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Chapter

Breakthrough Cancer Pain

Xue-Bin Yan

Abstract

Breakthrough cancer pain has attracted more and more attentions recently because it has become the biggest obstacle to control cancer pain. Pain can occur at any stage of cancer. Despite the aggressive treatment, some patients still experience high-intensity pain in the short term, which is commonly referred to as breakthrough pain. Typical breakthrough pain has clinical features such as rapid onset and short duration, and it has uncontrollable and unpredictable characteristics, which impact the overall life quality of patients and the therapeutic effect of cancer pain. It has always been a puzzle and difficult in clinical treatment of breakthrough cancer pain. This paper aims to provide a more detailed review of the definition, assessment tools, classification and characteristics, epidemiology, and mechanism and treatment of breakthrough cancer pain, in order to facilitate the future development of this work in clinical treatment.

Keywords: breakthrough cancer pain, characteristics, mechanisms, therapy

1. Introduction

Pain is one of the most common clinical symptoms associated with malignant tumors. Thirty to forty percent of patients suffer from pain at the beginning of diagnosis [1]. In actively treated patients, this proportion is higher, accounting for 50%, and in advanced cancer, even up to 90% [2]. Although it can effectively control the background pain of most cancer patients according to the WHO three-step analgesic principle, it still suffers from cancer pain. Cancer patients, indeed, may suffer from intense pain spikes that break through the control of chronic pain. Uncontrollable and unpredictable characteristics of a complex manifestation of cancer pain, termed as breakthrough cancer pain (BTP), have always baffled the treatment and the adverse effects including diet, sleep, daily activities, relationships with others, aggravating depression and anxiety and will impact patients' quality of life. Therefore, the control of breakthrough cancer pain is still a very difficult problem for clinicians. In view of the current lack of research data on outbreak pain in China, this paper aims to provide a more detailed review of the breakthrough cancer pain, in order to facilitate the future development of this work in clinical treatment.

2. The definition of breakthrough cancer pain

Background pain in cancer patients manifests as a persistent state of pain (most commonly 12 hours or longer), usually controlled by long-term administration. According to the WHO three-step analgesia program, general background cancer

pain can be adequately controlled in 70–90% of patients [3]. Despite good control of baseline pain, some patients have short-term, short-lived, intense pain episodes. This is called breakthrough cancer pain (BTP) [4].

The first definition of cancer pain is proposed by Portenoy and Hagen in 1989 as the following: BTP is a transient increase in pain, greater than moderate intensity, occurring on moderate- or lower-intensity baseline pain [5]. In the third edition of Oxford palliative medicine textbook, BTP is defined as a transient deterioration of pain experienced by patients with relatively stable and well-controlled baseline pain [6]. In 2009, the UK and Ireland Conservative Treatment Collaborative Committee (APM) put forward the following views on outbreak pain and concluded that as long as the following three conditions are met at the same time, it can be diagnosed as an BTP: (1) having background cancer pain, (2) the background cancer pain adequately controlled in the last week (NRS score ≤ 3 points), and (3) the pain temporarily acutely aggravated [7].

3. Evaluation tools for breakthrough cancer pain

For cancer patients, the intensity of pain should be assessed at each visit. The most common is the numerical score (NRS). The pain intensity level from 0 to 10 is evaluated as 0 indicating lack of pain (no pain) and 10 indicating the most extreme pain (the most imaginable pain). Visual analog scale (VAS) is also frequently used; patients use a 100 mm length digital scale to describe pain intensity (0, no pain; 100, the most powerful pain imaginable). The descriptive Likert scale (painless, mild pain, moderate pain, strong pain, severe pain) is the least accurate but is usually the most understandable for the patient.

But general tools may not be sufficient to adequately cover the complexity of BTP. Several specific features of BTP are reflected in background pain, treatment-related factors (including trigger events and predictability), and time factors. Key factors include relationship to background pain, time to last BTP, frequency, peak pain intensity, position, time from onset to maximum intensity, duration, cause, predictability, general remission, BTP relief, pain satisfaction with relief, the onset of pain relief, and satisfaction with the onset of pain relief. Other items completed by professionals include the etiology of BTP and the pathophysiology of BTP [8]. Understanding these factors is critical to being able to construct an effective analgesic strategy, which is the primary purpose of any pain assessment. The lack of BTP assessment tools may be related to the fact that some authors advocate the use of general pain tools without the need for a separate BTP assessment tool [9, 10]. Recently, a new evaluation tool was developed and validated for BTP (Webber's BAT tool). The assessment tool provides information about BTP and how the efficacy and toxicity of BTP drugs interfere with everyday life, and the reliability and effectiveness of testing in a group of patients is quite good [11].

Portenoy et al. used the Beck Depression Scale (BDI) questionnaire, the beck anxiety scale (BAI) questionnaire, and the baseline pain intensity measurement based on the VAS scale to assess the impact of BTP on quality of life. In 178 patients with well-controlled baseline pain, both groups were extracted and evaluated based on whether they had BTP. In 65% of patients, BTP is caused by cancer, and in other cases it is related to the treatment used. Baseline pain is more severe in patients with BTP. In addition, how pain affects mood, work, sleep, mobility, social relationships, and life satisfaction is also assessed. Each aspect is evaluated over a range of values from 0 to 10 (0, no effect; 10, overall impact). In the case of the BDI and BAI scales, the patient responded to 21 questions, ranging from 0 to 3 (0 for asymptomatic and 3 for highest symptom intensity) [12].

It is worth noting that BTP may have a negative impact on prognosis [13] and may also have an adverse effect on the duration of cancer treatment [14]. Accurate diagnosis of pain types and early introduction of appropriate treatments should be sought. Moreover, in the lack of exhaustive tools, successful BTP diagnosis (and management) is the result of the combination of adequate assessment, appropriate (tailored) treatment, and adequate reassessment.

4. Classification and characteristics of breakthrough cancer pain

Breakthrough cancer pain can be divided into sporadic pain (incidental pain), spontaneous or idiopathic pain, and discontinuation of drug withdrawal (end of dose). Mixing BTP can also be included as the fourth subtype [15]. Sporadic pain is a common type of BTP, with a shorter peak intensity and a shorter duration, more predictable, often caused directly after muscle or bone activity, such as getting up, turning over, going to toilets, coughs, etc. It can also be associated with contraction or spasm of visceral smooth muscle, such as bowel or bladder spasm, so patients are more willing to limit their activity to avoid triggering BTP, although the duration of pain is unpredictable even after cessation of activity. There is no obvious cause of self-explosive pain, and the duration of pain is more than 30 minutes. It is generally not directly related to regular analgesic treatment and has no significant correlation with physical activity [16]. In general, when there is sufficient analgesia for most of the day, three to four episodes per day are considered acceptable [17]. Insufficient analgesic drugs are relatively rare. It often occurs at the next point in the continuous analgesic treatment phase for 1–2 hours, and acute pain occurs on the basis of continuous pain treatment. APM believes that the analgesic drug dose-deficient outbreak is caused by insufficient control of the underlying cancer pain and that it is not a BTP [7].

BTP is characterized by a rapid onset, usually occurring in a matter of minutes or even seconds (average about 3 minutes), stronger than baseline pain, up to 7 points (NRS score), and very short duration (average 30 minutes) [1]. In a large study of 1412 patients, 80.6% of patients reported a significant negative impact of BTP on daily life. The average number of episodes was 2.4 per day with an average intensity of 7.4/10. In patients reporting a rapid onset of BTP, this is predictable in approximately half of the cases, while BTP with a gradual onset (>10 minutes) is less predictable. The average duration of an untreated episode of BTP was approximately 30 minutes [10]. These characteristics may change during the course of the disease. For example, patients who are receiving palliative care are older, have lower levels of Karnofsky, have fewer BTP episodes per day, and have slower BTP episodes than those assessed in the pain clinic or oncology ward. BTP is less predictable [18].

Davies et al. published the results of a multicenter clinical trial involving 1000 patients treated in 28 professional palliative care units in 13 European countries from 2008 to 2011. Patients were classified as eligible for trial according to a questionnaire on five questions. Forty-four percent of patients were induced by specific factors, 41.5% were idiopathic, and 14.5% were mixed. The results showed that specific factors caused by BTP patients' activity problems and basic daily activities were more frequent, while those with idiopathic pain were more common with changes in mood and sleep problems [18].

5. Epidemiology of breakthrough cancer pain

There are wide variations in the estimates of incidence reported in the literature, possibly due to the different backgrounds and implications of the definition

of BTP. A multicenter study in the four Nordic countries in 201,135 surveyed the incidence of BTP in 320 patients with cancer pain by issuing questionnaires, all from palliative care centers or pain treatment centers. Of these, 83% had breakthrough cancer pain, in which 44% had sporadic outbreaks, 39% had spontaneous outbreaks, and 17% had both types of pain. On average, there were three outbreaks of pain every 24 hours. The longest interval was 2 times/week, and the shortest interval was 24 times a day. According to the degree of pain, 3% of patients were mild, 37% were moderate, and 60% were severe [8].

In some epidemiological studies, although not verified, the patient's background pain may be uncontrolled or not receiving opioids. For example, in more than half of patients with severe background pain, a different phenomenon than other patients was observed, and patients without BTP had higher background pain intensity. In other studies, most patients had uncontrolled background pain, who received non-opioid analgesics or weak opioids or were dissatisfied with pain management.

6. Mechanisms of breakthrough cancer pain

The pathogenesis of cancer pain is very complicated. The most common causes are malignant tumor compression and infiltration of pain-sensitive organ structures such as bones, muscle soft tissue, peripheral nerves, internal organs, and the others. There is also atrophy and cancer cachexia, or it may be the result of aggressive anticancer treatment, but the real cause in some patients is unclear [19].

The most common nociceptors associated with cancer pain are afferent nerves, which can transmit various noxious stimuli to the central nervous system through the periphery. Nociceptors mainly have two major functions: transduction of pain signals and transmission of pain signals. Various noxious stimuli can directly activate the nociceptors, transmitting the electrochemical nerve impulse signals generated by the afferent nerves to the central nervous system of the patient, and the patient has a feeling of pain. Cancer and immune cells in the tumor mass region release several neuroimmune mediators that interact with multiple receptors on peripheral nociceptive nerve terminals to promote abnormal discharge and hyperexcitability. In addition, tumors that grow near the peripheral nerve can impair the integrity of the nerve and induce neurological conditions associated with persistent pain, hyperalgesia, or allodynia. Both of these effects of the tumor on the peripheral nerves can lead to central sensitization, which further enhances the efficacy of nociceptive transmission through the spinal dorsal horn and the perception of BTP [20].

During the operation, tissue damage associated with damage to the surrounding small nerves can be caused. After tissue damage, inflammatory mediators and other substances (e.g., histamine, serotonin, nerve growth factor, bradykinin, leukotrienes, prostaglandins, norepinephrine, cytokines, etc.) are damaged at the wound site tissue and inflammatory cells, and sympathetic nerve endings are released. The released material can alter the excitability of nociceptors by phosphorylating and upregulating the cell membrane or upregulating ion channels in the nerve. This peripheral sensitization can explain the increased sensitivity of early postoperative clinical manifestations to mechanical stimulation of the wound site. However, postoperative pain cannot be explained only by peripheral mechanisms. Repetitive, detrimental input from sensitized C fibers causes activation of the signal cascade within the dorsal horn cells, thereby facilitating the response. Central sensitization may explain the increased sensitivity of noninvasive tissue around the wound to mechanical stimulation. Under these conditions, mechanical stimulation caused by exercise and cough may cause BTP [21].

Recent studies have found that specific nuclei located in the posterior thalamus are associated with pain-related networks. Related studies have found that the most effective inhibitors of noxious stimuli are β-endorphin, enkephalin, and dynorphin. The most common precursor of β-endorphin is proopiomelanocortin; the precursor of enkephalin and leucine enkephalin is mainly proenkephalin-A (pro-ENK); the precursor of dynorphin is enkephalin original B. B-Endorphin mainly binds to opioid receptors, and enkephalin mainly binds to opioid receptors, and dynorphin mainly binds to opioid κ receptors. The commonly used opioids, oxycodone and morphine sustained-release tablets, are combined with receptors and/or K receptors to mimic the action of endogenous opioid peptides to achieve analgesic treatment [22].

Visceral pain may be located in the visceral or distant body parts. Two types of nociceptors dominate the internal organs: high threshold receptors and intensity-encoded mechanoreceptors. In addition, the presence of "silent" nociceptors has been found. "Silent" nociceptors are activated in the event of tissue damage or inflammation and may contribute to the signaling of chronic visceral pain. High threshold nociceptors may be activated in acute pain states. For example, prolonged stimulation of the internal organs, such as inflammation, may sensitize high threshold nociceptors and activate "silent" nociceptors. Sensitized nociceptors may now also respond to harmless stimuli. Increased peripheral neuronal activity results in increased excitability in the visceral-somatic neurons in the spinal cord (central sensitization). For example, BTP caused by food intake can be explained by sensitization of visceral mechanoreceptors, and the increase in pain area is due to central sensitization [23].

Our team found that the activation of astrocytes in the dorsal horn of spinal cord and connexin 43 (Cx43) protein is involved in the process of bone pain in bone metastases in mice. The total amount of Cx43 protein and phosphorylation may be important factors affecting cancer outbreak pain factor. Gap 26 blocks the gap junction channel of the spinal dorsal horn, which can improve the pain behavior index of mice with cancerous outbreak pain and downregulate the expression of Cx43 protein, which can regulate the pain of cancerous outbreak. The spinal dorsal horn EAAT1 protein is involved in the pathogenesis of mouse basic cancer pain, and EAAT2 protein has an effect on the occurrence and maintenance of bone metastases. Activation of EAAT2 by Cef improves its pain behavioral metrics and regulates burst pain. Cx43 can affect the protein expression of EAATs but EAAT2 does not affect the expression of Cx43 protein. Spinal dorsal horn Cx43-EAATs may play a role in cancerous outbreaks [24].

7. Treatment of breakthrough cancer pain

Treatment with BTP includes medication, nerve block, nerve damage, TNES, palliative exposure to bone lesions, the use of bisphosphonates, and identification and prevention of factors that induce BTP (e.g., excessive physical labor, persistent cough, constipation). The NCCN guidelines for adult cancer pain [25] recommends the use of 10–15% of immediate-release opioids in total daily analgesics to treat BTP. If the number of outbreaks of pain per day exceeds 4 times, the amount of the basic analgesic drug is raised. Opioid analgesics have no ceiling effect. For severe refractory pain, high-dose opioid controlled-release preparations are often needed for analgesic treatment. Large doses are defined as daily doses of oxycodone sustained-release tablets (or equivalent doses of other opioid analgesics such as fentanyl transdermal patches or MS contin) up to 150 mg/d.

7.1 Drugs

Opioids are still the most important and effective drugs for the treatment of breakthrough cancer pain [26]. The main opioids currently used to treat BTP are morphine immediate-release tablets, oxycodone sustained-release tablets, fentanyl sublingual tablets (SLF), morphine sustained-release tablets and controlled-release tablets, fentanyl nasal spray (INFS), fentanyl transmucosal citrate (OTFC), morphine sulfate (injection), sufentanil injection (injection), and so on. The above various types of morphine agonists work in combination with secretory opioid receptors, which produce analgesic effects after agonizing the receptor.

Oral administration is the most common route of administration for cancerous outbreaks and is the recommended route of administration by the WHO. The NICE guidelines recommend immediate-release of morphine for BTP first-line first-aid drugs and do not provide fentanyl as a first-line rescue drug but morphine. The onset and duration of immediate-release tablets may not be suitable for the treatment of many BTP events [27]. Oxycodone sustained-release tablets can be used as a two-step drug or as a three-step analgesic drug, which can simultaneously agonize both receptors and K receptor opioid receptors, with high bioavailability and clinical good analgesic effect and less drug-related adverse reactions [22]; the analgesic intensity is about twice that of morphine immediate-release tablets. After oral administration, there will be two release phases, which provide early onset of rapid analgesia. The fast release phase and the subsequent sustained-release phase, through the rapid release phase to achieve the purpose of treating burst pain, do not require conversion of the dosage form; clinical application of oxycodone controlled-release tablets is more and more extensive.

In order to evaluate the efficacy of oral morphine and oral transmucosal fentanyl preparations to provide further insight into their relative merits as treatments for BTP, we conducted an analysis to compare the effects of fentanyl, morphine, and placebo on BTP indirectly (**Table 1**, **Figures 1–6**). The therapeutic effect was evaluated by the difference in pain intensity difference (PID) score. We found that all opioids provided better analgesic effects during the first hour after dosing, whereas fentanyl may provide a higher level of pain relief than oral morphine. Participants administered a transmucosal fentanyl showed lower pain intensity and higher pain relief at all time points than placebo or oral morphine, and the fentanyl achieved significant pain relief faster. But there is no significant difference between the various transmucosal fentanyl preparations. From the PID score, the analgesic effect of fentanyl is stronger than oral morphine. And improvements in pain relief were apparent within 30 minutes of treatment, with the PID being larger for the fentanyl preparations than for MSIR during this period. This is of potential importance because most BTP episodes occur within 30 minutes. However, there are few existing studies, especially regarding the comparison of fentanyl with oral morphine, which is a limitation of this mixed treatment. Moreover, the possibility of systematic differences between undetected data sources for heterogeneity analysis cannot be ruled out. In conclusion, although oral morphine is still an appropriate treatment option for BTP, oral transmucosal fentanyl may be more clinically advantageous in some patients.

The recently published guidelines support this approach and recommend the use of fast- or short-acting opioids to treat BTP, whose pharmacodynamics reflect the rapid onset and short duration of pain [28]. The Cochrane review reported the utility of seven different transmucosal fentanyl compared to oral opioids. Oral and nasal transmucosal fentanyls are an effective treatment for BTP [29]. The drugs such as fentanyl oral effervescent tablets and fentanyl sublingual tablets have also

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Fentanyl (F) and placebo/morphine PID (C)												
Study	**5 minutes**		**10 minutes**		**15 minutes**		**30 minutes**		**45 minutes**		**60 minutes**	
	F	**C**	**F**	**C**	**F**	**C**	**F**	**C**	**F**	**C**	**F**	**C**
INFS vs. placebo (HANS2009 [33])	N	N	2.58	1.22	N	N	N	N	N	N	4.57	2.46
INFS vs. placebo (RUSSELL2010 [34])	0.59	0.49	1.32	0.93	1.96	1.33	2.69	1.73	3.19	2.08	3.57	2.21
INFS vs. placebo (MORTEN2015 [35])	N	N	2.4	1.5	N	N	N	N	N	N	N	N
INFS vs. IRMS (FALLON2011 [36])	1	1	2.02	1.8	3.22	2.68	4.38	3.64	4.95	4.47	5.58	5
SFT vs. placebo (NAOHITO2015 [37])	N	N	N	N	2.43	2.06	4.11	3.39	N	N	5.58	4.52
SFT vs. placebo (RANCK2009 [38])	N	N	1.2	0.92	2.04	1.51	2.94	2.1	N	N	3.45	2.51
SFT vs. placebo (NOVOTNA2014 [39])	0.7	0.5	1.6	1.1	2.6	1.8	3.5	2.5	N	N	3.9	2.7
SFT vs. placebo (NAOHITO2015 [40])	N	N	N	N	N	N	3.18	2.7	N	N	N	N
OTFC vs. placebo (RAUCK2009 [41])	0.3	0.3	0.8	0.7	1.4	1.2	2.5	1.9	3	2.3	3.3	2.4
OTFC vs. IRMS (PAUL2001 [42])	N	N	N	N	1.86	1.46	2.88	2.4	3.55	3.03	4.03	3.57

Table 1.
META analysis data

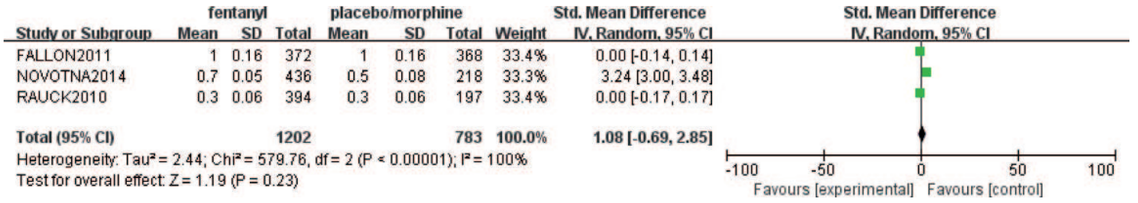

Figure 1.
Fentanyl versus placebo/morphine PID 5 minutes.

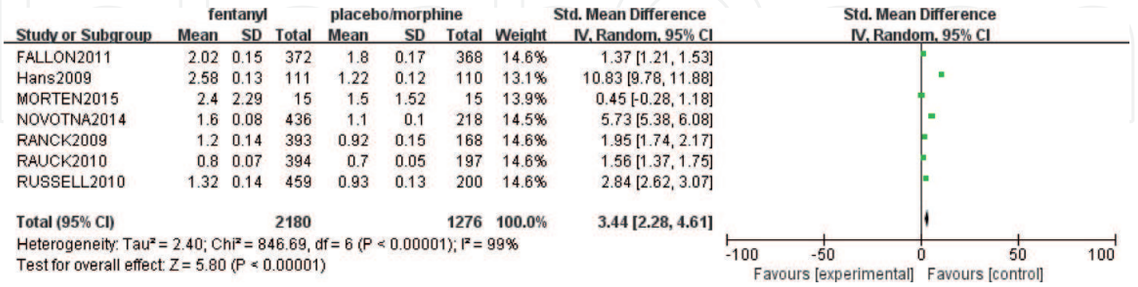

Figure 2.
Fentanyl versus placebo/morphine PID 10 minutes.

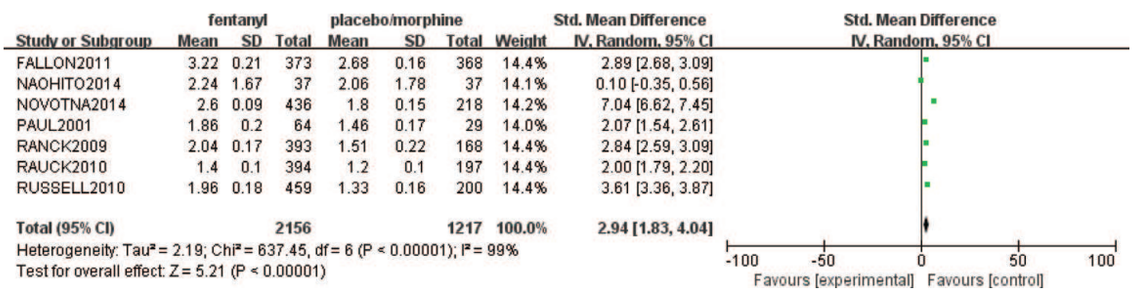

Figure 3.
Fentanyl versus placebo/morphine PID 15 minutes.

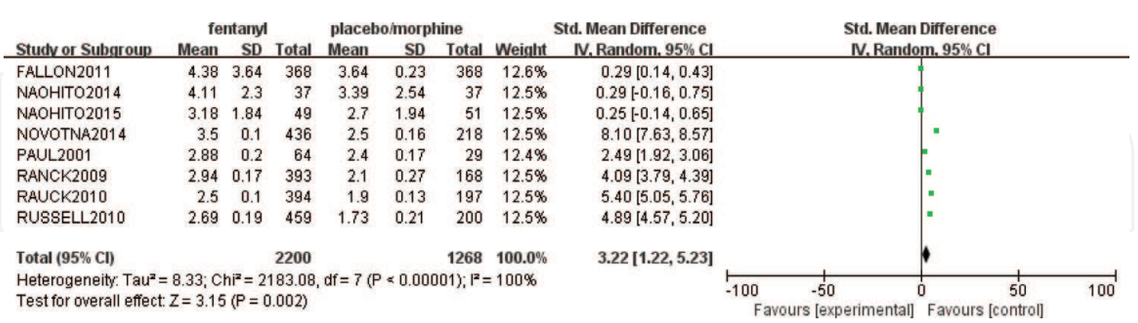

Figure 4.
Fentanyl versus placebo/morphine PID 30 minutes.

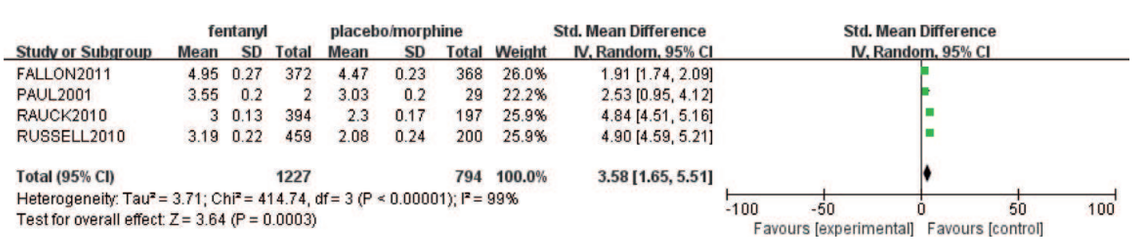

Figure 5.
Fentanyl versus placebo/morphine PID 45 minutes.

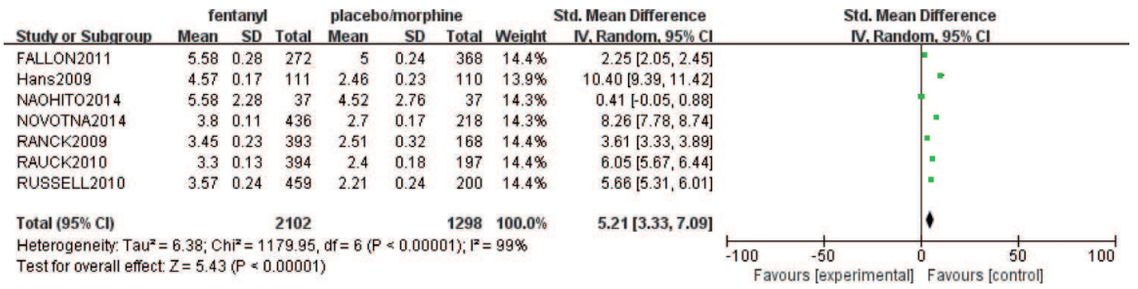

Figure 6.
Fentanyl versus placebo/morphine PID 60 minutes.

been approved for use in European and American countries. However, the state of oral mucosa, drug distribution, and oral infections will affect the absorption of drugs, thus affecting the analgesic effect of drugs. Fentanyl nasal spray (INFS) has been approved by the European Commission in 2009 and has been officially used in the clinic. It has been marketed globally and is mainly used for outbreak pain in cancer patients who maintain analgesic treatment with drugs such as oral opioids. Treatment: nasal mucosal sprays are suitable for those with oral mucosal damage or saliva dysfunction, but those with nasal mucosal bleeding or ulcers need to switch to other treatments [30].

Both morphine sulfate injection and sufentanil citrate injection can be administered intravenously. Intravenous use of opioids has a fast onset and a positive effect [31, 32]. However, it is necessary to evaluate the pain every 15 minutes, and should be alert to the acute side effects of drugs such as respiratory depression [32], vomiting, dizziness, acute urinary retention, etc., especially acute respiratory depression, severe cases can be directly life-threatening, so opioid veins The application should be performed in a ward with emergency conditions or in an emergency ward, and an opiate rescuer naloxone is prepared at the bedside.

Individualized doses and modes of administration can also be tailored to the condition, and stable morphine is delivered to the human body via intravenous (PCIA), epidural (PCEA), and subcutaneous (PCPA).

7.2 Cell therapy

Cell treatment is to return autologous cells cultured in vitro to patients. Through these cells with biological micro-pump function, they can continue to secrete analgesic substances to relieve pain or improve pain thresholds, such as serotonin, norepinephrine, dynorphin, enkephalin, neurotrophic factor, etc., to achieve the purpose of relieving cancer pain or improving the pain threshold of patients. The most extensive and intensive research is the analgesic effect of adrenal chromaffin cells, sympathetic ganglion cells, and some neurotumor cells.

7.3 Gene therapy

Gene therapy refers to a method of achieving analgesic effects by altering gene expression in a patient. It can be divided into in vivo pathways and in vitro pathways. In vitro route refers to the removal of target cells from the body or the adoption of cell lines and the in vitro introduction of therapeutic genes into the body for therapeutic purposes. In vivo route refers to the direct introduction of therapeutic genes into the body. In pain research, there are two main aspects of gene therapy, namely, by upregulating anti-pain gene expression and downregulating pain gene expression, specifically interfering with the biological behavior of pain for therapeutic purposes.

7.4 Interventional neuroradiologic therapy

Nerve block and nerve damage are one of the main treatments for cancer pain by blocking the pain transmission pathway. The current clinical damage treatment is damage to peripheral nerves, nerve roots, celiac plexus, subarachnoid space, and pituitary gland. Before the operation, physical examination and imaging methods were used to fully determine the pain range of the patient, and the nerves to be controlled were determined. Under the guidance of CT, the target nerve was destroyed by means of anhydrous alcohol, chemotherapy drugs such as doxorubicin, or physical ablation. Analgesic effect, with positive effect, fast onset, and little effect on other organ functions, has unique advantages for outbreak pain and intractable cancer pain that are ineffective for medical treatment. Currently, nerve blockers or lesions often have anesthesiologists, or the implementation of pain specialists in specialist hospitals has extremely high requirements for the operation of doctors in the positioning of nerves and imaging; otherwise it is likely to cause serious consequences.

8. Summary

Breakthrough cancer pain is a type of problem that clinicians urgently need to solve. There is currently no recognized definition and classification system for cancer BTP, and there are no well-proven BTP assessment tools that pose significant challenges to clinical management. Although breakthrough cancer pain has common clinical features, there are significant differences between individuals, which require clinicians to emphasize the importance of individualized, multidisciplinary analgesic programs on the basis of comprehensive treatment. In short, the current overall treatment effect of breakthrough cancer pain is not good; it is worthy of our attention.

Author details

Xue-Bin Yan
The Third Xiang-Ya Hospital of Central South University, Changsha, China

*Address all correspondence to: yanxb999@126.com

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