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Pain Control in Patients with Cancer

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Pain is common in cancer patients, although its prevalence varies with the primary site and stage of the malignancy. High rates of pain are observed with prostate, bone, and gynaecological primary cancers, while it is usually less problematic in haematological malignancies. Unfortunately, many patients and healthcare professionals still believe that the late stages of cancer are inevitably painful, which leads to therapeutic nihilism. Clinicians should recognize that 'cancer pain' may arise not only from the malignancy, but also from its treatment and the presence of concomitant conditions. Current research focuses on the mechanisms, treatment, and consequences of pain. Recent advances have been made with novel agents, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists, and new formulations, such as transdermal drug delivery systems. Non-analgesic approaches to pain control, such as the use of bisphosphonates or intravenous radionuclides for bone metastases, and the roles of nerve blocks and orthopaedic surgery, soon will be evaluated. Quality-of-life and satisfaction studies are needed to evaluate the impact of pain on patient functioning and its effects on family, social, and economic life. The World Health Organization has proposed a three-tier approach to cancer pain management, in which drugs ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to strong opiates are titrated to the level of pain. Oncologists have an important role in implementing this approach and in seeking more rational legislation concerning the prescribing of opioids for the treatment of cancer pain. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

PAIN REMAINS one of the major challenges in cancer therapy. It occurs frequently in patients with cancer and is the most feared symptom in patients with advanced cancer [1]. Unfortunately, many patients and physicians believe that the late stages of cancer are inevitably painful, an attitude which leads to therapeutic nihilism [2]. Ironically, the patient with cancer often is treated by a large team of physicians and other healthcare professionals, none of whom is specifically responsible for treating the patient's pain [3].

Recent research has confirmed that nearly all cancer pain is treatable. The Expert Working Group of the European Association for Palliative Care concluded that oral and subcutaneous administration of morphine can produce effective control of chronic cancer pain in approximately 80% of patients [4]. This conclusion is extremely encouraging, especially since the panel only focused on the administration of one drug. Most experts believe that the use of more aggressive techniques should result in adequate analgesia for an additional 10% of patients [2].

Despite the level of pain control that theoretically can be achieved with currently available treatments, the sobering reality is that only between 50 and 60% of patients with cancer achieve adequate pain relief. For example, in a recent French study, 57% of 605 patients with cancer reported that they had experienced pain due to their cancer during the previous week [5]. Of patients with pain, 69% said that their worst pain impaired their ability to function. Thirty per cent of patients with pain whose doctors reported information about their treatment were not receiving any pain medication and 51% were not receiving adequate pain management [5].

It has been estimated that 25 million people throughout the world die without adequate pain control every year [1]. This situation continues, not because of a lack of effective drugs and treatments, but because of widespread ignorance about how to use them [6]. Failure to recognise and to document patients' pain are two other major but easily remediable contributors to inadequate pain control [2, 5, 7].

THE EPIDEMIOLOGY OF CANCER PAIN

The prevalence of cancer pain varies according to the primary site and stage of the malignancy and the presence and location of metastases [5, 8]. In a survey of the entire inpatient cancer population of Memorial Sloan–Kettering Cancer Center during a 1 week period in the late 1970s, the rate of pain differed widely according to the type of cancer [9]. Pain was reported by only 5% of patients with leukaemia, but by 80% of those with cancer of the oral cavity and 85% of those with bone cancer. Fifty-two per cent of patients with breast cancer reported pain. In another study, 40% of patients with non-metastatic and 64% of patients with metastatic breast cancer reported pain, as did 30% of patients with non-metastatic and 75% of patients with metastatic prostate cancer [8]. The extensive bone metastases that occur in many patients with advanced prostate, breast, lung, and renal cancers result in severe pain management problems.

THE ROLE OF ONCOLOGISTS IN PAIN CONTROL

What is the role of oncologists in pain control? In addition to providing optimal pain management for their own patients, they must be highly vocal advocates in a number of areas. They should argue for the establishment and promotion of an academic base that supports the palliative care component of cancer management [3]. Armed with outcome data, they should advocate the establishment of a sufficient number of high-quality palliative care programmes in their respective countries [3, 10]. Finally, they must work to formulate and guide government policies on the necessary quotas of opioids requested from the International Narcotics Control Board [10]. Although access to potent opioids is no longer a major issue in the United States, Canada, or Great Britain, it remains an overwhelming problem in many other European countries and throughout much of the developing world. As data from the U.K. forcefully demonstrate, free access to opioid analgesics does not lead to indiscriminate use of these agents [11].

A regional survey was recently performed to determine the patterns of opioid use in patients being treated by specialist palliative care teams in the Trent Region of the U.K. [11]. Of a total of 1 007 patients receiving care in inpatient and community settings, 970 had cancer. A total of 42% of patients were not receiving opioids, 10% were receiving weak opioids only, and 45% were receiving potent opioids [11]. The fact that fewer than half of the patients were receiving potent opioids disproves the common belief that in the U.K., where there is a well-developed hospice system and free access to drugs, patients with advanced cancer who are in hospice care are invariably treated with morphine.

It also is instructive to examine the doses of opioids administered to the 535 patients receiving opioids at the time of the survey. The daily oral morphine equivalence of patients' latest recorded doses ranged from 0.4 to 3 600 mg, with a median of 60 mg [11]. Interestingly, a study of opioid use by 676 patients at St. Christopher's Hospice, Sydenham, U.K., which was published in 1983, showed that the median dose of oral morphine also was 60 mg [11]. These findings indicate that having free access to morphine has not markedly increased the amount of morphine consumption over a period of more than a decade. Despite the fears of some officials, rational prescribing still prevails.

Another important question that was addressed in the Trent Region study is what happens to opioid usage when patients receive specialist palliative care. With a median period of 200 days in palliative care, 43% of patients did not change their opioid dose, 10% reduced their dose but continued to receive opioids, and 5.8% discontinued opioids altogether [11]. Data such as these make a powerful argument for not restricting the availability of opioids but rather, for increasing the availability of specialist palliative care. Given optimal care, a considerable number of patients with advanced cancer may obtain adequate pain relief at reduced opioid doses.

PRINCIPLES OF PALLIATIVE MEDICINE

A large obstacle to the effective treatment of patients with advanced cancer is therapeutic nihilism. This is grounded in the erroneous assumptions that treatment has failed when a patient no longer has a potentially curable disease and that death from certain types of cancer is inevitably painful [3]. As has been eloquently argued in a recent paper by MacDonald, cancer management should not only be directed toward achieving a cure or even the prolongation of life, but also toward prevention of suffering through impeccable management of cancer symptoms. This principle should underlie the treatment of all patients with cancer and be consistently addressed in the training of new healthcare professionals who will work with cancer patients [3].

Palliative medicine is a new subspecialty of internal medicine that focuses on the care of terminally ill persons, including patients with cancer and those with other life-threatening diseases. Its aim is to achieve the best balance between length of life and quality of life for an individual. It is important to recognise that quality of life is not synonymous with freedom from suffering. Rather, it is a multidimensional concept that takes into account the nature and degree of well-being, satisfaction, achievement, and independence in several areas of daily living.

Palliative care is generally considered a modality that is applied late in the course of a terminal illness, after curative

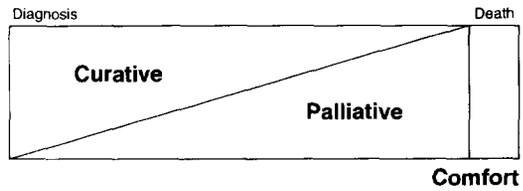

Figure 1. The current WHO approach to palliation in patients with cancer. Reprinted with permission from *Progress in Palliative Care*, 1996.

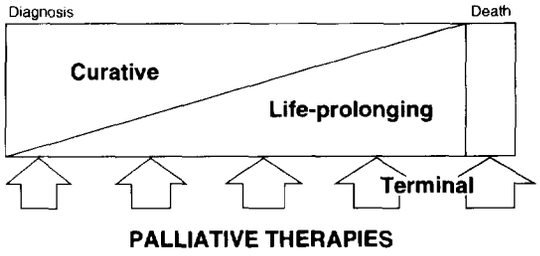

Figure 2. The Sheffield model for palliation in patients with cancer. This approach makes use of various palliative interventions at all stages of the disease, not just during the terminal phase. Reprinted with permission from *Progress in Palliative Care*, 1996.

Table 1. The major types of cancer pain [1]

Type of pain	Cause	Description
Somatic	Ongoing activation of peripheral nociceptors; usually results from involvement of skin, bone, and muscle structures	Well-localised, constant, aching or gnawing
Visceral	Injury to sympathetically innervated organs; probably results from inflammatory response and the release of noxious substances in the area of nociceptors	Constant, aching, poorly localised, commonly referred to cutaneous sites
Neuropathic	Injury of the peripheral or central neural structures and the resultant aberrant somatosensory processing at these sites; may be due to mechanical pressure of tumour on a nerve, nerve transection during tumour surgery, or biochemical changes associated with radiotherapy	Burning, tight, or lancinating jabs, following the path of the injured nerve

and life-prolonging approaches have failed (Figure 1). In the Sheffield model of palliative care, however, patients receive palliative care at every stage of their illness, beginning at the time of diagnosis [12]. It can and should coexist with curative, life- prolonging, and rehabilitative therapies (Figure 2).

CONSEQUENCES OF CANCER PAIN

The 'total pain concept' is well established among healthcare professionals working in palliative medicine [13]. It is based on the understanding that pain has a major impact on quality of life, that it affects not only patients but also family members and other caregivers, and that inadequate pain management often has serious economic consequences [6].

According to the total pain concept, the perception of physical pain has diverse components. The psychological consequences of physical pain have been extensively studied, and it is now known that anxiety and depression often are associated with chronic pain and that they are especially common in patients with cancer pain. Pain also has social consequences; social stresses within a family intensify a patient's perception of pain, and this heightened awareness of pain further intensifies the family's social stresses. Physical pain also can result in, or be exacerbated by, a spiritual distress that can overwhelm the patient and affect every aspect of his or her life [13].

In trying to relieve pain, a physician should address not only the patient's physical pain but also the consequences of that pain. However, most physicians are uncomfortable when attempting to deal with anything but physical pain because their training has not prepared them to deal with the psychosocial and spiritual dimensions of pain. The physician who is working as part of a multidisciplinary team may wisely conclude that other team members are better prepared to deal with certain aspects of the patient's pain [3].

Pain affects patients' quality of life in many ways. It can impede their mobility very quickly, thus limiting their independence. It can disrupt the sleep patterns not only of the patient, but also of the family member who may need to get up in the middle of the night to administer an extra dose of analgesic. Patients' and family members' quality of life may be further impaired by the adverse effects of pain management. The non-steroidal anti-inflammatory drugs (NSAIDs), which play a major role in the management of mild to moderate pain, can cause gastric upset and bleeding. The side effects of opioids, including constipation, nausea and vomiting, and excessive sedation, are well documented. Although radiotherapy and chemotherapy may relieve pain, their use may also be associated with transient adverse effects such as emesis and myelosuppression.

PRINCIPLES OF THERAPY FOR CANCER PAIN

In selecting a treatment for a patient's cancer pain, the physician should consider the cause of the pain, its severity, and any preferences about treatment that the patient might have.

Cause of pain

In determining the optimal treatment for cancer pain, the first step is to identify its cause and type on the basis of a detailed pain history, a physical examination, and the review of patient records, laboratory data, and imaging studies (Table 1) [2]. In practice, it is sometimes impossible to isolate the cause of pain; in other instances, the patient's pain may have multiple causes [13]. Such situations require a broad approach to pain management. Depending on the nature of the patient's malignancy and anticancer therapy, the status of the patient's pain may change substantially within a short period of time, necessitating frequent assessments and adjustments of the treatment regimen [2, 10].

One reality of palliative medicine is that, in addition to cancer pain, patients may have other types of pain, as well [13]; this is especially true of older patients. A survey conducted at Michael Sobell House in Oxford, a major palliative care centre in the U.K., showed that four-fifths of patients had two or more pains and one-third had four or more pains [14]. Furthermore, not all of these pains were associated with the malignancy. Physicians who treat cancer patients should realise that some kinds of pain, such as the pain of chronic rheumatoid arthritis, may actually be more severe and have a greater impact on the patient than the pain caused by a new cancer [2, 8]. In such a situation, simply addressing the patient's cancer pain accomplishes very little. Furthermore, the physician also must be alert to the presence of iatrogenic pain that may result from diagnostic or therapeutic interventions, such as biopsies, surgery, radiation, chemotherapy, or angiography. Debilitated patients also may have pain as a result of constipation, rectal or bladder spasms, or decubiti [1, 2].

Severity of pain

Therapy for pain also should be based on its severity; this issue was definitively addressed by the World Health Organization (WHO) in its set of guidelines entitled *Cancer Pain Relief*, which was released in 1986. An important component of these guidelines is a three-step analgesic ladder (Figure 3) [15]. This approach is based on the assumption that most patients should have adequate pain relief if healthcare professionals master the use of a few effective and relatively inexpensive drugs that are administered orally, on a regular

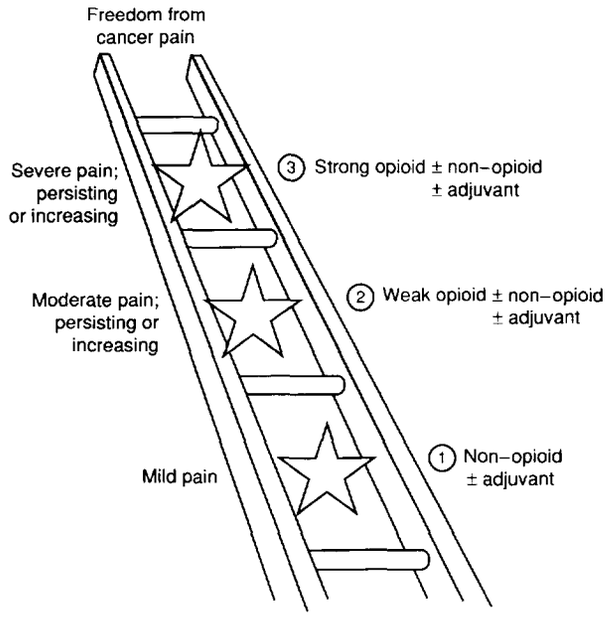

Figure 3. The three-step analgesic ladder described in the World Health Organization's guidelines on cancer pain relief. Reprinted with permission from *Hospital Update*, 1994.

basis, depending on the individual needs of the patient. More than 250 000 copies of this document had been distributed in over 22 languages by 1993, making it the second most translated publication in the history of the WHO [16].

Controlled studies have yet to be conducted to assess the proportion of patients in whom the use of this analgesic ladder results in adequate pain control, although it has been described as a simple and effective means of controlling cancer pain [16]. In an open-label prospective study of 2118 cancer patients who were referred to the anasthesiology-based pain service of the University of Cologne, it was demonstrated that following the WHO guidelines resulted in pain relief that was considered good in 76% of patients, satisfactory in 12% of patients, and inadequate in 12% [10]. The WHO guidelines also have served as the basis for highly specific and clinically effective treatment algorithms for patients with mild, moderate, or severe cancer pain [17].

Mild pain. Mild pain often is treated with NSAIDs alone. Because patients have variable responses to the different NSAIDs, sequential drug trials may be needed [6]. Acetaminophen and aspirin also are widely used in patients with mild cancer pain [2]. Adjuvant analgesic therapy with antidepressants and corticosteroids also may be used in some patients with mild cancer pain. In the case of neuropathic pains, anticonvulsants might also be used. Adjuvant analgesics that are commonly used in patients with cancer pain are summarised in Table 2 [1, 2, 6, 10].

Moderate pain. Patients who experience persistent or increasing pain while receiving a regimen recommended for the treatment of mild pain often are treated with one of the 'weak' opioids. These agents include codeine, propoxyphene, oxycodone (when combined with aspirin or acetaminophen), hydrocodone, dihydrocodeine, dextropropoxyphene, and tramadol [6]. The availability of these agents varies from country to country; therapy for moderate pain often is initiated by prescribing a commercial product that combines aspirin or acetaminophen with one of these opioids [6]. Some clinicians prescribe meperidine for moderate cancer pain, but it is best avoided because of its short half-life; in addition, the accumulation of its metabolite, normeperidine can result in tremulousness, myoclonus, and seizures [6].

Severe pain. The treatment of patients with severe cancer pain varies from country to country, based upon the opioid analgesics that have been approved for use in each country. Most patients receive morphine, hydromorphone, levorphanol, methadone, or fentanyl. A traditional means of treating patients with severe pain is to administer repeated intravenous doses of an analgesic every 15–30 min until pain is controlled [6]. However, there is usually no need to use the parenteral route for titrating or stabilising pain control, and it is feasible to use short-acting opioids until pain is controlled, and then convert the patient to the equivalent dose of a longer-acting opioid. Patients with severe cancer pain should ideally be treated by specialists in pain management.

Some patients who do not achieve adequate pain relief with opioid therapy benefit from the coadministration of adjuvant agents (Table 2). Thirty-eight per cent of the 2118 patients enrolled in the 10-year prospective study conducted at the University of Cologne received multiple analgesics during the terminal phase of their illness [10]. Other patients may benefit from transcutaneous electrical nerve stimulation, regional anaesthesia, and neuroablative procedures [2]. Some of the newer approaches to the treatment of severe pain are discussed in a later section of this review.

Table 2. Adjunct analgesics commonly used in patients with cancer pain [1, 2, 6, 10]

Class of drug	Main use	Commonly prescribed drugs
Tricyclic antidepressants	Supplemental treatment of neuropathic pain	Amitriptyline, desipramine, nortriptyline
Anticonvulsants	Supplemental treatment of lancinating neuropathic pain	Carbamazepine, phenytoin, valproate, clonazepam
Corticosteroids	Supplemental treatment of neuropathic pain or metastatic bone pain, spinal cord compression; may also improve appetite, mood, nausea, and malaise	Dexamethasone, prednisone, methylprednisolone
Local anaesthetics	Supplemental treatment of neuropathic pain; may be used in combination with long-acting corticosteroids	Mexiletine
Alpha$_2$ adrenergic agonists	Supplemental treatment of sympathetically mediated pain	Clonidine
Spasmolytics	Supplemental treatment of colicky visceral pain	Butylscopolamine

Patient preference

Whenever possible, pain therapy should reflect the preferences the patient might have; however, the physician should attempt to determine when these preferences are based on misinformation or prejudices that need to be dispelled. Many patients resist opioid therapy because they are under the erroneous impression that opioids cause addiction in persons with advanced cancer [18]. Other patients oppose opioid therapy because they see it as the harbinger of death. Clearly, there is a need for aggressive patient and family education about the appropriate use of opioid analgesia in the treatment of cancer pain [6].

Before physicians and other members of the multidisciplinary treatment team can provide this education, they must first address and overcome their own prejudices about opioid therapy [18]. For example, a recent Eastern Cooperative Oncology Group survey of physician attitudes and practice in cancer management found that nearly one-third of physicians waited until a patient's prognosis for survival was 6 months or less before beginning maximal analgesic therapy [19]. The WHO Cancer and Palliative Care Programme has set as one of its major goals for the years 1995–1999 the enhancement of healthcare professionals' knowledge about opioids and has scheduled a series of major worldwide conferences to address this topic [19].

OPIOID TREATMENT FOR CANCER PAIN

Improving the side-effect profile of opioid therapy

Over the years, many physicians have assumed that side-effects (e.g. chronic constipation, nausea and vomiting, pruritus, and sedation or mental clouding) are inevitable consequences of opioid therapy and that a smaller but sizeable proportion of patients are likely to experience agitated impaired mental status. Today, however, it is known that these side-effects can be prevented or minimised in many patients by *gradually* increasing the dosage of opioid analgesics or taking other simple precautions. The availability of newer opioids or different formulations of older agents has facilitated the elimination or amelioration of opioid side-effects in most patients.

An important principle in administering opioid analgesics is that doses must be increased gradually. For example, a patient can remain alert and unsedated on a dose of 1200 mg per 24 h of parenteral diamorphine, the equivalent of 3600 mg per 24 h of oral morphine, as long as the dose is titrated slowly. Some patients who experience sedation or mental clouding despite careful dose titration may benefit from short-term treatment with stimulants, such as dextroamphetamine, methylphenidate, or pemoline [2, 6].

Constipation is a problematic side-effect of opioid therapy, both because it has a detrimental effect on patients' quality of life and because it can result in fecal impaction, which may require hospitalisation. Most authorities recommend that patients start receiving prophylactic treatment for constipation as soon as opioid therapy begins [2]. Prophylaxis is especially important in elderly patients, those who have pre-existing bowel disease, those who are not ambulatory, and those who are taking other medications that can cause constipation [6]. Stool softeners, irritants, bulk laxatives, lubricants, and enemas can be used individually or in combination [2].

Nausea and vomiting should be treated promptly with antiemetics [2]. Patients with opioid-associated pruritus often obtain relief when they are treated with antihistamines, such as hydroxyzine and diphenhydramine [2]. Substituting another opiate for morphine may also eliminate or reduce pruritus.

Opioid rotation. Changing opioids may be one way of avoiding serious side-effects, such as nausea, vomiting, sedation, myoclonus, and agitated impaired mental status, which usually manifests as delirium [20]. With this approach, drugs such as morphine, methadone, hydromorphone, fentanyl, and diamorphine are rotated every few weeks or months [21]. This therapeutic strategy is said to maintain pain control, while preventing cumulative toxicities which are believed to be caused by the accumulation of opioid metabolites, especially in patients with diminished renal function, and by changes in receptor–effector relationships that are believed to occur following prolonged exposure to a single opioid [22]. In some centres, parenteral hydration is used in combination with opioid rotation to enhance the excretion of opioid metabolites [21].

A retrospective chart review of patients admitted to the Palliative Care Unit of Edmonton General Hospital, Alberta before and after the initiation of opioid rotation, with and without hydration, demonstrated that the incidence of agitated impaired mental status was significantly ($P < 0.001$) reduced following the adoption of opioid rotation and optional parenteral hydration [21]. In another retrospective study at the same institution, opioid rotation was associated with non-significant improvements in patients with hallucinations, uncontrolled pain, and nausea, and with significant improvements in patients with cognitive failure ($P < 0.01$) and myoclonus ($P < 0.002$) [22].

While opioid rotation appears to be a well-established practice in North America, where a wide selection of opioids is currently available, it is seldom used in Europe, owing to the narrower range of available drugs. In the near future, opioid rotation will become more feasible in the U.K. when hydromorphone is approved, and when clinicians become more familiar with fentanyl patches. However, it is necessary to test the validity of this approach by randomised, controlled trials.

Alternative formulations and routes of administration

Although a long-standing tenet of pain therapy was that analgesics should be administered orally and by the clock, other approaches to opioid administration are currently available or are under investigation. The following alternate routes of administration are now used in some countries or are under investigation for the treatment of patients with severe cancer pain: buccal, sublingual, rectal, transdermal, intranasal, subcutaneous, intravenous, intraspinal, and intraventricular [6].

Controlled-release oral formulations. Kapanol™ also branded as Kadian™ or Morcaps™, is one of several new controlled-release formulations of morphine that are now under evaluation [23]. In a recent randomised, double-blind, parallel-group study, the safety and efficacy of Kapanol™ administered every 12 and 24 h was compared with that of an older controlled-release morphine formulation, MS Contin®, which is administered every 12 h. Scores for patient global assessment of pain control were significantly ($P = 0.018$) better for patients receiving Kapanol™ every 24 h than for those receiving MS Contin®. As with other medications that can be given once daily, use of 24 h preparations may enhance patient compliance. They also may result in less toxicity than older morphine formulations, since they are associated with a more constant plasma morphine concentration and fewer peaks and troughs [24].

Parenteral formulations. Several formulations of parenteral opioids are now available. Many patients resist parenteral administration of analgesics, especially if they receive cytotoxic drugs through the parenteral route. However, patients are usually receptive to some of the more sophisticated methods of parenteral drug delivery. Patient-controlled analgesia utilises programmable pumps or even simple pumps that allow patients to press a button to obtain another dose of medication. The systems utilise a variety of mechanisms to prevent patients from administering more than the prescribed amount of drug within a given period of time. While this approach works very well in patients with acute pain, it is less suitable for patients with chronic pain because of the expense.

A more common approach to the administration of parenteral opioids is the use of a small battery-powered syringe driver. This system administers analgesics by slow subcutaneous infusion and has become a keystone of modern palliative therapy. It also can be used to administer antiemetics and various other types of drugs. Just as patients tend to resist opioid medication because they see it as a sign of terminal illness, they also may become apprehensive when asked if they would like to have a syringe driver. This is another area in which patient and family education is extremely important. Because of the excellent results that can be obtained with syringe drivers, they should be used during the earlier stages of cancer treatment, as well as during the final phase.

Nebulised formulations. Today, extensive research is being conducted in Europe on the nebulised route of opioid administration. This approach appeared promising because absorption of nebulised opioids occurs rapidly through the pulmonary circulation. The presence of opioid receptors in the airways was also thought to be potentially useful in the management of dyspnea by nebulising opioids.

Unfortunately, results to date have been negative [25, 26]. Only small doses are absorbed, and the route of administration is relatively inconvenient for caregivers. The use of nebulised fentanyl is now under evaluation [27]. It appears that this approach may be most appropriate for the treatment of breakthrough pain (or paroxysmal dyspnoea) rather than for long-term medication.

Rectal formulations. Some NSAIDs and opioids can be given via the rectal route, and additional studies of new rectal analgesic formulations are about to begin. Rectal formulations usually are prescribed for patients who are temporarily unable to use oral opioids [6, 28]. Because most patients dislike frequent insertion of suppositories, rectal formulations that have an extended duration of action are in development.

Transdermal drug delivery. Transdermal drug delivery already is extensively used in North America, and it is likely to become more important in Europe within the next few years. Fentanyl, one of the first of the synthetic opioids, is 70 times more potent and hundreds of times more lipophilic than morphine. When applied to the skin, it penetrates quickly and efficiently. A single transdermal fentanyl patch can be worn for 72 h, during which time it delivers consistent and predictable amounts of drug.

A randomised, controlled crossover study that was recently completed compared the safety and efficacy of transdermal fentanyl and oral morphine [29]. The study was particularly noteworthy as the first major research collaboration among palliative care units in the U.K. Patients were treated for 15 days on each treatment arm; all 202 patients enrolled in the study had cancer pain that was managed with oral morphine prior to study entry. The study confirmed that, at the doses administered, transdermal fentanyl and oral morphine were equally effective in relieving pain. Patients reported a mean of 20 fewer minutes of sleep per night while receiving fentanyl than while receiving morphine. Fentanyl also was associated with less daytime drowsiness. Side-effects were reported by 82% of patients receiving morphine and by 40% receiving fentanyl. At baseline, more than 20% of patients reported substantial constipation. During the study, the proportion of patients who reported 'quite a bit' or 'very much' constipation was 15.0% on the fentanyl arm and 34.8% on the morphine arm ($P < 0.001$). Patients on the fentanyl arm also reported significantly ($P < 0.04$) less nausea than those on the morphine arm. Fifty-four per cent of patients preferred fentanyl, and 36% morphine ($P = 0.037$). In view of these positive results, transdermal fentanyl is likely to play an important role in the treatment of severe cancer pain in the coming years. Interestingly, this study revealed that despite the apparent advantage of transdermal fentanyl in terms of side-effects and convenience, the patients' self-reported global quality of life did not differ between the two treatment groups.

NEW TREATMENTS FOR METASTATIC BONE PAIN

Various approaches to the treatment of metastatic bone pain are under investigation. Among the most promising are agents that inhibit bone resorption, radionuclide therapy, and specialised orthopaedic surgery.

Inhibitors of bone resorption

The pathophysiology of osteolysis in patients with advanced cancer is not fully understood, but the major cellular mechanism for bone loss appears to be related to an increased number of osteoclasts or increased osteoclast activity. Therefore, the use of inhibitors of osteoclast-mediated bone resorption for the treatment of bone pain has been investigated [30].

Calcitonin. Calcitonin, a polypeptide hormone secreted mainly by the thyroid and also by the thymus and parathyroids, reduces calcium and phosphate concentrations in plasma and inhibits bone resorption. It is beneficial in the short-term management of bone pain in patients who continue to have pain despite treatment with NSAIDs and opioids [1]. Side-effects include nausea, vomiting, flushing, faintness, and local skin irritation following subcutaneous administration. A major drawback of calcitonin is its cost.

Bisphosphonates. In advanced cancer, bone resorption by osteoclasts causes hypercalcaemia, bone fractures, and bone pain. Bisphosphonates such as clodronate and pamidronate (Aredia®) have been shown to inhibit osteoclastic bone resorption, thus relieving metastatic bone pain and preventing bone fractures and its associated pain [31].

A Phase II study evaluated the effect of a single intravenous (i.v.) infusion of high-dose (120 mg) pamidronate on pain, mobility, analgesic use, quality of life, and bone metabolism in 34 patients with progressive bone metastases [32]. There was a 68% improvement in pain control in patients with breast cancer, a 60% improvement for patients with prostate cancer, and a 59% overall response to pamidronate therapy. Following treatment, patients also reported a significant ($P < 0.01$) improvement in the ability to perform activities of daily living and to engage in social activities.

Treatment was well tolerated and adverse events were mild. These included fever, transient chills, diarrhoea, nausea, vomiting, and asymptomatic hypocalcaemia [32].

A randomised, placebo-controlled study of pamidronate in 382 patients with stage IV breast cancer confirmed that bone pain was reduced ($P = 0.046$) and performance status better maintained ($P = 0.027$) with pamidronate. In addition, time to developing first skeletal complication was delayed (13.1 versus 7.0 months, $P = 0.005$) and fewer patients had skeletal events (43% versus 56%, $P = 0.008$) [33].

The most common side-effects of bisphosphonate therapy include gastrointestinal intolerance, fever, leucopenia, oliguria, and thrombocytopenia [1]. Etidronate is not recommended for long-term use because of gastrointestinal intolerance, while long-term use of pamidronate is associated with inhibition of bone mineralisation.

Many other bisphosphonates are now under investigation. The new generation of agents is thousands of times more potent than older agents like pamidronate and, unlike pamidronate, can be given orally.

Radionuclide therapy

Radionuclides that bind to bone have long been used to diagnose cancers, but more recently they also have been used to treat bone metastases, often after conventional radiotherapy. In a recent randomised, double-blind, crossover study, 32 prostate cancer patients with bone metastases whose pain was not controlled with conventional therapy were treated with 150 MBq strontium-89 or placebo. Patients receiving strontium-89 were significantly ($P < 0.01$) more likely to achieve pain relief than those receiving placebo [34].

Radionuclides should not be used as a sole means of treating vertebral body metastasis because they rarely possess the potency or duration of action to prevent the progression of coexisting epidural spinal cord compression. Radionuclide therapy is expensive, and there is still limited evidence on its relative cost-effectiveness compared to conventional treatments.

Specialised orthopaedic surgery

Specialised orthopaedic surgery is used to treat metastatic bone pain that cannot be relieved by other means and to prevent or treat bone fractures caused by bone metastases [35]. Endoprosthetic replacement has shown promise in patients with both single and multiple metastases. Diaphyseal pathological fractures of proximal limb bones can be stabilised with interlocking nail systems, with or without polymethylmethacrylate cement [35]. These procedures allow early return to weight-bearing and other activities. As soon as the surgical wound has healed, adjunctive radiotherapy, chemotherapy, or hormone therapy can be administered.

OTHER NEW TREATMENTS FOR CANCER PAIN

Three other promising types of therapy for patients with severe cancer pain that has not responded to standard therapy are *N*-methyl-D-aspartate (NMDA) receptor antagonists, epidural infusions, and nerve blocks.

NMDA receptor antagonists

The NMDA receptors are found in the dorsal horn of the spinal cord, and are known to be involved in the modulation of chronic pain, through newly understood mechanisms of the 'plasticity' of the central nervous system. Stimulation of these receptors by noxious stimuli can lead to the phenomenon of increased sensitivity to further painful stimuli—so-called wind-up. The anaesthetic agent ketamine is an NMDA receptor blocker, and can be used at subanaesthetic doses to provide fine control of severe and refractory pain, even of the neuropathic type which is poorly responsive to morphine [36]. Most of the research and clinical experience has been in postoperative and acute pain management, but there is increasing experience in palliative care of cancer pain [37]. So far, there have been no randomised controlled trials in cancer patients, but several case reports and larger series have been published [38].

Ketamine is usually given as an i.v. bolus to induce immediate reduction in pain, and then continued as an intravenous (i.v.) or subcutaneous infusion. A significant problem associated with this drug is cerebral stimulation leading to dysphoria and hallucinations, observed when the dose is reduced or withdrawn—the so-called emergent phenomena. They may be minimised by the concurrent administration of a small dose of benzodiazepine, such as midazolam, alongside the ketamine. It remains to be seen if this potent drug can be used routinely in cancer pain management, outside of the specialist pain control settings.

Epidural infusions

In patients with chronic non-malignant back pain, the epidural administration of opioids, corticosteroids such as methylprednisolone, and local anaesthetics such as bupivacaine has been beneficial [39]. Epidural steroids are now being extensively used in patients with chronic back pain due to cancer [40]. Questions have been raised about the toxicity of high-dose corticosteroids and the potential dangers of the epidural route [41]. There has been particular concern about the possible connection between the injection of methylprednisolone into the spine and the development of subacute arachnoiditis [42]. However, this rare complication may be caused by some of the components of the vehicle used to deliver methylprednisolone, rather than by methylprednisolone itself. In any case, arachnoiditis is an irrelevant complication in patients with advanced cancer and concern about its development is not a legitimate reason for withholding epidural steroids from cancer patients.

Nerve blocks

With a carefully individualised combination of conventional medications and nerve blocks, it usually is possible to achieve effective pain control in patients with advanced cancer whose pain is not controlled adequately with opioids alone. Nerve blocks may consist of temporary blocks using a long-acting local anaesthetic such as bupivacaine, long-acting neurolytic blocks using alcohol or phenol, or regional opioid blocks [2]. Local anaesthetic blocks, which are particularly useful at trigger points in myofascial pain syndromes, may be complicated by hypotension, toxic reactions resulting from inadvertent subarachnoid or i.v. administration, or pneumothorax following needle placement [2].

In neurolytic blocks, alcohol or phenol is injected into the subarachnoid or epidural space to destroy nociceptive fibres in the dorsal rootlets. When performed in the thoracic region, this procedure is associated with few complications, but nearly 20% of patients with cervical or lumbar neurolytic blocks develop motor or sphincter dysfunction that may be permanent. Thus, the procedure is particularly appropriate

for patients with pre-existing paralysis of the lower extremities or a colostomy. Because they also may result in a chemical neuritis that develops within a few months of the procedure, neurolytic blocks usually are reserved for patients with a short life expectancy [2].

Regional opioid blocks have the advantage of producing analgesia without impairing other sensory, sympathetic, or motor functions [2]. Because intraspinal opioids usually are administered at a dose that is one-tenth to one-hundredth of an equi-analgesic dose of oral or parenteral opioids, they usually are associated with fewer systemic toxicities. Approximately 20% of patients experience nausea, vomiting, pruritus, urinary retention, or tolerance. The major shortcoming of intraspinal opioid therapy is its cost.

CONCLUSION

How can oncologists achieve greater professional satisfaction? We should argue for the restructuring of the medical curriculum so that future physicians recognise that the provision of optimal palliative care is no less important than the delivery of excellent curative and life-prolonging therapies [2]. We should insist that the clinical trials in which we participate have quality-of-life measures incorporated into their design [43]. Despite the demands on our time, we should ensure that our approach to the individual patient becomes less tumour-oriented and more person-centered. Although our patients rightly expect access to the most advanced medical therapies, their ultimate desire is for a sympathetic, personal approach to their situation.

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