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## Review paper

# Towards better pain treatment in cancer

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**This review focuses on ways to ameliorate diagnosis and treatment of cancer-related pain with currently available knowledge and methods. The first part indicates how to improve pain assessment and diagnosis in the cancer patient. The second part evaluates current views for adequate pain management based on evidence of double-blind analgesic trials in cancer-related pain and deals with misconceptions in established symptomatic therapy.**

*Key words*: Cancer, double-blind trial, neuropathic pain, nociceptive pain, pain.

## Scope of the problem

Pain is feared in cancer patients. Pain recalls to the presence of disease, mortality, and creates anticipatory suffering, anxiety and depression. In view of the discussions on euthanasia, cancer pain relief would lead to reducing its need.

Pain is among the most prevalent symptoms in cancer patients and affects approximately 50% at various stages of disease.[1–6] Pain is the presenting symptom in 15% of cancers—about one-third of patients with metastatic disease and 60–99% in the terminal stage complain of pain.[5,7–12] In advanced stages, pain is moderate in 40–50% and of excruciating severity in 25–30%.[13–15] Between 10 and 40% of all cancer patients die with unrelieved pain.[8,16,17]

Results obtained in routine clinical practice are often unsatisfactory.[17,18] Of all patients with cancer, 42–73% are undermedicated, with minorities, women and patients of 70 years or older being groups at risk.[2,17,19,20] Numerous studies suggest that many physicians lack knowledge of adequate pain assessment and the clinical pharmacological know-how of cancer pain management.[6,19,21–28] Other unfavorable prognostic factors for satisfactory pain relief in cancer patients are severe, but intermittent pain,[9,10] poor compliance with treatment and major emotional or family problems.[29]

Improvement of possibilities for better management has made unrelieved cancer-related pain unacceptable. In all stages of neoplastic disease, the rate of satisfactory pain relief applying the WHO guidelines for pain management is increasing. Complete pain relief is rarely achieved, but pain can often be maintained at about one-third of its severity.[28] According to recent reports, it should be possible to offer satisfactory pain treatment in 70–95% using the guidelines of the WHO.[17,19,28–36]

These data suggest that better pain management in cancer should be possible. This goal could be achieved by a more thorough analysis of the pain problem tailored to the type and cause of the pain.

## Towards better assessment of pain in cancer

Poor assessment of the pain is one of the important factors of inadequate management.[6] In analyzing pain in the cancer patient one distinguishes the terms nociception, pain and suffering.[37] Nociception is defined as the activity in the nervous system following potential or actual tissue damage. Pain is the perception of this activity with cognitive and affective processes in the brain. Pain may or may not be the result of active tissue damage. Although psychological processes influence the perception of pain, an organic lesion can ultimately be identified in most cancer patients. Suffering may be defined as a threat to the integrity of the personality.[38] Suffering in the cancer patient affects the quality of life. Although pain has an important influence on suffering, other factors as anxiety, depression, dependence, physical immobility and social isolation also

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affect the quality of life. Thus, assessing pain in cancer is more elaborate than simple nociception.[39,40]

## Pain mechanisms in cancer-related pain

Although the term 'cancer pain' is often used, it bears no relationship to the basic pathophysiological mechanism of the pain. Cancer-related pain is best classified as nociceptive pain and (non-nociceptive) deafferentation pain. The pathophysiologic mechanisms of these types of pain determine the choice of symptomatic therapy.

In nociceptive pain, potential or actual tissue damage, like tumor, trauma or inflammation, activates primary afferent neurons (nociceptors) by noxious mechanical, thermal or chemical stimuli. This activation is processed by inflammatory mediators, like bradykinin, prostaglandins PGE2 and PGF2α, histamine, and substance P. If pain is caused by activation of free unmyelinated nerve endings in the surrounding connective tissue of a peripheral nerve, the 'nervi nervorum', it is called nociceptive nerve pain.[35,41–45] Visceral pain is another type of nociceptive pain, and is caused by activation of nociceptors in the viscera of the thorax and abdomen. Facial pain as a result of a mediastinal tumorous lesion is an example of referred pain caused by nociceptive activation of visceral structures[46,47] (see Table 1). Nociceptive pain usually responds to opioids and interventional denervation of the peripheral lesion.

Deafferentation pain is an example of non-nociceptive pain, in which nerve injury causes pain sustained by aberrant somatosensory processing. Presence of active tissue damage is usually absent. The pain is no longer a warning signal for the integrity of the human being. In cancer, nerve injury often is the result of therapy. For example, pain in the axilla and the medioposterior aspect of the arm following a radical mastectomy may be produced by a lesion of the intercostobrachial nerve.[48] Pain is experienced over the skin area with a sensory disturbance. Non-painful stimuli, like slight touch and moderate cold, may produce pain. Another type of deafferentation pain results from damage to the central nervous system, and is called central pain. In cancer, spinal cord compression by epidural metastases is probably an often unrecognized cause of central pain.

**Table 1.** Classification of pain mechanisms in cancer-related pain

| Nociceptive | Non-nociceptive |
|---|---|
| Nociceptive pain *per se* | Deafferentation pain |
| | nerve injury pain |
| Nociceptive nerve pain | central pain |
| Visceral pain | Psychogenic pain |
| Referred pain | Idiopathic pain |

Deafferentation is not or less responsive to treatment with non-steroidal anti-inflammatory drugs (NSAIDs)[49,50] and opioids than nociceptive pain,[51,52] and tends not to respond to neurolytic procedures.[53,54] In contrast to nociceptive pain, deafferentation pain often precludes pain treatment directed at the underlying cause. Thus, the distinction between nociceptive and deafferentation pain is of crucial importance for the type and efficacy of symptomatic therapy. The clinical distinction is made by showing the presence of active tissue damage, like tumor or metastasis, corresponding to the site of the pain. Nociceptive pain in cancer often has an increasing intensity. In deafferentation pain, there usually is a short latent period following the onset of nerve injury. Furthermore, the presence of pathologic sensory phenomena, like hyperpathia and allodynia for cold and touch, are characteristic symptoms in deafferentation pain.[55] Of course, both nociceptive and deafferentation pain may occur together, and malignant nerve pain may be a good example of this. If a tumor compresses a nerve root or plexus, the mechanism consists in activation of free nerve endings in the connective tissue surrounding the nerve sheath. If no anti-tumor therapy is instituted, the tumor will invade the nerve fibers and this may lead to severing of the nerve with deafferentation. Consequently, mechanisms which lead to the development of deafferentation pain may appear.

## Pain assessment

Pain measurement is an important parameter for accurate diagnosis, monitoring of therapeutic efficacy and quality of life. The discrepancy between the physicians's and patient's estimate of the severity of the patient's pain seems to be the most powerful predictor for pain management, apart from risk-group analysis.[6,19,56] Poor pain assessment appeared to be an important barrier to good pain management.[19] According to the cognitive-behavioral model, pain has an intensity, an affective value and an evaluative dimension.[57,58] Pain intensity is measured by self-report on validated scales.[59] A new pain in a cancer patient is often the first sign of progressive disease, and may lead to anxiety,

denial and dysphoria. In contrast to patients with benign pain who may aggravate their pain, cancer patients often dissimulate out of fear for elaborate testing or morbidity induced by anti-cancer therapy.[60] The evaluative process of pain is based on cognitive strategy and personality traits, and colors the meaning for the individual patient. For example, headache could be a sign of a brain tumor or abdominal pain a sign of recurrent malignancy.

The goal of cancer pain assessment is identification of the underlying type of the pain, and clarification of the relationship between the neoplasm and the pain, thereby providing information about potential new anti-neoplastic therapy. In the assessment of pain in cancer, the physician should be familiar with the biological behavior of the primary neoplasm, with neurological and pain assessment, and with possible approaches to pain treatment and anti-tumor therapy. At the Pain Clinic of the Memorial Sloan-Kettering Cancer Center rigorous assessment lead to a new diagnosis of metastatic disease in 64% of the patients and in 36% to a new neurological diagnosis.[24] Although it is tempting to relate all new pain in cancer to progression of malignant disease, no fewer than one-third of pain problems in cancer patients are due to non-malignant causes.[61] It is widely accepted that 15–46% of patients with systemic cancer who are admitted to an oncological service have neurological symptoms.[62,63] About half of these neurological symptoms are explained by metastatic involvement of the nervous system.[64]

Early diagnosis of recurrent disease or progression of disease during anti-tumor therapy may lead to institution of a new anti-tumor treatment.[24] This may prevent permanent disability. For example, early diagnosis of spinal cord compression preserves mobility and independence. Thus, a specific pain diagnosis clarifying the pain syndrome, the pathophysiology of the pain and the status of the disease can enhance quality of life by more successful pain treatment, a better functional outcome and facilitates tumor control. One of the most important causes of inadequate pain management is due to inaccurate localization of the primary site of disease responsible for the pain syndrome. For example, referred pain and radicular pain should be carefully distinguished from pain experienced at the site of tissue damage.

## Towards a better pain treatment of the cancer patient

Following a thorough assessment providing a pain specific diagnosis, options for symptomatic and anti-tumor therapy can be chosen. In nociceptive pain treatment, systemically administered analgesics are the hallmark of symptomatic therapy. Most pains in cancer can adequately be treated by orally administered analgesics, although 10–20% would not respond satisfactorily to this type of management.[28]

### Drug selection

For analgesic drug selection in nociceptive pain in cancer, the three-step analgesic ladder is strongly advocated by the WHO.[31,65] A number of field studies have explored its validity.[28,29,66–69] Between 80 and 90% of patients can be treated adequately using this approach. Oral application around the clock in an individually titrated dosage is recommended.[70] With unsatisfactory results the patient should move to the next step. Side-effects should be pharmacologically prevented when possible.

The pharmacological treatment of pain in cancer as presented here is based on evidence from reviewed randomized double-blind analgesic trials using a literature search in the *Medline* database over the period 1976–1994. If earlier publications were mentioned, these were also reviewed.

*Step 1.* For mild pain the non-opioid analgesics acetoaminophen (paracetamol) and the NSAIDs are used. Acetoaminophen probably acts by a central mechanism.[71] It lacks the gastrointestinal, hematopoietic and renal adversities, but is less effective in inflammatory conditions than the NSAIDs. The latter exert their principal analgesic effect by inhibition of the enzyme cyclo-oxygenase preventing the release of PGE2.[72] There is increasing evidence that NSAIDs also exert a central analgesic action at the dorsal horn of the spinal cord.[73–76] NSAIDs may play a special role in metastatic bony disease.[49,77–79] Experimentally, aspirin inhibits tumor growth in metastatic bone tumors. Prostaglandins mediate the hormonal response of certain tumors in bone.[80,81] The onset of bone pain appears to be mediated primarily through PGE2, either produced by the tumor or indirectly by pressure of the tumor mass on adjacent tissues.[49,82]

There is evidence from controlled trials that NSAIDs provide better pain relief than weak opioids[83] in opioid-naive patients, while previous opioid users prefer weak narcotics over NSAIDs. This suggests that NSAIDs should be prescribed prior to initiating narcotic therapy in cancer patients suffering pain and may reinforce the application of the WHO stepladder.

**Table 2.** NSAIDs in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug(s)[a] | Dose (mg/day) | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Martino, 1978[282] | pain due to malignant tumors | indoprofen | 200 | 18 | S | NPCDBCO | NS |
| | | indoprofen | 250 | | | | |
| Sachetti, 1984[88] | nociceptive bone pain due to metastasis | k(etoprofen) i.v. | 100 | 36 | S | NPCDBCO | K 400 > K 100 = LAS 1000 |
| | | k(etoprofen) i.v. | 400 | | | | |
| | | lysine acetyl-salicylate (LAS) i.v. | 1000 | | | | |
| Lomen, 1986[283] | nociceptive bone pain due to metastatic breast cancer | flurbiprofen | NR | 26 | S | PCDBCO | NS |
| Turnbull, 1986[85] | nociceptive pain of various primary tumors | naproxen | 1000 | 28 | S + M | PCDBCO | NS |
| | | aspirin | 3600 | | | | |
| Levick, 1988[87] | nociceptive bone pain due to metastasis | naproxen | 1550 | 100 | M | NPCDBPa | 1650 mg > 825 mg naproxen |
| | | naproxen | 825 | | | | |
| Stambaugh, 1988[93] | nociceptive bone pain due to metastasis | ibuprofen | 2400 | 30 | M | PCDBPa | ibuprofen > p |
| Ventrafridda, 1990[284] | cancer pain | paracetamol | 1500 | 65 | M | NPCDBCO | NS |
| | | acetyl salicylic acid | 1800 | | | | |
| | | diclofenac | 200 | | | | |
| | | ibuprofen | 1800 | | | | |
| | | indomethacin | 150 | | | | |
| | | pirprofen | 1200 | | | | |
| | | sulindac | 600 | | | | |
| | | naproxen | 750 | | | | |
| | | suprofen | 600 | | | | |
| Ventafridda, 1990[86] | nociceptive static and/or continuous cancer pain | naproxen | 1100 | 100 | M | NPCSBPa | NS |
| | | diclofenac | 200 | | | | |
| Bjorkman 1993[91] | nociceptive pain due to primary tumor or metastasis | diclofenac | 150 | 16 | M | PCDBCO | morphine sparing effect with diclofenac |

[a] Administered p.o. unless indicated otherwise; s = single dose; M = multiple dose; (N)PC = (non) placebo-controlled; (N)DB = (non) double-blind; SB = single-blind; Pa = parallel group; CO = cross-over; NR = not reported; NS = not significant; p = placebo.

There are no conclusive studies showing which NSAID is more effective in nociceptive pain in cancer and neither the optimal dose nor the route of administration have been established in clinical trials in cancer patients (see Table 2). In a double-blind comparative cross-over study of eight NSAIDs and paracetamol in the treatment of nociceptive pain in cancer, naproxen, diclofenac and indomethacin were the most potent analgesics with approximately equal side-effects.[84] However, statistical significant differences in analgesic effect were not reported in this trial, as well as in two other studies.[85,86] In two controlled studies, a dose-dependent analgesic effect for ketotifen and naproxen was reported in nociceptive pain due to bone metastasis.[87,88] The potential for dose-dependent toxicity requires an upper limit for dose titration which is generally 1.5–2 times the standard recommended dose.[87]

*Step 2.* If an NSAID provides unsatisfactory pain relief, the next step of the analgesic ladder includes both an opioid and a non-steroidal drug. Several controlled studies provide evidence that the combination of an opioid with a NSAID provides better pain relief than an NSAID alone,[49,89–94] although not unequivocally[95–97] (see Table 3). In nociceptive pain, especially due to bone metastasis, some NSAIDs (zomepirac, ketoprofen, pirprofen, indoprofen) seem at least as potent analgesics as weak opioids in combination with aspirin/phenacitin.[83,96,97] The role for weak opioids, such as codeine and hydroxycodone, in cancer pain treatment is controversial. Codein is partially biotransformed in the liver to morphine. At the time of publication of the WHO guidelines, slow-release morphine preparations were not easily available throughout the world. We prefer to eliminate Step 2 in cancer pain treatment. As an alternative for codeine in step 2, the noradrenergic $\mu$-agonist tramadol has been advocated.[98–103]

*Step 3.* Morphine is considered as the drug of first choice. It can be administered orally with a dose individually tailored to each patient without an arbitrary upper limit. Slow-release morphine (MS Contin) gives peak plasma concentrations 2 h after oral intake, and can be dosed two or three times daily, and is as potent as immediate-release preparations[104–107] (see Table 4). Methadone is suggested as a good alternative in patients after they had prior exposure to morphine.[25,108]

## Causes for undertreatment with opioids

The lack of understanding and misconceptions about the use of opioids is probably one of the most important factors of inadequate pain relief in cancer patients. Practical aspects of opioid pharmacotherapy encompass drug selection and dosing considerations, including selection of an appropriate route of administration, dose titration and the management of side-effects. Lay citizens mostly fear the development of confusion, tolerance and addiction, and health care professionals fear opioid-induced addiction and respiratory depression.[27,109]

*Misconceptions: tolerance, addiction and dependence.* The presumption that opioids are addictive and concerns about tolerance and toxicity still leads to the undertreatment of pain.[22,28,60] The terms tolerance and (physical) dependence are often confused with (psychological) addiction.

Tolerance designates that with repeated administration, increasing doses are needed to obtain the desired effect. Tolerance may manifest with a shorter duration of the drug action or by breakthrough pain. In cancer-related pain, it is difficult to assess the development of tolerance. Higher dose requirements may reflect increased tissue damage, rather than the development of tolerance. Maybe for these reasons, the development of tolerance in cancer-related pain is rarely a clinical problem.[100,110–112] Tolerance can become a clinical problem if the physician refuses to prescribe larger than standard doses.[25] Cross-tolerance is incomplete, therefore switching to an alternate opioid and selecting 50% of the equianalgetic dose may result in effective analgesia.[25,90,113] Rapid tolerance develops for respiratory depression, in contrast to the slow tolerance to obstipation.

It is a critical issue to recognize that it is possible to become physically dependent without evidence of addiction.[25] Physical dependence may manifest by the presence of the abstinence syndrome following abrupt discontinuation of an opioid or administration of an antagonist (naloxone).

Addiction (psychological dependence) refers to compulsive drug-seeking behavior to obtain desired effects other than pain relief. It should be suspected to be present if subjects demonstrate compulsive use, loss of control over drug use, if medication is stolen, etc. The only controlled study to date indicated that addictive behavior rarely (four out of 11 882 patients without a history of addiction) occurs when opioids are used for pain relief.[114–120] There are no long-term studies documenting that

**Table 3.** NSAIDs versus opioids in randomized analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug(s)[a] | Dose (mg/day) | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Stambaugh, 1980[83] | nociceptive pain due to primary or metastatic cancer | zomepirac | 100 | 40 | S | PCDBCO | zomepirac > oxycodone + APC > p |
| | | oxycodone/APC | | | | | |
| | | zomepirac | 100 | 170 | M | PCDBPa | opioid users: oxycodone + APC > zomepirac > p |
| | | oxycodone/APC | | | | | opioid naive: zomepirac > oxycodone + APC > p |
| Stambaugh, 1981[95] | cancer pain | zomepirac | 100 | 40 | S | PCDBCO | zomepirac = oxycodone + APC > p |
| | | oxycodone/APC | | | | | |
| Buckert, 1982[285] | hospital patients with pain due to cancer | pirprofen | 200 | 168 | S | PCDBPa | pirprofen 400 > pirprofen 200 = pentazocin > p |
| | | pirprofen | 400 | | | | |
| | | pentazocin | 100 | | | | |
| Pellegrini, 1983[286] | nociceptive bone pain due to metastasis | indoprofen i.v. | 400 | 12 | S | PCDBCO | indoprofen = morphine > p |
| | | morphine i.m. | 10 | | | | |
| Stambaugh, 1988[96] | nociceptive pain due to primary or metastatic cancer | ketoprofen | 100 | 160 | S | PCDBPa | ketoprofen 100 = ketoprofen 300 = aspirin/codeine > p |
| | | ketoprofen | 300 | | | | |
| | | aspirin/codeine | 650/60 | | | | |
| Minotti, 1989[97] | chronic cancer pain | diclofenac | 200 | 99 | M | NPCDBPa | diclofenac = nefopam = ASA/codeine |
| | | nefopam | 240 | | | | |
| | | ASA/codeine | 2560/160 | | | | |
| Strobel, 1992[92] | tumor pain | diclofenac/codeine | 50 | 184 | S | NPCDBPa | diclofenac/codeine > diclofenac |
| | | diclofenac | 50 | | | | |
| Dellemijn, 1994[44] | nociceptive nerve pain | naproxen | 1500 | 20 | M | NPCDBCo | naproxen > SR-morphine |
| | | SRM | 60 | | | | |

[a] Percodan = oxycodone/APC: 224 mg aspirin, 162 mg phenacitin + 32 mg caffeine + 5.4 mg oxycodone–HCl + 0.38 mg oxycone terephthalate; see legend to Table 2.

**Table 4**. Opioids in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug(s)[a] | Dose (mg/day) | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Beaver, 1977[142] | chronic pain due to cancer | i.m. versus oral oxymorphone | graded | 28 | | NPCDBCO | oral oxymorphone = 1/6 × i.m. potency |
| | | i.m. oxymorphone versus i.m. morphine | | 26 | | NPCDBCO | oxymorphone = 8.7 × morphine potency |
| Beaver, 1978[143] | chronic pain due to cancer | i.m versus oral codeine | graded | 43 | | NPCDBCO | oral codeine = 6/10 × i.m. potency |
| | | i.m. versus oral oxycodone | | 17 | | NPCDBCO | oral oxycodone = 5/10 × i.m. potency |
| Beaver, 1978[144] | chronic pain due to cancer | oxycodone i.m. versus morphine i.m. | graded | 28 | | NPCDBCO | oxycodone = 2/3 × morphine potency |
| | | oxycodone i.m. versus codeine i.m. | | 26 | | NPCDBCO | oxycodone = 10 × codeine potency |
| Staquet, 1979[287] | continuous pain in advanced cancer | dezocine i.m. morphine i.m. | 10 versus 10 | 10 | | PCDBCO | morphine > p dezocine = p |
| Staquet, 1980[288] | continuous pain in advanced cancer | ciramadol oral | 20 60 | 15 | | PCDBCO | ciramadol 60 > ciramadol 20 > p |
| Staquet, 1980[289] | continuous pain due to cancer | dezocine i.m. sd | 10 | 20 | | PCDBCO | dezocine > p |
| Kaiko, 1987[290] | chronic malignant pain | morphine i.m. + cocaine (oral) morphine cocaine | 10/10 | 19 | | PCDBCO | negative interaction effects |
| Meyer-Lindau, 1988[291] | medium to severe tumor pain | caerulein i.m. morphine i.m. | 5 μg 10 mg | 36 | | NPCDBPa | NS |
| Thirlwell, 1989[107] | chronic cancer pain | oral morphine sulfate solution SRM | titration | 23 | | NPCDBCO | NS |
| Cundiff, 1989[106] | chronic cancer pain | IRM versus SRM SRM | titration | 14 | | NPCDBCO | NS |
| Tawfik, 1990[101] | pain due to cancer of varying etiology | oral tramadol SRM | titration | 64 | | PCDBPa | tramadol 87 versus SRM 100% adequate relief; significance NR |
| Kalso, 1990[160] | cancer pain | morphine oxycodone PCA-i.v. | titration | 20 | | NPCDBCO | NS |
| Moulin, 1991[292] | cancer pain | i.v. versus SC hydromorphone | titration | 15 | | NPCDBCO | NS |
| Vedrenne, 1991[293] | cancer pain | epidural morphine ± naloxon | 4 mg 0.4 mg + 5 μg/kg/h | 40 | | PCDBPa | NS |
| Walsh, 1992[105] | chronic cancer pain | IRM versus SRM | variable | 33 | | NPCDBCO | NS |
| Finn, 1993[104] | cancer pain | IRM versus SRM | 60 | 34 | | PCDBCO | NS |

[a]Administered p.o. unless indicated otherwise; IRM = immediate-release morphine; SRM = slow-release morphine; S = single dose; M = multiple dose; (N)PC = (non) placebo-controlled; (N)DB = (non) double-blind; NR = not reported; NS = not significant; p = placebo.

chronic use of opioids for pain would lead to addiction; in fact, one controlled study provides that it does not.[121] It is essential to inform health care providers, the patient and his/her family that the risk of addiction to opioids is extremely small.

*Dose selection and adjustment.* Administration of opioids in insufficient doses may lead to an increase in opioid consumption without the desired analgesic effect.[7] High doses are often misinterpreted by physicians, who therefore undermedicate patients rather than using the endpoint effective analgesia.[122] In this respect it is important to mention that there is no preset maximum dose for opioids and the inter-patient variation in oral bioavailability is large, e.g. 50% for morphine.[112] Each patient has their own optimal dose giving the balance between optimal pain relief and manageable adverse effects.

Other causes of undermedication are too long dose intervals and as-needed medication. Initially, patients can be titrated on immediate-release morphine tablets (10 mg q 4 h) and, once stabilized, converted to slow-release forms in a 12 h dosing schedule to ameliorate patient compliance.[123] Occasionally, a 12 h dosing schedule is useful when drowsiness occurs at about 4 h after administration.[124]

Apart from formulations with slow-release delivery, opioids should be dosed six to eight times in 24 h. It is better to prevent pain considering the time needed to achieve adequate blood levels of the analgesic and providing blood levels at about minimal effective concentrations for pain relief. In breakthrough pain the dose of morphine should be increased by at least 50%.[124]

Dose reductions should be considered with renal impairment and in patients over the age of 60 years.[125] Renal impairment may reduce the clearance of morphine-6-glucuronide,[126] an active metabolite of morphine, and alternative opioids are recommended in this setting, e.g. methadone.[122,127–132] In advanced liver disease, morphine hepatic extraction is diminished and this also requires dose reduction.[133,134]

*Sequential trials with other opioids.* Some patients may benefit from a sequential trial with another opioid, based on binding differences for $\mu$-, $\kappa$- and $\delta$-receptors, and incomplete cross-tolerance to analgesic and adverse effects of different opioids.[25,113,122,135] Switching from one opioid to another, 50% of the equivalent analgesic dose should be given as a starting dose.[108] This is based on the established empirical information that cross-tolerance among opioids is not complete and that the relative potency of opioids may change with repetitive dosing. Furthermore, there exists a large variation in oral bioavailability of the same opioid between patients (4-fold) and between different opioids, e.g. $26 \pm 13\%$ for morphine and $79 \pm 12\%$ for methadone.[112] For successful switching to another opioid with equianalgesic potency, we refer to other reviews.[2,25,61,136]

*Side-effects of opioids.* Side-effects or the fear for side-effects are potential hazards that may lead to underdosing of analgesics, in particular of opioids. Inappropriately managing adverse reactions is another cause of failure of opioid therapy.[7] The emergence of side-effects depends on age, concurrent administration of other drugs, prior opioid exposure, starting dose and the route of administration.

The management of adverse effects is necessary to optimize the potential benefit of these drugs. Nausea and vomiting may develop in 10–40%, especially after initiating opioid therapy at a rather high dose (60 mg/day).[44,137,138] The transient stimulation of the medullary chemoreceptor trigger zone and increased vestibular sensitivity usually disappears within 3–7 days and may easily be overcome by an anti-emetic, e.g. metoclopramide. Opioid-induced constipation is so frequent that every patient should receive prophylactic laxatives. Doses of these drugs should be increased as necessary. In refractory constipation, a trial with magnesium sulfate or with oral naloxone with low bioavailability and a relative selectivity of opioid receptors in the gut can be used.[139] Opioid-induced constipation may induce vomiting and lower opioid absorption with the emergence of breakthrough pain. Alternative routes of administration frequently provide a good alternative. Cognitive impairment is mainly seen in older patients with impaired renal function, and initial dosing should be lower, e.g. slow-release morphine 10 mg b.i.d. to avoid delirium. Cognitive dysfunction occurs acutely with elevation of opioid-dosing, but tolerance to this effect usually occurs within a few days.[140] Inordinate fear of opioid-induced respiratory depression is an important impediment to adequate pain control in cancer. The patient at risk has an abrupt absence of the respiratory-stimulating effect of pain, as for example in patients receiving high doses of opioids and undergoing a local anesthetic procedure.

*Alternative routes of delivery.* In patients with swallowing difficulties or with gastro-intestinal obstruc-

**Table 5.** Fentanyl patches and equianalgesic doses of morphine

| Oral 24 h morphine (mg/day) | Fentanyl patches TTS ($\mu$g/h)[294] |
|---|---|
| 45–134 | 25 |
| 135–224 | 50 |
| 225–314 | 75 |
| 315–404 | 100 |
| 405–494 | 125 |
| 495–584 | 150 |
| 585–674 | 175 |
| 675–764 | 200 |
| 765–854 | 225 |
| 855–944 | 250 |
| 945–1034 | 275 |
| 1035–1124 | 300 |

tion, when a rapid onset of analgesia is required or in highly tolerant patients who require ultra-high doses, alternative routes of delivery need to be considered. Recently, promising results were reported from rectal, transdermal, transmucosal and s.c. administration by new delivery systems. Nevertheless, alternative routes do not necessarily provide more effective analgesia,[141] although opioids are more potent given by the parenteral route[142–144] (see Table 4).

Controlled-release morphine can also be administered rectally in the same dose as the oral route, as the bioavailability is in general equal for oral and rectal delivery.[145,146] For patients with difficulty in swallowing and for children, oral controlled-release suspension is a valuable alternative.[147] A transdermal delivery system of fentanyl available in 25, 50, 75 and 100 $\mu$g/h has proven to be a safe, non-invasive and effective method of managing nociceptive pain in cancer.[69,148] Equivalent analgesic doses of morphine have a rather wide range due to variations in absorption profile (Table 5). Using these conversion tables, 50% of patients will obtain adequate pain relief, while the other half has to be titrated upwards.[149] Continuous delivery reaches a plateau after 4–6 days.[150,151] Patches should be changed every 72 h, although pharmacokinetic variability is large and some patients may require 48 h dosing intervals. Constipation seems less frequent with fentanyl than with morphine.[152] Limitations are poor adhesion of the patch and the time required to titrate to optimal dosing, sometimes as long as 2 weeks. However, it seems a valuable adjunct in patients with difficulties in swallowing such as head and neck tumors, and with gastro-intestinal side-effects.[148,153,154]

In an open label study, administration of oral transmucosal fentanyl citrate (OTFC) in a flavored candy base (lolly-pop) appeared to be a promising analgesic for incident and breakthrough pain.[155]

**Table 6.**

| Opioid treatment with persistent pain and unmanageable side-effects |
|---|
| Adjuvant analgesic |
| Alternative route of delivery (epidural, transdermal, etc.) |
| Sequential trial with other opioid |
| Anti-tumor therapy |
| Invasive neuroablative procedure |

Subcutaneous infusions provide an alternative to the transdermal or transmucosal route, and may be expected to become increasingly popular with the availability of new drug–electronic device systems.[156] The oral dose should be divided by 2 to obtain the equianalgesic s.c. dose of morphine.[157]

Patient controlled analgesia (PCA) is a mode of opioid administration that employs the concept of individualization of analgesic dosage wherein the patient, within limits, can titrate his analgesic requirements. PCA can be used safely and efficaciously in outpatients with pain due to cancer.[158,159] The equianalgesic i.v. dose of morphine is 30% of the oral dose.[160]

Continuous epidural opioids with an ambulant pump with or without the addition of local anesthetics diminishes the systemic requirements of opioids, thus alleviating systemic adverse effects.[110,141,161–165] Epidural or subarachnoidal opioids are indicated when oral opioids provide unsatisfactory pain relief or when dose escalation leads to intolerable or unmanageable side-effects. With these techniques, about 80% of outpatients enjoy satisfactory pain relief.[111] Rates of complications as obstruction, dislocation or infection of the catheter depend on the time period the catheter remains *in situ*. On the short term, i.e. the first 290 days, epidural opioid infusion appears to give a lower complication (8%) rate than spinal opioids (25%). After this period, the complication rate of epidural administration rises steeply up to 50% (obstruction and dislodgement of catheter). The subarachnoid route is preferred in patients with life expectancy of 1 month or more, and in patients with a shorter life expectancy an epidural catheter would yield satisfactory results.[115]

There is considerable controversy about the advantages of spinal and epidural opioids. The supposed spinal selectivity for opioid binding is questioned by pharmacological data. For example, after an epidural dose of an opioid, systemic uptake is comparable with a pharmacological profile following intramuscular injection.[90,166,167] The addition of

**Table 7.** Adjuvant analgesics in cancer-related pain syndromes

| Cause of pain | Use of adjuvant analgesics |
|---|---|
| Bone metastases | diphosphonates<br>radiopharmaceuticals |
| Nociceptive nerve pain | corticosteroids |
| Deafferentation pain | tricyclic antidepressants<br>carbamazepine<br>mexiletine<br>topicals: lidocaine, capsaicin, NSAIDs |
| Occult infection | antibiotics |
| Muscle spasm | baclofen |
| Increased intracranial pressure | corticosteroids |
| Hepatomegaly | corticosteroids |

adjuvants, such as local anesthetics and clonidine, probably provides the relative advantage that is obtained with the epidural administration route.[161,163–165]

Intramuscular administration of opioids is painful and is not advised in the management of cancer-treated pain.

*Unsatisfactory pain relief with uncontrollable side-effects.* If opioid administration does not lead to an acceptable balance between pain relief and side-effects preventing further dose escalation, several interventions can improve this equilibrium by reducing the opioid requirements. These include concurrent use of alternative pharmacologic approaches, appropriate anti-tumor therapy or the use of invasive neuro-ablative procedures (see Table 6).

## Adjuvants

Adjuvant analgesics may either enhance the analgesic effects of opioids or provide intrinsical analgesic activities in specific pain syndromes[108,168,169] (see Table 7).

*Glucocorticoids.* The only controlled study evaluating 16 mg methylprednisolone b.i.d. versus placebo during 5 days showed a significant reduction in both pain and analgesic consumption in terminally ill cancer patients.[170] Uncontrolled studies and anecdotal data suggest that corticosteroids improve pain control in malignant nerve pain,[13,171] increase intracranial pressure,[172,173] acute epidural spinal cord compression,[173,174] superior vena cava syndrome,[175] metastatic bone pain,[176–178] hypertrophic pulmonary arthropathy, symptomatic lymphedema and painful hepatic capsular distention.[169,179–183] Dexamethasone is the preferred corticosteroid based on its minimal sodium-retention activity and superior potency when compared with other steroids.[184] The commonly used initial dose of dexamethasone in spinal cord compression is 100 mg i.v. A controlled study has shown that initial bolus of 10 mg i.v. followed by 16 mg/day may act as well on pain relief and arresting neurological progression, and results in smaller risk on serious side-effects.[174]

Glucocorticoids inhibit phospholipase A2, an enzyme that liberates arachidonic acid from cell membranes providing a substrate for prostaglandin synthesis. Thus, corticosteroids may enhance pain control by inhibiting the inflammatory response. One assumes that the benefit of glucocorticoids in epidural spinal cord compression and brain metastases results from reduction in peritumoral edema. Experimental research in neuropathic pain suggest that steroids reduce neuronal hyperexcitability in neuromas, possibly by a direct effect on the cell membranes.[185]

*Tricyclic antidepressants.* The proven analgesic action of tricyclic antidepressants seems to be inde-

**Table 8. Antidepressants in randomized controlled analgesic trials in nociceptive cancer-related pain**

| First author and year | Pain mechanism | Drug[a] | Dose (mg/day) | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Fiorentino, 1967[193] | metastatic cancer pain | imipramine | 150 | 40 | M | PCDBPa | NS |
| Beaumont, 1980[194] | terminal cancer pain | clomipramine | 60 | 20 | M | PCDBPa | NS (trial failed: 12 drop outs) |
| Walsh, 1986[189] | chronic cancer pain | imipramine | 50–75 | 69 | M | PCDBPa | reduced morphine consumption |

[a] Administered p.o. unless indicated otherwise; M = multiple dose; PC = placebo controlled; DB = double blind; Pa = parallel group; NS = not significant; p = placebo.

pendent of mood and applied doses are usually lower than required for their antidepressant effect.[186–189] The primary indication is pain due to nerve injury without local ongoing tissue damage, i.e. deafferentation pain.[50,186–188,190–192] Their analgesic effect in nociceptive pain in cancer remains to be established in controlled studies.[189,193–196] No benefit has been shown by adding imipramine to pain regimens in nociceptive pain in cancer.[193] A controlled study on imipramine in chronic cancer pain patients showed a significant reduced morphine consumption independent of antidepressive action.[189] Adding clomipramine in outpatients with advanced cancer showed inconclusive results, although an opioid-sparing effect was suggested.[194] Co-administration of antidepressants increase the bioavailability of morphine,[197] although the potentiation of morphine analgesia is thought to be mediated by an intrinsic effect of the antidepressant.[196] Thus, at present there are no controlled studies that support intrinsic analgesic effects of antidepressants in nociceptive pain independent of their effect on mood (see Table 8). However, antidepressants seem to be quite useful in cancer patients who experience sleep disturbances or depression.

Doses should be started low (10 mg amitriptyline at night) and gradually increased until satisfactory pain relief is achieved or until the highest tolerable dose. Often doses of 50–75 mg/day are sufficient, although optimum dosages and schedules have not been established.[198] Onset of analgesia varies from 1 day to 10 weeks. Common side-effects include dry mouth, drowsiness, urinary retention, orthostatic hypotension and constipation.

*Anticonvulsants.* The use of anticonvulsants such as carbamazepine has been favored for lancinating and paroxysmal pains in analogy with the proven effectiveness in trigeminal neuralgia. However, this is currently unsupported by controlled studies.

*Local anesthetics—antidysrhythmics.* In two controlled studies i.v. lidocaine appeared to be ineffective for neuropathic cancer pain,[199,200] although it has a proven efficacy in deafferentation pain.[201] Several controlled studies have reported the oral local anesthetic mexiletine as an effective analgesic in deafferentation pain such as diabetic polyneuropathy,[202,203] while topical lidocaine has shown to be effective in two controlled studies on postherpetic neuralgia.[204,205] Thus, the use of local anesthetics in nociceptive cancer pain is currently limited to epidural and intrathecal techniques.[162–165]

*α-adrenergic agonists.* In a double-blind placebo controlled study intrathecal administration of the partial $\alpha_2$-agonist clonidine was shown to induce analgesic properties in postoperative patients.[206] Epidural clonidine was shown to be ineffective in a controlled study of post-thoracotomy pain.[207] In a double-blind randomized trial in 85 patients with nociceptive pain due to cancer, epidural clonidine showed a significant analgesic effect as an adjunct to morphine in patients with nociceptive nerve pain, but was ineffective in somatic and visceral (nociceptive) pain.[208] The latter was described by the lack of frequent dose titration in the study protocol. Uncontrolled clinical studies and anecdotal data report promising results with epidural and intrathecal clonidine, as well as in morphine-tolerant patients who suffer from nociceptive pain in cancer.[209–212] Oral, epidural and transdermal clonidine have been suggested as effective analgesics in deafferentation pain.[213] The analgesic action of clonidine is thought to be mediated by a local spinal action on $\alpha_2$-adreno-receptors without interacting with opioid receptors.[214] Thus, there is some evidence for epidural clonidine use as an adjunct to morphine in nociceptive nerve pain, but conflicting reports about the analgesic efficacy of clonidine in nociceptive pain of viseral and somatic origin.

In one controlled study of 52 patients oral flupirtine (up to 600 mg/day) was superior to pentazocin (300 mg/day) in the treatment of unspecified 'cancer-related' pain.[215] The analgesic activity of flupirtine was postulated to be mediated via $\alpha_2$-adrenergic mechanisms.

*Anxiolytics, antipsychotics and sedatives.* The benzodiazepine midazolam has a role in painful procedures exerting its anterograde anamnestic properties and has been shown to be superior to the short-acting opioid fentanyl in two controlled studies.[216,217]

There are no well designed controlled studies that support the analgesic efficacy of anxiolytics, antipsychotic drugs or sedatives in cancer-related pain. Therefore, these classes of drugs are to be avoided because they provide sedation without improving analgesia[139,218–221] (see Table 9). The weak antipsychotic tiapride has been promulgated in three double-blind controlled trials for the treatment of nociceptive cancer-related pain.[222–224] Its analgesic efficacy, however, is not superior to aspirin.[225]

*Amphetamines.* If opioid-induced sedation limits further dose escalation, adding the amphetamine methylphenidate (e.g. 10 mg at 8.00 h and 15 mg

**Table 9.** Antipsychotics and sedatives in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug(s)[a] | Dose (ng/day)/dy | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Beaver, 1966[218] | nociceptive pain due to cancer; bone–visceral–nerve | levopromazine i.m. | 7.5 and 15 | 40 | S | NPCSB | morphine > levopromazine |
| | | morphine i.m. | 8 and 16 | | | | |
| Staquet, 1978[295] | nociceptive pain | tetrahydrocannabidol (NIB) versus codeine | 4 versus 50 | 30 | S | PCDBCO | NIB = codeine = p |
| | | NIB versus secobarbital | 4 versus 50 | 15 | | | NIB > secobarbital = p |
| Dilhuydy, 1979[222] | nociceptive bone pain due to metastasis of primary head and neck tumors | tiapride i.v. | 300 | 30 | S | PCDBCO | tiapride > p |
| Clavel, 1980[223] | nociceptive pain due to various primary tumors and metastasis | tiapride i.m. | 200 | 29 | S | PCDBCO | tiapride > p |
| Le Derff, 1982[224] | nociceptive pain due to various primary tumors and metastasis | tiapride p.o. versus i.m. | 300–600 | 27 | S | NPCDB | i.m. > p.o. |
| Clavel, 1984[225] | pain due to active cancer | tiapride i.v. or i.m. | 300 | 24 | S | NPCDBCO | NS |
| | | aspirin i.v. or i.m. | 500 | 24 | S | | |
| Yosselson-Superstine, 1985[219] | mixed group: nociceptive pain due to various primary tumors and metastasis (6) and arthritic pain (3) | hydroxyzine | 75 | 9 | M | PCPCDBO | NS |
| | | prochlorperazine | 30 | | | | |
| | | chlordiazepoxide | 30 | | | | |

[a]Administered p.o. unless indicated otherwise, (N)PC = (non) placebo-controlled; (N)DB = (non) double-blind; SB = single-blind; S = single dose; M = multiple dose; NS = not significant.

**Table 10.** Amphetamines in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug[a] | Dose (mg/day) | No. of patients | No. of doses | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|---|
| Bruera, 1986[231] | nociceptive pain in terminal cancer patients | mazindol | 3 | 30 | M | PCDBCO | mazindol > p |
| Bruera, 1987[229] | nociceptive pain due to local recurrence or metastasis | methylphenidate | 15 | 32 | M | PCDBCO | methylphenidate > p |
| Bruera, 1992[230] | cancer pain | methylphenidate | 15 | 20 | M | PCDBCO | methylphenidate > p in cognitive function |

[a]Administered p.o. unless indicated otherwise, PC = placebo-controlled; DB = double-blind; SB = single-blind; S = single dose; M = multiple dose; p = placebo.

at 12.00 h) allows enhanced pain control both by potentiating the analgesic effect of opioids, and by raising opioid dose with less sedation and improved physical activity and cognitive function[226–230] (see Table 10). Mazindol has a similar effect on pain intensity, but seems to be hampered in clinical use by lack of a favorable effect on patient activity and appetite, and may cause delirium.[231]

*Diphosphonates.* The diphosphonates pamidronate (APD) and clodronate (CL2MDP) relieve bone pain from osseous metastases in breast cancer and multiple myeloma in several controlled studies[232–238] (see Table 11). Unfortunately, the analgesic effect is relatively small and the studies lack uniform validated methods of pain assessment.[239] Nevertheless, these drugs can be recommended in patients with refractory bone pain.[39,239–245] In controlled studies a reduction in analgesic consumption was observed in 50–60% of the patients starting after 6–8 days but for a sustained period.[237,246] Diphosphonates stabilize bone by increasing calcium absorption and inhibiting osteoclasts.[247,248] Pamidronate disodium and clodronate can both be administered orally and i.v. For example, APD may be started by i.v. infusion of 30–60 mg in 4–6 h., followed by 30 mg every 2 weeks i.v. or by 150 mg b.i.d. orally.[249]

*Radiopharmaceuticals.* Both placebo-controlled and open-label studies report that osteoblastic bone metastases in prostate and breast cancer show a response rate of 45–82% to strontium-89 by a reduction of new pain sites, analgesic consumption or radiotherapy and improving the quality of life[250–258] (see Table 12). Although the optimal dose has not been established, a dose–response relationship seems to be present.[257] This therapy can safely be repeated several times every 3 months. It is a useful adjunct to external beam radiation, even when external radiation to spinal cord tolerance was received.[250,253] A 20–30% drop in platelet count is to be expected at week 5–6 (advisable platelet count > 60 000) after injection without a significant drop in white blood cell count.[250] Patients with symptomatic metastatic prostate cancer in whom androgen blockade has failed are the preferential candidates for strontium-89.

*Antibiotics.* Local infection is a common cause of pain in local recurrence of head and neck tumors, and a prompt and sustained response to empirical antibiotic therapy may confirm the diagnosis and relieve the pain.[259,260]

*Calcitonin.* The first controlled study using salmon calcitonin (200 IU q.i.d. for 48 h) in 32 patients with nociceptive pain of various primary tumors, and in only 16 due to bone involvement, only four of 13 patients showed a analgesic response to calcitonin in contrast to none of 12 to placebo.[300] All the responders had nociceptive bone pain due to metastasis. In another controlled study 20 out of 42 patients with nociceptive bone pain due to metastasis reported partial pain relief after a single i.v. salmon calcitonin infusion of 200 IU. The 20 good responders entered a double-blind placebo-controlled trial showing significant pain relief and a significantly longer period before they required analgesics.[261] However, the analgesic effect of calcitonin seems quite small and more controlled studies are needed to define its role in the treatment of pain in bone metastasis.

## Neuroablative techniques

Nerve blocks and neuroablative procedures are nowadays seldom applied because of their high failure rate, transient effect, high incidence of side-effects, and refinement of oral and spinal opioid

**Table 11.** Diphosphonates in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug[a] | Dose (mg/day) | No. of patients | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|
| Delmas, 1982[232] | nociceptive bone pain in multiple myeloma | clodronate | p.o. 1600 | 13 | PCDB | clodronate > p |
| Siris, 1983[233] | nociceptive bone pain in metastatic breast cancer | clodronate | p.o. 3200 | 10 | PCDBCO | clodronate > p |
| Elomaa, 1983[234] | nociceptive bone pain in metastatic breast cancer | clodronate | p.o. 1600 | 34 | PCDB | clodronate > p |
| Canfield, 1987[235] | nociceptive bone pain in multiple myeloma | clodronate | p.o. 3200 | 12 | PCDBCO | 8/11 responders decreased bone pain |
| | nociceptive bone pain in metastatic breast cancer | clodronate | p.o. 3200 | 10 | PCDBCO | 'similar results' |
| Cleton, 1989[236] | nociceptive bone pain in metastatic breast cancer | pamidronate | p.o. 300 | 131 | NPCNDB controls | pamidronate > untreated controls |
| Smith, 1989[296] | nociceptive bone pain in metastatic prostate cancer | etidronate | i.v. 7.5 mg/kg × 3 days followed by p.o. 400 | 57 | PCDB | etidronate = p |
| Belch, 1991[297] | nociceptive bone pain in multiple myeloma | etidronate | i.v. 5/kg | 176 | PCDB | etidronate = p |
| Ernst, 1992[237] | metastatic bone pain in metastatic breast cancer | clodronate | i.v. 600 | 24 | PCDBCO | clodronate > p |
| Lahtinen, 1993[238] | nociceptive bone pain in multiple myeloma | clodronate | p.o. 2400 | 350 | PCDB | clodronate > p |

[a]Administered p.o. unless indicated otherwise; (N)PC = (non) placebo-controlled; (N)DB = (non) double-blind; CO = cross-over; S = single dose; M = multiple dose; p = placebo.

**Table 12.** Radiopharmaceuticals in randomized controlled analgesic trials in nociceptive cancer-related pain

| First author and year | Pain mechanism | Drug[a] | Dose (μCi/day) | No. of patients | Study design | Comparative analgesic efficacy significant? |
|---|---|---|---|---|---|---|
| Buchali, 1988[298] | nociceptive bone pain due to metastasis in prostate cancer | strontium-89 | 2.03 | 41 | PCDB | NS |
| Lewington, 1991[256] | nociceptive bone pain due to metastasis in prostate cancer | strontium-89 versus strontium (p) | 1 inj. | 32 | PCDB | strontium-89 > p |
| Maxon, 1991[299] | nociceptive bone pain due to metastasis of various primary tumors | rhenium-186(sn)HEDP | 30–35 | 20 | PCDBCO | rhenium-186 > p (= $^{99m}$Tc-MDP) |

[a]Administered p.o. unless indicated otherwise; (N)PC = (non) placebo-controlled; (N)DB = (non) double-blind; NS = not significant; p = placebo.

administration.[28,262,263] Diagnostic local anesthetic blocks are unreliable and do not represent a good prognostic indicator for the effect of neurolytic block. The best indication for neuroablative procedures, e.g. percutaneous cordotomy, is unilateral nociceptive pain in a patient with a limited life expectancy of less than a few months. Unilateral lumbar plexopathy by pelvic malignancy or true unilateral chest wall pain by invasion of a mesothelioma are other indications that enable relief for several months.[262,263] Bilateral nociceptive pains that cannot be managed by simpler means are handled by the more efficacious mesencephalic tractomy, which carries greater risk on morbidity, or the less effective medial thalamotomy.[53] Oral opioids should instantaneously be reduced dramatically when a successful block is performed to avoid respiratory depression.

## Alternative approaches in cancer-related pain treatment

Because the perception of pain has multidimensional aspects, pain treatment should also address cognitive and emotional domains. In this respect cognitive-behavioral training and coping skills appeared less effective than hypnosis training.[18] Both anxiety and depression enhance the pain experience and should therefore be treated.

## Problem areas: poor response of a specific pain syndrome to analgesics

Inadequate pain control may relate to a poor response of both nociceptive or neuropathic pain to analgesics. Both movement-related incident pains and neuropathic pain seem to be the main contributors.[9,10,158]

*In nociceptive pain.* In nociceptive pain, NSAIDs exert their specific analgesic effect by inhibiting the inflammatory response. Nociceptors can also be stimulated by mechanical pressure or stretch without the presence of inflammation. For example, back pain exclusively manifesting on coming to the upright position and disappearing at rest, may be the consequence of instability of the spinal column. This movement-related pain or incident pain on weight bearing responds poorly to pharmalogical approaches.[158] Enhancing spinal stability by an individual tailored corset or by orthopedic surgery often provides a satisfactory solution. Furthermore, in headaches due to increased intracranial pressure in meningeal carcinomatosis, conventional analgesics are usually ineffective. Drainage of cerebrospinal fluid by lumbar punction with or without intrathecal chemotherapy or employment of radiotherapy may yield the only effective pain relief. Finally, nociceptive pain due to pancreatic cancer is classically known to be relatively resistant to opioids and a celiac plexus block may be considered at an early stage.[264,265]

*In deafferentation pain.* Pain syndromes caused by the treatment of cancer are often due to lesions of the nervous system. Oncological surgery may sacrifice a peripheral nerve with anesthesia dolorosa. Radiotherapy can lead to a painful plexus neuritis, and immunotherapy may activate latent viruses, such as the herpes zoster virus with increased risk of post-therpetic neuralgia. These types of deafferentation pain without the presence of an inflammatory response are believed to be not or less responsive to conventional analgesics.[49,52,158,266]

Tricyclic antidepressants (amitriptyline, desipramine, nortriptyline, imipramine),[186–188,190–192] certain anticonvulsants (e.g. carbamazepine)[267,268] and topical approaches like capsaicin cream,[269,270] lidocaine patches or gel,[204,205] and NSAIDs in diethylether solutions[271–273] are the recommended therapies. However, about two-thirds of the patients have at best partial pain relief with these approaches. Neuroablative techniques are ineffective for deafferentation pain and often lead after a latent period to a new pain syndrome in a larger skin area with more difficult management problems.[54] The number of deafferented nerve fibres increases with more extensive nerve injury.

## Anti-tumor therapy for pain treatment in cancer

The assessment process may reveal a cause for the pain that is amenable to primary anti-tumor therapy. Approximately one-fifth of pain consultations in cancer patients lead to new anti-tumor therapy.[24] In a survey of 3500 cancer patients, 1423 patients had pain lasting more than 2 weeks due to malignant invasion. Of these, anti-tumor therapy with radiation, chemotherapy, hormone therapy and/or surgery supplied partial or complete relief in 75%.[36] Anti-tumor therapy has an important role in the treatment of cancer-related pain. The physician should be familiar with the therapeutic options of a specific primary tumor at a specific site.

Surgical treatment of a painful metastasis in an unstable bony structure may restore mobility and ameliorate analgesic-insensitive incident pain. Excellent results can be obtained after surgical decompression of the spinal cord, spinal stabilization, internal fixation of pathological fractures or potential fractures, and joint replacement.[274]

Radiotherapy has a pivotal role in the treatment of painful bone metastases, epidural malignancy and cerebral metastases.[275] Results of lumbosacral plexopathy pain with radiation seem promising and the initial results in painful hepatic capsular distention by metastases from colorectal cancer seem rewarding as well.[276–279] Re-irradiation of a local recurrence is sometimes possible depending on the dose received, the tissue involved and the time-lapse between the last irradiation. The radiopharmaceuticals strontium-89 and rhenium-186 form a relatively new method for the treatment of painful bone metastases, especially in hormone-dependent tumors.[256]

The discussion of chemotherapeutic regimens for the treatment of the primary malignancy is beyond the scope of this article. Interestingly, however, anecdotal data have reported analgesic effects of chemotherapy even in the absence of a tumor response.[280,281]

The goal of anti-tumor therapy in cancer-related pain is directed at local tumor control with concurrent pain relief without necessarily aiming for systemic remission of the malignancy. A favorable analgesic effect does not always parallel an objective response on the tumor.

A crucial problem with the use of anti-tumor therapy in pain control is the burden for the patient. This includes diagnostic investigations necessary for accurate localization of the pain syndrome[24] and the risk of complications of anti-tumor therapy in relation to predicted analgesic effects. The balance between the burden of necessary investigations and side-effects of anti-tumor therapy, on the one hand, and their potential advantages for pain control and quality of life, on the other, should be discussed with the patient. No patient with cancer should be inadequately evaluated because of poorly controlled pain.

## Conclusion

Many of the causes of inadequate pain control in cancer are potentially avoidable. Proper pain assessment includes medical and neurological knowledge on specific pain diagnosis, pain mechanism (nociceptive versus non-nociceptive) and location, and knowledge of the biological behavior of the primary tumor. Adequate pain treatment supposes practical knowledge on symptomatic pain control and options for anti-tumor therapy. Special problems are symptomatic treatment of deafferentation pain. In this respect, preventive measures such as avoiding nerve injury in cancer therapy may exert an important effect.

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