Cancer pain, pathophysiology, characteristics and syndromes

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Summary

In this study the pathophysiology and characteristics of cancer pain together with cancer pain syndromes and guidelines of management are reviewed.

Tumour-associated pain may be nociceptive (somatic or visceral) if the sustaining mechanisms are related to ongoing tissue pathology, or neuropathic when pain is associated with injury to neural tissues. The mechanism by which tumours produce pain include obstruction of lymphatic and vascular channels, distension of a hollow viscous, oedema and tissue inflammation or necrosis. Injury to tissues results in the local release of numerous chemicals that mediate transmission of pain stimulus.

Cancer pain syndromes result from one or more of three fundamental causes; direct tumour involvement of tissues, cancer-directed therapy, and mechanisms unrelated to cancer or its treatment. Cancer pain syndromes are also classified as acute or chronic.

Cancer pain characteristics provide some of the data essential for syndrome identification. These characteristics include intensity, quality, distribution and temporal relationships.

The principles of tumour-directed pain control include modifying the source of pain by treating the cancer and the inflammatory response to cancer, altering the central perception of pain and interfering with nociceptive transmission within the central nervous system.

Key words: Cancer pain; Cancer pain pathophysiology; Cancer pain characteristics; Cancer pain syndromes.

Introduction

Controlling the pain associated with cancer is a major health care problem [1, 2]. Thirty percent of patients with cancer have pain at the time of diagnosis, and 65% to 85% have pain when their disease is advanced [1-5]. Lack of expertise by clinicians in assessing and managing cancer pain has been listed as an important cause of poor pain control [6]. From this point of view it is clear that management of cancer pain requires a variety of assessment skills and the integration of knowledge about the pathophysiology of cancer pain, characteristics of cancer pain, cancer pain syndromes, pharmacology, and disease specifics.

Pathophysiology

Pain is defined as an unpleasant and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [7]. The sensory features and subjective qualities of pain vary, depending on its origin. Its emotional features depend in part on the social and physical context in which pain occurs, associated cognition, and the meaning of tissue trauma for the individual, but they are almost always negative [8].

From a sensory perspective, tumour-associated pain may be classified as nociceptive (somatic or visceral) and neuropathic. Pain is nociceptive if the sustaining mechanisms are related to ongoing tissue pathology, and it is neuropathic when evidence suggests that the pain stems from injury to neural tissues and abberant somatosensory processing in the periphery or in the central nervous system (CNS) [8].

Mechanisms by which tumours produce pain include obstruction of lymphatic and vascular channels, distension of a hollow viscous, oedema and tissue inflammation or necrosis.

Nociceptive pain

For each somatosensory receptor there is a preferred type of stimulus (mechanical, chemical, thermal, or a combination of these modalities) to which the neuron is most sensitive, called adequate stimulus. There are some receptors in tissues distinguished by a relatively high threshold to adequate stimulus, which are termed as nociceptors [9]. Adequate stimulus differs for the different functional states of a nociceptive neuron because the membrane chemistry changes. Each tissue has characteristic adequate stimuli for its custom designed nociceptive apparatus [10]. These stimuli cause some changes, and eventually sensory fibres provide information to the CNS [11].

Nociceptors are subclassified with respect to three criteria [11]:

1. Unmyelinated, C-fibre afferents (conduction velocity < 2 m/s) versus myelinated, A-fibre afferents (conduction velocity > 2 m/s).
2. Modalities of stimulation that evoke a response.
3. Response characteristics.

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Chemical sensitivity of nociceptors

Injury to tissues results in the local release of numerous chemicals (brodykinin, prostaglandins, arachidonic acid metabolites, adenosine and adenosine phosphates, serotonin, protons, histamine, cytokines, excitatory aminoacids, opioids) which mediate or facilitate the inflammatory process.

Bradykinin

Bradykinin is released upon tissue injury and is present in inflammatory excudates [12]. The administration of brodykinin results in evoked response in the fibres [13]. Sensitisation and excitation appear to be predominantly mediated via the B2 receptor, although in some fibres a B1 receptor-mediated effect has been observed [14].

Protons

Protons selectively activate nociceptors and produce a sensitisation of nociceptors to mechanical stimuli [15]. The low pH levels in inflamed tissue due to local acidosis may contribute to pain and is associated with protons. A synergistic excitatory effect of protons and a combination of inflammatory mediators has been reported [16].

Serotonin

Serotonin is released from platelets as a result of the effect of platelet activating factor, and can activate nociceptors. Serotonin can also potentiate the pain induced by bradykinin [17].

Histamine

The role of histamine in pain sensation is less clear, but it has been reported to excite polymodal visceral nociceptors and potentiate the responses of nociceptors to brodykinin [18]. Histamine is released from mast cells, which is caused by substance P that is released from nociceptor terminals [19].

Arachidonic acid metabolites

The prostaglandins, thromboxanes and leukotriens are a large family of arachidonic acid metabolites collectively known as eicosanoids. The eicosanoids are generally not considered to activate nociceptors directly, but rather to sensitise the nociceptors in skin and viscera to natural stimuli and other endogenous chemicals [20].

Adenosine and adenosine phosphates

During inflammation and tissue injury, adenosine and its derivatives (AMP, ADP, ATP) may be released or leak into the extracellular space and activate nociceptors [21]. Adenosine and its derivatives have been reported to induce pain in humans [22]. However, intradermal injection of ATP in humans is not painful [23].

Cytokines

During inflammation cytokines (e.g., interleukin 1β, IL-1β; tumour necrosis factor α, TNF-α; interleukin 6, IL-6; interleukin 8, IL-8) are released by a variety of cells (e.g. macrophages) and regulate the inflammatory response [24]. A direct excitation and sensitisation to thermal and mechanical stimuli of nociceptive afferent fibres have been shown for IL-1β and TNF-α [25].

Excitatory amino acids

An involvement of peripheral glutamate receptors in formalin-induced pain behaviours has been demonstrated [26]. Glutamate receptors have been identified on peripheral terminals of cutaneous nociceptors [27]. The peripheral application of glutamate activates nociceptors [28].

Opioids

Peripheral analgesia by opioids appears to be part of a physiological antinociceptive system because increased amounts of endogenous opioids have been found in inflamed tissues [29].

Nociceptive pain may be cutanous (superficial or deep) or visceral. Most cutanous pain is well localised, sharp, pricking or burning. Deep tissue pain usually seems diffuse and dull or aching in quality. Visceral pain is diffuse, often referred to the body surface, perseverating, and frequently associated with a queasy quality that patients describe as sickening [8].

Prolonged or repeated activation of nociceptive C fibres produces central sensitisation so that noxious stimuli produce pain (allodinia). This is called central sensitisation and occurs in any situation with prolonged or intense C fibre input [30]. Both substance P and glutamate acting at the N-metyl-D-aspartate (NMDA) receptor contribute to central sensitisation [31, 32].

Neuropathic Pain

Neuropathic pain involves injury to the nervous system and has different mechanisms from pain caused by chronic tissue inflammation. For nerve injury, the fibres are disconnected from the periphery and respond to axonal damage, local neuritis, atrophy, altered Schwann cell activity, and their own altered signalling. For inflammatory and neuropathic conditions, there are phenotypic changes in the peripheral nerve cells; increased excitation, disinhibition, or both of the dorsal horn and pain pathways; altered immune signals into the CNS; and usually some activation of stress endocrinology and alterations in sensory sympathetic interactions [33].

Cancer pain syndromes

Cancer pain syndromes are defined by the association of particular pain characteristics and physical signs with specific consequences of the underlying disease or its treatment, and have important prognostic and therapeutic implications. These syndromes result from one or more of three fundamental causes [8,34]; direct tumour involvement of pain sensitive tissues, cancer-directed therapy, and mechanisms unrelated to cancer or its treatment. Patients may present with complex patterns of pain that result from a combination of these categories [35].

Cancer pain syndromes are also classified as acute or chronic. However acute pain experienced by cancer patients is usually related to diagnostic and/or therapeutic interventions, whereas chronic pain is most commonly caused by direct tumour invasion (Tables 1 and 2) [36].

Acute pain is defined by a recent onset and natural history characterised by transience. The pain is often associated with anxiety and signs of sympathetic activity such as hypertension and tachycardia [36].

Chronic pain has been defined by persistence for three months or beyond the usual cause of an acute illness or injury, or by association of a chronic pathological process [37].

Cancer pain characteristics

The evaluation of pain characteristics provides some of the data essential for syndrome identification. These characteristics include intensity, quality, distribution and temporal relationships.

Intensity

The evaluation of pain intensity is pivotal to therapeutic decision-making [38, 39]. It indicates the urgency. The assessment of pain intensity may also help to characterise the pain mechanism and underlying syndrome. Patient self-reports are always the primary source of information for the measurement of symptoms. Observer ratings of symptom severity correlate poorly with patient ratings and are generally inadequate substitutes for patient reporting.

The three most commonly used instruments for assessing cancer pain intensity are as follows:

1. Visual Analog Scale (VAS): A slash mark corresponding to intensity of pain is placed on a 100-mm line ranging at one end from 'no pain' to the other end, 'pain as bad as it could possibly be' (e.g., birth pain).

Table 1. — *Cancer-related acute pain syndromes.*

Cancer-related acute pain syndromes
Acute pain associated with diagnostic and therapeutic interventions
Acute pain associated with diagnostic interventions
Lumbar puncture headache
Transthoracic needle biopsy
Arterial or venous blood sampling
Bone marrow biopsy
Lumbar puncture
Colonoscopy
Myelography
Percutaneous biopsy
Thoracentesis
Acute postoperative pain
Acute pain caused by other therapeutic interventions
Pleurodesis
Tumor embolization
Suprapubic catheterization
Intercostal catheter
Nephrostomy insertion
Cryosurgery-associated pain and cramping
Acute pain associated with analgesic techniques
Local anaesthetic infiltration pain
Opioid injection pain
Opioid headache
Spinal opioid hyperalgesia syndrome
Epidural injection pain
Strontium-89-induced pain flare
Acute pain associated with anticancer therapies
Acute pain associated with chemotherapy infusion techniques
Intravenous infusion pain
Hepatic artery infusion pain
Intraperitoneal chemotherapy abdominal pain
Acute pain associated with chemotherapy toxicity
Mucositis
Corticosteroid-induced perineal discomfort
Taxol-induced arthralgias
Steroid pseudorheumatism
Painful peripheral neuropathy
Headache
Intrathecal methotrexate meningitic syndrome
L-asparginase associated dural sinuses thrombosis
Trans-retionic acid headache
Diffuse bone pain
Trans-retionic acid
Colony stimulating factor
5-flurouracil-induced anginal chest pain
Palmar-plantar erythrodyesesthesa syndrome
Postchemotherapy gynecomastia
Chemotherapy-induced acute digital ischemia
Acute pain associated with hormonal therapy
Leutenizing hormone releasing factor tumor flare in prostate cancer
Hormone-induced pain flare in breast cancer
Acute pain associated with immunotherapy
Interferon induced acute pain
Acute pain associated with growth factors
Colony-stimulating factor induced musculoskeletal pains
Erythropoietin injection pain
Acute pain associated with radiotherapy
Incident pain associated with positoning
Oropharyngeal mucositis
Acute radiation enteritis and proctocolitis
Early onset brachial plexopathy
Strontium-89-induced pain flare
Acute pain associated with infection
Acute herpetic neuralgia
Acute pain associated with vascular events
Acute thrombosis pain
Lower extremity deep venous thrombosis
Upper extremity deep venous thrombosis
Superior vena cava obstruction

Table 2. — *Cancer-related chronic pain syndromes.*

Cancer-related chronic pain syndromes	
Tumor-related pain syndromes	
Bone pain	
Multifocal or generalised bone pain	
Multiple bony metastases	
Marrow expansion	
Vertebral syndromes	
Atlantoaxial destruction and odontoid fractures	
C7-T1 syndrome	
T12-L1 syndrome	
Sacral syndrome	
Back pain and epidural compression	
Pain syndromes of the bony pelvis and hip	
Hip joint syndrome	
Acrometastases	
Artritidies	
Hypertrophic pulmonary osteoarthropathy	
Other polyarthritidies	
Muscle pain	
Muscle cramps	
Skeletal muscle tumors	
Headache and facial pain	
Intracerebral tumor	
Leptomeningeal metastases	
Base of skull metastases	
Orbital syndrome	
Parasellar syndrome	
Middle cranial fossa syndrome	
Jugular foramen syndrome	
Occipital condyle syndrome	
Clivus syndrome	
Sphenoid sinus syndrome	
Painful cranial neuralgias	
Glossopharyngeal neuralgias	
Trigeminal neuralgia	
Eye and ear syndromes	
Otalgia	
Eye pain	
Tumor involvement of the peripheral nervous system	
Rumor-related radiculopathy	
Postherpetic neuralgia	
Cervical plexopathy	
Brachial plexopathy	
Malignant brachial plexopathy	
Idiopathic brachial plexopathy associated with Hodgkin's disease	
Malignant lumbosacral plexopathy	
Tumor-related mononeuropathy	
Paraneoplastic painful peripheral neuropathy	
Subacute sensory neuropathy	
Sensorimotor peripheral neuropathy	
Pain syndromes of the viscera and miscellaneous tumour-related syndromes	
Hepatic distension syndrome	
Midline retroperitoneal syndrome	
Chronic intestinal obstruction	
Peritoneal carcinomatosis	
Malignant perineal pain	
Malignant pelvic floor myalgia	
Adrenal pain syndrome	
Ureteric obstruction	
Ovarian cancer pain	
Lung cancer pain	
Paraneoplastic nociceptive pain syndromes	
Tumour-related gynecomastia	
Chronic pain syndromes associated with cancer therapy	
Postchemotherapy pain syndromes	
Chronic painful peripheral neuropathy	
Avascular necrosis of femoral or humeral head	
Plexopathy associated with intraarterial infusion	
Raynaud's phenomenon	
Chronic pain associated with hormonal therapy	
Gynaecomastia with hormonal therapy for prostate cancer	
Chronia postsurgical pain syndromes	
Postmastectomy pain syndromes	
Postradical neck dissection pain	
Postthoracotomy pain	
Postoperative frozen shoulder	
Phantom pain syndromes	
Phantom limb pain	
Phantom breast pain	
Phantom anus pain	
Phantom bladder pain	
Stump pain	
Postsurgical pelvic floor myalgia	
Chronic postradiation pain syndromes	
Plexopathies	
Radiation-induced brachial and lumbosacral plexopathies	
Radiation-induced peripheral nerve tumour	
Chronic radiation myelopathy	
Chronic radiation enteritis and proctitis	
Burning perineum syndrome	
Osteoradionecrosis	

2. Numeric Rating Scale: A number is assigned to the intensity of pain on a scale of 0 to 10; 0 reflecting 'no pain', and 10 reflecting the 'worst pain possible'.

3. Verbal Descriptor Scale: The patient chooses one of the following selections that best describes pain: no pain, mild pain, moderate pain, severe pain, or worst possible pain.

Many people, both with and without cancer function quite effectively with a background level of mild pain that does not seriously impair or distract them. As pain severity increases to moderate intensity, pain passes a threshold beyond which it is hard for the patient to ignore. The prevalence of moderate to severe pain was reported to be highest in gynaecologic cancer and in head and neck cancer, and severe pain was found to be most common in prostate cancer [40].

Quality

The quality of pain often suggests its pathophysiology. Somatic nociceptive pain is usually well localised and described as sharp, aching, throbbing or pressure-like. Visceral nociceptive pain is generally diffuse and may be gnawing or crampy when caused by obstruction of a hollow viscus, or aching, sharp or throbbing when caused by involvement of organ capsules or mesentery [41]. Neuropathic pain may be described as burning, tingling or shock-like (lancinating). Ovarian cancer patients generally describe pain occurring in the abdominopelvic or lower back region, as being frequent or almost constant, and moderate to severe in intensity. Patients with advanced ovarian cancer may experience pain in the lower extremities either from invasion of the lumbosacral plexus by tumour or by lymphoedema secondary to iliac vessel occlusion [42]. On the other hand pain in cervical cancer is usually seen due to metastatic lesions rather than the cancer itself [43].

Distribution

Patients with cancer pain commonly experience pain at more than one site [42,44]. The focal pain is used to donate a single site, and usually experienced in the region of the underlying lesion. Focal pain should be distinguished from those that are referred to a site remote from the lesion. Familiarity with pain referral patterns is essential to target appropriate diagnostic and therapeutic manoeuvres [45]. For example shoulder pain needs to be evaluated for possibility of diaphragmatic irritation, if there is no lesion in the shoulder region.

Principles of the management of cancer pain

Successful management of the cancer patient with pain depends on the ability of the clinician to assess initial problems, identify and evaluate pain syndromes, and formulate a plan for continuing care that is responsible to the evolving goals and needs of the patient and the patient's family. Pain management is, should be, an integral component of comprehensive cancer care [46]. The pain experienced by most cancer patients responds to direct and indirect modification of the source of the pain combined with pharmacologic and nonpharmacologic alteration of the central perception of pain [47-49]. However a multidisciplinary approach is necessary for successful evaluation of the cancer pain. Practice guidelines were reported by the American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section [50]. These guidelines are reported to be systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints. The purpose of these guidelines for cancer pain management was reported as:

1. To optimize pain control;
2. To minimize side-effects, adverse outcomes, and costs;
3. To enhance functional abilities and physical and psychological well-being; and
4. To enhance the quality of life for cancer patients.

The basic principles of tumour-directed pain control include [51];

1. Modifying the source of pain by treating the cancer and the inflammatory response to cancer.
2. Altering the central perception of pain (e.g., by the use of analgesics, antidepressants, anxiolytics, and psychotherapy).
3. Interfering with nociceptive transmission within the CNS (e.g., neuroaxial analgesia and spinal neurolysis, cordotomy and myelotomy).

Conclusions

1. Cancer pain may be due to an underlying nociceptive (somatic or visceral) or neuropathic mechanism.
2. Cancer pain experienced may appear as acute or chronic pain syndromes.
3. Characteristics of cancer pain are important together with other properties in evaluation of cancer pain.
4. The practitioner should be aware of all pain therapies available, and reassure their patients that there are a host of alternatives that can be employed to prevent or treat cancer-related pain.

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