Conclusion

Important factors in managing sporting injury

Prevention (general fitness, training regimen, equipment use)

Management

- History to establish cause(s) of injury and thus make correct diagnosis and prevent recurrence
- Examination (of athlete and equipment)
- Investigation
- Diagnosis—for correct treatment
- Treatment appropriate to injury (rest, drugs, physiotherapy, surgery)
- Maintenance of general fitness (of uninjured parts)
- Correction of poor training programmes
- Rehabilitation—gradual, structured regimen
- Emphasis of importance of wam up before, stretch after, exercise
- Prevention of too early return to sport—to avoid recurrence or second injury

Management of a sporting injury requires an assessment of why the injury occurred, treating the injury itself while maintaining fitness, and a gradual structured rehabilitation programme through to competition. Breakdown can occur at any stage along the path of return to sport. Doctors should liaise with the athlete's coach to alter bad training regimens and check the sporting history for other factors contributing to the risk of injury.

Athletes are enthusiastic and rewarding patients to treat. The British Association of Sport and Medicine runs an educational programme covering all aspects of sports medicine. Anyone interested should contact the author.

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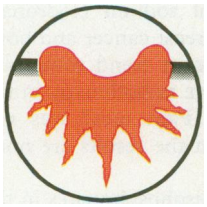
Current Issues in Cancer

Palliative care

Carol L Davis, Janet R Hardy



This is the 10th and concluding article in the series examining developments in cancer and updating what we know about the disease

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Though many of the treatment strategies used in palliative care have never been subjected to clinical trial, it has been argued that advances in palliative care have outstripped those in many other specialties. This article is not a comprehensive review of therapeutic options, nor even of recent advances in this topic, but concentrates on the latest developments and controversies in the pharmacological treatment of four frequent and important symptoms: neuropathic pain, anorexia and cachexia, intestinal obstruction, and breathlessness. It is difficult to perform blinded, randomised trials in patients with advanced disease and poor performance status, yet it is these patients who may gain most from the adoption of new well evaluated treatment strategies.

> *"Palliative treatment is no longer regarded as a negative lack-of-treatment, or as a ragbag of therapies which are vaguely thought of as supportive."*[1]

Palliative care has been defined in many ways, but perhaps the most apposite is that recently adopted by the World Health Organisation—"the active, total care of a person whose condition is not responsive to curative treatment."[2] This definition highlights the fact that such care should not be restricted to patients with malignant disease and that terminal care is but one aspect of palliative care, if a very important one. The concept of palliative care embraces optimal symptom control and quality of life as well as appropriate rehabilitation.[3] The patient is regarded as part of a unit which also includes his or her family, friends, and carers.

Issues in pain management

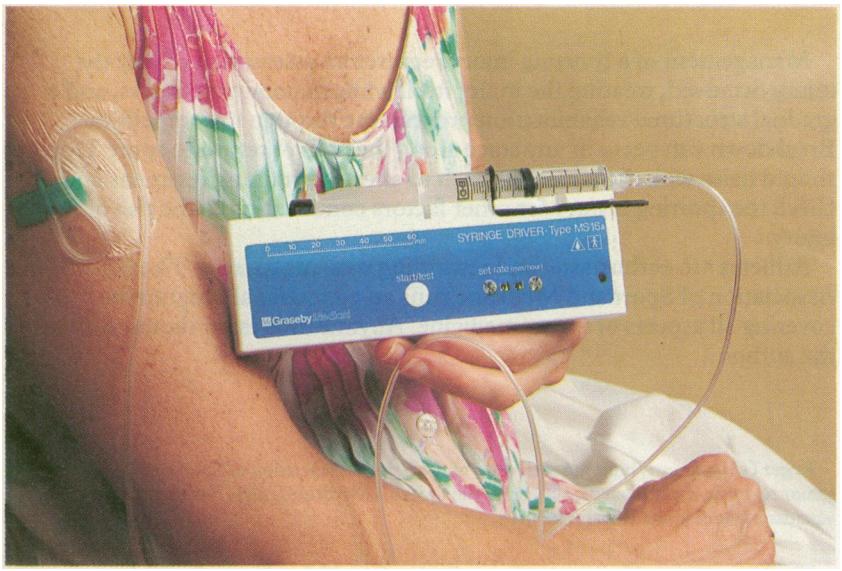
Pain is one of the most common and probably most feared symptoms of advanced cancer. A recent highly publicised court case centred on the symptomatic management of a patient with severe rheumatoid arthritis[4] served to illustrate that pain is not always responsive to conventional analgesics.

The semantics of pain are complicated and to some extent controversial. Total pain, as first described by Cicely Saunders, is recognised as pain comprising physical, psychological, emotional, and spiritual elements and underlines the importance of a multidisciplinary approach to its control. Paradoxical pain is described as pain that gets worse not better with increasing doses of opioids,[5,6] but there is controversy over the precise definition and, indeed, over whether this phenomenon actually exists.[7-11] Neuropathic pain is nearly always secondary to nerve damage, whether due to compression, infiltration, or destruction, whereas nociceptive pain is caused by ongoing activation of primary afferent neurones in response to noxious stimuli and can arise from either somatic or visceral lesions.

A full discussion of recent advances in pain control is beyond the scope of this article, but some current issues are reviewed.

Morphine-6-glucuronide

Recent advances in our understanding of morphine metabolism have led to the recognition of the importance of the active morphine metabolite morphine-6-glucuronide.[12,13] This substance has been isolated and synthesised.[14] Preliminary single dose studies have shown morphine-6-glucuronide to be less toxic than equipotent doses of morphine.[15,16] These findings are exciting but must be considered in the light of the fact that morphine, when properly employed, is an excellent strong analgesic which does not usually cause major, unmanageable toxicity. Until the results of



The subcutaneous route is still underutilised. Many drugs may be given in this way, including corticosteroids and non-steroidal inflammatory agents

current studies are available the use of this compound must remain experimental.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs have an established role in the control of pain associated with bone metastases and inflammatory tumours. Recently there has been a vogue for giving these agents by subcutaneous infusion. This may be of advantage in some cases but requires more evaluation, particularly in comparison with the rectal route.

Ketorolac is a new non-steroidal anti-inflammatory drug which appears to have a higher analgesic to anti-inflammatory ratio than other drugs in this class. Several studies have shown an opioid sparing effect in cases of postoperative pain[17 18] and there are anecdotal reports of its successful use in cancer related pain,[19] including some cases of neuropathic pain. The side effect profile seems similar to that of other non-steroidal anti-inflammatory drugs. Claims of its superior analgesic activity require substantiation.

Neuropathic pain

Confusion abounds regarding the correct terminology of pain resulting from damage to nerves and nerve endings, and Portenoy has produced an excellent review of the topic.[20] The most common cause of neuropathic pain in patients with cancer is progressive disease. It can also be caused by all modalities of anticancer treatment and by factors not directly related to either the disease or its treatment.

Several pharmacological and non-pharmacological treatment options exist for neuropathic pain. Traditionally the pain has been regarded as opioid insensitive but this view has been challenged and some workers believe that an element of the pain may be opioid responsive, though very high doses of opioids may be required. Even if the pain is partially responsive to morphine, treatment with at least one coanalgesic is nearly always required. The most commonly used drugs are listed in box 1.

Tricyclic antidepressants may be particularly useful in dysaesthetic pain—that is, pain associated with an area of abnormal sensation—while anticonvulsants, especially valproic acid and carbamazepine, are often effective in lancinating or stabbing pain. Early assessment of the therapeutic role of flecainide was encouraging,[21] but the randomised trial was curtailed when the drug was linked with fatal arrhythmias in patients with pre-existing myocardial ischaemia.[22 23] There is, however, little doubt that flecainide can be efficacious in refractory neuropathic pain. It is usually used as a second or third line agent in selected patients with advanced cancer and neither a history of, nor suspected, ischaemic heart disease.

Recent laboratory advances hold the key to the development of new therapeutic strategies.[24] In particular, both *N*-methyl-D-aspartate and cholecystokinin antagonists hold promise. Preliminary experience with ketamine, an *N*-methyl-D-aspartate receptor antagonist, is encouraging, but the optimal dose, schedule, and route of administration have yet to be established.

The non-drug treatment of neuropathic pain includes the use of both nerve stimulating and nerve blocking techniques as well as a range of psychological interventions, including relaxation therapy and the teaching of cognitive coping strategies.[25]

Despite this plethora of treatment options, neuropathic pain remains difficult to treat and its management requires an individualised approach. Neuropathic pain is not usually hard to diagnose but the lack of clinical trials and, in general, ignorance of the therapeutic possibilities conspire against optimal treatment.

Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption. Their exact mechanism of action is unclear but may include direct biochemical effects on the osteoclast, prevention of osteoclastic attachment to the bone matrix, and inhibition of osteoclastic differentiation and recruitment.[26] To date, the main clinical use of bisphosphonates has been in the treatment of hypercalcaemia of malignancy. Recently, however, treatment with bisphosphonates has been shown to bring about both subjective and objective improvement in painful metastatic bone disease.[27-29] In one large randomised study of oral sodium clodronate versus placebo in women with breast cancer and bony metastatic disease a non-significant trend towards a reduced requirement for palliative radiotherapy in the treatment arm was reported.[30] Pain relief was not measured as a specific entity but the results are none the less encouraging.

The therapeutic potential of bisphosphonates in the mangement of bone pain requires further investigation. Future studies must determine the clinical characteristics of the patients most likely to benefit as well as the correct formulation and dose of these agents when

Box 1—Pharmacological treatment options for neuropathic pain

Tricyclic antidepressants

Putative mode of action—Effect on monoamine mediated, pain modulating pathways

Examples—Amitriptyline, dothiepin

Anticonvulsants

Putative mode of action—Stabilisation of neuronal membrane

Examples—Valproic acid, carbamazepine, phenytoin, clonazepam

Antiarrhythmics

Putative mode of action—Stabilisation of neuronal membrane

Examples—Flecainide, mexiletine, tocainide

Steroids

Putative mode of action—Reduction of perineuronal oedema

Example—Dexamethasone

used for this indication. Absorption from the gastrointestinal tract is poor, and dietary restrictions are necessary to avoid precipitation in the gut. Hence many clinicians prefer to give bisphosphonates by intravenous infusion rather than by mouth. The frequent hospital or hospice attendances that this necessitates may be inconvenient and difficult, and most patients therefore prefer oral treatment. Issues of patient preference and compliance should be of paramount importance in the design of such studies.

Anorexia and cachexia

The anorexia-cachexia syndrome of advanced malignancy contributes substantially to the morbidity and mortality from the disease. It is recognised as a chronic abnormal metabolic state characterised by specific abnormalities of fat, protein, and carbohydrate metabolism. Tumour necrosis factor, or cachectin, was thought to be the primary causative factor, but now multiple cytokines are thought to be implicated. A complex cytokine cascade, triggered in the host by the tumour, is believed to result in the progressive weight loss, weakness, and relative hypophagia that characterise this condition.[31]

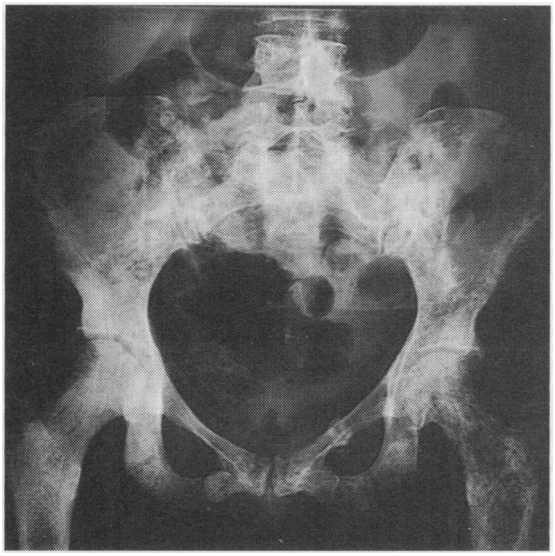
A multiplicity of drugs has been employed in the treatment of anorexia and cachexia (box 2), and some have been evaluated in clinical trials. Corticosteroids

Box 2—Drugs investigated for their therapeutic potential in anorexia and cachexia

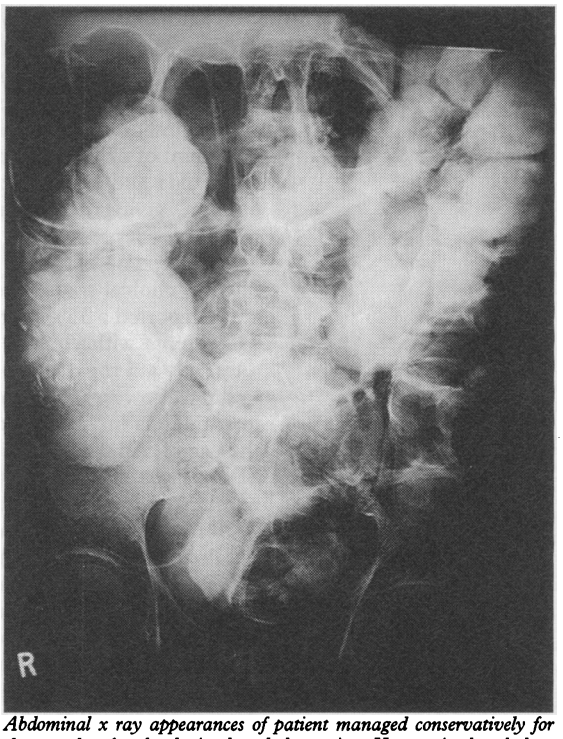
Corticosteroids	Metoclopramide
Anabolic steroids	Cannabinoids
Progestogens	Cytoproterone
$5HT_3$ antagonists	Insulin

are commonly used and have been shown to improve both quality of life and appetite. Improved appetite with corticosteroids, however, is rarely translated into non-fluid weight gain.[32] Improvement in both appetite and weight has been recorded in randomised trials of progestogens,[33] and these changes seem to be dose related, independent of tumour response, and not secondary to fluid accumulation. There is debate over the most appropriate dosage regimen and the mechanism of action remains unknown.

These results are encouraging but patients with advanced cachexia, poor performance status, and very limited prognosis are unlikely to have been recruited into the trtials. Hence an unrealistically optimistic view of the potential benefits of these therapeutic interventions may have been presented to date.



Pelvic x ray picture showing multiple bone metastases from carcinoma of breast. Maximal radiotherapy had already been given, and severe bone pain was managed successfully with opioids and intravenous bisphosphonates



Abdominal x ray appearances of patient managed conservatively for three weeks after developing bowel obstruction. He remained ambulant and went home for part of that time

Intestinal obstruction

Intestinal obstruction is a fairly common complication of advanced malignancy, particularly ovarian carcinoma. Treatment traditionally includes fasting, nasogastric suction, intravenous fluids, and consideration of surgery, but these interventions may not be appropriate in all patients. Various drugs including anticholinergics, antiemetics, and analgesics have an established place in the medical management of inoperable intestinal obstruction and an increasing range of alternative pharmacological and non-pharmacological strategies is available.

Perineoplastic inflammation of the bowel wall may partly be responsible for the mechanical component of intestinal obstruction, and there is considerable anecdotal evidence to support the use of high dose steroids in the short term management of small bowel and large bowel obstruction. There is no consensus on the duration of treatment that makes up an adequate therapeutic trial. The risk of toxicity and the possibility that such treatment might compromise subsequent surgery are cause for concern. These issues are currently being assessed in a multicentre trial.

Octreotide, an analogue of somatostatin, stimulates water and electrolyte absorption and inhibits water secretion in the small bowel.[34] This agent may be given either by subcutaneous bolus injection or, preferably, by subcutaneous infusion. Early reports support its use as an adjunct in bowel obstruction[35,36] and enterocolic fistulas.[37]

Gastrostomies, whether placed percutaneously via an endoscope or under ultrasound guidance, are usually employed for feeding but also have a role in the management of bowel obstruction.[38] The place of such venting gastrostomies is not yet established but there seems little doubt that in selected patients the procedure can adequately palliate symptoms and improve quality of life.

Breathlessness

Once disease oriented strategies are exhausted, and preferably alongside these measures, a range of symptom oriented measures can be employed in the treatment of breathlessness. The pharmacological treatment of this symptom centres on the judicious use of opioids and benzodiazepines. Contrary to popular opinion, giving morphine does not invariably cause respiratory depression.[39 40]

Nebulised opioids have been used for breathlessness but few clinical trials have been conducted. An initial study reported a 35% increase in exercise endurance in 11 patients with chronic non-malignant lung disease after only a 5 mg dose of nebulised morphine.[41] These findings, however, were not substantiated.[42] Nevertheless, there is increasing anecdotal evidence to support the use of nebulised opioids, particularly in breathlessness related to cancer.[43] Opioids are not licensed for administration by this route nor for this indication. Both morphine and diamorphine have been employed but their relative efficacy has not been established.

Nebulised morphine has been most widely used but clinical studies so far are sparse and there is no information on which breathless patients are most likely to benefit, nor on the optimum dose. Pharmacokinetic studies confirm that only a fraction of the total dose is absorbed; the bioavailability of a 10 mg dose relative to the intravenous route is less than 5%.[44] Toxicity seems rare, though bronchospasm secondary to histamine release, triggered by either the preservative or the drug itself, is at least theoretically possible. The low bioavailability of morphine delivered by this route precludes its use for analgesia.

Inhaled opioids might relieve breathlessness either by central effects on respiration and perception or through local mechanisms. The very low bioavailability of nebulised morphine favours a local effect in the lung, which could be modulated by pulmonary receptors.[45] If administration of opioids by this route is proved to relieve breathlessness, then more light may be shed on the interaction between pharmacological agents and mechanisms of ventilatory control.

Conclusion

Palliative care is increasingly recognised as an essential component of a cancer patient's care both throughout the course of the disease and regardless of whether that patient's disease is potentially curable. Moreover, clinical application of the principles of palliative care need not and should not be limited to patients suffering from malignant disease. Optimal symptom control and care of the whole person are an integral parts of the comprehensive care of any patient and deserve to be considered as such.

Recent therapeutic advances in palliative care, a few of which are described above, are exciting and some are controversial. They hold the potential to improve the quality of life of countless patients. To fulfil this role they require rigorous evaluation in properly conducted clinical trials.

We acknowledge Professor G Hank's helpful advice during the preparation of this paper.

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