 April, 2003 "Changes and integrations to the DM of 24 May, 2001"
- CIRCOLARE (memorandum) no.800 of 30 June, 2003
- CIRCOLARE (memorandum) no. 7990 of 4 November, 2003

With the approval of the law no. 38 of 15 March, 2010, the prescription of opioids for the treatment of pain in cancer patients is simplified and facilitated. This class of drugs may be prescribed through the national health system as a therapy lasting up to 30 days. This measure, created to facilitate access to treatment, encourages the use of these drug compounds by specialists and is an advancement on prescription rules initially established in DPR (president's decree) 309/90.

The analysis of the specific Italian context in the care framework offers an opportunity for some considerations which may help to explain why, like other European countries, BTcP in Italy is still probably insufficiently and often improperly treated (Davies, 2013). According to article 10 of Law 38/2010, GPs can prescribe all ROO (Rapid Onset Opiod) medications currently approved for sale in Italy; this is not the rule for all physicians operating within health and social welfare facilities.

In some regions, medical specialists – including palliativists and algologists – are not authorized to directly prescribe medications so that the medication costs can be reimbursed by the regional health system. In some situations, mostly in the public or private non-profit "hospital-at-home" model only available in certain regions (e.g., in Lombardy), the care team can supply medications (including ROOs) directly to the patient at home, provided that the drugs are included in the regional and/or local pharmacy formulary, or purchased from the facility to which the palliative care unit belongs. A first consequence of these limitations is that, where the specialist prescription is not direct but presented as a "therapeutic recommendation", the patient must have medications "registered" by the GP in the Italian NHS's prescription pad. This is not always automatic, since each practitioner has their own base of scientific opinions, knowledge, and experiences. Following the Law 38/2010 and related training projects, GPs have acquired a specific cultural basis in treating pain (Fanelli, 2010). Even where it is clearly indicated, through a specific legislative measure, that specialists must have and dispose all the active substances and products authorized for pain treatment, the disagreement with the application is strong at the peripheral level, it varies between one hospital, and one local health authority, and another (Decreto direttore generale sanità).

On the other hand, with a few exceptions, the technical bodies within each hospital and each local health authority since 2001, the Committees for a Pain-Free Hospital (COSD) – subsequently redefined by article 6 of the Law 38/2010 as the Committees for a Pain-Free Hospital/Community (COTSD) – have not been able to introduce useful elements to overcome this critical situation. Although contributed significantly to raising awareness among physicians and population on treatment of chronic pain, they have been established in a minority of registered healthcare facilities and, their functioning has not been continuous and they have no real powers of changing the current situation.

There are currently a few factors of inappropriateness in treating BTcP in Italy; first of all the lack of clinical recognition of this pain entity, due to an inadequate mode of detection and daily monitoring of pain, even though this is an obligation provided for by art. 7 of Law 38/2010 (Italian Law n. 38 of 2010). This serious shortcoming clearly emerges each year from the Reports that the Minister of Health must issue to the Parliament to comply with art. 11 of Law 38/2010. Secondly, the use of NSAIDs, especially via the intramuscular route, even for BTcP with repeated daily episodes. Thirdly, oral use of weak opioids even in the case of intense exacerbations. Another reason is the 'dogmatic" use of oral immediate-release morphine formulations, regardless of the comparative assessment of efficacy for each patient, especially concerning the rapidity of action and the effectiveness profile (efficacy/tolerability ratio) (Woodcock, 2012). Finally, the constant use of the same ROO system of fentanyl, among that approved for clinical use in Italy since 2005, without the prior assessment of the patient's clinical situation and preference, and of the potential support offered by the patient's family or caregiver to the therapeutic team.

The causes of these prescriptive behaviours are often independent on the level of specific knowledge of clini-

cians and result from variables outside of their control, such as a non-thorough application of pharmacoeconomic principles by purchasing decision makers. Use of lower cost medications is preferred, even though it is evident that they do not always represent the optimal treatment in BTcP. NSAIDs, for example, are associated with a large number of toxic effects (Fallon M, 2011). In addition, morphine per os, even in its immediate-release preparations, has an average time required to achieve the peak intensity which is significantly more prolonged than ROOs (Bhala, 2013). In the case of BP fluctuations, short-term oral morphine may find indications as a rescue medication, i.e., necessary to adjust the ATC treatment in relation to the circadian pain flares (Caraceni, 2012). Its uncritical use, however, in the case of a clear presence of BTcP, exposes patients to some risks: (a) the persistence of intense pain, even for 30 min after onset; (b) non-optimal control of the exacerbation; and (c) pharmacological effects of morphine needlessly longer than the duration of the BTcP episode in relation to the pharmacological and analgesic half-life of the opioid (3–4 h vs. the average BTcP duration of 60–90 min) (Zeppetella, 2009).

THE CONTEXT OF BTCP TREATMENT

It is clear that the social context and the degree of social and "collective" sensitivity to the issue of pain and suffering are elements which can facilitate, or create an obstacle to the treatment of BTcP.

Different variables may influence the initial choice of the active substance to be used, the possible switch of administration route, and the method in the BTcP treatment: characteristics of patient, family and support group, the composition of the healthcare team, the therapeutic setting, and the organizational-management-economic and local regulatory framework, more broadly defined as "context".

The management of BTcP requires an interdisciplinary approach that includes all the actors involved in cancer patients' treatment. Since BTcP affects the patient throughout the course of the disease, all specialists dealing with cancer must be familiarized with its detection and management – not only the specialist with an active part in the treatment but also primary care physicians. On the other hand, the management of BTcP should be multimodal. An integrated strategy is required that includes the availability of cancer-specific treatment, appropriate analgesic use, careful control of basal pain, and the adequate indication to interventional pain procedures (Margarit et al, 2012). Clinicians involved in cancer treatment, especially with patients in the advanced and progressive phases of disease, commonly experience that pain is not always adequately controlled, even when up-to-date treatment guidelines are followed. One of the most frequent causes of such difficulty relates to the observation that pain occurs in 80% of cancer patients in an advanced stage of disease, and it is highly intense in 30% of the cases. These pain fluctuations are often unexpected and unpredictable (Hagen, 2008). Sometimes, they can be due to predictable, though unavoidable, causes such as voluntary motor activity or automatic changes in sleeping position (Davies, 2009). In the last 20 years, the objective analysis of the clinical pathway in oncologic patients has allowed to identify, within these pain variations, a specific pain syndrome called breakthrough cancer pain (BTcP) by the international scientific community, also defined as intense episodic pain (dolore episodico intenso) by Italian physicians, although the introduction of this variation in terminology is burdened with some problems (Vellucci, 2015). BTcP is differentiated from background pain (BP) variations by: (a) its high intensity, generally 7 in a 0–10 Numerical Rating Scale (NRS); (b) a short time between onset and peak of intensity (a few minutes); (c) a short duration (approximately 60 min); (d) its potential recurrence during 24 h (3–4 daily episodes in most patients); and (e) non-responsiveness to treatment for BP, even when the daily dose of medication (primarily opioids) is increased (Corli, 2011). Even today, the clinical approach to BTcP varies markedly among physicians, from a complete negation of the syndrome to its over-estimation.

Moreover the misperception that ROO-administration

systems may be superimposed in clinical use as they all release an identical active molecule (fentanyl) is commonly held, and the idea that each product has its own specificity and appropriateness of use has not yet been sufficiently disseminated.

We need to make a rational choice based on therapy personalization through a careful evaluation of the variables, for which a definition as ''target BTcP opioid therapy'' is suggested.

BTCP BREAKTHROUGH CANCER PAIN

THE PATIENT

The choice of route and system of administration should be based primarily on patient's preference, if the patient has good cognitive functions and reasonable motor activity (Davies, 2011). The patient should be informed and educated about the four routes (gingival fornix, sublingual mucosa, oral mucosa, and nasal mucosa). The time dedicated to patient training is balanced by an increased adherence of the patient to the treatment scheme and by the reduced rates of inefficacy resulting from an incorrect use of the chosen system. The systems with easier administration instructions have a greater guarantee of success in patients who are already stressed by daily pain and suffering.

The situation is different if the patient has cognitive-relational problems, or motor activity difficulties, especially in the upper limbs and hands, or difficulty in the coordination of the complex buccal motor activity, particularly in case of automatic movements of ejection of liquids and solids from the mouth. In the more advanced stages of the disease, but also in elderly subjects, unconscious motions of sucking or ejection of what is introduced by others into the oral cavity may be present. In the first kind of patients, selection and method of administration become significant and imply an operability that is always ''active'' for the therapeutic team and more and more ''passive'' on the part of the patient. If the choice is made not to switch to intravenous bolus administration of opioids, the most appropriate ROOs for these patients are those specifically designed for the sublingual or nasal route. In the latter kind of patients, when difficulties are due to motor activity, an assessment and the preference of the patients should always be requested.

FAMILY AND CAREGIVERS

The family unit, the caregiver in particular, plays a central role in the evaluation of pain and in the interaction with the therapeutic team, also regarding drug administration and the monitoring of medication efficacy, especially in the context of home care, but sometimes even for assisted patients in residential care homes or hospices. The constant presence of a family caregiver is the most important selection criterion in taking charge of home care by a palliative care team, but this prerequisite is often not fulfilled. The presence of ''expanded'' family units is common in the composition of the Italian family, with a turnover of different relatives in the home during the day. Another point is the presence of non-family caregivers, without specific healthcare training and of non-Italian nationality, culture, and language. Increasingly, the patient is assisted by an elderly partner, who may have problems of reduced autonomy, physical and neuropsychiatric comorbidities, that limit his own ability to give care.

Regarding BTcP treatment, the care team should investigate the potential support that can be provided by the family unit or caregiver to formulate a proper therapeutic plan.

CARE SETTING

BTcP could occur in every care setting which provides assistance to cancer patients in the advanced stages of therapy: outpatient care, day hospital, inpatient care in a hospital specialist unit or hospice, residential care home, or at home.

When a health and social care team is constantly present and specifically trained in pain therapy and palliative care, the variables related to accessibility to the product

become less important, unless the care team delegates the administration of the medication to the patient or caregiver. In each setting, in the choice of BTcP treatment, the referring clinician and care team should consider all the variables described, relating to the patient and family member/caregiver. The ease of use is a "transversal" variable in the training and prescription process in all care settings. Settings characterized by a greater intensity of care can adopt more complex treatments including intravenous administration of bolus of short-term opioids or infusion systems for PCA methods.

THE ACTORS INVOLVED

The care network (multidisciplinarity) of the various health professionals (GP – oncologist – radiotherapist – surgeon and organ specialist – pain therapist – nurse) is essential to clarify the context, the objectives and the therapeutic possibilities, with the aim of better guaranteeing care continuity and to keep the patient's quality of life at the highest possible level. Managing the patient in a multidisciplinary way with the help of a team who deals with support treatments and symptom management is useful in the early disease stages to facilitate etiologic treatments and guarantee a continuity of care in the switch to palliative care. It is of basic importance and absolutely necessary to involve patients in the discussion of the treatment choices, in order to clarify the advantages and toxicity of all treatments and to agree on the best option for the single patient.

It is important to reassert the importance of a correct communication and understanding between nurse and clinician, with a constant readiness to interact with the GP and all those participating in the healthcare pathway (physiotherapist, hospital clinicians, psychologist, volunteers, family members, etc.). Especially in the initial stages of the disease, the palliative care clinician or algologist provide support to the GP or oncologist, in case of difficulty in controlling pain. In the more advanced stages of disease, when the patient is taken into care by the palliative care team, a contact with the GP is necessary at the beginning of the pathway to draft the individual assistance plan (PAI, piano di assistenza individuale) and, later on, in key therapeutic moments such as the need of sedation because of the impossibility to control the pain symptom in other ways. The contact with oncologists and radiotherapists will be ongoing, in order to evaluate the patient's pathway as a team.

GENERAL PRACTITIONER (GP)

The Law 38 of 2010 puts great emphasis in this physician. The General Practioner is a precious resource, both on the sheer professional level and on the human level, in so far as they can offer an effective and competent approach to cancer pain in all the disease phases. Since the assistance plan must increase the quality of life by taking care of the ill person in their totality, involving their family in the care process, keeping under careful and punctual control not only pain but also all other disturbing symptoms, recognizing the moment when therapies aiming to recovery or to significantly prolong survival must give way to palliative care. The GP's closeness and authority, gained through years of proximity with the family and their problems, make it possible to have them better accept and manage the most difficult health situations involving chronic diseases or a new or newly serious disease.

ONCOLOGY SPECIALIST/RADIOTHERAPIST

The oncology specialist/radiotherapist has a primary and essential role. Cancer pain relief must be a priority purpose in every phase of the disease and can be achieved by means of drug therapy alone in the majority of cases. The oncologist specialist/radiotherapist should approach the patient with a priority objective: decreasing the impact of pain on self-sufficiency and on the daily activities and relationships, i.e., the reduction of disability. To this purpose they can both directly manage pain with all the painkillers and therapeutic modalities mentioned above, and directly tackle the cause of pain, i.e., the tumor itself or any iatrogenic damage, through drug, radiant, and surgical therapies. In the first three stages, it is essential that clinicians act without hesitation, using all the pain-relieving (even opioid) drugs and, at the same time, treat the causes: the tumor itself

or any iatrogenic damage. The dual action will allow the patient to eliminate the pain and overcome disability quickly and lastingly, obtaining the progressive reduction/elimination of painkillers, as the tumor responds to the effective therapy.

ALGOLOGIST OR PAIN THERAPIST

The algologic diagnosis involves determining the anatomical source of pain, and the mechanisms producing it and causing its persistence in time. Its duty is therefore to recognize pathogenesis and features of pain so he can suggest the most adequate therapeutic strategy in each case. Therapy must involve the correct use of drugs, preferably taken orally, as recommended in the World Health Organization (WHO) guidelines, allowing to control pain syndromes in 80 to 90% of the cases. In the last years, the knowledge of pain therapy has rapidly developed, allowing to set up particular effective invasive procedures that need to be reserved to patients with specific and/or extremely complex pain syndromes thanks to the advice and involvement of the pain therapy specialist. The contribution of the pain specialist is therefore essential for a good success of the therapeutic project of pain control, both in solving "difficult" cases, and for consultation in the cases where it is possible to optimize the approach by exploiting the best options offered by medicine today. The question is not using invasive techniques as opposed to non-invasive ones, but to make justified choices.

PALLIATIVE CARE TEAM

The aim of Palliative Care is the quality of life in the presence of active, progressive and advanced-stage disease, and this is attainable by controlling not only pain, but also other physical symptoms and psychological, social, and spiritual issues.

In order to cope with the complexity of this "global" assistance, the action of various professionals is often required, who should be able to work together and always be aware of the central role of the patient with respect to the course of treatment. This is the reason for the term palliative care team. The team is organized and coordinated by a health director and all its members meet periodically. For cancer patients with (physical) pain symptoms, the prevalent roles in the team are obviously the clinician and the nurse, who have the responsibility to define the patient's individual assistance plan (PAI, Piano di Assistenza Individuale), together and/or in accordance with the GP, and to regularly update the assistance report.

An accurate case history is of utmost importance to know the patient's clinical history and past therapies, with particular respect to pain therapy, with the aim of guaranteeing the necessary assistance continuity and therapeutic efficacy in care. It is indeed likely that the Palliative Care team is involved at the end of a preceding pathway which also involved therapies, and of which the team must be aware.

CEAD – INTEGRATED HOME CARE (IHC)

CeAD is the centro dell'assistenza domiciliare (Center for Home Care), which operates by integrating municipalities, hospitals, GPs and all the network actors concurring to give integrated answers to the subjects needing assistance and care. In this setting, the IHC offers home assistance to citizen of any age in frail or non-self-sufficient conditions, whose permanent or temporary health or socio-sanitary situation prevents them from accessing local outpatient services with normal means.

CARE GIVER/VOLUNTEER ASSOCIATIONS

Cancer volunteer work has a crucial role, since it stands in for institutional functions and anticipate new solutions and methods in response to the patients' needs. Especially in this setting, however, volunteer work must not and cannot only have a supply role to institutional deficiencies, but it needs to go much further. Especially in the last years, organizations have developed a specific approach to every stage of the disease, revealing planning and directing capabilities, being the first to understand the need of good assistance continuity which takes into account non only the strictly sanitary needs,

but also the psychological, social, assistance, and spiritual needs: a multidimensional approach that goes together with the treatment of physical pain. Pain control should be a primary objective in each stage of cancer disease, not only in the final phase but also at the onset. The management of cancer and existential pain cannot and must not be limited to the final stages of the disease, but should develop within a structured pathway starting from the very moment when the diagnosis is made. Volunteer networking, together with the other involved actors, contribute to this process by listening to and assisting patients, by trying to offer a meaning, even when there seems to be none, and hope whatever may happen. In this way, in every moment of their journey, patients are not left alone in managing both issues linked to daily life and dignified and conscious end-of-life choices (ASL MB: PDTA Dolore 2012).

CONCLUSIONS

In a complex situation such is the cancer patient with severe pain, and with BTcP in particular, the possibility of globally taking charge the patient and, if necessary, the whole family, is a way to improve assistance and therapy effectiveness. This objective is best pursued by means of a diagnostic and therapeutic care pathway (PTDA). The PDTA for breakthrough cancer pain and generally for cancer pain is a useful managing tool to support the physician who is treating the patient. The PDTA main objective is to favor uniformity in the various health structures that take charge of patients, to stimulate the creation of a participatory and cooperation culture, and to encourage the management and the control of global results. The building of a technical-managerial process in BTcP, as a "pathway", defines the objectives, the roles and the fields of intervention, guarantees clarity of information for the user and a clear definition of the operators' tasks, helps improving the reproducibility and uniformity of provided services and, at same time, helps anticipating and therefore reducing extraordinary events, increasing flexibility and adaptation to changes. Sharing a diagnostic and therapeutic care pathway does not imply losing independence and flexibility, but using a tool that supports operators in carrying out their tasks, with a constant adaptation to the specific setting and a constant check of updates and improvements. In the current context of decrease and containment of public healthcare expenditure, implementing a shared PDTA at the professional level and at the political-managerial level in clinical practice involves better efficiency of the services provided, owing to a rationalization and optimization of the available resources, a higher appropriateness of services and, therefore, more qualified and more focused responses to the multiple needs expressed by the patients. This new managerial approach using pathways calls attention on the theme of punctual computing of costs and consumptions, as a prerequisite for a more correct allocation of available resources and, at the same time, pushes forward the satisfaction of health needs and the organizational appropriateness within healthcare structures.

With this view, the PDTA indicates where, when and what to do to timely make a diagnosis, to appropriately implement specific therapeutic actions, and to permanently manage the patient in the structure. It also focuses attention on activity as an object to manage in order to obtain better control on the causes of cost formation (e.g., reducing the variability of resource consumption for the treatment of one disease) and to improve the quality aspects perceived as relevant by the patient (e.g., a timely communication of the contents of their clinical treatment).

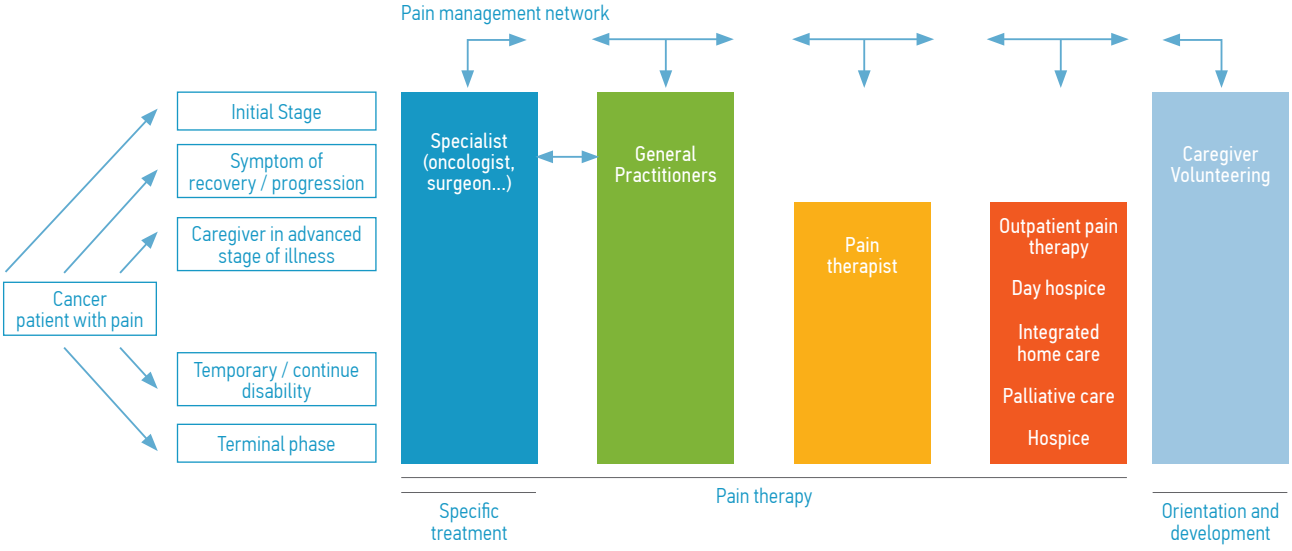
The choice to use the expression "diagnostic and therapeutic care pathway" (percorso diagnostico terapeutico assistenziale – PDTA) to define this issue has two advantages: the term "pathway" highlights the citizen/patient's experience and the organizational impact that PDTA as a tool can have on the body that uses it.

Moreover, the terms "diagnostic", "therapeutic" and "assistance" underline an active and total management (from prevention to rehabilitation) of the patient, which often need to be dealt with by means of multi-profes-

FIGURE 1

Synthesis of the cancer patient's pathway for the evaluation and management of pain

The patient with cancer pain can contact the GP and/or hospital specialist who, after appropriate evaluation, prescribe a drug therapy. Working in synergy, the GP and/or specialist can involve a pain therapist and palliative care service in the process if pain cannot be controlled with drug therapy alone any longer. In the advanced stages of disease, IHC/Palliative car also contribute to pain control, providing different therapy settings (hospice, outpatient, home care) depending on the patient's disability degree (temporary, permanent). The result of pain and relief evaluation and the applied therapy are always shared among the various actors in the patient's treatment network.



sional and multidisciplinary interventions, tackling diverse psycho-physical and social issues.

The PDTA is finally a local/regional model that, based on the guidelines and relatively to the available resources, allow to analyze the differences between the expected and the observed situation in view of improving quality.

LITERATURE

» Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382:769–79.

» Caraceni A, Hanks G, Kaasa S, et al; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012; 13(2):e58–e68

» Conferenza stato regioni 14/131/CR08b/C8 . Proposta di accordo stato-regioni sulla definizione dei percorsi di cura da attivare nei dipartimenti di salute mentale per i disturbi schizofrenici, i disturbi dell'umore e i disturbi gravi di personalità 2014. http://www.regioni.it/newsletter/n-2596/del-31-10-2014/schizofrenia-disturbi-dellumore-e-della-personalita-percorsi-di-cura-13129/

» Corli C, Pizzuto M, OICP Research Group. Per qualche dolore in meno... Capire e trattare il breakthrough cancer pain. Roma: CIC EdizioniInternazionali; 2011. (Corli, 2011)

» Davies A, Dickman A, Reid C, Science Committee of the Association for Palliative Medicine of Great Britain

and Ireland, et al. 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. 2009;13:331–8.

» Davies A, Zeppetella G, Andersen S, et al. Multicentre European study of breakthrough cancer pain: pain characteristics and patient perceptions of current and potential management strategies. Eur J Pain. 2011;15:756–63)

» Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. 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. 2009;13(4):331–338.

» Fallon M, Reale C, Davies A, et al. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, doubleblind, double-dummy multiple-crossover study. J SupportOncol. 2011;9:224–31.

» Fanelli C, Ventriglia G (eds). Il dolorecronico in medicinagenerale. Ministerodella Salute 2010.

» Hagen NA, Biondo P, Stiles C. Assessment and management of breakthrough pain in cancer patients: current approaches and emerging research. CurrPainHeadache Rep. 2008;12:241–8.

» Il percorso del paziente oncologico con sintomo dolore: diagnosi e trattamento, continuità ospedale territorio. ASLMB: PDTA Dolore 2012.

» Le 10 Raccomandazioni. DecretoDirettoreGeneraleSanità, RegioneLombardia, n. 23454, 30/12/2004 con Oggetto: Determinazioni per la costituzione del ComitatoOspedaleSenzaDolore (COSD) presso le StruttureSanitarie di ricovero e cura e adozione del "ManualeApplicativo per la realizzazionedell'OspedalesenzaDolore". pag. 22. Available from: http://www.fedcp.org/pdf/ospedale_senza_dolore.pdf.

» Margarit C, Juliá J, López R et al. Breakthroughcancerpain – still a challenge. Journal of PainResearch 2012:5 559–566

» Tola M. R., Montanari E. Baldi E et al. Il PercorsoDiagnosticoTerapeuticoAssistenzialenellaSclerosiMultipladellaRegione Emilia-Romagna: impatto sull'organizzazione, e suicosti di gestione della malattia attraverso l'impiego di un software di valorizzazione economica. ClinicoEconomics – Italian Articles on Outcomes Research, 2013 8:13-24.

» Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for non bioequivalence. N Engl J Med. 2012;367:2463–2465. doi: 10.1056/NEJMp1212969

» Zeppetella G. Breakthrough pain in cancer patients. ClinOncol (R CollRadiol). 2011;23:393–8.

» Zeppetella G. Dynamics of breakthrough pain vs. pharmacokinetics of oral morphine: implications for management. Eur J Cancer Care (Engl). 2009;18:331–7.

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