

# *Bailey & Love's* SHORT PRACTICE of SURGERY

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tumours have the V600E *BRAF* mutation; cetuximab is only effective in patients with colorectal cancer who have wild-type (non-mutated) *ras*; imatinib is particularly effective in patients with gastrointestinal stromal tumours who have mutations in exon 11 of the *Kit* gene – patients with mutations in exon 9 may still respond to imatinib but will require higher doses and patients without mutations in *Kit* are far less likely to respond to imatinib.

Treatment choice therefore requires a molecular analysis of the patient's tumour. It is this determination of treatment at the individual level that has led to the concept of 'personalised medicine'. Although major advances have been made, important targets such as *ras* remain elusive at present, although several *ras*-targeted molecules are in development.

### Immunotherapy

Treatments to activate the immune system against cancer have a long history, stimulated by the observation that up to half of the volume of certain tumours was known to be made up of immune cells, which appeared to be inactive or dead. There is now an appreciation that multiple malignancies activate mechanisms whose normal purpose is to down-regulate the immune system after elimination of an infectious organism. These mechanisms are called T-cell checkpoints. Inhibition of these checkpoints can reactivate the immune cells and has had remarkable success in previously virtually untreatable diseases such as metastatic melanoma. This novel form of treatment is generally much better tolerated than cytotoxic chemotherapy but may result in side effects owing to the uncontrolled activation of the immune system. Side effects such as pneumonitis, colitis, adrenal failure and hypophysitis (pituitary inflammation) may be life-changing or life-threatening and are more common when using a combination of checkpoint inhibitors.

Immunotherapy is a very active field of research and it is likely that vaccines and engineered immune cells will increasingly enter treatment protocols in the coming years.

### Principles of combined treatment

Non-surgical treatments are often used in combination. For example, radiotherapy and chemotherapy are often given together as an alternative to surgery, e.g. in the treatment of rectal, cervical, head and neck or brain cancers (Table 12.5). The rationale behind combination, as opposed to single-modality therapy, is straightforward and is somewhat analogous to that used for combined antibiotic therapy: it is a strategy designed to combat resistance. By the time of diagnosis many tumours will contain cancer cells that, through spontaneous mutation, have acquired resistance to individual modalities of treatment. Unlike antibiotic resistance, there is no need for previous exposure to the treatment. Spontaneous mutation rates are high enough to allow chance to permit the occurrence, and subsequent expansion, of clones of cells resistant to a treatment to which they have never been exposed. If only single-modality treatments were used, then the further expansion of these *de novo* resistant subclones would limit cure. The problem can be mitigated by, from the outset of treatment, combining treatment modalities.

There are three main principles upon which the choice of drugs for combination therapy is based: (i) use drugs active against the diseases in question; (ii) use drugs with distinct modes of action; (iii) use drugs with non-overlapping toxicities. By using drugs with different biological effects, for example by combining an antimetabolite with an agent that actively damages DNA, it may be possible to obtain a truly synergistic effect, i.e. where the effects of the two modalities together are superior to the additive effects of both separately. It is inadvisable to combine drugs with similar adverse effects: combining two highly myelosuppressive drugs may produce an unacceptably high risk of neutropenic sepsis. Where possible, combinations should be based upon a consideration of the toxicity profiles of the drugs concerned.

In considering the combination of radiotherapy and chemotherapy, radiation could be considered as just another drug. There is, in addition to synergy and toxicity, another factor to consider in the combination of drugs and radiation – the concept of spatial cooperation. Chemotherapy is a systemic treatment, radiotherapy is not. Radiotherapy is, however, able to reach sites, such as the central nervous system and testis, that drugs may not reach effectively. This is why, for example in patients treated primarily with chemotherapy for leukaemias, lymphomas and small cell lung cancer, prophylactic cranial irradiation may be part of the treatment protocol.

#### Summary box 12.4

##### Principles of combined treatment

- Use effective agents
- Use agents with different modes of action (synergy)
- Use agents with non-overlapping toxicities
- Consider spatial cooperation

### Oncological emergencies

There are a limited number of true emergencies in oncology. Those that require immediate recognition and management are:

- **Cord compression:** rapid diagnosis and management to relieve pressure on the spinal cord is essential to obtain the best results for patients. Ideally, treatment should be instituted when cord compression is threatened rather than when it has already occurred. Management is likely to include steroids and either neurosurgery or radiotherapy.
- **Neutropenic sepsis:** rapid diagnosis and antibiotic therapy are essential. There is a strong inverse relationship between the time taken to start antibiotics and the chance of patient survival.
- **Immune side effects** including hypophysitis, adrenal failure and insulin-dependent diabetes.

In contrast, there are many urgent oncological situations that are very unpleasant for the patient or that can rapidly deteriorate if not recognised quickly. These include thrombosis, effusion, superior vena cava obstruction and pain, among many others.

## Life after cancer

As early diagnosis becomes more common and treatment outcomes improve, so an increasing number of people are cured of cancer. However, the impact of a cancer diagnosis and its treatment is profound. Organisations such as UK-based Macmillan Cancer Support can provide information and support to patients facing the health, work and financial sequelae of cancer.

## Symptom control and palliative care

The distinction between palliative and curative treatment is not always clear-cut and will become increasingly blurred as professional and public attitudes towards the management of cancer change. Twenty years ago cancer was perceived as a disease that was either cured or it was not; patients either lived or died. There was little appreciation that, for many patients, cancer might be a chronic disease. Nowadays, it is appreciated that many patients will have multiple different treatment options during their cancer journey. Five-year survival is not necessarily tantamount to cure. With the development of targeted therapies that regulate, rather than eradicate, cancer this state of affairs is likely to continue. The aim of treatment will be growth control rather than the extirpation of every last cancer cell. Patients will live with their cancers, perhaps for years. They will die with cancer, but not necessarily of cancer.

Patients fear the symptoms, distress and disruption associated with cancer almost as much as they fear the disease itself. Palliative treatment has as its goal the relief of symptoms. Sometimes this will involve treating the underlying problem, as with palliative radiotherapy for bone metastases; sometimes it will not. Sometimes it may be inappropriate to treat the cancer itself, but that does not imply that there is nothing more to be done – it simply means that there may be better ways to assuage the distress and discomfort caused by the tumour. Palliative medicine in the twenty-first century is about far more than optimal control of pain: its scope is wide and its impact immense (Table 12.7). The most important factor in the successful palliative management of a patient with cancer is early referral. Transition between curative and palliative modes of management should be seamless.

Common problems that may be effectively palliated include:

- **Cerebral metastases:** stereotactic radiosurgery for small lesions is highly effective, although limited to patients who are likely to survive long enough to benefit.
- **Effusions:** pleural and ascitic drains may control these chronic problems. In the case of pleural effusion pleurodesis may prevent reaccumulation.
- **Thrombosis:** increased coagulability and pressure on blood vessels make this a common problem in oncology.
- **Hypercalcaemia:** bisphosphonates may control the patient's calcium level and regular infusions will be necessary when the underlying tumour process is not controlled by other means.

**TABLE 12.7** An outline of the domains and interventions included within palliative and supportive care.

Holistic needs assessment	Pain, anorexia, fatigue, dyspnoea, etc.		
	Treatment-related toxicity		
Symptom relief	Drugs		
	Surgery		
	Radiotherapy		
	Complementary therapies:	Acupuncture	
		Homeopathy	
Aromatherapy, etc.			
Psychosocial interventions	Psychological support Relaxation techniques Cognitive behavioural therapy Counselling Group therapy Music therapy Emotional support		
Physical and practical support	Physiotherapy Occupational therapy Speech therapy		
Information and knowledge	Macmillan		
	Maggie's centres		
Nutritional support	Dietary advice		
	Nutritional supplements		
Social support	Patients		
	Relatives and carers		
Financial support	Ensure uptake of entitlements		
	Grants from charities, e.g. Macmillan		
Spiritual support			

- **Fatigue:** this is often a difficult symptom, which is partly due to the tumour and partly due to its treatment. Encouraging aerobic exercise, even at a low level, can improve fatigue and also stimulate appetite.
- **Weight loss:** patients often lose their appetite and consequently lose weight. Eating little and often with food supplements as necessary may be effective in mitigating weight loss.
- **Fever:** recurrent fevers are a feature of certain tumours such as lymphoma and renal cell cancer. Tumour fever must be distinguished from infection and this can often only be done by exclusion.
- **Paraneoplastic syndromes:** these are varied and often difficult to recognise. Management of the underlying malignancy may not necessarily resolve the syndrome.

## End-of-life care

End-of-life care is distinct from palliative care. Patients treated palliatively may survive for many years; end-of-life care concerns the last few months of a patient's life. Many issues, such as symptom control, are common to both palliative care



selective root blocks in the epidural space are used for the pain of nerve root irritation associated with or without minor disc prolapse, followed by active physiotherapy and rehabilitation to promote mobility.

Nerve stimulation procedures such as **acupuncture** and transcutaneous nerve stimulation increase endorphin production in the central nervous system. Nerve decompression craniotomy rather than percutaneous coagulation of the ganglion is now performed for trigeminal neuralgia.

Spinal cord stimulation (SCS) by dorsal column stimulation is now a recognised and effective management of intractable neuropathic pain (**Figure 23.9**). This involves placement of electrodes in the posterior epidural space to allow dorsal column stimulation through an implantable pulse generator inserted in the body. In the UK this has been recommended by National Institute for Health and Care Excellence (NICE) guidance for intractable neuropathic pain management. Robust evidence exists for its clinical and health economic benefit in failed back surgery syndrome, in which patients have undergone previous spinal surgery. Early use of SCS in surgery-naïve patients might lead to better outcomes. National guidelines in the UK do not recommend disc replacements or spinal fusions in patients with lower back pain unless the latter are part of a trial, rendering a large part of the patient population ineligible for surgery. In these instances, SCS could prove to be an effective solution.

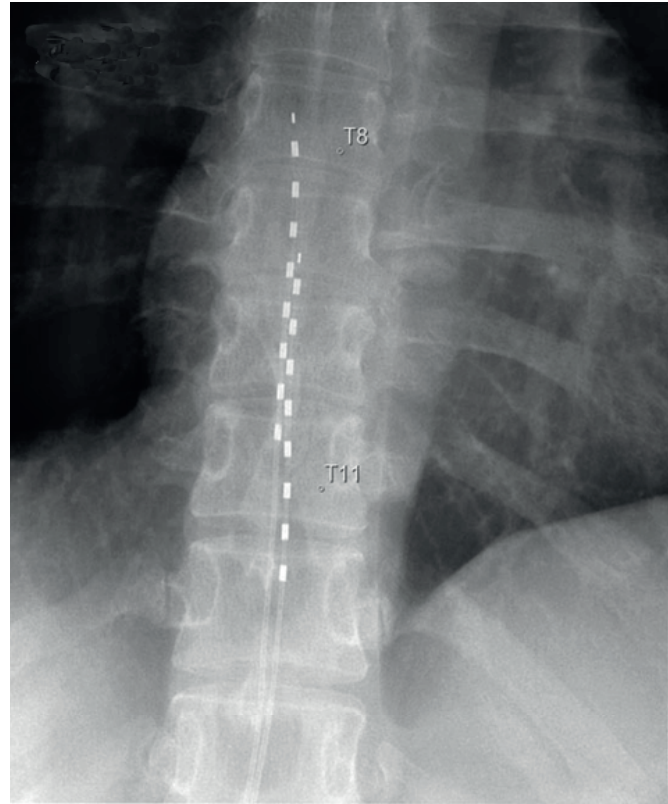
## Pain control in malignant disease

Pain is a common symptom associated with cancer, even more so during the advanced stages. In intractable pain, the underlying principle of treatment is to encourage independence of the patient and an active life in spite of the symptom. WHO advises use of the 'WHO analgesic ladder':

- first step: simple analgesics – paracetamol, NSAIDs, tricyclic drugs or anticonvulsant drugs;
- second step: intermediate-strength opioids – codeine, tramadol;
- third step: strong opioids – morphine (pethidine has now been withdrawn).

Oral opiate analgesia is necessary when the less powerful analgesic agents no longer control pain on movement or enable the patient to sleep. Opioids may exhibit both dependence and addiction with long-term use. It is important to distinguish between addiction and dependence; the former is a psychosocial phenomenon whereas the latter is a purely physiological response to a given drug. Some patients experience 'breakthrough pain' (acute, excruciating and incapacitating), which occurs either spontaneously or in relation to a specific predictable or unpredictable trigger experienced by patients who have relatively stable and adequately controlled background pain. Opioid rotation or switching may be considered if a patient obtains pain relief with one opioid and has severe adverse effects.

Oral morphine, which is often used for chronic pain, can be prescribed in short-acting liquid or tablet form and should be administered regularly every 4 hours until an adequate dose of drug has been titrated to control the pain over 24 hours. Once this is established, the daily dose can be divided into



**Figure 23.9** Dual-lead spinal cord stimulator in the epidural space.

two separate administrations of enteric-coated, slow-release morphine tablets (MST morphine) every 12 hours. Additional short-acting opioids (morphine/fentanyl) can then be used to cover episodes of 'breakthrough pain'. Nausea treated using antiemetic agents does not usually persist, but constipation is a frequent and persistent complication requiring regular prevention by laxatives.

### *Infusion of subcutaneous, intravenous, intrathecal or epidural opiate drugs*

The infusion of an opiate is necessary if a patient is unable to take oral drugs. Subcutaneous infusion of diamorphine is effective and simple to administer. Epidural infusions of diamorphine with an external pump can be used in mobile patients. Intrathecal infusions with pumps programmed by external computers are used; however, there is a possibility of the patient developing an infection with catastrophic effects. Intravenous narcotic agents may be reserved for acute crises, such as pathological fractures.

### *Neurolytic techniques in cancer pain*

These should only be used if life expectancy is limited and the diagnosis is certain. The useful procedures are:

- subcostal phenol injection for a rib metastasis;
- coeliac plexus neurolytic block with alcohol for the pain caused by pancreatic, gastric or hepatic cancer;
- intrathecal neurolytic injection of hyperbaric phenol;