Pain

Management of cancer pain

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Patients with cancer have diverse symptoms, impairments in physical and psychological functioning, and other difficulties that can undermine their quality of life. If inadequately controlled, pain can have a profoundly adverse impact on the patient and his or her family. The critical importance of pain management as part of routine cancer care has been forcefully advanced by WHO, internationlal and national professional organisations, and governmental agencies. The prevalence of chronic pain is about 30–50% among patients with cancer who are undergoing active treatment for a solid tumour and 70–90% among those with advanced disease. Prospective surveys indicate that as many as 90% of patients could attain adequate relief with simple drug therapies, but this success rate is not achieved in routine practice. Inadequate management of pain is the result of various issues that include: undertreatment by clinicians with insufficient knowledge of pain assessment and therapy; inappropriate concerns about opioid side-effects and addiction; a tendency to give lower priority to symptom control than to disease management; patients under-reporting of pain and non-compliance with therapy; and impediments to optimum analgesic therapy in the health-care system. To improve the management of cancer pain, every practitioner involved in the care of these patients must ensure that his or her medical information is current and that patients receive appropriate education.

Assessment of cancer pain

The management of cancer pain depends on a comprehensive assessment that characterises the symptom in terms of phenomenology and pathogenesis, assesses the relation between the pain and the disease, and clarifies the impact of the pain and comorbid conditions on the patient's quality of life. This assessment requires the use of a standard nomenclature and an approach that explores the many dimensions of pain and other features of cancer.

Because pain is inherently subjective, a patient's self-report is the gold standard for assessment. The information elicited from the patient should focus on: temporal features (onset, pattern, and course); location (primary sites and patterns of radiation); severity (usually measured with a verbal rating scale, eg, mild, moderate, or severe, or a 0–10 numeric scale); quality; and factors that exacerbate or relieve the pain. These characteristics, combined with information from the physical examination and review of laboratory and imaging studies, usually define a discrete pain syndrome, clarify the known extent of disease and the relation between the pain and specific lesions, and allow inferences about pain pathophysiology. This information influences the decision to undertake further assessments or attempt specific therapies.

In the past few years, inferences about the pathophysiology of pain have informed therapeutic decision making. The term nociceptive is applied to pains that are presumed to be maintained by continual tissue injury. Nociceptive pain is called somatic when the continued activation is related to primary afferent nerves in somatic tissues, such as bone, joint, or muscle, and is called visceral when viscera afferents are activated by injury.

The term neuropathic is used when the pain is believed to be sustained by aberrant somatosensory processing in the peripheral or central nervous system. This label encompasses diverse syndromes. The broad subtypes comprise the deafferentation pains (such as central pain, phantom pain, and postherpetic neuralgia), peripheral mononeuropathies and polyneuropathies, and the complex regional pain syndromes (reflex sympathetic dystrophy or causalgia). Although neuropathic pains can respond well to conventional analgesics, these syndromes are disproportionately represented among patients whose pain responds poorly to opioid drugs.[1] As a result, the diagnosis of a neuropathic pain syndrome often indicates other therapies, including the use of specific non-traditional analgesic drugs.

Cancer pain syndromes

Recognition of pain syndromes can help identify the specific aetiology responsible for the pain, guide the need for additional evaluation, suggest specific therapies, or assist in assessments of patients' outcome. Although most acute pain syndromes are caused by common diagnostic or therapeutic interventions[2] (panel 1), acute flare ups of pain are also common among patients with chronic pain. Up to two-thirds of patients with well-controlled chronic pain have transitory breakthrough pains.[3] The potential for new therapies for breakthrough pain, such as oral transmucosal fentanyl citrate,[4] is likely to increase understanding of this type of pain.

As many as three-quarters of chronic pain syndromes result from a direct effect of the neoplasm; others are related to therapies administered to manage the disease or to disorders unrelated to the disease or its treatment. Clinicians who manage cancer pain must be able to recognise common syndromes.[5]

Tumour-related nociceptive pain syndromes

Neoplastic invasion of bone, joint, muscle, or connective tissue can cause a persistent somatic pain; bone pain syndromes are the most common. Only a small proportion of bone metastases become painful, and the factors that

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convert a painless lesion into a painful one are unknown. The spine is the most common site of bone metastases and many patients with cancer have back pain. Extension of a neoplasm from the vertebra has the potential to damage the spinal cord or nerve roots, and thereby produce substantial neurological compromise. Back pain from vertebral metastasis is, therefore, a marker of potential epidural spinal cord or cauda equina compression. Recognition of the specific patterns of pain (eg, "crescendo" pain, pain flare with recumbency, or radicular pain) and the neurological findings that predict impending epidural compression allow the selection of patients at high risk of this complication for specific imaging of the epidural space with magnetic resonance imaging or myelography. With early diagnosis and treatment of the tumour, the neurological disorder can be prevented. This is a compelling example of the need for syndrome recognition in the assessment of cancer pain.

Panel 1: **Acute pain syndromes**

Due to procedures and therapies

Acute pain associated with diagnostic procedures
- Lumbar puncture headache
- Bone marrow biopsy
- Lumbar puncture
- Venepuncture
- Paracentesis
- Thoracentesis

Acute pain associated with analgesic techniques
- Spinal opioid hyperalgesia syndrome
- Acute pain after Strontium-89 therapy of metastatic bone pain

Acute postoperative pain

Acute pain associated with other therapeutic procedures
- Pleurodesis
- Tumour embolisation
- Nephrostomy insertion
- Pain associated with bone marrow transplantation (oral mucositis, hepatopathy)

Acute pain associated with chemotherapy
- Pain from intravenous or intra-arterial infusion
- Intraperitoneal chemotherapy
- Headache due to intrathecal chemotherapy
- Painful oropharyngeal mucositis
- Painful peripheral neuropathy
- Diffuse bone or muscle pain from colony-stimulating factors or chemotherapies
- 5-fluorouracil-induced angina

Acute pain associated with hormonal therapy
- Painful gynaecomastia
- Luteinising hormone-releasing factor tumour flare in prostate cancer
- Hormone-induced acute pain flare in breast cancer

Acute pain associated with immunotherapy
- Arthralgia and myalgia from interferon and interleukin

Acute pain associated with radiation therapy
- Painful oropharyngeal mucositis
- Acute radiation enteritis and protocolitis
- Early onset brachial plexopathy after radiation for breast cancer

Due to neoplasm or related pathology

Acute tumour-related pain
- Vertebral collapse and other pathological fractures
- Acute obstruction of hollow viscus (eg, bowel, ureter, bladder outlet)
- Headache from intracranial hypertension
- Haemorrhage into tumour

Acute pain associated with infection
- Myalgia and arthralgia associated with sepsis
- Pain associated with superficial wounds or abscesses

Adapted from Portenoy.[2]

Panel 2: **Chronic pain syndromes in patients with cancer: tumour-related pain syndromes**

Nociceptive pain syndromes

Bone, joint, and soft-tissue pain syndromes
- Multifocal or generalised pain (focal metastases or marrow expansion)
- Base of skull metastases
- Vertebral syndromes
- Pain syndromes of the bony pelvis and hip
- Tumour invasion of joint, or soft tissue, or both

Paraneoplastic pain syndromes
- Hypertrophic osteoarthropathy
- Tumour-related gynaecomastia

Neoplastic involvement of viscera
- Hepatic distension syndrome
- Rostral retroperitoneal syndrome
- Chronic intestinal obstruction and peritoneal carcinomatosis
- Malignant pelvic and perineal pain
- Chronic ureteral obstruction

Neuropathic pain syndromes

Painful peripheral mononeuropathies

Painful polyneuropathies

Plexopathy
- Cervical
- Brachial
- Lumbosacral
- Sacral

Radiculopathy

Epidural spinal cord compression

Obstruction, infiltration, or compression of visceral structures, including hollow viscus and supporting connective tissues, produce various visceral nociceptive pain syndromes (panel 2). Most of these syndromes are easy to diagnose. A few syndromes can pose diagnostic challenges, particularly when they precede the diagnosis of the neoplasm.

Tumour-related neuropathic pain syndromes

Neuropathic pain syndromes may be caused by tumour infiltration or compression of nerve, plexus, or roots, or by the remote effects of malignant disease on peripheral nerves (panel 2). The syndromes are highly variable; patients may have aching pains or dysesthesias (abnormal pain sensations such as burning) anywhere in the dermatomal region innervated by the damaged neural structure.

Treatment-related pain syndromes

Nociceptive pain syndromes related to chemotherapy, radiation therapy, or surgery are rare (panel 3). Somatic pain related to osteonoecrosis of bone can be caused by radiation or corticosteroid-based chemotherapy regimens, and chronic visceral pain can follow intraperitoneal chemotherapy or abdominal radiation therapy. These syndromes can mimic tumour-related pains and in the assessment it is important to exclude recurrence.

Most post-treatment pain syndromes are neuropathic. The factors that predispose some patients to chronic neuropathic pain after nerve injury, the extent or severity of which may be minor, are unknown. Any surgical incision could lead to a neuropathic pain syndrome in a small proportion of pateints. Repeated assessments are often needed to exclude tumour recurrence. Chronic pain after any amputation can result in neuroma formation at the amputation site, the underlying cause of stump pain, or central-nervous-system processes that presumably underlie the development of phantom pain.

Panel 3: **Chronic pain syndromes in patients with cancer: treatment-related pain syndromes**

Nociceptive pain syndromes
Painful osteonecrosis
Radiation-induced or corticosteroid-induced necrosis of femoral or humeral head
Osteoradionecrosis of other bones
Painful lymphoedema
Painful gynaecomastia
Chronic abdominal pain
Due to intraperitoneal chemotherapy
Due to radiation theapy
Radiation-induced chronic pelvic pain

Neuropathic pain syndromes
Postsurgical neuropathic pain syndromes
Postmastectomy syndrome
Post-thoracotomy syndrome
Postradical neck dissection syndrome
Postnephrectomy syndrome
Stump pain and phantom pain
Postradiotherapy pain syndrome
Radiation fibrosis of cervical, brachial, or lumbosacral plexus
Radiation-induced neoplasm
Radiation myelopathy
Postchemotherapy pain syndromes
Polyneuropathies

Radiation-induced fibrosis can damage a peripheral nerve or nerves and cause chronic neuropathic pain; symptoms usually occur months to years after treatment. The neuropathic pain tends to be less prominent than the pain caused by neoplasm, and can also be associated with slowly progressive weakness, sensory disturbances, radiation changes of the skin, and lymphoedema. The diagnosis may be complicated by previous surgery and the risk of cancer recurrence.

Other issues in assessment of cancer pain

Most patients with cancer who experience chronic pain also develop other physical and psychological symptoms. Studies have shown that pain, fatigue, and psychological distress are the most common symptoms in patients with cancer.[6–8] A broad assessment of symptoms is an essential part of the management of cancer pain.

Assesment of pain and symptoms, in turn, is only one of a range of issues that contribute to the suffering of the patient and the family.[9] Suffering has been compared to overall impairment in quality of life[10] and defined as "total pain".[11,12] Both suffering and quality of life are multidimensional constructs and the assessment needed to explore them must examine impairments in multiple domains, including the physical, psychological, social, spiritual, existential, and others.[13] The foundation for this assessment is constant, open communication between the clinician and the patient.

The assessment and management of difficulties that arise in the multiple quality of life domains is fundamental to the therapeutic model known as palliative care. Palliative care is a model of care focused on patients with progressive incurable illness and their families. It is a therapeutic approach that aims to improve the quality of life of the patient and family throughout the course of the disease and help them face the prospect of death. Palliative care must intensify at the end of life, when it must ensure that comfort is a priority, values and decisions are respected, practical support is available, and opportunities exist for growth and resolution.

Panel 4: **Guidelines for conventional management of chronic opioid therapy**

Comprehensive assessment
Define pain syndrome, functional status, psychosocial disturbance, and concurrent diseases. Consider previous substance abuse.
Consider efficacy of opioids in the defined pain syndrome and the role of this treatment in a multimodal approach.

Drug selection
Consider age and whether major organ failure is present, especially renal, hepatic, or respiratory.
Consider pharmacological issues.
Consider drug-selective differences in side-effect or toxicity profile.
Consider the effects of concurrent drugs with possible pharmacokinetic and pharmacodynamic interactions.
Consider individual differences (note previous treatment outcomes) and patient's preference.
Be aware of available preparations for route (eg, oral, intravenous, subcutaneous injection, topical) and formulation (eg, immediate or controlled release).
Be aware of cost differences.

Route selection
Use least invasive route possible.
Consider the convenience and compliance of patient.

Dosing and dose treatment
Consider previous dosing requirements and relative anlgesic potencies when initiating therapy.
Start with low dose and increase until adequate analgesia occurs or dose-limiting side-effects occur.
Consider dosing schedule (eg, around-the-clock or as needed) depending on the expected duration of pain.
Consider rescue medication for breakthrough pain.
Recognise that tolerance is rarely the driving force for dose escalation; consider disease progression when increasing dose requirements occur.

Trial of alternative opioids
Note individual differences in the response to various opioids; consider a trial of another opioid following treatment failure.

Treatment of side-effects
Consider treatment for constipation, nausea, somnolence or itch.

Monitoring
Monitor treatment efficacy and pain status over time and consider modification if necessary

Adapted with permission from Ingham and Portenoy.[17]

All clinicians who care for patients with cancer provide palliative care as a part of good medical practice. Effective treatment for pain is an essential part of this care. Palliative care is currently evolving as a medical specialty in many countries. Referral to specialists in palliative care is appropriate whenever symptom distress cannot be managed, a high degree of global suffering exists, or the need for a comprehensive team approach to care is required, which commonly occurs as patients approach the end of life. Some countries have specialised programmes for the provision of palliative care at the end of life, such as hospice programmes.

Management of cancer pain

Although the mainstay approach for the management of cancer pain is opioid-based pharmacotherapy, a range of potential strategies should be considered for each patient. In many cases, the assessment of pain indicates an intervention targeted at the aetiology of pain. Radiation therapy is commonly used for pain, and palliative chemotherapy is occasionally given with the major goal being analgesia. Recently, the US Food and Drug Administration approved two chemotherapeutic drugs,

Drug	Dose (mg) equianalgesic to morphine 10 mg intramuscular*				Comment
	Oral	Intramuscular	Half-life (h)	Duration (h)	
Morphine	20–30†	10	2–3	2–4	Standard for comparison
Controlled-release morphine	20–30	10	2–3	8–12	Various formulations are not bioequivalent
Sustained-release morphine	20–30	10	2–3	24	
Oxycodone	20	. .	2–3	3–4	
Controlled-release oxycodone	20	. .	2–3	8–12	
Hydromorphone	7·5	1·5	2–3	2–4	Potency may be greater—ie, hydromorphone:morphine is 3:1 rather than 6·7:1, during long-term use.
Methadone	20	10	12–190	4–12	Although 1:1 ratio with morphine was in single dose study, there is a change with chronic dosing and large dose reduction (75–90%) is needed when switching to methadone.
Oxymorphone	10	1	2–3	2–4	Available in rectal and injectable formulations.
Levorphanol	4	2	12–15	4–6	
Fentanyl	. .	. .	7–12	. .	Can be administered as a continuous intravenous or subcutaneous infusion; based on clinical experience, 100 µg/h is roughly equianalgesic to morphine 4 mg/h.
Transdermal fentanyl	. .	. .	16–24	48–72	Based on clinical experience, 100 µg/h is roughly equianalgesic to morphine 4 mg/h. A ratio of oral morphine to transdermal fentanyl of 70:1 may also be used clinically.

*Studies to assess equinalgesic doses of opioids have used morphine by the intramuscular route. The intramuscular and intravenous routes are deemed to be equivalent and intravenous is the most common route used in clinical practice.
†Although the oral/intramuscular morphine ratio was 6:1 in a single-dose study, other observations indicate a ratio of 2–3:1 with repeated administration.
Adapted from Derby and colleagues.[21]

Opioid analgesics used for the treatment of chronic pain

gemcitabine and mitoxantrone, specifically for symptomatic relief in pancreas cancer and prostate cancer, respectively.[14] The use of these therapies as a component of pain management must be consistent with the patient's medical status and goals of care.

Pharmacological approaches

Opioid therapy

Given its effectiveness and safety, opioid therapy should be administered routinely to patients with moderate to severe cancer pain. The "analgesic ladder" approach of WHO is widely accepted as the basis for treatment guidelines.[3,15,16] Although this approach originally emphasised the role of morphine, it is now recognised that individual patients vary greatly in their response to different opioids. Sequential opioid trials (so-called opioid rotation) may be needed to identify the drug that yields the most favourable balance betwen analgesia and side-effects. Panel 4 summarises the guidelines for conventional management of chronic opioid therapy.[17]

The oral route for opioid delivery is effective and acceptable to most patients and it is generally preferred for chronic opioid therapy. Other routes may be useful, however, in selected patients. The transdermal route of administration is available for the highly lipophilic opioid, fentanyl. Comparative trials against controlled-release oral morphine indicate that this formulation is preferred by some patients and may be associated with less constipation than other formulations;[18] it is also commonly used if the oral route is compromised by dysphagia or impaired gastrointestinal function, if compliance has been difficult with oral agents, or if a trial with fentanyl is desired. Continuous subcutaneous infusion, with or without bolus injections for breakthrough pain, may be delivered by an ambulatory infusion pump.[19] In the future, these pumps may be partly supplanted by the advent of iontophoretic devices that can provide similar drug delivery characteristics through the skin. Intraspinal approaches can be valuable among a highly selected group of cancer patients who are unable to benefit from systemic therapy. There are various approaches to implement long-term epidural or intrathecal infusions.[20]

Dosing guidelines for opioid therapy are well established (panel 4). Fixed scheduled dosing has replaced as-needed dosing in the treatment of continuous or frequently recurring pain. An as-needed rescue dose tends to be combined with the fixed regimen for the treatment of breakthrough pains. The size of the starting dose varies with the severity of the pain, previous exposure to opioid, and the medical condition of the patient. Among patients with limited exposure to opioid, the starting dose is usually equivalent to 5–10 mg of parenteral morphine every 4 h. The size of the rescue dose typically ranges from 5% to 15% of the total daily dose and the dosing interval is long enough to observe the full effect of each dose. With oral dosing, the minimum interval is usually 2 h, whereas with intravenous administration it can be as short as 10–15 min. Individualisation of the dose is the key principle in opioid therapy. The goal is to achieve a favourable balance between analgesia and side-effects through gradual adjustment of the dose. The size of each dose increment is usually either the total of the rescue doses consumed during the previous 24 h, or 30–50% of the current daily dose (sometimes higher in patients with severe pain).

Information about the relative potency betwen opioid drugs is needed for changes in drugs or routes of administration (table).[21] This information derives from single-dose studies in selected populations and should be taken as a guideline for the selection of a starting dose of a new drug or route. When switching from one opioid to another, the dose of the new drug is typically reduced by 30–50%, and more (>90%) when the new drug is methadone.[22]

There is no maximum dose or ceiling dose for the pure µ-agonist opioids. Dose titration should continue until the outcome is satisfactory or intolerable side-effects occur. The management of side-effects is fundamental to therapy and can open the therapeutic window by permiting the use of higher, more effective doses. The most common side-effects are related to gastrointestinal function (constipation, nausea, and vomiting) and neuropsychological function (somnolence and impairment of cognition). There are numerous therapeutic strategies for each of these phenomena.[23–25] Some patients do not attain a favourable balance between analgesia and side-effects during opioid titration. For these patients, other strategies may be appropriate, for example, other drug approaches, or the use of non-pharmacological interventions such as a nerve block, surgical procedure, or psychological therapy (panel 5).

Non-opioid and adjuvant analgesics

The non-opioid analgesics include acetaminophen and the non-steroidal anti-inflammatory drugs (NSAIDs). Adjuvant analgesics are drugs that have a primary indication other than pain but are analgesic in certain circumstances.

Acetaminophen and the NSAIDs are widely used, produce dose-dependent analgesic effects, and have dose-response relations characterised by a minimum effective dose and a ceiling dose for analgesia. Acetaminophen is usually safer but does not have substantial anti-inflammatory effects; anecdotally, evidence indicates less efficacious in bone pain and pains associated with grossly inflammatory processes. NSAIDs can be useful and should be considered for co-administration with the opioids. The maximum efficacy and side-effects of each NSAID vary between patients; similarly, different NSAIDs produce varied effects in the same patient. Given the variability in the minimum effective dose and ceiling dose, dose titration is usually justified. The use of NSAIDs is limited by side-effects and concerns about gastrointestinal and renal toxic effects. The use of these drugs is likely to improve with the advent of cyclo-oxygenase-2 selective inhibitors, which lack significant gastrointestinal and renal toxicity.[26]

Adjuvant analgesics include drugs in diverse classes (panel 6). Among patients with cancer, these drugs tend to be administered after opioid therapy has been optimised. Corticosteroids are multipurpose drugs and are used commonly in patients with advanced disease to improve pain, anorexia, nausea, and malaise. Many other adjuvant analgesics, including antidepressants, anticonvulsants, and oral local anaesthetics, are used for neuropathic pain that does not respond adequately to an opioid.[27] Sequential trials are sometimes needed to identify a useful drug. Other adjuvant analgesics are used to manage opioid-refractory malignant bone pain. These include bisphosphonates, radiopharmaceutical drugs, and calcitonin. With increasing evidence that the bisphosphonates improve overall morbidity associated with bone metastases, the use of these drugs is expanding.[28] The pain associated with malignant bowel obstruction may be difficult to treat. Anticholinergic drugs, octreotide, and corticosteroids may be useful adjuvant drugs that reduce pain and vomiting.[29]

Panel 5: **Alternative therapeutic options when an opioid regimen fails**

Approach	Therapeutic options
Administer a pharmacological technique to reduce the requirement for systemic opioid	Use of adjuvant analgesics Use of spinal opioids
Identify an opioid with a more favourable balance between analgesia and side-effects	Sequential opioid trials (opioid rotation)
Improve the tolerability of the opioid	More aggressive management of side-effects (eg, use of stimulant for opioid-induced sedation)
Try non-pharmacologic techniques to reduce requirement for systemic opioid	Anaesthetic approaches (eg, blocks) Surgical approaches (eg, cordotomy) Rehabilitative approaches (eg, bracing) Psychologic approaches (eg, cognitive therapy)

Adapted from Portenoy.[2]

Panel 6: **Adjuvant analgesics**

Indication	Examples
Multipurpose drugs	Corticosteroids Dexamethasone Prednisone
Neuropathic pain	Antidepressants (multipurpose but used for neuropathic pain) Tricyclic antidepressants Amitriptyline Desipramine Newer antidepressants Fluoxetine Paroxetine α-2 adrenergic agonists (multipurpose but used for neuropathic pain) Clonidine Tizanidine NMDA receptor antagonists Ketamine Dextromethorphan Anticonvulsants Gabapentin Carbamazepine Phenytoin Valproate Clonazepam Lamotrigine Oral local anaesthetics Mexiletine Tocainide Neuroleptics Pimozide Miscellaneous Baclofen Calcitonin
Drugs used for complex regional pain syndrome or suspected sympathetically-maintained pain	Calcitonin Clonidine Prazosin
Topical agents	Capsaicin Phenoxybenzamine Local anaesthetics
Drugs for bone pain	Bisphosphonates (eg, pamidronate) Calcitonin Radiopharmaceuticals (eg, strontium-89 and samarium-153)
Drugs for bowel obstruction	Scopolamine Glycopyrrolate Octreotide

Other analgesic techniques

For patients who do not respond adequately to drug therapy, alternative analgesic therapies must be considered. These therapies include many anaesthetic, surgical, neurostimulatory, physiatric, and psychological interventions (panel 5). Some patients pursue alternative medicine to obtain relief. There have been no comparative studies of any of these interventions and therapeutic decisions are made on the basis of an assessment of the patient's pain, medical and psychosocial status, extent of disease, and therapeutic goals. In each case, the clinician must assess the benefits and burdens associated with the therapy. Open communication about these issues is essential to provide long-term support to patients with refractory pain syndromes.

Conclusion

Cancer pain occurs mostly in the context of a progressive illness that may result in multiple other physical and psychological symptoms, functional decline, spiritual or existential distress, family disruption, financial worries, and many other issues that may undermine the quality of life of the patient and his or her family. Optimum management of pain should be viewed from the broad perspective of palliative care that aims to maintain quality of life throughout the course of disease and manage the complex difficulties that can occur as patients approach the end of life. All clinicians who treat patients with cancer must acknowledge the importance of palliative care as part of good medical practice and focus appropriately on the knowledge and practical skills needed to address concerns about quality of life, such as pain. The ability to provide a comprehensive assessment, competently administer analgesic drugs, and communicate with the patient and family is the basis of pain management in patients with cancer.

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