Review

Cancer Pain Management -current concepts, strategies and techniques

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Abstract: Pain is frequently reported during cancer disease, and still remains poorly controlled in 40% of patients. Recent developments in oncology have helped to better control pain. Targeted treatments may cure cancer disease and significantly increase survival. Thereby, a novel population of patients (cancer survivors) has emerged, also enduring chronic pain (27.6% moderate to severe pain). The present review discuss the different options currently available to manage pain in (former) cancer patients in the light of progress made in the last decade. Major progress in the field are recent development of a chronic cancer pain taxonomy now included in International Classification of Diseases (ICD-11) and update of WHO analgesic ladder. Until recently, cancer pain management has mostly relied on pharmacotherapy, opioids being considered as mainstay. The opioids crisis has prompted the reassessment of opioids use, both in cancer patients and cancer survivors. The review focuses on the current utilization of opioids, on the neuropathic pain component often neglected and on techniques and non-pharmacological strategies available which help to personalize patient's treatment. Cancer pain management is now closer to the management of chronic non-cancer pain i.e. "an integrative pain care" aiming to improve patient's quality of life.

Keywords: cancer pain; cancer survivors; neuropathic pain; WHO analgesic ladder; opioid analgesics; non-pharmacological treatements; integrative pain care

1. Introduction

Many peoples are affected by cancer and the prevalence is increasing as the population is ageeing. Pain is a common symptom of cancer diagnosis and rises in prevalence throughout and beyond cancer treatment [1,2]. In a recent systematic review, from 2014 to 2021, the overall prevalence of pain in cancer patients was 44.5% [2]. Moderate to severe pain was experienced by 30.6% of the patients (vs 38% of the patients in 2016). Pain prevalence in advanced metastatic and terminal cancer was 54.6% (vs 66.4% in 2016). Thus, both pain prevalence and pain intensity have declined in the past decade. Nevertheless, the presence of poorly controlled pain still remains a problem for many cancer patients, an evidence pointed out by a recent systematic review (including papers from 2014 to 2020) [3]. An analgesic treatment inadequate to the intensity of pain was identified in about 40.2% of cancer patients, particularly in elderly patients who usually present with several comorbidities and in patients from countries with a low-medium economic level where the access to analgesic drugs may be restricted (due to high costs or health policy).

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Further, it is worth noting that pain management often remains secondary to other cancer treatments what contributes to pain undertreatment [4].

Whether pain itself is not immediately life threatening, chronic pain remains one of the most frequent and disabling symptom of cancer. Chronic pain is always associated with poorer quality of life due to psychological distress (fatigue, depression) and reduced functioning [1]. That is particularly worrying because some data indicate that the presence of poorly relieved pain may decrease survival rates in cancer [5,6].

Recent developments in oncology which allow better control of tumor growth and thereby reduce the associated phenomena of inflammation, ischemia and compression [7], also have contributed to reduce cancer pain prevalence and severity, improving the patients quality of life [2]. Targeted treatments have also increased patients survival and for some patients have led to a disease-free outcome (curative treatment). By consequence, a novel population of patients called "cancer survivors" has now emerged. According to a recent systematic review, 47% of cancer survivors report the presence of some chronic pain (moderate to severe pain: 27.6%) in relation with previous treatments like chemotherapy, radiotherapy or curative surgery or even in relation with a concomitant chronic pain condition unrelated to cancer or cancer treatment [6,8]. The management of chronic pain in this specific population requires a different approach of that used for peoples with a limited prognosis.

These last years have shown substantial evolution and relevant improvements in chronic cancer pain management. A major progress in the field is the recent development of a chronic cancer pain taxonomy and its inclusion in the International Classification of Diseases (ICD-11) thanks to a collaboration between WHO (World Health Organization and IASP (International Association for the Study of Pain) [1]. There was clearly a need for a standardized classification of cancer-related pain allowing a greater visibility of the problem and facilitating its recognition in public policy decisions, particularly in low-middle income countries where chronic is as prevalent as in high-income countries but pain management is often inadequate due to both limited resources and low prioritization of the problem. The general diagnostic code "cancer-related pain" only demands that the pain arose in relation to cancer and lasted/recurred for 3 months [1]. Cancer patients experience at least two different types of pain [1] and a neuropathic component is present in 20.9% to 40% of the patients, associated to higher pain intensity, poorer quality of life and higher analgesics intake [9]. Correct identification of the nature and the cause of pain is mandatory to achieve optimal pain control in any chronic pain patient, including cancer patient and cancer survivor. Accurate diagnosis and classification may lead to important benefits for patients: tailored treatment, better supportive therapies and more specialist referrals [1].

Another important improvement in cancer pain management is the recent adaptation of the WHO analgesic ladder used as a simple and valuable guidance since 1986. Until recently, cancer pain management has mostly relied on pharmacotherapy, opioids being considered as the mainstay. The opioids crisis which has highlighted the life threatening side effects of opioids has prompted the reassessment of opioids use to treat pain (acute pain, chronic non-cancer and cancer pain). Opioids dependence, abuse and misuse, problems most feared in chronic non-cancer pain patients, are now scrutinized in cancer patients and cancer survivors [10,11]. More, the interest for non-pharmacologic treatments in pain management is increasing.

Finally, like in other medical specialities, patient-reported outcomes (PROs) are now considered as key elements in making appropriate treatment decisions. In the past, cancer patients did not report pain spontaneously [12] but today the health-related quality of life has gained in interest for cancer patients, including for the older ones [13]. There is an important trend towards taking the patient's preferences and symptoms into consideration instead of only basing the treatment choice on patient comorbidities and drugs toxicity profile [12].

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In summary, cancer pain management is now closer to the management of chronic non-cancer pain and should be considered as "integrative pain care". By definition, integrative care includes the combination of two or more healthcare strategies in a multidisciplinary, interdisciplinary, collaborative, consultative and coordinated context (definition of IASP Global Year 2023). Integrative pain care may combine treatment strategies from different areas of alternative medicine, traditional medicine, or both. Such therapeutic approach better fits to the complexity of the pain experience and promotes individual preference as well as engagement of the person being treated when developing a pain treatment plan.

The present review is aimed to present and discuss the different options currently available to manage pain in (former) cancer patients in the light of progress made in the last decade. A particular attention has been paid to the literature published during the last ten years in the field, in the light of recent guidelines from specific societies like ASCO (American Society of Clinical Oncology), ESMO (European Society for Medical Oncology) or EAPC (European Association of Palliative Care). The review focuses on the current utilization of opioid analgesics, including the concerns of opioid adverses effects in the era of "opioid epidemic", on the presence of a neuropathic component too often poorly diagnosed and treated, as well as on the techniques and non-pharmacological strategies available which may help to personalize the treatment of the patient.

2. Opioids in cancer pain management: an update of the mainstay approach

Opioids still remain the mainstay of moderate to severe cancer pain treatment. Consequently, a skilled use of opioid analgesics is crucial to an adequate pain relief taking into account their potential harms. Several guidelines from different societies (EAPC, ASCO, ESMO and WHO) have been published and regularly updated [14-16]. Opioids prescribing relies on the WHO three steps ladder first released in 1986.

Weak opioids (codeine, hydrocodone, tramadol) are recommended to initiate pain relief in opioid naïve patients when pain is reported as mild to moderate, with no difference regarding the drugs efficacy [15-17]. Weak opioids are usually combined with non-opioid analgesics like paracetamol/acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs). There is no evidence showing that initiating opioid therapy by using a weak drug (step II) will improve the overall management of cancer pain. Similar observation was made regarding the strong opioids (step III drugs).

Strong opioids (morphine, oxycodone, hydromorphone) are recommended when the pain intensity is moderate to severe. To begin with low dose and to titrate up to obtain an optimal balance between satisfactory analgesia and tolerated side effects is mandatory. Analgesic efficacy seems to be similar among oral morphine, oxycodone and hydromorphone [17]. According to an overview of Cochrane Reviews (9 reviews, 152 RCTs, N=13524), more than 90% of the patients engaged in opioid treatment will get meaningful pain relief from oral morphine or fentanyl patch within 10 to 14 days [18]. The Cochrane Review also pointed out that up to 77% of the patients report at least one opioid side effect (mainly constipation and nausea) and 10-20% of cancer patients under opioid treatment need to change the treatment [18].

Opioid response varies among patients and the "interchangeability" of four morphine-like opioids has been questioned in an interesting multicenter, randomized, phase IV trial among cancer patients (N=520) receiving oral morphine, oral oxycodone, transdermal fentanyl or transdermal buprenorphine for 28 days [19]. Worst and average pain intensities decreased in a similar way among the four treatment groups. A daily dose increase occurred in each group (from 33% in oral morphine to 121% in transdermal fentanyl). Switch to an other opioid varied from 22% (morphine) to 12% (oxycodone) and discontinuation of treatment varied from 27% (morphine) to 14.5% for transdermal fentanyl. Drowsiness, constipation and dry mouth occurred in half of the patients. Opioids side effects did not differ regarding gastro-intestinal side effects (although transdermal fentanyl was previously found to cause less constipation than oral opioids). In contrast, central nervous system side effects e.g. myoclonus, confusion, hallucinations… were more

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prevalent with oral morphine (13.2% vs 2.4% in transdermal fentanyl group) [19]. In their conclusion, the authors pointed out the high percentage of non responders (8.9-14.4%) and poor responders (11-15.3%) to treatment, meaning that 22% to 26% of the patients had less than 30% reduction of pain intensity after 28 days opioid treatment. Even patients with a good response needed frequent adjustements in opioid therapy [19]. Although the trial suffered several limitations, it underlines the difficulty to provide an adequate and stable/sustainable management of chronic pain in cancer patients for various reasons like opioid tolerance or opioid poorly tolerated side effects, disease rapid progression or pain component poorly responsive to opioid treatment.

Sparing strong opioids for the WHO step III ladder has been longtime questioned and the use of low dose of a strong opioid as an alternative to a weak opioid has been suggested [17]. Indeed, early studies have reported that more than 50% of patients needed to switch from step II to step III within two weeks of treatment, due to lack of pain control [20]. Beside a lack of efficacy, some weak opioids demonstrate genetic polymorphisms that cause an unpredictable analgesic effect [21]. More, weak opioids are often expensive in low- and middle-income countries. A recent international open-label RCT (N=153) has compared a two-step approach versus the standard three-step approach WHO analgesic ladder [20]. The results showed no difference in time to get stable pain control between the control group (paracetamol, weak opioid i.e. tramadol or codeine up to maximal doses) and the experimental group (paracetamol, strong opioid i.e. morphine or oxycodone titration). Further, in the control group, 53% of the patients needed to change to a strong opioid due to ineffective analgesia within 6 days of treatment initiation (IQR 4-11 days). Patients under strong opioid experimented no more side effects, but had less nausea, and the costs were less. The trial provides some evidence that a two-step approach may be considered as a valuable alternative option for cancer pain management.

Optimizing opioids utilisation when pain remains poorly controlled deserves attention. As aforementioned, up to 26% of patients are non-responders or poor-responders to opioids [19]. Several causes explain the phenomenon including disease progression, negative psychological conditions, the pain features involving a neuropathic component and breakthrough pain (BTP) [22]. Moreover, an opioid misuse [10] and the possible development of some opioid tolerance and/or hyperalgesia may be questioned [23].

Opioid rotation or switching is common practice to optimize pain management. Opioid rotation is defined as switching from one opioid drug to another or changing an opioid's administration route (useful when patient's clinical state impairs pharmacokinetic or metabolism of opioid drugs) [24]. Two recent reviews on the topic including respectively 9 publications [25] and 20 publications [24] concluded that pain control was achieved while frequency of opioids side effects was rarely lessened. Further, no opioid drug could be found to be the best. Finally, equianalgesic tables commonly used are not based on high-level scientific evidence and very often the dose of the new opioid needed to be increased above the dose initially calculated, with the exception of rotations to methadone, and the ratio for a given opioid may change over time. Some authors [25] recommend to use methadone as second opioid when high doses of the first line opioid are already prescribed. It is here worth noting that opioids combinations are currently not recommended as evidence is limited.

Methadone developed in the 1930s is a potent synthetic opoid analgesic, with high oral bioavailability (67-95%), lack of active metabolites, long half life and low cost [26]. Methadone displays unique analgesic properties as it binds to μ-opioid receptors but also possess anti-NMDA (N-methyl-D-aspartate) properties and may affect serotonin and noradrenaline reuptake (activation of central nociceptive inhibitory systems and antidepressant effect). Methadone has two isomers: d-methadone displays antagonist activity at the NMDA receptor and l-methadone interacts synergistically with morphine at μ-opioid receptor. More, its continuous administration as μ-agonist induces much less NMDA overexpression, expression which is associated to opioid tolerance and hyperalgesia [27]. To date, methadone has been reported to be very effective *in opioid switching*, specifically when high doses of opioid are already used. Because of its complex pharmacokinetic

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profile, methadone prescription should be made by experienced professionals, i.e. pain specialists (according to guidelines like EAPC) [28]. When used as first line opioid in an opioid responsive pain, methadone does not provide superior analgesia to morphine [29]. A recent study assessed the efficacy and adverse effects of methadone used *as first-line therapy* in cancer patients that were either receiving low doses of opioids (weak opioids or others, at dose < 60 mg oral morphine equivalent/day) or none (i.e. opioid-naïve patients) [27]. Opioid-naïve patients started methadone at 6 mg/day and other patients at 9 mg/day. In both groups of treatment, methadone provided good analgesia with limited adverse effects and a minimal opioid-induced tolerance (low methadone escalation index). However, in high level socio-economic countries, methadone is rarely used as first line opioid but instead kept to treat complex pain due to neuropathic involvement or tolerance/hyperalgesia development. Besides its prescription as second-line opioid after switching as aforementioned, methadone can also be used *as a co-analgesic*. Low dose of methadone (e.g. 5 mg/day at start) as an adjunct to other opioids has been reported in the treatment of cancer pain in palliative care patients and seems to be both effective and safe [30,31]. In these reports (N=146 [29]; N=410 [31]), methadone as co-analgesic allowed a significant reduction in pain intensity in 49% to 94% of the treated patients, with a low incidence of side effects (20% of patients, no severe side effects).

Buprenorphine is not typically used as first-line analgesic in cancer pain. Buprenorphine is a strong opioid with mixed agonist and antagonist properties [32,33]. It is a semi-synthetic partial μ-opioid receptor and ORL-1 receptor agonist and a ƙ- and δ-opioid receptors antagonist. The drug binds to the μ-opioid receptor with a high affinity and has a slow dissociation, that contributes to a long duration of action and milder withdrawal symptoms. Unlike other opioids, buprenorphine does not induce μ-opioid receptors internalization that contributes to explain a reduced risk of tolerance phenomenon. Further, the drug demonstrates antihyperalgesic effects that last longer than the analgesic effect and that might be linked to its ƙ-opioid receptor antagonism. For these reasons, buprenorphine has been approved for opioid withdrawal and maintenance treatment of opioid dependance. Further, compared with other opioids, buprenorphine cause little to no immunosuppression at therapeutic analgesic doses [33]. In humans, a ceiling effect is observed for respiratory depression but not for analgesia. The oral bioavailability is low (15%) due to an extensive first-pass metabolism in the gastrointestinal mucosa and the liver. Buprenorphine does not accumulate in renal failure and is not removed by haemodialysis, keeping analgesia unaffected under these circumstances. In cancer patients, buprenorphine is usually prescribed as transdermal formulation in case of opioid switching and when suitable for some patients e.g. renal failure, patients with mixed pain including a neuropathic component [34]. It is worth noting that the drug is now recommended as first-line treatment of chronic pain in *cancer survivors* [7].

Tapentadol demonstrates strong analgesic effects in relation with its dual mechanism of action. The drug belongs to a novel class of analgesics as it binds to the μ-opioid receptor with an affinity 10- to 20-fold lower than morphine or oxycodone but also acts as a central norepinephrine reuptake inhibitor (NRI). Both mechanisms of action are synergistic and contribute to the analgesic potency of the drug [35]. The use of tapentadol in cancer pain management is recent, particularly because the drug is only available as oral tablets. In opioid-naïve patients with moderate to severe pain, tapentadol 25-200 mg twice daily is non inferior to oxycodone 5-40 mg twice daily as well as non inferior to morphine at a dose ratio 2.5:1 [35]. Tapentadol treatment is associated to less gastrointestinal and central nervous system side effects. It is interesting to note that switching from tramadol (a drug with dual mechanism of action involving both weak μ-opioid receptor binding and serotonin-norepinephrine reuptake inhibition) to tapentadol may be associated to improved analgesic efficacy. In opposite to tramadol, tapentadol is safe in patients with hepatic decompensation. Switching from high doses of a strong μ-opioid agonist to equianalgesic doses of tapentadol is also feasible but may induce features of mild opioid with-

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drawal. Tapentadol is particularly effective in cancer patients with *mixed pain and neuropathic pain* (hematological malignancies, bone metastasis, chemotherapy induced) with >75% response to treatment and neuropathic pain symptoms reduction [36].

Ketamine was synthetized in the early 1960s as a dissociative anesthetic and potent analgesic [37]. The drug is a racemic mixture with S(+) isomer being 3 to 4 times more potent than the R(-) isomer. Ketamine can be administered by multiple routes (intraveinous, intramuscular, intranasal…) but oral and rectal routes display poor bioavailability (17 and 25%, respectively) due to a first pass metabolism. Norketamine is an active metabolite with weak potency. Ketamine interacts with several systems (opioid, nicotinic, muscarinic) but its major mechanism of action relies on NMDA-receptor antagonism in the central nervous system. Further, ketamine is called a "use-dependent" drug i.e. it blocks NMDA channels only if they have already been open by intense or repeated noxious stimuli. Opioids administration also activates NMDA receptors resulting in opioids tolerance and hyperalgesia [23]. The administration of ketamine at sub-anesthetic doses (low doses: < 0.5 mg/kg) provides significant analgesic effects with limited side effects i.e. psychodysleptic or dysphoric effects [37]. Finally, rapid and potent antidepressant effects of ketamine have been recently highlighted. For all the aforementioned reasons, ketamine may be a useful adjuvant in the treatment of refractory chronic pain. In contrast to intraveinous administration, oral ketamine has a limited utility [38]. Whether a recent Cochrane review [39] found insufficient evidence to recommend ketamine as an adjunctive therapy in cancer pain, several clinical reports underline the benefit of low dose ketamine infusion (started at 100 mg/24h, up to 300 mg/24h) added to opioid analgesics in palliative care unit [40,41]. In these reports (N=70), ketamine infusion significantly reduced pain intensity in 56 to 74% of the patients, with an acceptable tolerance.

Magnesium deserves a few comments in the field of pain management, particularly as adjuvants to opioids in perioperative pain. Magnesium ions regulate the conduction of NMDA receptor channels in the central nervous system. Hypomagnesemia may occur in advanced cancer disease for various reasons and may be associated to refractory pain episodes [42]. Consequently, in case of poorly controlled pain despite strong opioid intake, blood magnesium levels should be checked. In experimental studies, magnesium sulfate enhance the effect of analgesics acting as NMDA receptor antagonists like ketamine and methadone [43].

Adverse effects and harms related to long-term opioids intake

Besides their analgesic effects mediated into the central nervous system, exogenous opioid analgesics also interact with various systems like mood, immune system… where they disturb endogenous opioids functioning. Common side effects of opioids are well know e.g. nausea and vomiting, constipation, sedation, dizziness, hallucinations, respiratory depression. The development of tolerance and, in rare cases, the development of hyperalgesia also may occur and necessitate treatment adaptation [23]. Other side effects like endocrine changes i.e. androgens deficiency and bone demineralization remain too often underestimated. More recently, the risk of depression associated to long term opioid prescription has been questioned [44]. Finally, psychological dependence and opioid use disorders (OUD) have gained in interest these last years in relation with the "opioids crisis". Opioid side effects may affect the quality of life of cancer patients and longterm opioid use even may affect survival, a question which is actually debated [8]. Both inadequate pain relief and opioids administration negatively impact the patient's immune response (either directly on tumor growth or indirectly on immune cells functioning). More well designed prospective studies are needed, taking into account that adequate pain relief remains a priority in cancer patients.

It is worth noting that side effects, and specifically harmful side effects of opioids, are actually pointed out and even more feared in the "cancer survivors" population [8]. Among opioids harms, the risks of *opioid use disorders (OUD)* have longtime been perceived as extremely low by health care providers in cancer treated patients. In a recent systematic review (literature review of the last 20 years), OUD prevalence reached 8% (up

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to 20%) among patients with cancer-related pain [10]. These findings clearly demonstrate that aberrant opioid analgesic behaviors (i.e. chemical coping), misuse and addiction also occur in cancer patients under chronic opioid treatment. In relation to the large definition of "OUD" used in the review, the studies heterogeneity precluded to define a profile of higher risk patient. Nevertheless, male patients seem to be at higher risk and opioids overdoses are more frequent in patients treated for head and neck cancers and myeloma. Opioid prescribing and use among cancer survivors is currently under consideration as it is in non-cancer chronic pain patients [11]. Besides the effects of chronic opioid intake on the immune system functioning, longterm opioid therapy may induce a state called "hyperkatifeia" i.e. a negative emotional state involving malaise, irritability, dysphoria, alexithymia, anxiety and in fine, mood depression [44]. To fight these negative feelings, patients increase opioids intake (i.e. negative reinforcement) what may lead to overdose, suicide and mortality. In a recent retrospective-based cohort study (N=54509), among the 6.1% of preoperative opioid-naïve patients who still used opioid analgesics at 6 months after lung cancer surgery, the authors found a 40% higher risk of 2-year all-causes mortality like cancer recurrence and opioids overdose [45]. More, longterm users of strong opioids were at higher risk of poorer survival than users of less potent opioids (OR 1.92 vs 1.22). Consequently, close follow up of chronic opioid prescriptions is recommended in cancer survivors [8], lowest doses of opioids, opioid tapering as soon as possible and prescription of specific drug like buprenorphine for maintenance [46].

3. The problem of neuropathic feature in cancer pain

Between 20 and 40% of cancer patients will experience neuropathic pain, defined by the International Association for the Study of Pain (IASP) as pain caused by a lesion or disease of the somatosensory nervous system [47]. In these patients, the peripheral or central nervous system can be affected either by the tumor itself or by its treatment (surgery, chemo- and radiotherapy) [1]. A particularity of cancer-related neuropathic pain is the frequent joint presence of nociceptive pain secondary to the mass effect of the tumor or its metastases, a situation referred to as mixed pain [1,48]. Neuropathic mechanisms play an important role in the pathophysiology of cancer-induced bone pain and may cause metastatic bone pain refractory to standard pain treatments. Presence of neuropathic features was found in 30.8% (95% CI: 23.6 to 39.1%) of the patients suffering from cancer-induced bone pain [49]. A recent large Korean observational study confirmed that the presence of neuropathic pain in cancer patients was associated with higher pain intensity, higher pain interference in daily life, and lower quality of life [50]. In this cohort, less than half the patients suffering from neuropathic cancer pain received the recommended adjuvant analgesics [50], highlighting the fact that despite the recent addition of specific codes in the latest International Classification of Diseases (ICD-11), neuropathic cancer pain remains under-treated [1].

Since there are specific treatment options available for neuropathic cancer pain (NCP), it is important that a correct diagnosis is established. The diagnosis of neuropathic cancer pain can be challenging and requires a comprehensive evaluation, including a detailed medical history, physical examination, and possibly diagnostic tests. In the absence of a gold standard for the diagnosis of neuropathic pain, the revised grading system for neuropathic pain remains the most widely used set of assessment criteria [51]. These criteria are (1) a history of a lesion or disease of the somatosensory nervous system *and* pain in a plausible neuroanatomical distribution, (2) pain associated with sensory signs in the same neuroanatomical distribution, and (3) confirmatory diagnostic tests indicating the presence of a lesion or disease of the somatosensory nervous. According to the number of satisfied criteria, the pain can be classified as possibly, probably, or definitively neuropathic [51]. While not formally validated in NCP patients, this approach has been endorsed by the IASP Cancer Pain Special Interest Group [48]. Neuropathic pain screening questionnaires, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Douleur Neuropathique 4 (DN4), and the PainDetect, can be valuable tools

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to assess the likelihood of neuropathic pain in individuals, including those with neuropathic cancer pain [52].

The guidelines on the management of cancer pain from the European Society for Medical Oncology recommend that NCP be treated with a combination of opioids and adjuvants when opioids alone are not sufficient [14].

First-line medications used to manage neuropathic pain include tricyclic antidepressants (TCAs, amitriptyline and nortriptyline), serotonin and norepinephrine reuptake inhibitors (SNRIs, duloxetine and venlafaxine), and anticonvulsant drugs (mainly gabapentin and pregabalin) [53]. While fewer studies have specifically investigated these drugs in NCP patients, a 2016 systematic review and meta-analysis found that adding antidepressants or anticonvulsants to opioids reduces pain intensity more than opioids alone [54]. Two more recent studies have reached similar conclusions. A randomized controlled trial enrolled 70 patients with NCP poorly controlled by a combination treatment of opioids and pregabalin and randomized them to receive either duloxetine 40 mg or a placebo. Significantly more patients in the duloxetine group reported a pain reduction of ≥ 50% (32 vs. 3%, $p = 0.002$). A retrospective chart review included 43 patients and showed that the combination of duloxetine and methadone resulted in a modest reduction of NCP intensity compared to methadone or duloxetine monotherapy [55]. Clinicians should always balance the potential benefits of these medications with their potential side effects. TCAs possess anticholinergic properties and can induce sedation, dry mouth, blurred vision, urinary retention, orthostatic hypotension, and tachycardia. Adverse effects of SNRIs include nausea, headache, dizziness, sweating, and arterial hypertension. Patients on gabapentinoids frequently complain of dizziness or somnolence, but both pregabalin and gabapentin are also associated with more serious adverse events, such as respiratory depression [56] and abuse [57].

Since patients with NCP often present with mixed pain, opioids are commonly prescribed in combination with first-line anti-neuropathic pain drugs [48]. Indeed, the guidelines on the management of cancer pain from the European Society for Medical Oncology recommend that NCP be treated with a combination of opioids and adjuvants when opioids alone are not sufficient [14]. There is no conclusive literature about the superiority of one opioid over another in the treatment of NCP, but some molecules with a dual mode of action might achieve better results in this indication. *Tramadol* is a weak opioid agonist but also inhibits the reuptake of serotonin and noradrenaline. It is recommended as a second-line treatment for neuropathic pain [53]. Its use in NCP is supported by a small placebo-controlled randomized trial [58]. The recently introduced opioid *tapentadol* acts both as a MOR agonist and selective noradrenaline reuptake inhibitor [59]. Kress et al. randomized nearly 500 patients with moderate to severe chronic malignant tumor-related pain—three-quarters reporting NCP—to receive either tapentadol, morphine sulfate, or a placebo. Both treatment arms were superior to the placebo, and tapentadol was non-inferior to morphine. Gastrointestinal side effects were less frequent in the tapentadol group [60]. More recently, a retrospective cohort study compared the evolution of pain intensity in 127 patients suffering from NCP who started treatment with tapentadol, methadone, oxycodone, fentanyl, or hydromorphone. The reduction in pain intensity was more pronounced with tapentadol, but this was statistically significant only when compared with oxycodone [36]. Finally, switching from another opioid to *methadone*—a MOR agonist and N-methyl-D-aspartate (NMDA) antagonist—has been shown to improve pain scores in patients with NCP in a recently published prospective cohort pilot study. Allodynia and the pressure/squeezing sensations were the most markedly reduced [61]. Methadone's complex pharmacokinetic profile—most notably its long half-life—complicates its use in clinical practice [28].

4. Personalized treatment: is it possible?

The presence of a multidisciplinary team is mandatory to manage refractory pain [62]. However, application of the fourth step in the WHO ladder should be considered,

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before refractory pain appears, and even before application of the step 3 in some patients who could benefit of more personalized therapeutic strategies [62]. The European Society for Medical Oncology (ESMO) recommends to adopt an integrative approach which includes primary antitumour treatments, interventional analgesic therapy and variety of non-invasive techniques [14]. While those treatments have a growing body of evidence for cancer pain, studies considering the benefit of such approach in breakthrough cancer pain are still lacking [14]. Radiotherapy, hormonotherapy, chemotherapy and surgery can be effective for pain relief in certain cancers [62]. Other more specific strategies, somehow more invasive, need to be considered on a basis of "case by case".

Neuromodulation consist of "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" [63]. This can be achieved by spinal cord stimulation, neuraxial drug delivery system, peripheral nerve stimulation or peripheral nerve field stimulation [62].

Deep brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation or motor cortex stimulation are in field of research [62].

Spinal Cord Stimulation (SCS) and dorsal root ganglion stimulation provide pain relief in neuropathic pain but studies dedicated to cancer pain are missing. Data are promising, with pain relief of at least 50%, but only case reports have been published up to now [62,64,65].

Neuraxial drug delivery is an option for some patients i.e. refractory pain, opioids intolerance, widespread bone metastases, specific locations like pancreatic cancer. Through an intrathecal (IT) catheter, drugs are infused directly near the spinal dorsal horn, bypassing the brain-blood barrier [66,67]. As for now, only ziconotide and opioids have FDA approval and have been proven to be effective and safe by this route. These drugs can be used in association with local anesthetics, baclofen, clonidine or ketamine (low to moderate evidence for those later drugs) [62]. The use of the IT route is associated with a better pain management and quality of life (QoL), a reduction of systemic opioid needs (ranging from 300 to 700 mg.d-1) and fewer systemic side effects due to the lower doses of opioids used [67-69]. Some authors note that it could also increase patient survival [14,62,69]. The use of an intrathecal drug delivery system (IDDS) is associated with a reduction of health care utilization for the patients [68]. Complications related to the technique (i.e. pump failure, implantation surgery, programming) are rare. Side effects related to the drugs administered can occurs, depending on the dosage. Morphine may induce similar side effects as systemic route, though less frequent, and development of granuloma at the catheter tip has been reported. Ziconotide is associated with dizziness, nausea and confusion [67]. Before implantation, clinicians should consider diagnosis, expected survival, previous use of opioids, location and type of pain. Thus, internal IT catheter should be reserved for patients who have long term survival expectation (>3 months) while external IT catheter might be considered for the others patients. The catheter implantation should be decided after appropriate consideration, and never proposed as a rescue treatment, which could lead to a failure in pain management [66]. A recent systematic review has highlighted the fact that preimplantation opioid consumption is usually high, suggesting that IDDS remains often a last resort option [68]. A multidisciplinary team and a specialized pain centre are mandatory to manage patients with such devices [62]. Regular routine evaluations and multidisciplinary re-assessment are recommended [62]. It is however worth noting that recent expert consensus proposes wider application of intrathecal analgesia in cancer pain treatment, including to ensure comfort at the end of life [66].

Technics of percutaneous neurolysis include cryoanalgesia, thermal neurotomy or pulsed radiofrequency, with the duration of effects depending on the lesion of the nerve.

Percutaneous neurolysis can be use for neuropathic refractory pain in patient with short life expectancy. The block usually lasts for 3-6 months [14,62,70]. A multimodal guidance with combined imagery techniques is requested to perform the technique [62]. Spinal neurolytic block with ethanol or phenol allows to infiltrate the dorsal roots. This

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technique is limited to pain localized to a few dermatomes and requires a highly skilled team. One should be cautious about low emergence of Adamkiewicz artery and the occurrence of a vasospasm leading to spinal paralysis [14,62].

Stellate ganglia block can be performed for breast, upper limb or posterior cervical spine cancer pain and seems to provide a reduction of the pain in more than 50 % of patients [62].

Coeliac plexus or splanchnic neurolytic block are used for abdominal and epigastric cancer pain, but the results are mixed, depending on the tumour location. The dispersion of the neurolytic solution might be unpredictable and even ineffective when local anatomy is modified by the tumour growth [66]. Severe complications like Adamkiewicz artery vasospasm are rare. Vasodilatation induced by the block increases the upper abdomen temperature and the intestinal motility [62,70].

Hypogastric plexus neurolytic block has been studied in pelvic cancer pain of visceral origin. Only a few studies are available on the topic [62] as well as on effectiveness of ganglion impar block which is applied to relieve lower rectal and perianal burns [62,70].

The aforementioned neurolysis techniques may provide good pain relief at short- and mid-term and contribute to reduce the consumption of systemic drugs. They are usually applied in patients with a short life expectancy and they can be repeated if needed [14,70]. A cancer progression should be suspected when the analgesic effect is of short duration while some nerve regeneration may explain the recurrence of pain after a longer time period [62].

Cordotomy is a surgical procedure which consist of provoking lesions to spinothalamic tract, thus blocking the pain pathway. This therapeutic approach should be reserved for patients who have a short term survival and suffer severe nociceptive or neuropathic pain. The technique should be performed in hospitals offering specialized palliative medicine, oncology and pain medicine teams [62].

Percutaneous ablation of metastasis can be achieved through either radiofrequency or cryotherapy. This technique is safe and provides significant pain relief for metastatic bone lesions [62].

Vertebral instability and spinal cord compression are usually treated by surgical procedure. **Vertebroplasty or kyphoplasty** are now the first approach, as they can be achieved percutaneously and under local anaesthesia. Cement is injected under radioscopic guidance, with good pain relief [62,71,72]. Cement leakage is common but significant complications are rare [71]. These minimally invasive techniques represent a safe alternative to manage vertebral compression consecutive to fracture [71,72].

Botulinum toxin (BT) is well known for its effects on muscle contracture, with paresis occurring a few days after injection and lasting for up to 3 months. In addition, BT displays analgesics effects, through the reduction of the release of substance P, glutamate and calcitonine gene-related peptide. A central analgesic effect has also been suggested [73-75]. The administration of BT has shown positive effects in the treatment of migraine and peripheral neuropathic pain conditions [74]. Local BT reduced neuropathic pain and muscle spasm when injected in the vicinity of radiotherapy area or surgical area, and beneficial effects could last for 12 weeks at least [74-76]. Additionally, in vitro and in vivo studies have demonstrated that BT could induce cellular apoptosis and tumour size reduction [74,75,77]. However, some patients might not respond to BT injection, possibly due to development of some immune resistance (an effect observed in some patients who underwent repeated BT injections, hence cumulative doses) [77]. BT injection induces few side effects and appears safer than potent analgesic drugs [74,77]. Moreover, potential effects on cancer cell lines are also promising and deserve future developments [74].

Cannabis-related medicines (CBM) have gained attention, and recent legalization of cannabinoid consumption in many countries has increased their interest in pain management [78]. Recent reviews however agree on the fact that CBM provide low to no effect on chronic pain, including cancer-related pain. Moreover, CBM are associated with central nervous, psychiatric and gastrointestinal side effects (i.e. nausea, dizziness). Besides, the long term effects of regular longlasting use of CBM remain poorly known [78-81].

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Integrative medicine also involve non-pharmacological therapies which may reinforce the other therapeutic strategies and are mainly dedicated to improve the patient's comfort and quality of life. Mind-body practice is based on the interactions between brain, mind, body and behaviour. Mind is used to improve physical function and health. Different techniques are available (i.e. meditation, hypnosis, tai chi, biofeedback, etc), allowing for a personalized approach according to the patient preference. These technique have demonstrated benefits on anxiety, depression, fatigue and emotional wellness [70,82].

Hypnosis induces a modified state of consciousness with increased response to suggestion. Self-induced hypnosis is effective to manage pain and to improve the quality of life of chronic pain patients, being more effective in highly hypnotizable patients. Nevertheless, evidence remains limited and more studies are needed in the field of chronic cancer pain [82].

Yoga practice improves the quality of life but, up to now, has show beneficial effect on pain only in patients presenting with aromatase inhibitor-related joint pain [83,84]. Studies have related some promising effects of Tai Chi and Qi Gong on emotional wellbeing (i.e. better control of anxiety, depression, stress and then enhanced quality of life). More studies are still required to support these findings [70,82,85].

Mindfulness and meditation are effective for cancer-related symptoms (i.e. anxiety, fatigue, depression). They improve the global patient's quality of life and might reduce pain severity, as reported in recent systematic review including American and Danish clinical trials [86]. Mindfulness might be more effective for some patients, based on clinical and psychological characteristics [87].

Cognitive behavioural strategies and pain coping are easily accessible techniques with beneficial impact on pain symptoms, but their use remain poorly studied in cancer population [87].

Music therapy, either receptive or active (i.e. playing, singing), can reduce pain, emotional distress and analgesic drugs consumption. Music therapy interventions can also improve quality of life and fatigue, as shown in recent systematic reviews [87-89].

Acupuncture is used worldwide for diverse reasons, including pain and its application is growing in oncologic practice [90-92]. Moreover, recent systematic reviews seem to demonstrate that acupuncture might be beneficial for cancer pain management including cancer pain in palliative care patients, allowing the reduction of some analgesic drugs intake (quality evidence however remains weak [85,90,93-95]. Considering the safety of the technique and the limited side effects, acupuncture is then considered by several authors as part of the integrative approach of cancer pain, and recommended by international societies like ASCO [83,92,95].

Massage therapy has shown beneficial effect on cancer pain, fatigue and anxiety in recent systematic reviews but evidence is limited and weak [84,96,97]. When considered, caution should be warranted and massages shouldn't be applied on soft tumor tissues or bones metastasis sites. [82]

A systematic review of quality measures for palliative care in oncology has shown that psychological, *social and spiritual aspects* of patient suffering are often neglected [98]. In the general population, religious and spiritual interventions may have a small beneficial effect on pain, contributing to reduce physical symptoms and to increase the quality of life, especially in patients enduring a chronic condition (i.e. obesity, cancer) [99]. Spiritual and Religious interventions have shown moderate effect on the quality of life in cancer patients, with little impact on pain reduction [100,101]. Considering the safety and the acceptance of these interventions, their use in an holistic approach of the patient is certainly beneficial and even recommended by some authors [70,101].

As future therapeutic approach, *virtual reality* is gaining interest, due to recent technological progress. Its use can improve the patient's overall well-being and reduce anxiety. Evidence for pain management, especially chronic pain, is still unconclusive and more studies are needed in this field [102-104].

5. Conclusion

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Pain is frequently reported during cancer disease, and still remains poorly controlled in around 40% of patients. Recent developments in oncology have helped to better control pain. These targeted treatments may cure cancer disease and significantly increase survival. Thereby, a novel population of patients (also called "cancer survivors") has emerged, with some of them enduring chronic pain (27.6% reported incidence of moderate to severe pain). Pain management in these patietns requires different strategies than treatment of patients with limited life expectancy. Major progress have been made in the last decade which include the recent development of a chronic cancer pain taxonomy now part of the International Classification of Diseases (ICD-11) as well as the update of WHO analgesic ladder. Until recently, cancer pain management mostly relied on pharmacotherapy, opioids being considered as the mainstay. The ""opioids crisis has prompted the reassessment of opioids use, in both cancer patients and cancer survivors. Recent literature review demonstrates that cancer pain management is now closer to the management of chronic non-cancer pain and should be considered as "integrative pain care". Clinicians should switch to dynamic interdisciplinary pain management. Alternative interventional therapies should be available when primary approach (i.e. traditional WHO ladder approach) has failed. Since cancer pain is multimorphic, optimal management always requires a dynamic evaluation to constantly adapt the therapeutic approach. Highly specialized teams with appropriate technical support are mandatory [62,87]. Further, the different scientific societies strongly recommend to use a multimodal approach i.e. pharmacological, physical and psychotherapeutic treatments [62,82,83,87] to better fit with personalized treatment. The goal should be to improve the patient's quality of life, not to increase the lifespan at the expense of its quality. The later observation has became a priority among the patients' requests.

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