



A clinical approach to the management of cancer-related pain in emergency situations

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Received: 9 August 2018 / Accepted: 23 April 2019 / Published online: 11 May 2019
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Abstract

Purpose Most cancer patients experience many pain episodes depending on disruptive elements, leading them to the emergency room. The objective of the article is to describe common pitfalls that need to be avoided, as well as opportunities to be seized for repositioning patients back on their care pathway.

Methods Critical reflection based on literature analysis and clinical practice.

Results Most forms of cancer are now chronic, evolving diseases, and patients are treated with high-technology targeted therapies with iatrogenic effects. Moreover, the multimorphic nature of cancer-related pain requires dynamic, interdisciplinary assessments addressing its etiology, its pathophysiology, its dimensions (sensory-discriminatory, cognitive, emotional, and behavioral), and the patient's perception of it, in order to propose the most adapted therapies. However, for most patients, cancer pain remains underestimated, poorly assessed, and under-treated.

In this context, the key steps in emergency cancer pain management are as follows:

- *Quick relief of uncontrolled cancer pain*: after eliminating potential medical or surgical emergencies revealed by pain, a brief questioning will make the use of carefully titrated morphine in most situations possible.
- *Assessment and re-assessment of the pain and the patient*, screening specific elements, to better understand the situation and its consequences.
- *Identification of disruptive elements leading to uncontrolled pain*, with an interdisciplinary confrontation to find a mid to long-term approach, involving the appropriate pharmaceutical and/or non-pharmaceutical strategies, possibly including interventions.

Conclusions Pain emergencies should be part of the cancer care pathway and, through supportive care, provide an opportunity to help cancer patients both maintain their physical, psychological, and social balance and anticipate further painful episodes.

Keywords Pain management · Personalized management · Multimorphic pain · Cancer pain · Emergency · Supportive care

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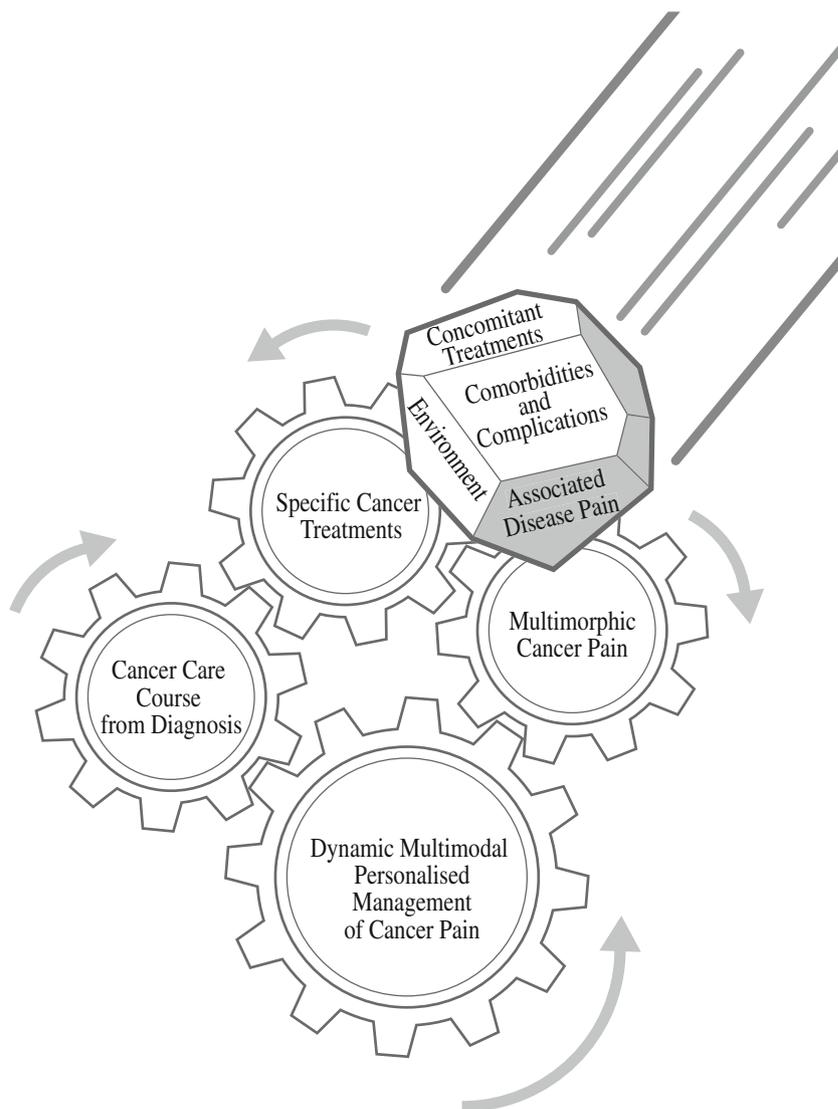
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Introduction

Patients with cancer-related pain remain with more frequent visitors to emergency rooms than other patients with chronic, non-cancerous conditions [1]. The importance of pain emergencies reflects the need for the optimized management of cancer pain in real life, as corroborated in epidemiological studies. Currently, cancer-related pain remains underestimated, poorly assessed, and under-treated [2–10].

Cancer pain is multimorphic, with frequent changes possibly related to cancer progression from diagnosis and/or to its treatments. It can also be affected by disruptive events such as changes in concomitant treatments, associated disease pains, comorbidities and complications, or modifications of the environment (Fig. 1). Faced with an evolving, chronic condition,

Fig. 1 Disruption key elements in the dynamic, multimodal, targeted, individualized management of multimorphic cancer pain



requiring state-of-the-art treatments not without major side effects, cancer pain management has become part of a specific approach [10].

In parallel to improved understanding of the pathophysiological mechanisms of pain, the analgesic pharmacopeia has been significantly enhanced, and the use of both interventional and non-interventional procedures is becoming more generalized, including in the early stages [10–18]. On the other hand, the considerable progress made in oncology therapies has revolutionized the management of cancer patients, many of whom now have a chronic disease with improved life expectancy and quality of life [19–21].

In this context, cancer pain can only be understood and relieved if it is the subject of an exhaustive and interdisciplinary assessment period that is essential for establishing the cause, pathophysiological mechanisms, and any disruptive elements (Fig. 1). Insufficient assessment may result in chronic

pain being underestimated, with the addition of often-avoidable medicine-related pain [22].

In the course of their care pathway, cancer patients undergo many episodes of pain in a complex process [23]. The goal is to prevent the development of a long-term vicious circle of pain (Fig. 2), as this profoundly modifies the patients' quality of life. As a result of the psychological fragility brought on by cancer and pain, the consultation for cancer pain in an emergency is a further occasion for gaining the patients' trust and including them in a targeted, positive approach.

The aim of this article is to identify the philosophy of care that drives clinicians in emergency situations when faced with pain patients, and how this situation must be integrated into multimodal management (within the context of supportive care). Facing cancer patients often suffering from undertreated pain, at their consultations, the authors have carried out a critical reflection based on a literature analysis and their

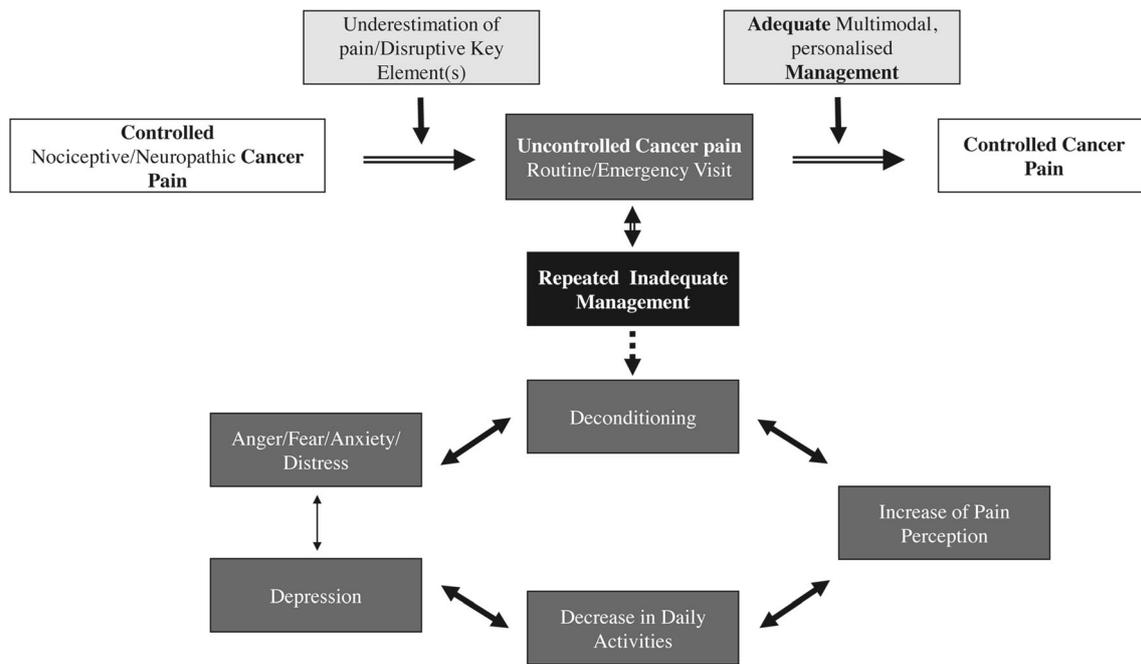


Fig. 2 The vicious circle of chronic cancer pain related to repeated inadequate management in patients with underestimated cancer pain or in the presence of disruption key element(s)

clinical practice. For each domain, the literature search was set up on recent reviews and the latest English and French publications on Medline.

From medical or surgical emergency to quick relief of uncontrolled pain

Experienced acute pain is not necessarily a medical emergency even if the patient claims the relief as soon as possible. Thus, the first step will be to distinguish true medical or surgical emergencies revealed by pain, whether or not directly related to cancer (e.g., myocardial infarction, appendicitis, and spinal cord compression), from exacerbations or new kind of pain(s) requiring adjusted management. These medical or surgical emergencies situations revealed by pain will involve specific approaches such as surgery or interventional procedures.

In other situations, patients identify pain emergencies through their unusual nature in terms of presentation, intensity, localization, and psychological impact. The time before needing relief and the pain threshold vary from one individual to another, as well as over time in a single patient. For instance, the emotional sensitivity of the moment, asthenia, anxiety, and depression are all factors influencing the experience of pain exacerbations [24–26]. The way this emergency is dealt with by caregivers has a considerable impact on the patients' subsequent pain history, its cognitive process, and their apprehension [24, 27].

Although the first objective at the emergency room or even at home is to relieve the patients' pain, a short initial

interview is needed to identify both similar past histories and the treatments that successfully brought relief. As mentioned earlier, the initial clinical examination will first allow eliminating a potential medical or surgical emergency revealed by acute pain. Otherwise, the reference treatment will be intravenous (IV) or immediate release (IR) oral morphine following the rules of titration, taking into account the patient's singularities (morphine naïve or not, fragile patients, etc.) [10].

The titration should take into account on-going treatments (treatment(s) and interdoses) [10, 28]. The treatment must also consider the possible increase in anxiety caused by the pain and the situation. The aim is to carry out the opioid titration to obtain the smallest effective dose possible, with repeated reassessments of the pain [10, 28]. Depending on the analgesic treatments taken prior to the pain emergency, the choice of dose to be prescribed is based on characteristics specific to the patient, and in particular, his or her current morphine uptake, fragility, and previous tolerance [29]. Given the need for immediate relief, the intravenous approach should be privileged, but the sublingual or intranasal treatments with rapid onset opioids (ROO) can be relevant in breakthrough cancer pain (BTcP), especially at home. BTcP is an episode of severe pain that occurs in patients receiving a stable opioid regimen for persistent pain sufficient to provide at least mild sustained analgesia [10, 30–32]. Eight patients out of ten cease their usual activities when experiencing BTcP [33]. If not properly managed, it leads to pain emergencies, and hospitalization rates are higher than those of patients without BTcP (37% versus 23%) [34].

Following the interdisciplinary assessments and understanding the cause of the decompensation, the most appropriate relay treatment can be then prescribed in a mid- and long-term perspective.

Assessment and re-assessment of pain and patient: key points in cancer pain emergencies

Assessment and re-assessment of the pain and the patient are key points in cancer pain management [10] and also in emergencies situations, which could be considered as a point of entry for providing better further care [1]. We propose a basic and practical screening tool based on seven elements, which can be searched for with no particular order and could lead to an exhaustive initial assessment of pain in emergency situations (Table 1).

Given the multimorphic nature of cancer pain, patients themselves are the best at describing their own pain and treatment response [35]. Consequently, in conscious subjects, pain should not be assessed only by a third party [36]. Cancer can evolve, and the etiology of pain exacerbation may be new, transitory, recurrent, or installed. Different types of pain can coexist: mixed, overlapped, combined, and associated (Table 2).

The evolving nature of cancer means that patients must be assessed and re-assessed continually [10] to not stigmatize worsening of background chronic cancer pain too quickly, but instead screen for complications, altered psychological status, episodes of paroxysmal pain, or new elements (neuropathic, for example) in the pain. This will prevent analgesic escalations, in particular, strong opioids, themselves a possible source of hyperalgesia [10, 37], and make it possible, if applicable, to diagnose and treat comorbidities or underlying complications.

The aim is thus to assess the patient, characterize the multimorphic pain and its evolution, and assess the care

pathway in its entirety (diagnosis, cure, relapse, palliative situation) and its psycho-social repercussions, as well as past and current cancer treatments (cancer pharmaceutical therapy, surgery, radiotherapy), which may all have contributed to a state of pain that has become unbearable (Figs. 1 and 4). The assessments involve clinical examinations, and patient-reported outcome (PRO) measures to establish the impact of pain emergencies, as well as complementary examinations to confirm its diagnosis. The ability to inform and to communicate with the patient and the family is fundamental [10], especially when pain leads to emergency consultations.

The response must therefore focus on the aspects concerned and break the damaging momentum (Fig. 2). In case of insufficient assessment or management, repeated pain emergencies worsen the patient's quality of life over time.

A clinical pathway to identify disruptive elements leading to uncontrolled pain

Once pain has been assessed and relieved rapidly, practitioners search to identify disruptive elements with patients so as to treat the cause if possible and help them return to a state of balance and stability (Fig. 3). Knowing the cause of a pain emergency, above all, if it is reversible, makes it possible to treat it without necessarily increasing the previous prescription of analgesics. Depending on the cause and/or disruptive elements in the emergency, it is an opportunity for the interdisciplinary team to adapt the analgesic management and adapt a complementary interventional approach, whether invasive or not. We propose a clinical pathway to identify disruptive elements leading to uncontrolled pain in emergency situations (Fig. 3). In each case, recommended treatments including invasive or non-drug approaches will be applied [10], but we will not specifically develop it in this article. Relieving pain exacerbations means thinking immediately of a lasting and appropriate relay treatment to decrease the level of suffering over time. Depending on the disruptive elements, the

Table 1 Basic elements to assess cancer pain in emergencies situations, after having screened out medical or surgical emergency situations revealed by pain

Elements	Assessment
Treatments	Evaluation of on-going treatments, current/past cancer treatments, compliance, inappropriate treatments and/or dosages, misuses, drugs interactions
Pain localization	Pain linked to actual cancer, possible metastasis evolution, differential diagnosis
Temporality of pain	Inaugural acute pain, exacerbation on chronic pain, new kind of acute pain, BTcP
Intensity of pain	Quantization using specific scales to quickly measure improvements (VAS, VRS, NRS)
Pathophysiological nature of pain	Nociceptive, neuropathic Mixed, overlapped, combined, associated
Consequences of pain	Anxiety, depression, malnutrition, deconditioning, social impacts
Diagnosis of pain	Identify the etiology(-ies) of pain to propose the best-personalized management

VAS, visual analogue scale; VRS, verbal rating scale; NRS, numerical rating scale

Table 2 The characteristics of the multiple forms of complex pain presented by cancer patients

	Etiology		Location		Pathophysiology	
	Identical	Different	Identical	Different	Neuropathology	Inflammatory
Mixed ^a	Yes	No	Yes	No	Yes	Yes
Overlapped ^b	No	Yes	Yes	No	Yes	Yes/no
Combined ^c	Yes	No	No	Yes	Yes	No
Associated ^d	No	Yes	No	Yes	Yes	Yes/no

^a Example of mixed pain: bone metastases and Pancoast syndrome pain

^b Example of overlapped pain: bone metastases and lumbago

^c Example of combined pain: cancer and taxanes

^d Example of associated pain: cancer and rheumatoid arthritis

interdisciplinary assessment may lead to hormone therapy and chemotherapy and/or interventional treatments such as radiotherapy, cementoplasty, peripheral nerve block analgesia, or a perimedullary catheter [10, 14–18]. As a complement to analgesics, other non-drug approaches should be considered, such as psychotherapy, hypnotherapy, and transcutaneous electrical nerve stimulation. [11–13].

Pain emergency related to cancer and its comorbidities

Pain in emergency situations can be first linked to the primary cancer but also to possible secondary localization(s) of the disease. In both cases, pain can reveal tumor progression or

extension and be the first symptom leading to a new diagnosis, sometimes weeks or months after initial cancer pain management. Tendon, joint, and muscle pain are also common, exacerbated by the muscle and joint deconditioning imposed by the illness and often associated with malnutrition [38].

Pain emergency related to cancer treatments

Anti-cancer therapies can be directly responsible for drug-induced pain leading to emergency consultations (for example, neuropathy with taxanes, post-radiotherapy burns, neuropathic pain following surgery, or muscle or joint pain from hormone therapy and immunotherapy) [10, 39]. Present in about 20 to 40% of cancer patients, and the main etiology in

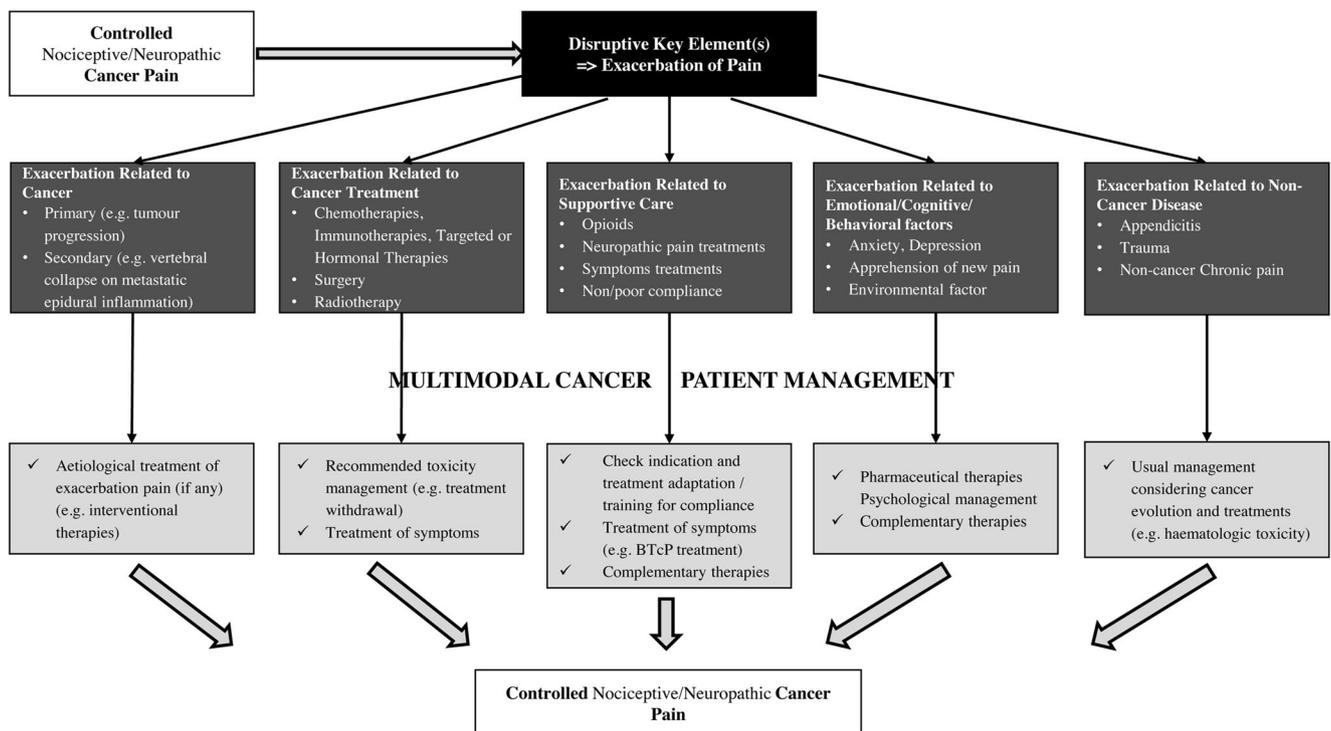


Fig. 3 Options of multimodal, personalized management of pain exacerbation in patients with underestimated cancer pain or in the presence of disruptive key element(s) leading to emergency unit

about one-third of patients [3, 40], neuropathic pain is often under-diagnosed and under-treated, and can be responsible for emergency consultations [40–42]. Neuropathic pain can be caused by cancer treatments but often appears to be multifactorial, as it can be linked to several associated causes including the cancer itself. Tricyclic antidepressants, gabapentin, pregabalin, and duloxetine are strongly recommended as first-line treatments for neuropathic pain [10] but are not suitable in emergency situations.

In some emergency situations, and if possible, discussing the indication of anti-cancer treatments with oncologists may be relevant in order to reconsider potential specific curative options with fewer side effects.

Pain emergency related to supportive treatments

An exhaustive evaluation of treatments, if possible with the help of clinical pharmacists, can in itself be a good way to find reasons for uncontrolled pain [43]. Poor compliance to pain killers, insufficient doses, inappropriate analgesics, misuses or abuses, and drug interactions with on-going treatments can explain uncontrolled pain. If the analgesia fails, it is thus necessary to verify that there has been good compliance. Failure to comply with analgesic treatments is known to be significant because of fear of side effects: 8% of patients declare that they fail to comply and 20% do not answer questions about their compliance [3]. Supportive care treatments can also be incriminated in certain painful situations. For instance, opioids, mainly combined with other treatments, can also be responsible for pain through their undesirable effects, such as constipation, occlusive syndrome, acute urine retention, and vomiting. These symptoms, along with hyperalgesia [37], must be systematically screened for and corrected. Hyperalgesia rarely affects patients who, through the use of opioids and for no other detectable reason, suddenly become hypersensitive to pain with generalized allodynia [44, 45]. Long-term steroid therapy can be responsible for pain too, due to skin lesions, mucositis, infections, or osteonecrosis, as well as bisphosphonate drugs which can be complicated by osteonecrosis of the jaw [10].

Poor knowledge of these undesirable effects may lead to an inappropriate and harmful escalation in opioid prescription, whereas managing these effects requires specific treatments [46, 47].

Pain emergency related to emotional, cognitive, or behavioral factors

In comparison to the general population, the rate of depression in cancer patients is up to three times higher [48, 49]. Cancer pain is associated with higher levels of depression [50] and depressed cancer patients are at increased risk of outcomes and mortality [51]. Depression and anxiety are frequently

associated with cancer patients [51]. In palliative situations, patients can develop a stronger desire for premature death, a concept that includes requests for euthanasia, suicide, or medically assisted suicide [48].

Based on this background, and considering the close relationship between pain and anxiety or depression, it appears important to consider it in emergency situations: depression and anxiety can be the consequence of high levels of mental distress for sustained periods in time [51]. Age and potential cognitive impairments have to be taken into consideration as well [52].

Pain emergency related to non-cancer diseases

As for any patient, acute pain leading to emergency consultations can have a non-related cancer etiology. The clinician should not be too conditioned by the cancer and always keep a diagnosis-focused approach considering the frequency of possible differential diagnosis in pain emergency. Given that other conditions, notably cardiovascular, renal, or endocrine, are favored by cancer or its treatments, patients should thus benefit from the sometimes-specific standard circuits for emergency management (e.g., chest pain) to prevent delayed diagnoses or inappropriate treatments.

From healthcare facilities to care pathway management

In all cases, multimodal management of a patient's recurrent or refractory pain should not be delayed [14, 17]. After interdisciplinary assessment of the pain, new management should be proposed, as much for the around-the-clock analgesia as for any exacerbation of the pain, whether or not it is predictable. In addition, information must be provided on what to do in case of a recurrent pain emergency. If patients are compliant, anticipated prescriptions could be established, considering the risks associated with this practice. Through trust-based relationships, therapists must give patients the key to finding relief and care by themselves whenever possible: this is therapeutic education [53]. Providing patients with new training should allow them to fully understand the treatment strategy initiated. Therapeutic education is plenty of evidence of its utility for making self-management of symptoms easier, reducing worry about acute events, improving quality of life, and maintaining better autonomy and mood [54–57]. Education can be completed with coaching, nursing support, and the use of a diary for pain intensity and analgesic intake [58, 59]. Attention should also be paid to the family and friends, who may be natural assistants through the support they provide, or aggravators of the situation because of their anxiety [60]. Knowledge of what to do, and the patient's care pathway, plays a part in reassuring them.

Managing cancer pain emergencies thus means implementing a dedicated patient care pathway. Healthcare establishments must organize themselves so that they have a common plan in response to such emergencies, with a patient circuit whose modalities (including phone number for example) are transmitted to the patient as well as possibly to his/her family or friends.

For each of these situations, an interdisciplinary confrontation will make it possible to find an adapted, personalized response, integrated into the cancer patient's multimodal management (Fig. 3).

In addition, a patient-dedicated pathway for pain emergencies integrated into the multimodal supportive care management will help limit these emergency consultations. In France for example, hospital pain management centers and consultations must provide a dedicated pain pathway for cancer patients including emergency and palliative situations; this facility is however hardly implemented in hospitals except in cancer centers [61]. The aim is to control cancer-related pain with a decreased risk of exacerbations, to improve quality of life, and a possible extension of life expectancy, as shown in recent studies [62–67].

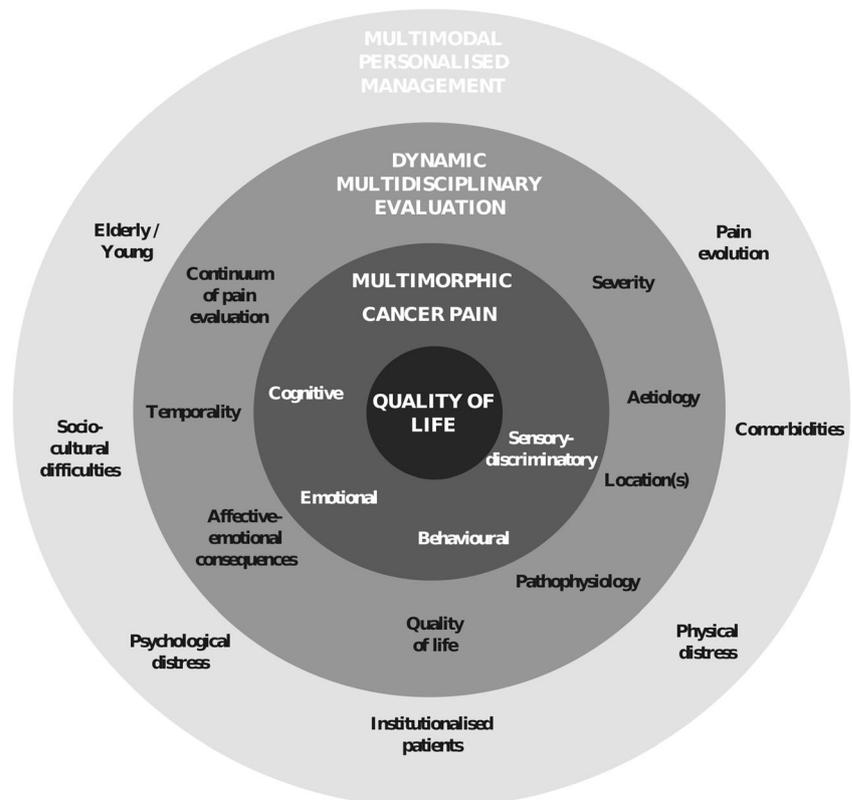
Medical advice given by telephone to relieve pain emergencies is common, but it can only be considered in patients who are already known [68]. In addition to the risk of misdiagnosis, the call runs the risk of resulting in a systematic

increase in the dose of analgesics. In some pain centers, clinical pharmacists are in charge of cancer patient's follow-up by telephone, to adjust treatments or provide best advices in case of exacerbation of pain, including in palliative situations [43]; this solution appears to be relevant as it allows decreasing hospitalizations or consultations, and it brings the best answer to a particular situation, interacting with cancer pain physicians and general practitioners.

As in the case of a consultation at the emergency department, patients must systematically be questioned about their current and past treatments, and the usual or unusual nature of the event in terms of its localization, intensity, and type (Table 1). On the basis of these simple questions, an appropriate treatment can be proposed from those available to the patient at home, while awaiting a consultation and clinical examination, scheduled for as soon as possible. If no appropriate treatments are available, and before the next prescription, the least dissatisfying treatment should be recommended to the patient—generally an increased dose of the current analgesic.

Telemedicine networks have been set up in several countries [68–72], facilitating a fast, advisory opinion of good quality, based on questioning and clinical examination of the patient, without removing the need for a face-to-face consultation as soon as possible if necessary. Furthermore, automated patient-reported outcome (PRO) using mobile healthcare

Fig. 4 Model of multimodal, targeted, personalized management of multimorphic cancer-related pain



applications could be relevant in the field of cancer pain management in order to improve patient's quality of life and prevent emergency consultations.

Given the importance of the multimorphic nature of cancer pain, management of pain emergencies thus requires a multimodal response for relief, understanding, prevention, and the appropriate management of future recurrences [73].

Discussion

As seen, management of cancer patients in pain emergency situations is complex. We insist here on the need to not limit oneself to simply increasing opioid analgesics, but rather to explore the disruptive element(s) and all the components of the pain that have played a part, in order to find the most appropriate and most durable care. The etiology of the pain is not necessarily cancer-related. All the treatments in progress that are potential sources of pain need to be assessed, and other non-drug-based techniques capable of bringing effective relief must be sought.

Recognizing the pathophysiological nature of pain (neuropathic, nociceptive, and nociplastic) and its different types (mixed, overlapped, combined, and associated) (Table 2) is essential for choosing the best management [74]. This multimorphic pain requires a management approach that is early, interdisciplinary, multimodal, personalized, and dynamic (Fig. 4). It is thus a question of teamwork, in which patients themselves play a full part.

On the other hand, pain exacerbations involve deep memorization, so it is important not to trivialize either the situation or the response. Nowadays, however, this is not the standard management offered to patients with cancer pain, as shown by epidemiological studies [2–9]. The management presented requires education, time, cooperation, and support from the family or friends, which is only encountered in certain specific cancer centers/departments in certain countries.

Emergency management of cancer patients with pain thus requires education in care for patients and caregivers, including the patient's general practitioner, for a more appropriate response. In parallel, while primary care physicians report a lack of knowledge in the management of chronic pain in cancer survivors, most of them are open to receiving medical education on treatment options and clinical practice guidelines [75].

Integrative models in cancer have demonstrated their positive impact in terms of patient quality of life, management of symptoms, and optimization of care pathways, regardless of the place of management (outpatient, at hospital, home care) [76]. Their relevance relies on other means of looking at cancer medicine: interdisciplinarity, development of paramedical skills, decompartmentalization of hospital and community medicine, a personalized approach to the patient's care

pathway, anticipation and prevention of disruptions [66], and a continuum in order to abolish the palliative/curative dichotomy in favor of adaptation to patients, their issues, and their environment. They must become standards when it comes to structuring care in oncology at a larger scale.

Conclusions and perspectives

Nothing can be taken for granted, and each pain emergency situation is unique and changing. Pain emergencies should be part of, and organized within, the patient's cancer care pathway. Cancer pain emergencies thus require teamwork in a spirit of exhaustive supportive care and knowledge of the different approaches and techniques that bring relief.

The emergency consultation is an opportunity to help cancer patients both maintain their physical, psychological, and social balance, and anticipate further painful episodes.

Acknowledgments Support was provided by Xavier Amores, M.D. and Viorica Braniste, M.D. & Ph.D. (Kyowa Kirin), and Robert Campos Oriola, Ph.D, and Marie-Odile Barbaza, MD (Auxesia) for manuscript preparation.

Funding information This article was funded by Kyowa Kirin.

Compliance with ethical standards

Conflict of interest Alexis Burnod reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; non-financial support from Kyowa Kirin, outside the submitted work. Caroline Maindet reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Mundipharma, and non-financial support from Kyowa Kirin, Grunenthal, Hospira, Takeda, and Janssen Cilag, outside the submitted work. Brigitte George reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Mundipharma, non-financial support from Grunenthal and Kyowa Kirin, outside the submitted work; participation to a clinical study without honoraria from Bouchara. Christian Minello reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Takeda, and non-financial support from Kyowa Kirin, Mundi Pharma, Mylan Pharma, and Grunenthal, outside the submitted work. Gilles Allano reports non-financial support from Kyowa Kirin, during the conduct of the submitted work; personal fees and non-financial support from Grunenthal, Mundipharma, and Medtronic, and non-financial support from Kyowa Kirin, outside the submitted work. Antoine Lemaire reports non-financial support from Kyowa Kirin France, during the conduct of the submitted work; personal fees and non-financial support from Kyowa Kirin International, Mundi Pharma, Grunenthal and Takeda, personal fees from Mylan, and non-financial support from Kyowa Kirin France, Archimèdes Pharma, Teva, Prostrakan, outside the submitted work.

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