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ADAPTA project: adequacy of treatment in breakthrough cancer pain

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ABSTRACT

Introduction: Transmucosal fentanyl has specific properties which make it ideal for the treatment of breakthrough cancer pain (BTCP). Although there is a broad consensus for the administration of transmucosal fentanyl for BTCP in Spain, there is uncertainty as to the way oncologists adjust their prescription to the patient and what are the determinants of the choice of different pharmaceutical forms.

Objectives: The main objective of this study was to analyze and prioritize the attributes that Spanish oncologists consider when assessing treatment options with transmucosal fentanyl in patients with BTCP.

Methods: A Scientific Committee performed a classification of 14 relevant attributes in the prescription of transmucosal fentanyl for BTCP. Subsequently, a dossier of scientific evidence was generated comparing these 14 attributes among the different available transmucosal fentanyl formulations, which was shared with the panel of experts (115 Medical Oncologists). After a thorough review of the document, the participants carried out an online vote for the prioritization of the attributes.

RESUMEN

Introducción: El fentanilo de administración transmucosa tiene características específicas que lo convierten en el fármaco adecuado para el tratamiento del dolor irruptivo oncológico (DIO). Aunque en España existe un amplio consenso sobre la idoneidad de la administración de fentanilo transmucoso para el DIO, es relevante conocer cómo los oncólogos adecuan su prescripción al paciente y cuáles son los factores determinantes de la elección de las diferentes formas farmacéuticas.

Objetivos: El objetivo principal de este proyecto fue identificar y priorizar los atributos que los oncólogos médicos españoles tienen en cuenta cuando valoran las opciones de tratamiento con fentanilo transmucoso en pacientes con DIO.

Métodos: Un comité científico realizó una tipificación de 14 atributos relevantes en la prescripción de fentanilo transmucoso para el DIO. Posteriormente se generó un dossier de evidencia científica comparando estos 14 atributos entre los distintos fentanilos transmucosos disponibles, que se compartió con el panel de expertos (115 oncólogos médicos). Tras una exhaustiva revisión del documento, los participantes realizaron una votación online de priorización de los atributos.

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Results: Out of fourteen attributes analyzed, seven achieved a consensus of ≥ 50 % of the participants: the start of the analgesic action (84 %), the adequacy of the effect of fentanyl to the BTCP episode (72 %), the ease of use (58 %), the presence of mucositis (57 %), the ease of titration of the optimal dose (57%), and the variety of presentations and doses available (59 %).

Conclusions: The most valued attributes were those related to the speed of action of the analgesic treatment and its adaptation to the BTCP profile, something to be expected given the spontaneous, unpredictable, and transitory nature of BTCP. As less valued attributes appear the risk of abuse or aberrant behavior and the presence of rhinitis for its administration, which indicates that the existence of these factors do not influence the choice of treatment for BTCP. These results will allow medical oncologists to know what attributes should be taken into account when customizing the patient's treatment of BTCP in order to improve the adequacy of rescue analgesia.

Key words: Breakthrough cancer pain, opioids, fentanyl, cancer pain management.

Resultados: De catorce atributos analizados, siete consiguieron un consenso de ≥ 50 % de los participantes: el inicio de la acción analgésica (84 %), la adecuación del efecto del fentanilo al perfil del episodio de DIO (72 %), la facilidad de uso por los pacientes y cuidadores (69 %), la duración del efecto (58 %), la presencia de mucositis (57 %), la facilidad de titulación de la dosis óptima (57 %) y las presentaciones y dosis disponibles (59 %).

Conclusiones: Los atributos más valorados fueron los relativos a la rapidez de acción del tratamiento analgésico y su adaptación al perfil del DIO, algo esperable dadas las características clínicas del episodio de DIO. Como atributos menos valorados aparecen el riesgo de abuso o conductas aberrantes y la presencia de rinitis para su administración, lo que indica que la existencia de estos factores no tiene tanta influencia en la elección del tratamiento para el abordaje del DIO. Estos resultados permitirán a los oncólogos médicos conocer qué atributos deben ser tenidos en cuenta a la hora de personalizar los tratamientos del paciente con DIO con el objetivo de mejorar la adecuación de la analgesia de rescate.

Palabras clave: Cáncer, dolor crónico oncológico, factores de riesgo, catastrofismo, método Delphi.

INTRODUCTION

Breakthrough pain is defined as a transient exacerbation of pain occurring spontaneously or in relation to a specific trigger, predictable or unpredictable, despite stable and adequately controlled baseline pain (1). Although breakthrough pain may occur in the context of several baseline pains (2), it has been better characterized in the oncology field. Breakthrough cancer pain (BTcP) can appear as a direct consequence of the tumor (70-80% of all cases), as a result of cancer therapy (10-20% of patients) or unrelated to the tumor or treatment (<10% of all cases) (3). The specific trigger factors of the BTcP can be identified in about half of the cases (4).

In 2013, a group of Spanish experts including specialists in Medical Oncology, Radiation Oncology, Pain Treatment Units and Palliative Care Units adopted a consensus document on the diagnosis and treatment of BTcP, which they defined as "an acute exacerbation of pain of rapid onset, short duration and of moderate to high intensity, that the patient suffers when he/she presents a stable baseline pain and controlled with opioids" (5). According to this consensus document, the ideal drug for the treatment of BTcP should meet the following specifications: a) be a powerful analgesic; b) have a rapid onset of action of 10 minutes or less; c) have a short duration of the effect (2 hours or less); d) have minimal side effects; and e) be easy to administer (easy, non-invasive and self-administered) (5). These attributes have been described in other studies by both Spanish oncologists (6) and foreign oncologists (7,8), and the consensus document has been adopted by the Spanish Society of Medical Oncology (SEOM), the Spanish Society of Radiation Oncology (SEOR), the Spanish Society of Palliative Care (SECPAL) and the Spanish Society of Pain (SED).

The various formulations of transmucosal fentanyl, for both buccal or nasal administration, have been a worthnoting improvement available to the physician for the therapy of breakthrough pain in cancer patients (9). These formulations have improved the efficacy and rapidity of action of classical opioids, including morphine, and their tolerability by patients is equivalent. Thus, the aforementioned consensus document indicates that "currently fentanyl is the active principle that best suits the analgesic needs of breakthrough pain due to its high analgesic potency and high lipophilicity, regardless of the major opioid used for the control of baseline pain" (5).

In 2010, the Declaration of Montreal proposed at the International Pain Summit recognized access to pain management as "a fundamental human right" (10). However, the prevalence of BTcP has been estimated that can reach up to 95% depending on the type of cancer and the diagnostic criteria, and about 60-90% of cancer patients die with pain (11). In Spain, considering that the prevalence of pain is very high in advanced stages of cancer (70-90%), it is estimated that at least 75,000 people face pain caused by cancer each year,

with pain being the most feared symptom among these patients (12).

Clearly, the definition of BTcP, its diagnosis, assessment and monitoring can influence the choice of a treatment and, consequently, the patient's outcomes. Therefore, reaching a consensus on these issues among a wide group of experts in this type of pain is important. The objectives of this study was, on the one hand, to review the available evidence to analyze and differentiate the attributes that oncologists consider to evaluate treatment options with transmucosal fentanyl in patients with BTcP. On the other hand, the objective was also to prioritize and generate recommendations on what attributes should be taken into account when customizing patient's treatments with BTcP in order to improve the adequacy of rescue analgesia.

METHODS

This project was conducted between May 21 and June 20, 2017 through the use of an online participatory tool. This collective intelligence tool was developed in three steps. In the first phase, a Scientific Committee comprised of Dr. Luis Cabezón Gutiérrez (Medical Oncology Service, University Hospital of Torrejón de Ardoz, Madrid) and Dr. Cecilio Álamo González (Department of Pharmacology, University of Alcalá, Madrid) drafted a list of 14 attributes relevant to the prescription of transmucosal fentanyl for the BTcP (Table I). During the second phase, a review of the available evidence based on technical data sheets and literature was coducted to analyze and differentiate these attributes among the different available transmucosal fentanyls. Then, a complete Dossier of Evidence and an executive summary (Table II) were generated and shared, via electronic mail, with 115 medical oncologists from all over Spain. After the review of the dossier, the third and final phase began, the experts voted online through an online application for the prioritization of the 14 attributes.

TABLE I
ATTRIBUTES IDENTIFIED BY THE SCIENTIFIC COMMITTEE

- Onset of the analgesic action
- Duration of the analgesic effect
- Administration time requirements
- Need for saliva
- Presence of mucositis
- Presence of rhinitis
- Local adverse effects
- Ease of use
- Ease of dose titration
- Time require to explain the correct administration by heatlh staff
- Risk of abuse and aberrant behavior
- Available doses and presentations
- Level of evidence
- Adaptation (adequacy of the effect to the profile of the BTcP episode)

RESULTS

The key question "What attributes do you consider most important when prescribing a treatment with transmucosal fentanyl for BTcP?" was asked to 115 oncologists. A total of 105 complete answers were obtained (94% participation).

Figure 1 shows the ranking of attributes obtained after the analysis of the voting. A total of 7 attributes out of the 14 established attributes obtained a majority of ≥ 50% of the participants: the onset of the analgesic action (84%), the adequacy of the effect of fentanyl on the profile of the BTcP episode (72%), ease of use (69%), duration of the analgesic effect (58%), presence of mucositis (57%), ease of dose titration (57%), and the availability of doses and presentations (50%). In contrast, the three attributes that had less relevance when prescribing a transmucosal fentanyl for BTcP were: the possible occurrence of adverse effects (35%), the risk of abuse or aberrant behavior (27%) and the presence of rhinitis (23 %).

DISCUSSION

The attribute reaching the highest level of consensus (84% of the participants) was the "onset of the analgesic action". The rapidity with which the decrease or disappearance of pain due to therapy occurs is a primary requirement in the management of spontaneous or incidental breakthrough pain in the cancer patient. In this sense, despite the average time of onset of an episode of breakthrough pain is 2 to 3 minutes, the pain may last up to 1 hour, although approximately 73% of the episodes last less than 30 minutes. Among the currently available fentanyl formulations, fentanyl pectin intranasal spray provides the fastest onset of analgesia: 5 minutes after administration (25). Transmucosal fentanyls of buccal or sublingual administration have longer analgesic times, reaching in some cases even 15 minutes (11). In contrast, oral forms of immediate release of morphine or oxycodone show their analgesic effect approximately 30-40 minutes after oral administration, being clearly insufficient to adequately control the BTcP. Despite this, a recent survey showed that oral forms these are still widely administered (up to 98% of patients) in some northern

TABLE II
EXECUTIVE SUMMARY OF EVIDENCE

	Transmucosal buccal fentanyl			*Transmucosal sublingual fentanyl*		*Intranasal fentanyl*	
	Compressed lozenge with integral oromucosal applicator (Actiq®)	*Fentanyl buccal tables (Effentora®)*	*Fentanyl buccal soluble film (Breakyl®)*	*Fentanyl sublingual tablets (Abstral®)*	*Fentanyl sublingual tablets (Avaric®)*	*Nasal spray solution (Instanyl®)*	*Nasal spray solution with pectin (PecFent®)*
Onset of analgesic action (minutes)	15 min (13,14)	10-15 min (15)	15 min (16,17)	10 min (18)	6 min (19)	10 min (20)	5 min (21,22)
Duration of the analgesic effect	In general, it is considered that the duration of the analgesic effect of an opioid administered in this context should provide a minimum coverage of 30 min. All transmucosal fentanyls with indication for BTcP provide analgesic control of at least 30 min (14-27)						
Administration time requirements	It should be placed in the mouth against the cheek and move through the mouth with the help of the applicator, so that the mucous area exposed to the product is maximized. It should be sucked and not chewed, since the absorption of fentanyl via the oral mucosa is rapid in comparison with the systemic absorption by gastrointestinal route. It should be consumed within 15 min (14)	The tablet should be removed from the blister alveolus and immediately placed in the buccal cavity (near a molar, between the cheek and the gum). It must be kept inside the buccal cavity for the time necessary for the disintegration of the tablet, which usually takes about 14-25 min. Alternatively, the tablet can be placed in the sublingual space. If after 30 min there are still remnants of the tablet, it can be swallowed with a glass of water (15)	With dry hands, take the Breakyl buccal film between your forefinger and thumb with the pink side facing to the thumb Place the Breakyl buccal film inside your mouth, so that the pink side makes smooth contact with the inner lining of your cheek • Press and hold it in place for 5 seconds. When applying more than one film, it is possible to apply them to both left and right side of the buccal mucosa. In general it would be completely dissolved in 15 - 30 min (5). In certain cases, the complete dissolution of the product may take more than 30 minutes, but this does not affect the absorption of the drug (17)	The tablet should be placed directly under the tongue as far as possible. It should not be swallowed. Patient should let it it dissolve completely in the buccal cavity without sucking or chewing it. Patients should not drink or eat anything until the tables is completely dissolved (18). In patients with dry mouth, water can be used to moisten the oral mucosa before taking Abstral® (18)	The tablet should be placed directly under the tongue as far as possible. It should not be swallowed. Patient should let it it dissolve completely in the buccal cavity without sucking or chewing it. Patients should not drink or eat anything until the tables is completely dissolved. If after 30 min some rest of the tablet remains, it should be swallowed (19)	The sprayer must be purged with 3 to 4 pulses in ventilated areas. It is recommended that the patient remain seated or standing upright during administration. After each use it is necessary to clean the end of the nasal spray (20)	The bottle should be primmed prior to the first use. For the use, the nozzle should be put at short distance (about 1 cm) into the nostril. Point it towards the wall of the nose. Firmly press down on the finger grips to spray it into the nostril and let it go to the grips.. A click will be heard and a number counter will move forward 1 unit after each use (21).

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TABLE II (CONT.)
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Need of saliva	YES (28) In patients with dry mouth, water can be used to moisten the oral mucosa (14)	YES (28) It is recommended that patients with xerostomia drink water to moisten the oral cavity before administration (15)	YES (28) The use of the tongue to wet the inside of the cheek or rinse the mouth with water to moisten it (17).	YES (28) In patients with dry mouth, water can be used to moisten the oral mucosa before the administration (18)	YES (28) It is recommended that patients with xerostomia drink water to moisten the oral cavity before administration (19)	NO (28)	NO (28)
Presence of mucositis	It is administered by sliding on the surface of the buccal mucosa, without chewing (14)	In a clinical trial of patients with grade 1 mucositis, differences in exposure to Effentora® were found. The Cmax and AUC-8 were 1% and 25% higher in patients with mucositis than in patients without mucositis, respectively. The differences observed were not clinically significant (15)	Patients with grade 1 mucositis should be closely monitored and dose adjustments can be considered. The efficacy and safety of Breakyl® in patients with mucositis greater than 1 have not been studied (17)	Studies in patients with mouth ulcers or mucositis have not been conducted for Abstral®. In these patients there may be a risk of increased systemic exposure and, therefore, special cautions are recommended during the dose adjustment phase mucositis. (18)	Studies in patients with mouth ulcers or mucositis have not been conducted for Avaric®. patients there may be a risk of increased systemic exposure and, therefore, special cautions are recommended during the dose adjustment phase (19)	Alternative in patients with tumors of the head and neck and other areas presenting mucositis due to chemotherapy and/or radiation therapy, in case of nausea and vomiting, in patients in whom oral administration is difficult or painful due to the presence of candidiasis and xerostomia (29-31)	Alternative for patients with tumors of the head and neck, and other areas that present mucositis due to chemotherapy and/or radiation therapy, in case of nausea and vomiting, in patients in whom oral administration is difficult or painful due to the presence of candidiasis and xerostomia o (29-31)

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Presence of rhinitis	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	The total exposure to fentanyl in patients with allergic rhinitis without previous treatment with a nasal vasoconstrictor is comparable to that observed in healthy subjects. Adrenergic vasoconstrictors (oxymetazoline) should be avoided, since they can alter the pharmacokinetics of fentanyl (20).	In patients with allergic rhinitis there was no effect on Cmax, Tmax or total exposure to fentanyl, when non-exposed and exposed status were compared acutely. In patients with allergic rhinitis there was no effect on Cmax, Tmax or total exposure to fentanyl, when states not exposed and exposed were compared acutely. Adrenergic vasoconstrictors (oxymetazoline) should be avoided because it can inlfuence the pharmacokinetics of fentanyl (21).
Systemic and local adverse effects	Very common: drowsiness, dizziness, headache, dyspnea, nausea, vomiting, constipation, abdominal pain and asthenia. Very common reactions at the site of application: Bleeding, irritation, pain and ulcers of the gums (14).	Very common: dizziness, headache, nause, vomiting. Very common reactions at the site of application: bleeding, pain, ulcers, irritations, paresthesia, anesthesia, erythema, edema, swelling and spots (15).	Common: confusion, drowsiness, headache, dizziness and sedation, abnormal vision, nausea, constipation, dry mouth, itching, tiredness. Uncommon local reactions: stomatitis, gingival bleeding, dyspepsia, mouth ulcerations, mouth pain, odynophagia (17).	Common: dizziness, headache, drowsiness, dyspnea, vomiting, constipation, hyperhidrosis, fatigue. Common reactions at the site of application: stomatitis, dry mouth (18).	Very common: drowsiness, sedation, dizziness, nausea, constipation. Frequent reactions at the site of application site: dry mouth (19).	Frequent: drowsiness, headache, dizziness, vertigo, flushing, feeling very warm, nausea, vomiting, hyperhidrosis, throat irritation. Infrequent reactions at the site of application: epistaxis, nasal ulcers, rhinorrhea (20).	Frequent side effects: change in taste, dizziness, drowsiness, headache, vomiting, nausea, constipation, disorientation and itchy skin. Frequent reactions at the site of application: epistaxis, rhinorrhea and nasal discomfort (21).

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Easiness of use (patient and/or caregiver)	The consumption must be done within 15 min. Must be placed in the mouth against the cheek and move through the mouth with the help of the applicator (14).	It is important to avoid humidity when handling the tablet, otherwise an effervescent reaction is initiated in which the active ingredient is released. Patients should extract the tablet from the alveolus blister and immediately place the whole tablet in the oral cavity (near a molar, between the cheek and the gum) (15).	Place the Breakyl buccal film inside the mouth, so that the pink side makes smooth contact with the inner lining of the cheek and then press and hold it in place for a minimum of 5 seconds until it sticks firmly. Now the white side should be visible (17).	Sublingual tablets should be administered directly under the tongue as far as possible (18).	Sublingual tablets should be administered directly under the tongue as far as possible (19).	Priming and administration procedure. It is an important alternative in cases in which the active collaboration of the patient is not possible (20,29).	Priming and administration procedure. It is an important alternative in cases in which the active collaboration of the patient is not possible (21,29).

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Easy titration (lower number of steps)	Starting dose: 200 mcg. 30 min. Second dose: 200 mcg. If it is not controlled, consider increasing the dose in the next episode of BTcP. Maximum 4 BTcP episodes per day (14)	Starting dose: 100 mcg. 30 min. Second dose: 100 mcg. If it is not controlled, consider increasing the dose in the next episode of BTcP. Maximum 4 BTcP episodes per day (15).	Starting dose: 200 mcg. There is no rescue with a second dose. If it is not controlled, consider increasing the dose in the next episode of BTcP. Maximum 4 BTcP episodes per day (17).	Starting dose: 100 mcg. 15-30 min. Second dose: 100 mcg. If it is not controlled, consider increasing the dose in the next episode of BTcP. Maximum 4 BTcP episodes per day (18).	Starting dose: 133 mcg. 15-30 min. Second dose: 133 mcg. If it is not controlled, in 15-30 min. conside increasing the dose in the following BTcP episode. In general, maximum 4 BTcP episodes per day (19).	Starting dose: 50 mcg in a single nostril 10 min. Second dose: 50 mcg. If it is not controlled, consider increasing the dose in the next episode of BTcP. The high bioavailability of Instanyl® requires a dose of 50 mcg to avoid initially very high Cmax peaks (9). Maximum 4 episodes of BTcP (20).	Starting dose: 100 mcg. This is a single spray into one nostril. If not controlled, increase the dose in the next episode of BTcP. Maximum 4 episodes per day of BTcP (21).
Risk of abuse. Aberrant behaviour	Repeated administration of opioids such as fentanyl can produce tolerance and physical and/or physiological dependence. The occurrence of iatrogenic addiction after the therapeutic use of opioids is rare (14,15, 17-21)						
Presentations (Dosage strength)	200, 400, 600, 800, 1200 y 1.600 (14).	100, 200, 400, 600 y 800 (15).	200, 400, 600, 800 y 1200 (17).	100, 200, 300, 400, 600 y 800 (18).	133, 267, 400, 533, 800 y 67 como dosis intermedia (19).	50, 100, y 200 (20).	100 y 400 (21).

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Doses available	200, 400, 600, 800, 1200 y 1600 (14)	100, 200, 400, 600 y 800 (15)	200, 400, 600, 800 y 1200 (17)	100, 200, 300, 400, 600 y 800 (18)	133, 267, 400, 533 y 800 (19)	50, 100, 200 y 400 (20)	100, 200, 400 y 800 (21)
Adaptation (adequation of the effect of fentanyl to the profile of the BTcP episode	Onset of action: 15 min Cmax: 0.39-2.51 ng/ml Tmax: 20-480 min Bioavailability: absolute 50 % (14)	Onset of action: 10-15 min Cmax: 1.02-0.42 ng/ml Tmax: 20-240 min Bioavailability: absolute 65 % (15)	Onset of action: 15 min Cmax: 0.38-2.19 ng/ml Tmax: 45-240 min Bioavailability: absolute 71 % (17)	Onset of action: 10 min Cmax: 0.2-1.3 ng/ml Tmax: 22.5-240 min Bioavailability: 54 % (18)	Onset of action: 6 min Cmax: 0.36-2.07 ng/ml Tmax: 22.5-240 min Bioavailability: 70 % (absolute, estimated) (19)	Onset of action: 10 min Cmax: 0.35-1.2 ng/ml Tmax: 12-15 min Bioavailability: absolute 89 % (20)	Onset of action: 5 min Cmax: 0.35-2.84 ng/ml Tmax: 15-21 min Bioavailability: relative compared to 200 µg citrate fentanyl buccal transmucosa: is of 120 % (21)

European countries (32). A study conducted in 1000 cancer patients in 13 European countries showed that only 19% of patients received transmucosal fentanyl for the treatment of BTcP (33).

In an exploratory Delphi study conducted in Spain (6), the vast majority of respondents (97.8%) indicated that the ideal time for the onset of the analgesic effect should be a maximum of 15 minutes and the "onset of analgesic action" received a score of 6.5 in a scale of 1-7, in which 7 was "extremely important" (6).

The second attribute, with a level of consensus of 72%, was the "adequacy of the effect of fentanyl to the profile of the BTcP episode". In this sense, the ideal drug for the treatment of BTcP should be a potent analgesic that can alleviate the high pain intensity. Given the pain transience, it should be a rapid absorption drug with rapid onset of action, its route of administration should be simple, easy and with high patients' acceptance. This drug should not add additional side effects to the baseline treatment with opioids and the duration of the effect should not exceed 120 minutes. The new rapid-acting fentanyl formulations adapt to the profile of breakthrough pain and provide better efficacy and less toxicity (9). The number of episodes per day, the need to repeat the dose due to insufficient relief, and the degree of relief are important aspects that should be considered when titrating the medication to control the BTcP. (6). Some authors have proposed the establishment of doses that are proportional to baseline opioid regimens for baseline pain, because this seems to be effective and safe in most patients (34). In any case, the different aspects related to the ease of dose titration, the clinical characteristics of each patient and the patient's need for social support are critical when choosing the treatment with fentanyl (6).

The third attribute, with a level of consensus of 69% of participants. was the "ease of use by the patient or the caregiver". An added value when selecting a therapeutic option among different formulations is the simplicity of the administration device, which will facilitate patient's adherence and compliance. The results of a survey conducted to Spanish oncologists showed that written instructions and information to the patient are often missing, a confirmation of whether the patient has understood the instructions and a systematic evaluation of pain (35). The study concluded that oncologists need to improve their communication skills, providing patients with written and verbal information about their illness and the plan for pain control (35). The intranasal formulation of fentanyl can be easily administered by a caregiver if the patient can not collaborate, avoiding the need for training if the patient is treated at home. In this sense, transmucosal fentanyl delivered via nasal has demonstrated to be in general faster than that administered buccally, since the nasal mucosa is more vascularized and more permeable (7).

The fourth attribute, with a level of consensus of 58%, was the "duration of the analgesic effect". Breakthrough pain is a heterogeneous pain, with intra and interindividual variations. The episodes, even in the same subject, may have very different characteristics, which hamper their proper identification and assessment. The duration of analgesia was the second most important criterion for selecting a drug for BTcP in the above mentioned Delphi study of Spanish (6). A total of 74.1% of the respondents indicated that the duration of the analgesic effect should last a maximum of 1-2 hours (6).

The fifth attribute, with a level of consensus of 57%, was the "presence of mucositis". The mucosa is an adequate route for the release of fast-acting drugs. However, the integrity of the mucosal epithelium, vascularization and hydration of the surfaces is important for the correct absorption of the different forms of buccal or sublingual transmucosal fentanyl. The presence of cancer processes in the oral cavity or alterations in the oral cavity as a side effect of certain treatments may interfere with the response to treatment. Patients receiving chemotherapy and/or radiation therapy may experience mucositis as a complication of such treatments. Pain related to mucositis hampers oral drugs delivery and leads to a decrease in fluid and food intake (36). Therefore, of course, this is an attribute that has a decisive influence when choosing a treatment with transmucosal fentanyl. However, a related attribute, the "need for saliva", obtained only 36% of consensus among respondents (Figure 1).

The "administration time requirements", or time that the applicator, tablet or film should remain in contact with the absorption surface in order to obtain the maximum absorption, did not reach a high consensus level (48% of the participants). It is possible that the participants assumed that the application is equally rapid for all the pharmaceutical forms of transmucosal fentanyl, or that this factor is not decisive for the speed of onset of analgesic effect.

The "level of scientific evidence" was not a main decisive attribute (47% of the participants). The studies that have rigorously addressed the comparison between the different options to establish which ones have a better risk-benefit balance are scarce (9). However, a Spanish survey published in 2010 showed that a high percentage of oncologists are unaware of some concepts of potential clinical importance, such as the actions of drugs on different opioid receptors (37). The consensus is clear regarding the administration of fast-acting fentanyl for the treatment of BTcP and Spanish oncologists see transmucosal fentanyl as an effective therapy. However, an effort to

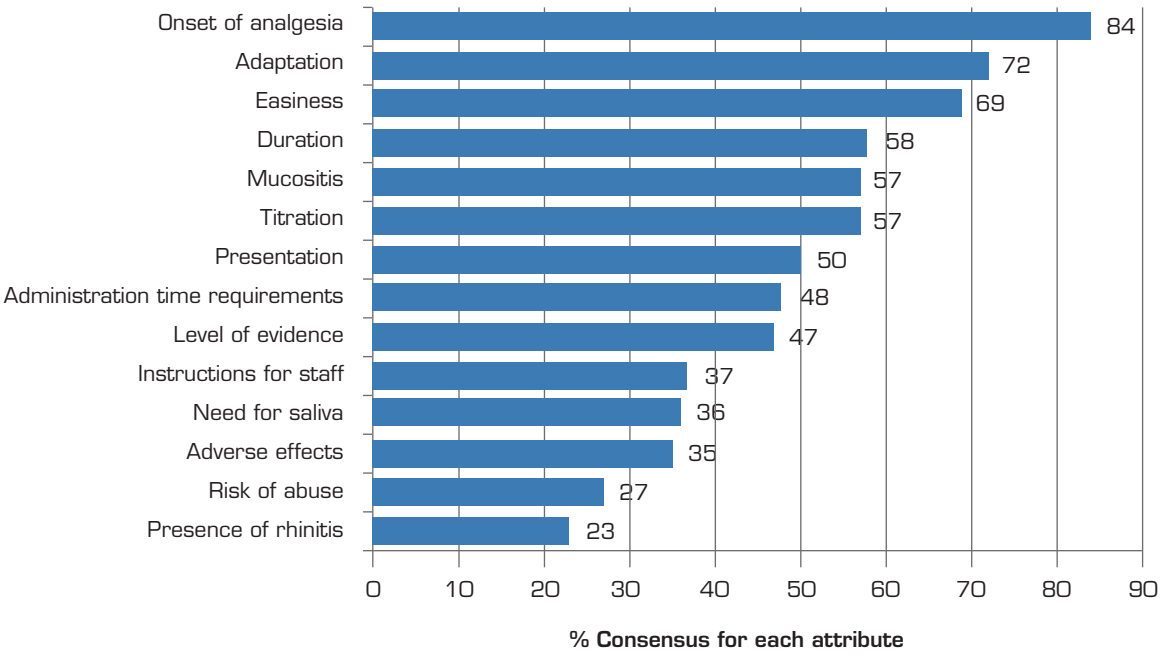

Fig. 1. Ranking of attributes according to Spanish oncologists.

disseminate the technical aspects that would allow oncologists to know thoroughly the different therapeutic options seems to be a priority. In addition, despite the prevalence of BTcP and being a negative prognostic factor in cancer patients, the BTcP is underdiagnosed and poorly treated. A qualitative study conducted in Spain determined the adherence to the Clinical Guideline for the Treatment of Cancer Pain of the Spanish Society of Medical Oncology (38). This study showed that, despite unanimity (100%) regarding the need for specific treatment for the BTcP and in the use of fentanyl as the first-choice drug (99%) was found among oncologists (n = 83), the guideline suffers from a limited compliance, in part because of its low diffusion and in part because of the potential confusion regarding certain recommendations (39). Also, a study conducted with American oncologists showed that one of the barriers identified for the adequate treatment of pain was the need for specific training in this field (40). Despite transmucosal fentanyl is clearly perceived by Spanish oncologists as a safe and well tolerated therapy against BTcP, it is necessary to continue training healthcare staff at all levels.

The variety in the pharmaceutical forms of transmucosal fentanyl eases that each patient can be treated with the formulation that best suits his/her clinical characteristics and preferences. Therefore, the collaboration of trained health personnel is necessary to explain how to manage the BTcP. Even so, the attribute "time necessary to explain the correct administration of transmucosal fentanyl" only reached a 37% consensus among participating oncologists. However, nurses, pharmacists, caregivers and family members must be involved to ensure patient's safety and to optimize the effectiveness of treatment.

It is notable that the occurrence of local adverse effects (related to the route of administration) in our analysis did not seem relevant when prescribing the different forms of transmucosal fentanyl (consensus of 35% of the participants). It is possible that oncologists are assuming that these forms of administration are equally safe and that adverse effects are common to all types of opioids (nausea, constipation, headache and sleepiness). It is also notorious that the participants in our study do not consider important the possibility of risk of aberrant behavior or abuse (27% of the participants). Finally, most oncologists do not considered the presence of rhinitis as a relevant attribute when prescribing medication, reaching this attribute only 23% consensus.

CONCLUSIONS

The present study regarding the priorities for prescribing transmucosal fentanyl for the treatment of BTcP showed that participating oncologists especially value the rapidity of the analgesic effect, the adequacy of the drug to the profile of the pain episode, the ease of use and the duration of the effect. These priorities are aligned with the needs of an effective treatment of the BTcP according to the consensus documents and currently available clinical practice guidelines. The low prioritization of attributes such as the possible occurrence of adverse effects, the risk of abuse, or the level of available scientific evidence stress the fact that Spanish oncologists perceive the different formulations of transmucosal fentanyl as safe, well tolerated, and effective drugs.

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