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Opioids in context: relieving the pain of cancer. The role of comprehensive cancer management*

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Optimal pain control requires detailed appraisal of each symptom; in many cases definitive treatment of the underlying cause will be the most effective means of pain control. As an example back pain may be due not only to bone metastases but also enlarging lymph nodes, renal pain or retroperitoneal tumour. Benign causes including degenerative joint disease should also be considered and each cause treated specifically alongside the use of analgesics. *Palliative Medicine* (2008); **22**: 303–309

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Introduction

There are several models of cancer pain which have been proposed, but all support the view that it is a multifactorial problem composed of several components whose relative contribution to the total pain experienced by the patient may vary. There will, however in almost all cases, be an underlying physical pain modified by both affective and spiritual responses and interpretations. Thus a somatic source of pain underpins the problem and addressing this specific component will have a significant impact on pain control.

It is recognized that many factors need to be considered in the management of cancer pain. The fundamental principle of cancer pain control is that before defining a treatment regimen careful assessment of the individual pains experienced by the patient and their specific cause should be undertaken. The presence of multiple underlying somatic pain sources is well recognized as is the presence of pain which may not be directly related to the cancer but rather related to treatment, medical complications of the weakened state including constipation and catheter use. In addition, patients will still suffer non-malignant causes of pain from co-existing chronic conditions.[1]

The fundamental principle of cancer pain management invoking the analgesic ladder remains an essential underpinning of other treatment options. The escalation of analgesic strength to strong opioids of which morphine remains the preferred drug for many patients is an inviolate concept in palliative medicine. There are, however, a number of difficulties with the use of morphine, which may explain its failure to control pain for all patients and persisting reluctance in some quarters to introduce the drug or use it in adequate doses. These may be considered as follows:

1) Morphine is ineffective against non-somatic causes of pain and when identified these will be a clear indication for other interventions either pharmacologically with the use of anxiolytics or anti-depressants or non-pharmacologically with the use of appropriate psychological treatments and spiritual support.
2) Compliance with morphine is often poor,[2] despite the well-established dogma that it works best taken on a regular basis by the clock rather than awaiting the development of pain. Many patients are very anxious about the possibility of intrusive side effects in particular constipation, others may have troublesome nausea and anorexia and many patients starting morphine or during periods of dose titration will have disturbing drowsiness, confusion and perhaps even hallucinations. These events unless managed appropriately will lead the patient and sometimes their physician to abandon morphine despite its potential efficacy with the misapprehension that morphine intolerance has been observed.
3) Incident pain remains a very difficult management problem. Adequate levels of opioid analgesia for incident pain will usually result in intrusive side effects during the pain free periods.[3] In contrast, appropriate doses for the pain free period will fail to control the incident pain.
4) Finally, despite its widespread use and inclusion in national and international guidelines for the management of cancer pain, the evidence base for the role of morphine in this setting and the evidence for specific dosing schedules remains scanty. For example, the commonly recommended approach of opioid dose type titration for severe cancer pain has been subject to a systematic evidence-based review which identified

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only nine studies in this area of which only two were randomized with a median number of patients of only 49.[4] The conclusion was that the data available was too meagre to support any recommendations and that there was a clear need for additional systematic research.

Against the above background, it is clear that the analgesic ladder and the use of regular opioids, none of which has a strong evidence base but is inculcated in standard practice guidelines for cancer pain, is not of itself a panacea in treating this complex phenomenon of cancer pain. An analytical approach to the patient is essential in which somatic pain is identified distinct from the other components of cancer pain and within this individual physical causes of pain are clearly identified. These will then be a target for further treatment harnessing the vast array of both specific cancer treatments and adjuvant pharmacological measures.

Specific cancer therapy

Oncological treatments are becoming more complex and widely available. They range from the use of simple radiotherapy or surgical procedures to complex biological-targeted systemic therapy. Any of these may have a role for an individual patient depending upon the nature of their underlying pain and the specific tumour which is being treated.

- Surgery has a vital role in the management of pathological fracture where pain relief is best achieved by internal fixation rather than ever-escalating doses of opioids. Similarly stenting for dysphagia, gastrojejunostomy for gastric outflow obstruction and defunctioning colostomy for large bowel obstruction can all be simple, but critical procedures in addressing causation of cancer pain.
- Radiotherapy has a well-established role in the management of bone metastases with efficacy against metastatic bone pain and also associated neuropathic pain. It is also useful in the management of headache from brain metastases and other sites of soft tissue infiltration including massive hepatomegaly from metastatic disease.
- Chemotherapy will be indicated for certain tumours particularly those which are highly responsive including myeloma, lymphoma and small cell lung cancer. It has also been shown to result in substantial gains in quality of life including pain in less responsive tumours, such as non-small cell lung cancer, pancreatic cancer and prostate cancer.[5–7] Concerns that chemotherapy may be associated with undue toxicity are often ill-founded and should not be used to dissuade a patient from appropriate treatment where there is a clear evidence base for overall improvement such as those cited above.
- Hormone therapy can have a vital and dramatic effect in cancers, which are hormone sensitive. The most striking is the response of metastatic prostate cancer to anti-androgen therapy where widespread bone pain can resolve within 24–48 h.[8] It is also effective and in widespread use for breast cancer and less commonly endometrial cancer.

Pain-specific therapy for cancer pain

Multifactorial causes of pain

Back pain

An illustration of the various issues that need to be considered in the comprehensive management of cancer pain can be seen in the example of a patient presenting with back pain. Potential causes are shown in Table 1 each of which demands a different management approach.

Bone metastasis

Bone metastases are undoubtedly the most common cause for metastatic back pain in a patient who has a primary tumour particularly one which is recognized as one which commonly spreads to bone. These will be cancer of the breast, prostate, lung, kidney and thyroid.

The preferred management of patients with simple bone pain from metastatic disease remains radiotherapy. Over the last two decades, a vast body of evidence has accumulated culminating in three meta-analyses[9,10,11] all of which confirm that low single doses of radiation in the range 8–10 Gy are as effective as any other radiation dose in this setting and should be considered the treatment of choice. There are, however, still areas of bone pain management which have a less secure evidence base and are still under investigation.

Table 1 Potential causes of back pain in a patient with metastatic malignancy

Malignant
Bone metastases
Para-aortic lymphadenopathy
Renal pain
Primary renal tumour
Obstructive hydronephrosis
Retroperitoneal tumour
Primary soft tissue sarcoma
Metastasis
Non malignant
Osteoarthritis
Prolapsed intervertebral disc
Osteoporotic collapse
Renal colic

- Pathological fracture as mentioned previously is best managed surgically, but the role of radiotherapy post operatively has not been systematically studied. It is common practice to offer radiotherapy and many reviews recommend this particularly in patients who are considered likely to have a prognosis extending beyond 3 months. The rationale is to prevent tumour regrowth in the area of fracture, which can result in further pain and displacement of the fixation device. Doses ranging from single doses to 20 or 30 Gy in 5–10 fractions are used but with no comparative data to support this. Radiotherapy also undoubtedly has a role in pathological fractures which are not amenable to surgical fixation, for example ribs, vertebral bodies and pelvis and scapulae. Irradiation of high-risk lesions, particularly those with >50% cortical erosion or axial cortical erosion >3 cm to prevent fracture if surgery is not feasible is also recommended. Again optimal dose fractionation remains uncertain.[11]
- Spinal canal compression is a relatively common complication of spinal bone metastasis. Primary tumours of the breast, lung and prostate account for most patients. In patients with good performance status, localized disease and a well-controlled primary then initial surgery is the best option to maintain function.[12] Again the role of post operative radiotherapy in this setting remains uncertain but is common practice. Many patients, however, present within the setting of widespread metastatic disease and 30% or so have multiple spinal levels involved. In these patients, primary radiotherapy is the treatment of choice together with moderate dose steroids. Again dose fractionation remains a matter of varied practice with some evidence that single doses are as effective as prolonged fractionated courses, although case series suggest that in selected patients, particularly those with haematological malignancies, more prolonged fractionation may be of value.[1,13,14] This is currently the subject of a randomized trial recently launched in the UK. Another area of debate and investigation is the role of prophylactic irradiation in patients considered at high risk of spinal cord compression. With increased access to magnetic resonance imaging (MRI), screening becomes possible and asymptomatic extradural deposits or bone metastases impinging on the spinal canal can be identified. No prospective study has evaluated the efficacy of prophylactic irradiation in this setting, although data does now suggest that those patients with known bone metastases and persisting spinal pain are at increased risk of subsequent spinal canal compression.[13]
- Neuropathic pain can be associated with spinal metastasis and may be a dominant component of the pain presented by a patient complaining of back pain. There is now good evidence that radiotherapy is effective in neuropathic pain and a recent large-randomized trial has reported that single doses of 8 Gy are not inferior to a more prolonged dose fractionation schedule delivering 30 Gy in 10 fractions.[15]
- Retreatment is a current area of active investigation and interest. Whilst primary treatment with radiotherapy is effective with a probability of response at 1 month around 70%, some patients having a more prolonged survival will experience recurrent pain. It does appear from the meta-analyses that this is more common in patients who receive a single dose compared with fractionated treatment and is the one argument raised to justify a prolonged fractionation schedule in patients with a longer prognosis. An alternative approach is to give a single dose and then anticipate retreatment, which is given in 25% of patients in previous randomized trials. This may not be an accurate reflection of retreatment need because in those studies there were no criteria for introducing retreatment and this was, therefore, a reflection of individual practice. A large international intergroup study is currently investigating the role of retreatment and optimal fractionation.[16] Historical data suggests that response rates to retreatment are similar to those for primary treatment and this is not predicted by prior response.[17]
- Wide-field irradiation is, perhaps, less commonly used than is appropriate. It has been shown in case series to be highly effective in achieving pain control for patients with scattered sites of bone metastasis. Optimal dose fractionation has been evaluated in one randomized controlled trial which suggested that 4 Gy given twice daily to the lower hemibody was equivalent to more prolonged fractionation.[18] Common practice, however, is to deliver single doses of 8 Gy to the lower half body and 6 Gy to the upper half body, reducing the dose where lung tolerance becomes the critical organ at risk, and again similar response rates are identified. Currently dose fractionation and retreatment in wide-field radiotherapy is being investigated further in an international trial coordinated through the International Atomic Energy Agency.
- Radioisotopes are increasingly used to treat scattered bone pain particularly from carcinoma of the prostate where most of the published data in randomized trials has been derived. It is undoubtedly highly effective with low toxicity rates. The common agents are strontium, rhenium or samarium. Recent interest is focusing on radium 223, which is a pure alpha emitter providing very short range high energy deposition potentially reducing the likelihood of bone marrow toxicity, which is the main dose limiting action when beta emitting isotopes are used. This agent then has the potential to deliver fractionated doses with the

possibility of not only symptom control but also longer term tumour control.[19]

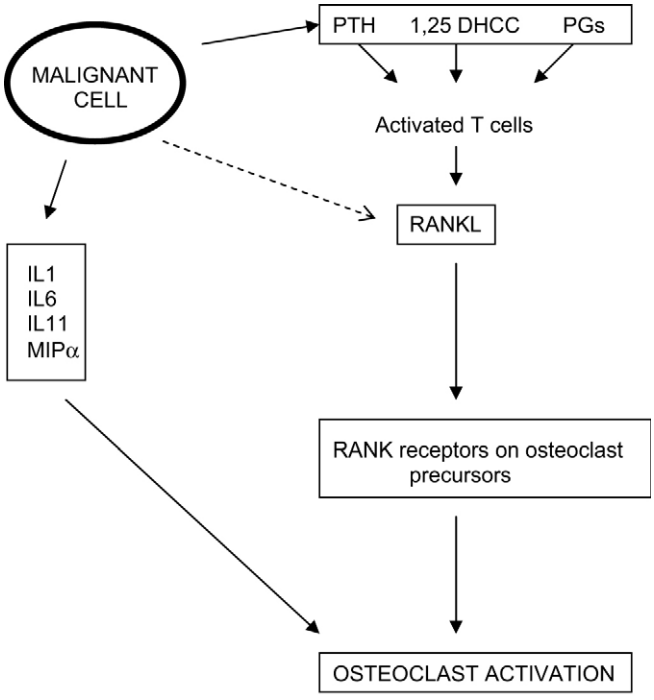
- Vertebroplasty is increasingly recognized as a safe and effective treatment in the face of vertebral collapse involving a far-less invasive procedure than open spinal surgery with computer tomography (CT) guided techniques to expand the vertebra and consolidate with cement. It should be considered where there is significant collapse of the vertebral body, whether from malignant or benign causes, such as osteoporosis.[20]
- MR-guided focused ultrasound is a new approach to the management of bone metastases; high frequency ultrasound is focussed at the site of bone metastasis under MR control. Because the penetration of such non-ionizing radiation is limited most of the effect is thought due to periosteal damage disrupting the afferent nerves. Adjacent soft tissue may also absorb some of the ultrasound energy and, therefore, it is currently not recommended for use in vertebral lesions for fear of spinal cord damage. At present, this remains an experimental technique but early data suggests a high level of efficacy even in bones previously irradiated.[21]

Pharmacological treatment of metastatic bone pain

There has been a considerable increase in the understanding of the pathophysiology of metastatic bone pain. A simplified diagram of the recognized cascade leading to osteoclast activation by tumour cells is shown in Figure 1.

Osteoclast activation is clearly a pivotal event in bone metastasis development and there is some evidence that osteoclasts are also important in evoking the pain stimulus. Inhibition of osteoclasts by bisphosphonates is undoubtedly effective in reducing morbidity from bone metastasis in those patents at high risk and also to a lesser extent reducing bone pain. Their relative role to radiotherapy is under investigation in a randomized trial within the UK and a role in combination with radiotherapy may prove to be the optimal use of the two agents.[22]

- Denosumab is a new monoclonal antibody developed for the control of bone metastasis and treatment of bone pain. This also results in osteoclast inhibition, but does so by targeting RANK. Early data suggests that it is well tolerated and effective,[23] and clearly its role relative to bisphosphonates will be an important area of research in the near future.



Il: Interleukin
MIPα: macrophage inhibitory protein alpha
RANK: receptor activator of nuclear factor κB
RANKL: receptor activator of nuclear factor κB ligand

Figure 1 Mechanism for bone destruction in metastatic disease.

- Pregabalin may have an important role in metastatic bone pain[24] and again its combination with radiotherapy may prove to be the optimal use of this agent.
- Chemotherapy has an important role in the control of metastatic disease for many types of malignant disease. There is limited published data on its efficacy specifically for metastatic bone pain, however, the results from detailed quality of life assessments are available which imply a significant impact on pain control is achieved with chemotherapy in many settings. Chemosensitive tumours which commonly cause metastatic bone pain include multiple myeloma for which a combination of melphalan, prednisolone and thalidomide is now first-line treatment for older patients[25] and high-dose steroid-based schedules leading to autologous stem cell procedures to enable high-dose chemotherapy are standard for younger patients.[26] Breast cancer is now treated with a wide range of chemotherapy drugs including not only the traditional schedules, such as cyclophosphamide, methotrexate and 5FU (CMF) or 5FU, epirubicin, cyclophosphamide (FEC) but also the taxanes, capecitabine and carboplatin. Chemotherapy is a recognized treatment for advanced inoperable non-small cell lung cancer using combinations of a platinum drug with gemcitabine, vinorelbine or paclitaxel[5] and small cell lung cancer is similarly highly sensitive to combination schedules of which etoposide and cisplatin is now the standard first line.[27] Prostate cancer which was long considered a relatively chemoresistant tumour has now been shown to benefit from treatment with docetaxel in terms of quality of life as well as a modest prolongation in survival.[7] Substantial improvements in the management of metastatic renal cell carcinoma have been achieved with the use of drugs, such as sorafenib and sunitinib, which have wide-ranging activity against tyrosine kinase resulting in anti-angiogenic and anti-proliferative actions.[28,29]

Hormone therapy

For breast and prostate cancer, this remains a widely used highly effective management option having limited toxicity with high response rates. First-line therapy for metastatic carcinoma of the prostate remains anti-androgen treatment with over 90% of patients having hormone responsive disease resulting in a dramatic improvement in symptom control.[30] Whilst many breast cancer patients will have adjuvant hormone therapy, second- and third-line treatments with the ever more potent and effective aromatase inhibitors, such as exemestane and anastrazole, provide further opportunities for symptom control in patients having previous adjuvant tamoxifen.[31] There are, however, few other examples of effective hormone treatment because most other tumours are not sensitive. Progestrogens or anti-oestrogens, such as goserelin, have a 30–40% response rate in metastatic endometrial carcinoma in which bone metastases can feature. Previous reports that renal cancer was sensitive to progestrogens are now largely discredited and this is no longer standard practice. Anecdotal reports of responses to tamoxifen with ovary cancer and melanoma are not sufficient to justify their routine adoption in these primary tumours.

Para-aortic lymphadenopathy

Back pain caused by enlarging para-aortic lymph nodes pushing on paraspinal structures is a well-recognized presentation of both lymphoma and testicular tumours. With advanced metastatic disease a similar mechanism may also ensue. Appropriate management of such patients will, therefore, demand an accurate diagnosis, which will be based on cross-sectional imaging with either CT or MRI. In addition to lymphoma and testicular tumours, other primary tumours within the abdomen and pelvis may also result in para-aortic lymphadenopathy. The management of each individual tumour must be considered in the context of their chemosensitivity and radiosensitivity alongside the wider picture of the disease. Thus a patient with lymphoma which is involving multiple sites will undoubtedly require chemotherapy, whilst if there is localized para-aortic lymphadenopathy after previous chemotherapy then local radiotherapy may be more appropriate. Similarly, lymphadenopathy from testicular tumours presenting in the context of widespread germ cell neoplasia will be best treated with chemotherapy, such as bleomycin etoposide prednisolone, whilst localized lymphadenopathy after chemotherapy will be managed by retroperitoneal lymph node dissection or if inoperable local radiotherapy.

Other tumours which may present with metastatic para-aortic lymphadenopathy causing back pain include bowel, pancreas, cervix and ovary. These may be amenable to chemotherapy or local radiotherapy to achieve tumour shrinkage and pain relief . This is summarized in Table 2.

Renal pain

A further site of origin for back pain can be the kidney.

- Renal tumours may also present with back pain. This may be the only presentation or associated with haematuria and other systemic symptoms. Again cross-sectional imaging is essential to define the primary tumour. Where operable nephrectomy will be the treatment of choice and may even be considered as a palliative measure for pain relief or persistent haematuria. Radiotherapy to the kidney has a limited role in palliation and as mentioned above newer chemotherapy drugs, such as sorafenib and sunitinib, are of increasing value.

Table 2 Indications for chemotherapy in metastatic para-aortic lymphadenopathy

Highly sensitive (>70% response rate*)
Lymphoma
NonHodgkins
Hodgkins
Testicular germ cell tumour
Seminoma
Teratoma
Moderately sensitive (50–60% response rate)
First line
Breast cancer
Small cell lung cancer
Bladder cancer
Ovary cancer
Second line
Breast cancer
Small cell lung cancer
Ovary cancer
Poorly sensitive (30–40% response rate)
First line
Cervical cancer
Endometrial cancer
Prostate cancer
Renal cancer
Soft tissue sarcoma
Non-small cell lung cancer
Second line
Non-small cell lung cancer
Bladder cancer

*Response defined by objective tumour shrinkage criteria of >50% reduction in maximum diameter for at least 1 month.

- Hydronephrosis occurs typically in the setting of locally advanced pelvic tumours in particular carcinoma of the cervix, bladder or prostate. The patient may present with back pain and varying degrees of renal failure evidenced by a rising serum creatinine and urea. In this setting, decompression of the kidneys is essential if active management is considered and this can be readily achieved by percutaneous nephrostomy performed under ultrasound or CT guidance followed by the insertion of ureteric stents. It is also important to consider the possibility of urethral obstruction typically due to a locally advanced prostate cancer or even benign prostatic hypertrophy and in women a vulvovaginal tumour. In such cases, urethral catheterization or suprapubic catheterization will decompress the kidneys resulting in pain relief and enabling the further treatment of the underlying malignancy if appropriate.
- Renal stones may occur in patients with advanced malignancy and should not be ignored as a potential diagnosis.

Retroperitoneal tumours

In addition to para-aortic lymphadenopathy primary retroperitoneal tumours may arise, typically soft tissue sarcomas. Longstanding backache is often a prominent feature of the history and once again cross-sectional imaging will identify the soft tissue tumour. The management of soft tissue sarcomas in this setting is often difficult because radical resection may not be feasible and the surrounding critical normal tissues including bowel and kidneys limit the total radiation dose that can be delivered. For this reason, chronic back pain in these patients may become a problem in the advanced stages as the primary progresses despite active management.

Benign conditions

Back pain is a common symptom in the general population and as with any other symptom in advanced malignancy benign causes should always be considered. In this setting, it will be particularly degenerative spinal disease and prolapsed intervertebral discs which may mimic metastatic spinal pain. Again where there is doubt and concern cross-sectional imaging, MR being superior in this setting, complemented by an isotope bone scan should elucidate the underlying problem.

Comprehensive pain management

The above illustrations demonstrate that pain presenting in a patient with advanced malignancy may have a vast range of causes not all of which will be best managed simply by the use of analgesics or even the combination of analgesics with co-analgesics. These will of course underpin other treatments and should not be ignored or left out but an accurate diagnosis for which cross-sectional imaging with CT or MRI is often sufficient should always be sought. Appropriate intervention can then be introduced and in this way close interaction between palliative medicine and oncology embracing the multidisciplinary approach to symptom diagnosis and pain control will optimize the outcome for the patient.

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