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REVIEW

High-rate breakthrough cancer pain and tumour characteristics – literature review and case series

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Abstract

Cancer pain requires careful comprehensive patient evaluation and an appropriate and personalized clinical approach by a trained multidisciplinary team. The proper assessment of breakthrough cancer pain (BTcP) is part of an all-inclusive multidimensional evaluation of the patient. The aim of this narrative review is to explore the relationship between high-rate BTcP, which strongly impacts health-related quality of life and tumour characteristics, in the face of novel approaches that should provide guidance for future clinical practice. The presentation of short, emblematic clinical reports also promotes knowledge of BTcP, which, despite the availability of numerous therapeutic approaches, remains underdiagnosed and undertreated.

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Introduction

Pain is a very personal experience that feels different for everyone[1,2] and can affect physical and emotional functions differently, with a global impact on the quality of life (QoL).[3–6] Pain is one of the most common symptoms in patients with cancer[7] and can be caused by several factors, including the tumour itself, treatment or a combination of both. There is evidence that moderate-to-severe pain intensity[8,9] and breakthrough cancer pain (BTcP)[10–13] correlate with worse outcomes and greater impairment of overall QoL in patients with cancer.

The 2009 definition of BTcP by the Scientific Committee Working Group of the Association for Palliative Medicine of Great Britain and Ireland[14] remains valid and states that BTcP is an acute, transient exacerbation of severe pain that occurs spontaneously or due to a specific trigger in a patient whose baseline cancer pain is stable and controlled most of the time. Usually, BTcP is described as sudden, acute pain with high intensity that is clearly distinguishable from background pain. Most BTcP episodes peak in intensity within a few minutes and last for 30–60 minutes.[12,15–17] Idiopathic or spontaneous BTcP occurs in the absence of a relationship to any specific, recognizable cause, whereas incident pain can be volitional if triggered by a voluntary act (e.g. walking, weightbearing, food/liquid ingestion, and changes in sleeping position) or non-volitional if related to an involuntary act (e.g. coughing, chewing, swallowing, vomiting, intestinal peristalsis, and bladder spasm).[14,16,18–20] In their observational study of 1000 patients, Davies et al. stated that 44% of patients with cancer reported incident pain, whereas 41.5% reported spontaneous pain and 14.5% both types.[12] In the Italian Oncologic Pain multiSetting Multicentric Survey (IOPS-MS) study of 4,016 patients with cancer, BTcP was reported to be idiopathic by 69.5%.[21]

Procedural breakthrough pain is considered a particular type of predictable pain caused by care procedures. It is therefore highly predictable and is often amenable to preventive treatment[22] and administration of rescue medications.[23] Temporary exacerbations of cancer pain despite adequate baseline pain control with strong opioids make the assessment and management of cancer pain particularly critical.[24] The high intensity of sudden pain along with its unpredictability, rapid onset and a

negative impact on life activities and sleep quality define a 'high-rate BTcP' or 'worst BTcP' phenotype. High-rate BTcP requires intensive pain re-evaluation, frequent therapeutic adjustments and close patient follow-up.

Indeed, successful relief of breakthrough pain with careful management from baseline is crucial to improve physical and emotional function[25] and several aspects of health-related QoL.[24] Therefore, BTcP should be systematically screened in all patients with cancer who report pain, and properly treated with fast-acting fentanyl-based products, commonly referred to as transmucosal immediate-release fentanyl (TIRF).[26] The ESMO guidelines[27] recommend the use of TIRF as the first choice for the treatment of rapid-onset BTcP, limiting oral opioids, such as morphine immediate-release, to the treatment of procedural and well predictable pain. Transmucosal fentanyl provides rapid analgesia and different TIRF formulations based on innovative technologies have been developed to provide a personalized therapeutic response for patients with BTcP.[28–31]

All patients with cancer should be screened for pain at the initial evaluation, at each subsequent contact, and whenever new therapy has initiated. The intensity of pain and the treatment outcomes should be evaluated regularly and assessed using a visual analogue scale, verbal scale, or numeric rating scale (NRS).[32,33] Assessment of BTcP is part of an all-inclusive multidimensional evaluation of the patient and is essential for optimal cancer pain management.[33] A comprehensive pain assessment must consider the type and stage of cancer, care setting, causes of cancer pain, patient QoL, and treatment preferences. Some patients may experience multifactorial pain or pain syndromes that require complex approaches and intense analgesic schedules.[34]

Recent studies[35,36] have suggested a relationship between the worst BTcP phenotype and specific cancer characteristics. The aim of this narrative review is to highlight the direct correlation between high-rate BTcP and tumour characteristics or background pain types. We also report three emblematic case studies with the aim of sensitizing clinicians to the correct assessment and management of high-rate BTcP associated with certain types of cancer and to contribute significantly to preventing missed or delayed diagnosis of BTcP. The first case report involves BTcP caused by multiple bone metastases in a man with lung cancer; the second discusses BTcP in a woman with breast cancer and comorbidities; and the third discusses visceral BTcP, which is less common.

Methods

A literature search was performed in PubMed database using the key term "breakthrough pain" in the title of the article. The search was limited to humans, adults, English language and publication years 2012–2022. Clinical trials, meta-analyses and multicentre studies were included, and we selected studies reporting both BTcP characteristics and tumour types. Some included studies were identified from the reference lists of previous narrative reviews, systematic reviews and meta-analyses on cancer pain. A manual search of the reference lists of identified papers was also performed. We used the process of creating an interpretive understanding typical of a hermeneutic review and we finally considered the studies listed in Table 1.

Review

The estimated prevalence of BTcP is approximatively 70% in patients with cancer though some discrepancies persist amongst different studies.[15,37] Although we are aware of the limitations of comparing data collected from studies with different purposes, we nevertheless observed that BTcP is more frequently associated with breast and lung cancer.

Approximately half of the patients with lung cancer reported neuropathic pain,[38,39] approximately half had bone metastases, and approximately one-quarter reported frequent BTcP episodes.[34] In breast cancer, the prevalence of neuropathic pain was higher than that in other types of cancer.[40] Chronic neuropathic pain can be attributed to multiple aetiologies[41]; the tumour[42] or metastases[43] can damage soft tissue, bones, viscera or nervous plexuses, causing chronic peripheral neuropathic pain perceived in the distribution of affected nerves.[1,44,45] Symptoms of peripheral nerve damage include tingling, burning pain, electrical sensation, hyposensitivity, numbness and muscle weakness, sensorimotor deficits, and allodynia or hyperalgesia.[41,46]

Anti-cancer treatments further contribute to the development of chronic neuropathic pain.[47,48] Neuropathic mechanisms were predominant in postsurgical pain,[1] affecting 63% of women after mastectomy and 33% of patients after thoracotomy for lung cancer. Postsurgical pain was reported to be moderate to severe in 11–25% of cases.[1,49,50]

Moreover, chemotherapy (i.e. taxanes, platinum-based drugs, vinca alkaloids, thalidomide and proteasome inhibitors) can induce chronic painful polyneuropathy.[1] Neuropathic pain is highly prevalent in patients who are candidates for radiotherapy for breast and lung cancer.[51,52] However, radiotherapy can cause neuropathic pain due to cranial or peripheral nerve injury.

The most frequent clinical manifestations after radiotherapy for intracranial and extracranial metastases are

Table 1. Main studies reviewed on BTcP.

Authors	Development method	Country/ region	Enrolled patient background	Number of patients with BTcP	Sex	Mean age (years)	Spontaneous BTcP	Incident BTcP	BTcP episodes (per day)	Mean duration	Onset time	Intensity	Primary tumour localization
Albiach et al.[76]	Survey (pain management specialists)	Spain	BTcP caused by bone metastases	386	Men 68.1%	65.7	50%	50%; volitional 44.3%; non-volitional 55.4%	3.5±1.8	20.2 minutes	Rapid 61.1%; slow 38.9%	Severe 71.2%; moderate 26.7%; mild 2.1%	Lung 25.4%
Baek et al.[77]	Multicentre nationwide study	Korea	Cancer pain (hospitalized patients)	177/609	Men 59%	>65			1.95–2				Lung 25.4%; prostate 22.0% (80 % stage IV)
Davies et al.[12]	Multicentre study	Europe	BTcP (palliative care)	1000	Men 51%	62	41.5% 14.5% spontaneous+ incident	44%; volitional 44.9%; non-volitional 15.2%; mixed 7.9%; procedural 11.3%; ND 20.5%	3	<10 min 15%; 10–30 min 25%; 30–60 min 23%; >60 min 37%	Time to peak 10 min	Severe 61.8%; moderate 33.7%; mild 3.6%	Gastrointestinal 26.4%; lung 17.2%; urological 16%; breast 12.5%
Bedard et al.[4]	Multicentre study	Canada	BTcP (palliative care)	94	Women 57 %	67	6.4 % 28.7 % spontaneous+ incident	64.9%	2–3	<10 min 16.6% 10–30 min 15.2%; 30–60 min 15.2%; >60 min 50%	Time to peak 10 min	Severe 61.8%; moderate 33.7%; mild, 3.6% (European data) Mean 7.8/10 (Canadian data)	Lung 21.3%; breast 21.3% gastrointestinal 11.7%; urological 10.6%

(*Continued*)

Table 1. (Continued)

Authors	Development method	Country/ region	Enrolled patient background	Number of patients with BTcP	Sex	Mean age (years)	Spontaneous BTcP	Incident BTcP	BTcP episodes (per day)	Mean duration	Onset time	Intensity	Primary tumour localization
Mercadante et al.[78]	Secondary analysis of a multicentre study						70.5%	29.5%; procedural 5.7%	2.2	Mean 52.6 min	≤10 min 65.5%; >10 min 35.5%	7.3	Gastrointestinal 34.3%; pancreas 24.1%; liver 8.7%; gynaecological 7.5%
Shi et al.[34]	Retrospective study	China	Cancer pain (lung cancer)	39/152	Men 65.1%	58							Bone metastasis 44.1%
Husic et al.[17]	Prospective study	Bosnia and Herzegovina	Cancer pain (palliative care)	80/433	Men 62.6%	62			2.41	16–20 min		Mean 8.04	Lung 33.1%; gastrointestinal 21.1%; otorhinolaryngological 15.6%; breast 15.1%
Mercadante et al.[21]	Multicentre study	Italy	BTcP (cancer at any stage)	4056	Men 54.8%	64.6		Predictable 33%	2.5	43 min		Mean 7.5	Lung 24.0%; breast 11.3%; gastrointestinal 25.4%; prostate 4.9%
Magnani et al.[22]	Prospective, observational and cross-sectional study	Italy	Cancer pain (palliative care)	149/1180	Women 55.7%	71.5				15–30 min 53.0%	0–10 min 51.0%; 10–20 min 44.3%	1–4 (34.2) 5–6 (43.6) ≥7–10 (22.1)	Lung cancer 24.8%; gastrointestinal 18.8%; urological 11.4%; breast 10.1%; multiple metastasis 65.1%; bone metastasis 6.0%
Mercadante et al.[79]	Secondary analysis of IOPS-MS multicentre study	Italy	Visceral cancer pain	414/470	Women 50.5%	65	70%	21%; procedural 9%	2.7				Lung 33.1%; gastrointestinal 13.0%; breast/ gynaecological 7.8%

(*Continued*)

Table 1. (Continued)

Authors	Development method	Country/ region	Enrolled patient background	Number of patients with BTcP	Sex	Mean age (years)	Spontaneous BTcP	Incident BTcP	BTcP episodes (per day)	Mean duration	Onset time	Intensity	Primary tumour localization
Cuomo et al.[24]	Clinical study	Italy	BTcP (solid tumours at any stage)	154	Men 55.8%	63.5	71.1%	72.7%		>30 min, 73.9%		8.24	Gastrointestinal 21.6%; breast 17.6%; otorhinolaryngological 15.7%; haematological 15.7%; gynaecological 11.8%
Brant et al.[80]	Prospective, quantitative, longitudinal, single-arm pilot study	USA	BTcP (advanced cancer)	51	Women 62.7%	56.3						≥7 (84.1%)	Lung 29.95%; colorectal 11.15%; otorhinolaryngological 7.14%; stage III or IV bone metastasis 31.1%
Fan et al.[81]	Retrospective cross-sectional analysis	China	BTcP (cancer stage III or IV, 55.8% metastatic)	428/798	Men 56.6%	56.7							

BTcP, breakthrough cancer pain; IOPS-MS, Italian Oncologic Pain multiSetting Multicentric Survey; ND, not determined.

cranial neuralgias after radiotherapy for intracranial and extracranial metastases[53] and painful brachial plexopathy in breast and apical lung cancer. In addition, stereotaxic body radiotherapy for apical lung cancer should improve the risk of brachial plexopathy.[54]

Finally, lung, breast and prostate cancers account for more than 50% of cases of metastatic spinal cord compression[55] caused by prolonged direct pressure from the tumour mass or by tumour-induced pathological collapse of the vertebral bone metastases.[56] The most common location for cord compression is the thoracic spine, followed by the lumbosacral spine and the cervical level.[43] Patients with epidural spinal cord compression experience back pain, weakness, sensory changes and autonomic dysfunction; therefore, prompt diagnosis is essential.

Neuropathic pain is associated with poor outcomes in cancer pain control[57] with greater analgesic requirements and disability.[44] When associated with BTcP, neuropathic pain causes not only an overall impairment of health-related QoL but also a substantial increase in healthcare costs.[58]

Patients with cancer often complain of pain caused by bone metastases, which are common in breast, prostate and lung cancer.[59–61] Post-mortem studies have estimated that 70–90% of patients with breast or prostate cancer have evidence of bone metastasis.[62] The most common sites of metastases are the vertebrae, pelvis, long bones, and ribs[63] and innocuous movement, bumps or falls may result in painful pathological fractures,[1] which might reduce mobility and increase anxiety, significantly worsening QoL.[64] Many breakthrough pain episodes of greater intensity in the advanced stages of cancer are due to bone pain caused by metastasis[17] and require additional proper therapy. Albiach et al.[76] collected data from patients with metastatic bone disease and BTcP and demonstrated that primary cancer was mainly localized in the lungs and prostate (85 out of 386 patients or 22%), and BTcP occurred spontaneously and suddenly with high pain intensity in 70.6% of cases.

Mercadante et al.[65] conducted a secondary analysis of the IOPS-MS study including 4056 patients with BTcP and showed that patients with lung cancer had higher levels of background pain, higher BTcP intensity, and greater interference with daily activities. The main causes of BTcP were cough and movement related to bone metastases. Shi et al.[34] reported moderate-to-severe chronic neuropathic pain in 46.7% of 152 patients with lung cancer and BTcP in 25.7%, mostly associated with a high intensity of background pain. Cuomo et al.[24] and Brant et al.[80] found high percentages (70% and 71.1%, respectively) of spontaneous BTcP, and the episodes of BTcP had a high average intensity (NRS ≥7).

A recent univariate analysis[36] based on the IOPS-MS study[15] analyzed data from 2671 patients with non-predictable BTcP, resulting in the identification of four BTcP phenotypes. The worst unpredictable BTcP had a fast onset time of <10 minutes and was mainly managed with TIRF.[26] This phenotype is significantly associated with younger age and lung cancer. Pantano et al.[35] published a similar study aimed at identifying novel sub-types of BTcP by using unsupervised learning algorithms. The study demonstrated that specific BTcP clusters, each associated with specific clinical features, were linked to therapy satisfaction or dissatisfaction. Finally, approximately 55% of patients with abdominal cancer pain developed BTcP episodes, with a higher percentage (90%) of patients with previous uncontrolled background pain.[66]

Mercadante et al.,[66] in their secondary analysis of the IOPS-MS study, observed that postprandial BTcP in visceral cancer pain is mainly associated with pancreatic cancer. In these patients, BTcP showed a lower intensity (mean NRS 6.9), faster onset and shorter duration (mean 45.8 minutes) in comparison with other causes of predictable BTcP and unpredictable BTcP.

Prevalence data on pancreatic cancer-related pain vary from 47% to 63% at diagnosis and 82% in advanced-stage cancer in patients referred to palliative care, with a positive correlation between pain and disease progression or poor outcomes. Patients with pancreatic cancer reported high intensity cancer pain and severe interference with activities of daily living.[67–69] The most common sites of metastatic disease are peritoneum, liver and lung.[69] Abdominal pain is usually referred to as lower mid-back pain and is accompanied by weight loss and sometimes jaundice. Local pain may be related to intraluminal activation of pancreatic enzymes and malignant obstruction and distention of the pancreatobiliary tree, whereas anterior mass progression may cause small bowel distension and severe abdominal or intestinal colic pain, usually accompanied by nausea and vomiting.[69] Involvement of the peritoneum, abdominal wall, retroperitoneal tissues, and both intrapancreatic and extra pancreatic nerve plexuses, including the celiac plexus, determines mixed nociceptive and neuropathic pain.[1,66,69]

Despite the World Health Organization guidelines regarding mild-to-moderate cancer pain treatment, only 40–49.6% of patients with pain due to pancreatic cancer receive a combination of opioids, adjuvant analgesic drugs and TIRF as the first choice for the treatment of unpredictable and rapid-onset BTcP.[41,57,68,70]

Case reports

Three clinical reports from real-life experiences in cancer pain management have been described with the intent of exemplifying pain management in complex cases. In these case series, the worst BTcP phenotypes were correlated with specific cancer characteristics and background pain types. All the data referring to the patients were published anonymously without any details allowing re-identification of the patient, and in accordance with the World Medical Association Declaration of Helsinki.

Case report 1

A 56-year-old male patient complained of dry cough, chest tightness, and cervical-dorsal pain for 2 months due to C3 and T1 vertebral body metastases. A contrast-enhanced chest CT scan demonstrated an 18-mm abnormal mass in the left lung, a solid left hilar mass and several bone metastases confirmed by ^{18}F-fluoro-2-deoxyglucose (FDG)-fluorodeoxyglucose positron emission (PET)/computed tomography (CT).

Stage IV lung adenocarcinoma was diagnosed. Genetic tests using next-generation sequencing of the lung lesion biopsy revealed *KRAS* G12C mutation, whereas other tested driver genes were absent. PDL1 expression was 10%. After active discussions, a multidisciplinary team (including oncologist, pathologist, respiratory physician, thoracic surgeons, radiologist and radiotherapist) agreed to treat the patient with chemotherapy plus immunotherapy (carboplatin plus pemetrexed plus pembrolizumab) and radiotherapy (8 Gy in a single fraction) on the bone metastases at risk for fracture and pain (C3, T1 and sacrum).

The patient experienced severe pain (NRS >7) for most of the day, causing reduced daily activity, sadness, low concentration, and a significant decrease in appetite and time spent sleeping. Paracetamol 1000 mg three times/day was not enough for a real benefit, so an oral controlled-release formulation of oxycodone was added (at a dose of 5 mg every 12 h gradually increased to 20 mg every 12 h), without side-effects related to opioids. Fairly good control of the baseline pain was achieved (NRS 2), but the patient reported sudden, severe and short-lasting pain, two to three times per day, in the neck and sometimes in the left leg when walking. A sub-lingual formulation of transmucosal immediate-release fentanyl at a dose of 133 µg was added for the BTcP episodes. Since no adequate analgesia was obtained within 15–30 minutes of administration of a single tablet, a supplemental 133 µg tablet was administered. BTcP episodes were controlled with 267 µg of fentanyl sublingual tablets. The recommendation was to use one sublingual tablet (267 µg) no more than four times per day.

After three cycles of chemo-immunotherapy, evaluation of the therapeutic effect presented a partial response based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

As a result of our prescription, the patient had strong relief of pain with optimal pain control, and there was also an improvement in quality of life and daily activities.

Case report 2

The patient was a 63-year-old woman with chronic kidney disease, type 2 diabetes and dyslipidaemia. In 2001, at the age of 43 years, she underwent left super external quadrantectomy and ipsilateral axillary lymphadenectomy for breast cancer (invasive ductal carcinoma, grade 2). The patient received standard radiotherapy after surgery, adjuvant therapy with six cycles of cyclophosphamide–methotrexate–5 fluorouracil, and triptorelin combined with tamoxifen for 5 years. In 2018, following the occurrence of left leg pain, clinical examination and whole-body ^{18}FDG-PET/CT scans revealed high FDG uptake in the vertebral (T4, T5, L1, L3, L5, S) scapulae, right IV rib, left femur and lymph nodes from the left supraclavicular and ilio-pulmonary areas. Supraclavicular lymph node biopsy confirmed metastasis of infiltrating ductal carcinoma, and letrozole (2.5 mg once daily) and denosumab (120 mg IV every 4 weeks) were administered. Magnetic resonance imaging (MRI) in the T1, T2 and STIR sequences of the spine excluded the presence of vertebral collapse. Radiotherapy on T10–S1 (25 Gy) and the left femur (30 Gy) was performed for palliative, analgesic and decompressive purposes and for the prevention of severe bone events.

The patient complained of moderate-to-severe pain (mean NRS 6–7) throughout the day and night, causing a reduction in sleep quality and duration. The pain was localized mainly in the lumbar spine and left hip and increased when sitting or standing, forcing the use of walking aids. She reported only partial benefit from paracetamol/codeine 500/30 (two tablets three times a day) and moderate benefit with the use of oral ketorolac (up to 40 mg/day), as needed. In view of chronic kidney disease stage 3, a buprenorphine transdermal system of 35 µg/h was applied and replaced every 96 hours (twice a week at regular intervals). The dosage was gradually increased over the weeks to 52.5 µg/h, and paracetamol was continued at a dose of 3 g/day. The patient was advised to complete a daily pain diary.

At the next control, the patient reported a reduction in baseline pain intensity. Average NRS was 5, but the pain diary showed several peaks of very intense pain (NRS 8–9), of variable duration, both spontaneous and mainly triggered by movement. The high frequency of these pain peaks and their increase near the transdermal patch replacement suggested that background pain was still not fully controlled. Therefore, the dosage of transdermal buprenorphine was increased to 70 µg/h, and naldemedine 200 µg tablets (once daily) was associated with the control of opioid-induced constipation. The subsequent pain diary showed the clear presence of BTcP episodes, for which 133 µg sublingual fentanyl was recommended, advising the patient to take it 5 minutes before triggering activities (i.e. standing or walking) or immediately at the onset of the unpredictable pain flair, and in any case no more than four times a day.

At the next telemedicine clinical follow-up, the patient reported good background pain control (NRS 3) and two to three BTcP episodes per day, well managed with sublingual fentanyl, which was increased to 267 µg.

Case report 3

A 56-year-old male patient was treated for abdominal pain and upper abdominal heaviness for approximately 3 months, with over-the-counter pain medication (mainly paracetamol up to 3 g/day or non-steroidal anti-inflammatory drugs) and weak opioids (tramadol as needed), which allowed unsatisfactory pain relief. Imaging studies showed a 3.5-cm pancreatic adenocarcinoma (cT2N0) that was borderline resectable. Neoadjuvant chemotherapy with the mFOLFIRINOX regimen (irinotecan/oxaliplatin/leucovorin/5-fluorouracil) was started. The patient reported visceral pain in the upper abdominal area and under the ribs, sometimes spreading to the back and worsening after eating or drinking. The pain intensity was moderate to severe (NRS 5–6).

The patient was started with transdermal fentanyl 12 µg/h subsequently increased to 25 µg/h due to nausea and vomiting that limited the regular intake of oral therapy.

After 2 weeks, the patient reported very good control of his pain (NRS <3) for most of the day but complained of two to three episodes per day of unpredictable flares of severe pain (NRS 7–8) with short duration, occasionally associated with big meals or defecation.

Sublingual fentanyl 133 µg up to four times a day was prescribed for BTcP, and constipation was better managed with a peripherally acting µ-opioid receptor antagonist (naloxegol 25 mg once a day).

Due to depressed mood and sleep disorders, after psychological consultation, the multidisciplinary team agreed to include duloxetine 30 mg once daily in the morning in order to treat symptoms of reactive depression secondary to cancer and chronic pain with a neuropathic component. Pain was then well controlled, and the patient started working again almost at full capacity and had an active family and social life.

After four cycles of chemotherapy, the patient started radiation therapy with concomitant use of capecitabine. Treatment showed a decrease in tumour diameter (1.5 cm) yet it was still in contact with the superior mesenteric artery. Pain decreased and opioid therapy was gradually discontinued. The patient was placed under observation, and new staging studies are expected.

Future perspectives

As cancer pain requires complex and multidisciplinary treatment modalities, patient management should be improved through technological advances. Telemedicine, as a remote system, could be seen as an opportunity for access to care and ongoing support as well as an opportunity to achieve the challenging goal of personalized cancer pain management.[71,72] Hybrid models appear to be a valid, modern, tailored approach to cancer pain management, improving patient satisfaction and healthcare costs, combining face-to-face visits and a scheduled remote follow-up programme with hospital readmissions as needed.[71] The implementation of telemedicine must be supported by the development of information technology infrastructure[71] and the training of patients and caregivers in the use of the telemedicine system.[73]

Additionally, new tools such as artificial intelligence (AI) and machine learning will soon become critical and indispensable resources that can improve care pathways, identify urgent activities and provide an appropriate response to the specific needs of the patient.[73,74] AI is also able to optimize drug discovery processes, their commercialization and associated costs.[75] This, combined with innovative drug delivery technologies, will allow improved customization of cancer pain therapy.

Finally, the implementation of AI-based applications could be useful for the future development of clinical trials. Recent studies have offered a novel approach to study BTcP through AI-based patient enrolment and stratification.[35,36]

Conclusion

Cancer pain requires careful comprehensive patient evaluation, individualized assessment and treatment by a trained multidisciplinary team. Specific treatment

must be planned for each patient, considering comorbidities and drug side-effects. Cancer pain intensity and the use of high doses of opioids are independent risk factors for poor prognosis and shorter survival in patients with cancer. Conversely, effective management of cancer-related pain improves the patient-perceived value of cancer treatment.

Alongside telemedicine, AI could represent a promising scenario, enabling physicians to make effective and data-driven decisions in a real-life context. The available evidence suggests that the worst BTcP phenotypes can be correlated with specific cancer characteristics or background pain types. BTcP should be systematically assessed in all patients with cancer. When background pain is controlled by strong opioids, BTcP must be properly treated with TIRF, limiting the use of immediate-release or intravenous morphine to selected cases according to BTcP characteristics, patient requirements and safety.

A challenge for BTcP management is the implementation of novel approaches, which should provide guidance for the future clinical practice of healthcare professionals involved in the multidisciplinary and tailored management of cancer pain.

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