

# Malignant disease

# 9

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The term 'malignant disease' encompasses a wide range of illnesses, including common ones such as lung, breast and colorectal cancer (Table 9.1), as well as rare ones, like the acute leukaemias. Malignant disease is widely prevalent and, in the West, almost a third of the population will develop cancer at some time during their life. It is second only to cardiovascular disease as the cause of death. Although the mortality of cancer is high, many advances have been made, both in terms of treatment, and in understanding the biology of the disease at the molecular level.

Treatment is given with curative or palliative intent, depending upon the evidence from continuing clinical trials. For many people, the word 'cancer' implies certain death, although this is clearly not always the case. Physicians have an obligation to be honest with their patients, combining realism about the prognosis with compassion and understanding so that patients can take an informed part in treatment decisions.

## AETIOLOGY AND EPIDEMIOLOGY

In most patients the cause of their cancer remains unknown and is probably multifactorial. Several environmental factors have, however, been identified as being associated with the development of malignancy (Table 9.2).

### Tobacco

The incidence of lung cancer in both men and women has increased dramatically in the last 25 years. The association of smoking with lung cancer is indisputable and causative mechanisms have been identified: cigarette tobacco is responsible for one-third of all deaths from cancer in the UK. Smoking not only causes lung cancer, it

**Table 9.1** Epidemiology of cancer by site of origin in England and Wales

Type	% of all cancers (1998)	% of cancer deaths	M : F
Oral cavity/pharynx	1	1.2	2.3 : 1
Oesophagus	2.3	4.4	2 : 1
Stomach	3.7	4.7	2.4 : 1
Colorectal	11.1	11.0	1.4 : 1
Pancreas	2.3	4.3	1.5 : 1
Lung	13.6	22.2	1.6 : 1
Melanoma	1.8	1.0	0.6 : 1
Other skin	14.1	0.3	1.5 : 1
Breast	12.2	8.6	0.01 : 1
Cervix	1.2	1.1	
Uterus	1.5	0.7	
Ovary	2.0	2.9	
Prostate	7.4	6.3	
Bladder	4.5	3.5	3.6 : 1
Kidney	1.8	2.0	2.1 : 1
Brain	1.3	2.1	1.4 : 1
Non-Hodgkin's lymphoma	2.8	2.9	1.5 : 1
Myeloma	1.1	1.6	1.5 : 1
Leukaemias	2.1	2.6	1.5 : 1

Cancers < 1% have been excluded

Derived from Doll R, Peto R (2003) In: *Oxford Textbook of Medicine*. 4th edn. Oxford: Oxford University Press

is also associated with cancer of the mouth, larynx, oesophagus and bladder. Smoking is discussed on page 893.

### Alcohol

Alcohol is associated with cancers of the upper respiratory and gastrointestinal tracts (Table 9.2), and it also interacts

## Malignant disease

**Table 9.2** Some causative factors associated with the development of cancer at various sites

Smoking	Mouth, pharynx, oesophagus, larynx, lung, bladder, lip
Alcohol	Mouth, pharynx, larynx, oesophagus, colorectal
<b>Iatrogenic:</b>	
Alkylating agents	Bladder, bone marrow
Oestrogens	Endometrium, vagina, breast
Androgens	Prostate
Radiotherapy	e.g. mantle radiotherapy – carcinoma of breast and bronchus
<b>Diet:</b>	
High-fat diet	Colorectal cancer
<b>Environmental/occupation:</b>	
Vinyl chloride	Liver (angiosarcoma)
Polycyclic hydrocarbons	Skin, lung, bladder, myeloid leukaemia
Aromatic amines	Bladder
Asbestos	Lung, mesothelium
Ultraviolet light	Skin, lip
Radiation	e.g. leukaemia, thyroid cancer
Aflatoxin	Liver
<b>Biological agents:</b>	
Hepatitis B virus	Liver (hepatocellular carcinoma)
Hepatitis C virus	Liver (hepatocellular carcinoma)
Human T cell leukaemia virus	Leukaemia/lymphoma
Epstein–Barr virus	Burkitt's lymphoma Hodgkin's lymphoma
<i>Schistosoma japonicum</i>	Bladder
<i>Helicobacter pylori</i>	Stomach

with tobacco in the aetiology of these tumours. It may be associated with an increased risk of breast cancer.

### Diet

Dietary factors have been attributed to account for a third of cancer deaths, although it is often difficult to differentiate these from other epidemiological factors. For example, the incidence of stomach cancer is particularly high in the Far East, while breast and colon cancers are more common in the western, economically more developed countries. Many associations have been observed without a causative mechanism being identified between the incidence of cancer and the consumption of dietary fibre, red meat, saturated fats, salted fish, vitamin E, vitamin A and many others. Food and its role in the causation of gastrointestinal cancer is discussed in Chapter 5.

### Environmental/occupational

**Ultraviolet light** is known to increase the risk of skin cancer (basal cell, squamous cell and melanoma). The incidence of melanoma is therefore particularly high in the white Anglo-Celtic population of Australia, New Zealand and South Africa, where exposure to UV light is combined with a genetically predisposed population.

**Occupational factors.** In 1775, Percival Pott described the association between carcinogenic hydrocarbons in soot and the development of scrotal epitheliomas in chimney sweeps.

The principal causes now are asbestos (lung and mesothelial cancer) and combustion of fossil fuels releasing polycyclic hydrocarbons (skin, lung, bladder cancers). Organic chemicals such as benzene may cause molecular abnormalities associated with the development of myeloid leukaemia.

### Infectious agents

The geographical distribution of a rare malignancy may suggest that it might be caused by, or associated with, an infective agent. For example, a specific type of T-cell leukaemia, seen almost exclusively in residents of the southern island of Japan and in the West Indies, is caused by infection with the retrovirus, HTLV-1 (human T-cell leukaemia virus) which is endemic in these areas.

Hepatocellular carcinoma occurs in patients with hepatitis B and C virus infections, and Burkitt's lymphoma and nasopharyngeal carcinoma are associated with the Epstein–Barr virus. EBV is also linked with Hodgkin's lymphoma (p. 508). Patients with HIV infection or immunosuppression from organ transplantation have an increased incidence of EBV-related lymphoma and herpesvirus-8-associated Kaposi's sarcoma. The incidence of cervical cancer is increasing amongst younger women in association with human papillomavirus infection. Early sexual activity and multiple sexual partners have both been found to be associated with increased risk.

Bacterial infection with *Helicobacter pylori* predisposes to the development of gastric cancer and gastric lymphoma, while *Schistosoma japonicum* infection predisposes to the development of squamous carcinomas in the bladder.

### Iatrogenic

**Drugs.** Oestrogens have been implicated in the development of vaginal, endometrial and breast carcinoma. Alkylating agents and radiotherapy given, for example, for Hodgkin's lymphoma (see later) are themselves associated with an increased incidence of secondary acute myelogenous leukaemia (AML), bladder and lung cancer. The epipodophyllotoxin drug, etoposide, has also been shown to be associated with the development of secondary AML.

**Radiation.** The nuclear disasters of Hiroshima, Nagasaki and Chernobyl led to an increased incidence of leukaemia after 5–10 years in the exposed population. Increased incidences of thyroid and breast cancer have also been reported. Radiotherapy used, for example, in ankylosing spondylitis and Hodgkin's lymphoma, has led to increased incidences of cancer.

### Geographical distribution

The incidence of specific tumours varies with geographical location but the cause varies; for example England, Scotland and Wales have the highest death rate from malignant disease in the world, mainly because of the very

high incidence of lung cancer due to smoking. India also has the highest incidence of cancers of the gall bladder, mouth and lower pharynx. Breast, colon and prostatic cancer have a relatively low incidence in Asian countries. Liver cancer occurs world-wide but is rare in Europe and North America where the HBV carrier rate is low. Stomach cancer is particularly prevalent in Japan and is thought to be due to dietary factors.

Environmental factors have been clearly implicated. For example, subsequent generations of people moving from countries with a low incidence to those with a high incidence of breast or colon cancer acquire the cancer incidence of the country to which they have moved. This suggests that for these specific cancers, environmental factors are more significant than genetic ones.

## THE BIOLOGY OF CANCER

Most human neoplasms are monoclonal in origin, i.e. they arise from genetic mutations within a single affected cell. However, over subsequent cell divisions heterogeneity develops with the accumulation of further abnormalities. The genes most commonly affected can be characterized as those controlling cell cycle check points, DNA repair and DNA damage recognition, apoptosis, differentiation, and growth signalling. Proliferation may continue at the expense of differentiation, which together with the failure of apoptosis leads to tumour formation with the accumulation of abnormal cells varying in size, shape and nuclear morphology as viewed down the light microscope.

The *kinetics* of cancer cell growth are exponential; however, the doubling times of human tumours are enormously variable. Mutations are common in the genes controlling a series of intracellular proteins, such as the cyclins and cyclin-dependent kinases (p. 157), and oncogene products such as *c-myc*, and the *ras* proteins (see Cancer genetics, p. 188) that regulate proliferation. Proliferation may also be abnormal due to defects in the nuclear enzyme telomerase, contact with other cells, nutrient supply or cytokine signalling. Telomerase is an enzyme that prevents the normal shortening of DNA with each cell division that leads to senescence. Persistent telomerase activity helps to maintain the neoplastic state in cancer cells.

Epithelial growth factor (EGF) and its receptors are overexpressed in many human epithelial tumours, constitutively switching on unrestrained growth of these tumours. Transforming growth factor- $\beta$  (TGF- $\beta$ ), a cytokine which has effects on extracellular matrix proteins, angiogenesis (see below) and immune effector cells, is also often overexpressed in tumour cells, and defects in TGF- $\beta$  signalling are often found in cancer cells. This signalling pathway is activated by cytoplasmic proteins, e.g. MADH4. Defects in tumour suppressor genes such as *MADH4* (*SMAD4* or *DPC4*) and *p53* (see p. 189) have a major part to play and occur, for example, in most pancreatic cancers.

## Apoptosis and growth

Tumour cell death may also be dysregulated. Normal cells usually die by an active and tightly regulated process known as apoptosis, or 'programmed cell death' (p. 162). Apoptosis can occur in response to a number of physiological or pathological stimuli (tumour necrosis factor, Fas ligand, and DNA-damaging cytotoxic drugs) and is mediated within the cell by a family of proteins known as caspases. Caspase activity is, in turn, regulated by intracellular inhibitors such as the Bcl-2 family of proteins and the inhibitor of apoptosis proteins (IAPs). Disturbances in the normal balance of these various proteins have been identified which favour survival of tumour cells over their normal counterparts. An example is the upregulation of the bcl-2 protein in follicular non-Hodgkin's lymphoma.

## Tumour immunology

Tumour cells are usually not recognized and killed by the immune system. There are two main causes. The first is failure to express molecules such as HLA and costimulatory B7 molecules which are required for activation of cytotoxic, or 'killer', T lymphocytes, since expression of these 'costimulatory' molecules following gene transfection may augment an immune response. Secondly, tumours may also actively secrete immunosuppressive cytokines and cause a generalized immunosuppression, leading for example to the reactivation of latent herpes zoster in shingles associated with malignancy.

## Angiogenesis

For many tumours, there is a progressive slowing of the rate of growth as the tumours become larger. This occurs for many reasons, but outgrowing the blood supply is paramount. Tumours need to establish a new blood supply. This new vessel formation (angiogenesis) is stimulated by a variety of peptides produced both by tumour cells and by host inflammatory cells, such as basic fibroblast growth factor (bFGF), angiopoietin 2 and vascular endothelial growth factors (VEGFs), which are stimulated by hypoxia. Inhibition of angiogenesis is a potentially novel method of cancer therapy, as new vessel formation within and around tumours not only provides the cancer with nutrients and oxygen, but permits haematogenous spread, or metastasis.

## Invasion and metastasis

Cancers spread by both local invasion and by metastasis in vessels of the blood or lymphatic systems. Infiltration into surrounding tissues is associated with loss of cell-cell cohesion. Cohesion is mediated by active homotypic cell adhesion molecules (CAMs). The cadherin molecules are transmembrane glycoproteins able to mediate cellular attachment. Epithelial cadherin (E-cadherin) is expressed by many carcinomas, e.g. gastric carcinoma (p. 289), and

loss of E-cadherin expression is associated with an increase in invasion of the tumour.

Invasion is partly determined by the balance of activators to inhibitors of proteolysis. Secretion of proteolytic enzymes, including the matrix metalloproteinases (particularly the collagenases), occurs from adjacent fibroblasts owing to failure of production of tissue inhibitors. The balance between the expression and activity of the matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) is involved in tumour growth, invasion, metastasis and angiogenesis. Some TIMPs may regulate cell proliferation and survival of cancer cells independently of MMP activity.

Dissemination of tumour cells occurs when they enter the vascular and lymphatic vessels. Here they must survive host-defence mechanisms so as to spread throughout the body. The disseminated cancer cells lodge in distant sites, partly by chance, but also because of specific interactions between receptors/ligands found on endothelial cells and on tumour cells. This may account for the specific pattern of metastases with certain tumours; for example, breast tumours frequently metastasize to long bones (see below).

The attachment of tumour cells to the endothelial cells is partly through adhesion molecules. Integrins are transmembrane heterodimeric glycoproteins formed by non-covalent association of  $\alpha$  and  $\beta$  chains. These molecules are normally responsible for cell-substrate adhesion. Patterns of integrin expression in tumours are complex but, nevertheless, certain tumours demonstrate up-regulation of specific integrins, such as the  $\alpha v$  family, during tumour progression, and this may allow migration of tumour cells through the extracellular matrix substrate and invasion through the basement membrane and formation of a metastatic deposit. Integrins also act as receptors for signals regulating gene expression and apoptosis.

**Bone metastases.** These occur in 75% of patients with advanced breast and prostate cancer and in 25% of patients with other solid tumours, e.g. lung, GI tract, thyroid, bladder or kidney.

Metastases are either osteolytic or osteoblastic with some patients having both.

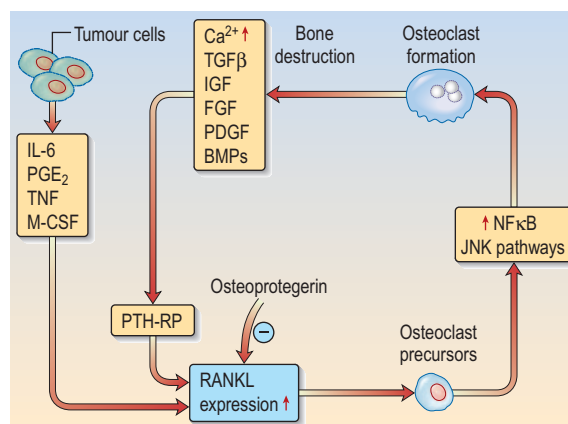
Prostate cancer is predominantly osteoblastic while most patients with breast cancer have osteolytic lesions.

In multiple myeloma (p. 517) the lesions are purely osteolytic.

Bone is a frequent site of metastases due to:

- high blood flow
- tumour cell production of adhesins which bind them to marrow stromal cells
- growth factors in bone, including TGF $\beta$ , insulin-like growth factor (ILG)-1 and 2, platelet-derived growth factor and fibroblastic growth factors.

**Osteolytic metastases** (Fig. 9.1). The destruction of bone is mediated by osteoclasts and not the tumour cells. Tumour cells produce parathyroid hormone-related peptide, IL-6, prostaglandin E<sub>2</sub>, TNF and macrophage



**Fig. 9.1 Mechanisms of osteolytic metastases.** Tumour cells secrete hormones as shown. These increase various factors, e.g. RANKL, and lead to increased osteoclastic activity. Bone destruction (resorption) in turn produces factors which increase tumour growth. Osteoprotegerin (see p. 592) has an inhibitory effect on RANKL. BMPs, bone morphogenic proteins; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL-6, interleukin 6; JNK, jun N-terminal kinase; M-CSF, macrophage colony-stimulating factor; NF $\kappa$ B, nuclear factor kappa B; PDGF, platelet-derived growth factor; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; PTH-RP, parathyroid hormone-related peptide; RANKL, receptor activator of NF $\kappa$ B ligand; TGF, transforming growth factor; TNF, tumour necrosis factor.

colony-stimulating factor (M-CSF) which increase the expression of receptor activity of nuclear factor  $\kappa$ B ligand (RANKL) which directly induces formation of osteoclasts and bone resorption. Bone destruction increases calcium levels, which promotes both tumour growth and the production of PTH-related peptide, which is a major factor in osteolytic bone destruction in many tumours. In multiple myeloma there is, additionally, inhibition of osteoblast activity (p. 517).

**Osteoblastic metastases.** The mechanism for this is less clear. It has been suggested that osteoclastic activity precedes osteoblastic activity and bone formation. It is also possible that the vicious circle (as in osteoclastic activity) may be in action, whereby the tumour induces osteoblastic activity and the release of growth factors for osteoblasts, which then increases the growth of tumours. Endothelin 1 has been shown to stimulate bone formation and its levels are increased in, for example, prostate and breast cancers.

## Cancer genetics

The development of cancer is associated with a fundamental genetic change within the cell. Evidence for the genetic origin of cancer is based on the following:

- Some cancers show a familial predisposition.
- Most known carcinogens act through induced mutations.

- Susceptibility to some carcinogens depends on the ability of cellular enzymes to convert them to a mutagenic form.
- Genetically determined traits associated with a deficiency in the enzymes required for DNA repair are associated with an increased risk of cancer.
- Some cancers are associated with chromosome 'instability' because of deficiencies in mismatch repair genes.
- Many malignant tumours represent clonal proliferations of neoplastic cells.
- Many tumours contain well-described cytogenetic abnormalities, which involve mutated or abnormally regulated oncogenes and tumour suppressor genes with transforming activity in cell lines.

Mutations may occur in the germline and therefore be present in every cell in the body, or they may occur by somatic mutation in response, for example, to carcinogens, and therefore be present only in the cells of the tumour.

Expression of the mutation and hence carcinogenesis will depend upon the penetrance (due to level of expression and presence of other genetic events) of the gene and whether the mutated allele has a dominant or recessive effect. There are a small group of autosomal dominant inherited mutations such as *RB* (in retinoblastoma) and a small group of recessive mutations (Table 9.3). Carriers of the recessive mutations are at risk of developing cancer if the second allele becomes mutated, leading to 'loss of heterozygosity' within the tumour, although this is seldom sufficient as carcinogenesis is a multistep process.

Malignant transformation may result from a gain in function as cellular proto-oncogenes become mutated, (e.g. *ras*), amplified (e.g. *HER2*), or translocated (e.g. *BCR-ABL*). However, these mutations are insufficient to cause malignant transformation by themselves. Alternatively, there may be a loss of function of tumour suppressor genes that normally suppress growth and differentiation. A third mechanism involves alterations in the genes controlling the transcription of the oncogenes or tumour suppressor genes (e.g. p. 189) (Tables 9.3 and 9.4).

## DNA repair

### Autosomal recessive

Some relatively rare autosomal *recessive* diseases associated with abnormalities of DNA repair predispose to the development of cancer (Table 9.3).

- *Xeroderma pigmentosum*. There is an inability to repair DNA damage caused by ultraviolet light and by some chemicals, leading to a high incidence of skin cancer.
- *Ataxia telangiectasia*. Mutation results in an increased sensitivity to ionizing radiation and an increased incidence of lymphoid tumours.
- *Bloom's syndrome and Fanconi's anaemia*. An increased susceptibility to lymphoid malignancy is seen.

It is not known why these chromosome-break syndromes predispose to tumours of lymphatic tissue.

### Autosomal dominant

The following are examples of cancer syndromes that exhibit *dominant* inheritance (Table 9.3):

- *Retinoblastoma*, an eye tumour found in young children. It occurs in both hereditary (40%) and non-hereditary (60%) forms. The 40% of patients with the hereditary form have a germline mutation on the long arm of chromosome 13 that predisposes to retinoblastoma. In addition to the latter, children inheriting this mutation

**Table 9.3** Familial cancer syndromes

	Gene	Neoplasms
<b>Autosomal dominant</b>		
Retinoblastoma	<i>RB1</i>	Eye
Wilms' tumour	<i>WT1</i>	Kidney
Li-Fraumeni	<i>p53</i>	Sarcoma/ brain/ leukaemia
Neurofibromatosis type 1	<i>NF1</i>	Neurofibromas
Familial adenomatous polyposis (FAP)	<i>APC</i>	Colon
Hereditary non- polyposis colon cancer (HNPCC)	<i>MLH1</i> and <i>MSH2</i>	Colon, endometrium
Breast ovary families	<i>BRCA1</i> and <i>BRCA2</i>	Breast/ovary
Melanoma	<i>p16</i>	Skin
Von Hippel-Lindau	<i>VHL</i>	Renal cell carcinoma and haemangio- blastoma
Multiple endocrine neoplasia Type 1	<i>MEN1</i>	Pituitary, pancreas, parathyroid
Multiple endocrine neoplasia Type 2	<i>RET</i>	Thyroid, adrenal medulla
<b>Autosomal recessive</b>		
Xeroderma pigmentosa	<i>XP</i>	Skin
Ataxia telangiectasia	<i>AT</i>	Leukaemia, lymphoma
Fanconi's anaemia	<i>FA</i>	Leukaemia, lymphoma
Bloom's syndrome	<i>BS</i>	Leukaemia, lymphoma

**Table 9.4** Examples of acquired/somatic mutations and proto-oncogenes

<b>Point mutation</b>	
<i>K-ras</i>	Pancreatic cancer
<b>DNA amplification</b>	
<i>myc</i>	Neuroblastoma
<i>HER2-neu</i>	Breast cancer
<b>Chromosome translocation</b>	
<i>BCR-ABL</i>	CML, ALL
<i>PML-RAR</i>	APML
<i>Bcl-2/IgH</i>	Follicular lymphoma
<i>c-myc</i> and <i>Ig</i>	Burkitt's lymphoma
CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; APML, acute promyelocytic leukaemia	

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at the so-called *RB1* locus are at risk for developing other tumours, particularly osteosarcoma.

- *Breast and ovarian cancer.* Two genes have been identified – *BRCA1* and *BRCA2*. A strong family history along with germline mutation of these genes accounts for most cases of familial breast cancer and over half of ovarian cancers. *BRCA1* and 2 proteins bind to the DNA repair enzyme Rad51 to make it functional in repairing DNA breaks. Mutations in the *BRCA* genes will lead to accumulation of unrepaired mutations in tumour-suppressor genes and crucial oncogenes.
- *Neurofibromatosis.* Inactivation of the *NF1* gene will lead to constitutive activation of *ras* proteins.
- *Multiple-endocrine-adenomatosis syndromes* (p. 1099). Multiple endocrine neoplasia type 1 is associated with the *MEN1* gene and type 2 (*MEN2*) is associated with mutations in the *RET* proto-oncogene on chromosome 10 and as such are the exception to all the other syndromes which involve tumour suppressor genes.

## FURTHER READING

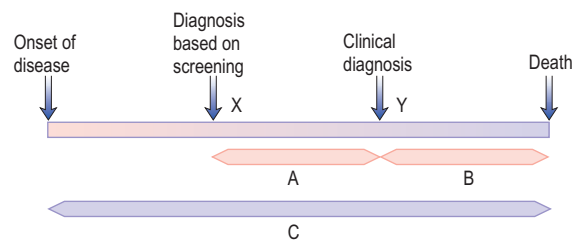
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## THE DIAGNOSIS OF MALIGNANCY

Most common cancers (but not the haematological cancers) start as focal microscopic clones of transformed cells, and diagnosis only becomes likely once sufficient tumour bulk has accumulated to cause symptoms or signs. In order to try to make an earlier diagnosis and increase the curative possibilities, an increasing number of screening programmes are being investigated which target the asymptomatic or preinvasive stages of the cancer.

## Screening

Genetic screening is used to target screening to those people at most risk of developing cancer. The aim is to improve individual and/or population survival. This strategy is dependent upon finding tests that are sufficiently sensitive and specific, using detection methods that identify cancer before it has spread, and having curative treatments that are practical and consistent with maintenance of a normal lifestyle and quality of life.



**Fig. 9.2** Lead time bias. Earlier diagnosis, at X, made by screening tests before the clinical diagnosis, at Y, suggests an increased survival time of A + B. The actual survival time (C) remains unchanged.

The ability to detect cancer at its very early stages when the patient is asymptomatic is the goal of every healthcare system.

Screening is provided to populations, e.g. for breast and cervical cancer in the UK, and also to individuals via annual check-ups, or opportunistic when patients see their doctor for other reasons.

Unfortunately, earlier diagnosis does not necessarily mean longer survival. The patient is merely treated at an earlier date and hence the survival appears longer, death still occurs at the same time from the point of genesis of the cancer. This is called lead time bias (Fig. 9.2). With length time bias, a greater number of slowly growing tumours are detected when screening asymptomatic individuals.

An effective screening procedure should:

- be affordable to the healthcare system
- be acceptable to all social groups so that they attend the screening session
- have a good discriminatory index between benign and malignant lesions
- show a reduction in mortality from the cancer.

## Cervical cancer

This test is cheap and safe but cervical smears require a well-trained cytologist to identify the early changes (dyskaryosis and cervical intraepithelial neoplasia (CIN)). This test reduces the incidence and mortality from cervical cancer.

## Breast cancer

The UK NHS Breast Screening Programme (i.e. mammography) for women aged 50–64 years has been shown to reduce mortality from breast cancer, and randomized control studies from other countries have also shown reductions in mortality. The test is acceptable to most women with 75% of women attending for screening.

The cost is estimated to be between £250 000 and £1.3 million per life saved, money which according to critics of screening, could be used more appropriately in better treatment.

Other population-based screening programmes that are being used or are in trials are:

### Prostate cancer

There is an easy, cheap, effective test – serum prostate-specific antigen (PSA) for the detection of this cancer, which is on the increase. The problems are that no easy acceptable treatment is available (p. 686) and the natural history of the disease is unclear (many men over 70 have evidence of prostate cancer at post-mortem with no symptoms of the disease) and no survival advantage has yet been shown.

### Colorectal cancer (CRC)

Faecal occult blood is an acceptable and cheap test for the detection of CRC. The false-positive rates are high, meaning many unnecessary colonoscopies (p. 330). Screening with flexible sigmoidoscopy is discussed on p. 331. No clear benefit on survival has yet been shown.

### Symptoms of cancer

Patients present with tumour site-specific symptoms, e.g. pain, and physical signs, e.g. a mass, which readily identify the primary site of the cancer. On the other hand, many seek medical attention when more systemic and non-specific symptoms occur such as weight loss, fatigue, and anorexia. These usually indicate a more advanced stage of the disease except in some paraneoplastic and ectopic endocrine syndromes (see below). Other patients are only diagnosed upon the discovery of established metastases such as the back pain of metastatic prostatic

cancer or the liver enlargement of metastatic gastrointestinal cancer.

Other indirect effects of the cancer manifest as paraneoplastic syndromes (Box 9.1) that are often associated with specific types of cancer and are reversible with treatment of the cancer. The effects and mechanisms can be very variable. For example in the Lambert–Eaton syndrome (p. 1269) there is cross-reactivity between tumour antigens and the normal tissues, e.g. the acetylcholine release at neuromuscular junctions.

The *coagulopathy of cancer* may present with thrombophlebitis, deep venous thrombosis and pulmonary emboli, particularly in association with cancers of pancreas, stomach and breast.

Other symptoms are related to peptide or hormone release, e.g. carcinoid or Cushing's syndrome.

*Cachexia of advanced cancer* is due to release of chemokines such as tumour necrosis factor (TNF), as well as the fact that patients have a loss of appetite.

*Cancer-associated immunosuppression* can lead to reactivation of latent infections such as herpes zoster.

### Physical examination

A general examination should be performed to include:

- main symptomatic areas, e.g. site, size of mass and associated lymphadenopathy
- precursor lesions, e.g. solar keratosis, dysplastic naevi
- general signs, e.g. jaundice, clubbing
- functional capacity (see Table 9.6).



#### Box 9.1 Paraneoplastic syndromes

Syndrome	Tumour
<b>Neurological</b>	
Lambert–Eaton syndrome	Lung (small cell)
Peripheral sensory neuropathy	Lung (small cell), breast and ovary
Cerebellar degeneration	Lung (particularly small cell)
<b>Endocrine/metabolic</b>	
SIADH	Lung (small cell)
Ectopic ACTH secretion	Lung (small cell)
Hypercalcaemia	Renal, breast
<b>Musculoskeletal</b>	
Hypertrophic pulmonary osteoarthropathy	Lung (non-small cell)
Clubbing	Lung
<b>Skin</b>	
Dermatomyositis/polymyositis	Lung and upper GI
Acanthosis nigricans	Mainly gastric
Hyperpigmentation	Lung (small cell)
Pemphigus	
<b>Haematological</b>	
Erythrocytosis	Renal cell carcinoma, hepatocellular carcinoma, cerebellar haemangioblastoma
Migratory thrombophlebitis	Pancreatic adenocarcinoma
DIC	Adenocarcinoma

SIADH, syndrome of inappropriate antidiuretic hormone secretion; ACTH, adrenocorticotrophic hormone; DIC, disseminated intravascular coagulation

## Malignant disease

### Histology

The diagnosis of cancer may be suspected by both patient and doctor but advice about treatment can usually only be given on the basis of a tissue diagnosis. This may be obtained by surgical biopsy or on the basis of cytology (e.g. lung cancer diagnosed by sputum cytology or cervix cancer diagnosed on the basis of a cervical smear). Malignant lesions can be distinguished morphologically from benign by the pleomorphic nature of the cells, increased numbers of mitoses, nuclear abnormalities in size, chromatin pattern and nucleolar organization, and evidence of invasion into surrounding tissues.

The degree of differentiation (or conversely of anaplasia) of the tumour has prognostic significance: generally speaking, more differentiated tumours have a better prognosis than poorly differentiated ones. Immunocytochemistry, using monoclonal antibodies against tumour antigens, is very helpful in differentiating between lymphoid and epithelial tumours and between some subsets of these, for example T and B cell lymphomas, germ cell tumours, prostatic tumours, neuroendocrine tumours, melanomas, and sarcomas. However, many adenocarcinomas and squamous carcinomas do not bear any distinctive immunohistochemical markers that are diagnostic of their primary site of origin.

There are several tests for genetic markers in tissue sections. For example, fluorescent in situ hybridization (FISH, p. 177) can be used to look for characteristic chromosomal translocations, deletions or duplications (see genetic basis of cancer, p. 486). Tissue microarrays can identify genomic imbalances, e.g. in breast cell cancer lines and lymphoma (see p. 170).

### Staging

Before a decision about treatment can be made, not only the type of tumour but also its extent and distribution need to be established. Various 'staging investigations' are therefore performed before a treatment decision is made. To be useful clinically the staging system must subdivide the patients into groups of different prognosis which can guide treatment selection.

The staging systems vary according to the type of tumour and may be site specific (see Hodgkin's lymphoma, p. 510), or the TNM (tumour, node, metastases) classification shown in Table 9.5 which can be applied to most common cancers.

### Performance status

In addition to anatomical staging, the person's age and general state of health need to be taken into account when planning treatment. The latter has been called 'performance status' and is of great prognostic significance for all tumour types (Table 9.6). Performance status reflects the effects of the cancer on the patient's functional capacity. An alternative performance rating scale is by Karnofsky.

### Tumour markers (Table 9.7)

Tumour markers are intracellular proteins or cell surface glycoproteins released into the circulation and detected

by immunoassays. Alpha-fetoprotein,  $\beta$ -human chorionic gonadotrophin and prostate-specific antigen are useful in the diagnosis of cancer but the remainder in Table 9.7 should be used with great care in diagnosis because of low specificity. They can be useful in the serial monitoring of response to treatment, as they can be quite sensitive to changes in the tumour burden.

## CANCER TREATMENT

### Aims of treatment

Cancer treatment requires the cooperation of a multi-disciplinary team to coordinate the delivery of the appropriate treatment (surgery, chemotherapy, radiotherapy and biological/endocrine therapy), supportive and symptomatic care, and psychosocial support. While all members will have the patient's care as their central concern, someone, often the oncologist, has to take responsibility for the coordination of the many professionals involved. Central to this endeavour is the

**Table 9.5** TNM classification as used for lung cancer

T = extent of primary tumour; N = extent of regional lymph node involvement; M = presence of distant metastases

Tx	Positive cytology only
T1	< 3 cm diameter
T2	> 3 cm/extends to hilar region/invades visceral pleura/partial atelectasis
T3	Involvement of chest wall, diaphragm, pericardium, mediastinum, pleura, total atelectasis
T4	Involvement of heart, great vessels, trachea, oesophagus, malignant effusion
N1	Peribronchial, ipsilateral hilar lymph node involvement
N2	Ipsilateral mediastinal
N3	Contralateral mediastinal, scalene or supraclavicular
M0	No distant metastases
M1	Metastases present

**Table 9.6** Eastern Cooperative Oncology Group (ECOG) performance status scale

Status	Description
0	Asymptomatic, fully active and able to carry out all predisease performance without restrictions
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, e.g. light housework, office work
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bedridden
4	Completely disabled. Cannot carry out any self-care. Totally bedridden

**Table 9.7 Serum tumour markers**

$\alpha$ -Fetoprotein	Hepatocellular carcinoma, and non-seminomatous germ cell tumours of the gonads
$\beta$ -Human chorionic gonadotrophin ( $\beta$ -HCG)	Choriocarcinomas, germ cell tumours and lung cancers
Prostate-specific antigen (PSA)	Carcinoma of prostate
Carcinoma embryonic antigen (CEA)	Gastrointestinal cancers
CA-125	Ovarian cancer
CA-19-9	Gastrointestinal cancers particularly pancreatic cancer
CA-15-3	Breast cancer

involvement of the patient, through education as to the nature of their disease and the treatment options available. An informed choice can then be made, even if in the end it is simply to abide by the decisions made by the professionals. Good communication embodies a humane approach which preserves hope at an appropriate level through empathy and understanding of the patient's position.

### Curing cancer

For most solid tumours local control is possible but not sufficient for cure because of the presence of systemic (microscopic) disease, while haematological cancers are usually disseminated from the outset. Improvement in the rate of cure of most cancers is thus dependent upon earlier detection and effective systemic treatment. The likelihood of cure of the systemic disease depends upon the type of cancer, its chemo-/hormonal sensitivity, and tumour bulk (microscopic or clinically detectable). A few rare cancers are so chemosensitive that even bulky metastases can be cured, e.g. leukaemia, lymphoma, gonadal germ cell tumours, and choriocarcinoma. For most common solid tumours such as breast and colorectal cancer, there is no current cure of bulky (clinically detectable) metastases, but micrometastatic disease treated by adjuvant chemotherapy (see below) after surgery can be cured in 10–20% of patients.

### Palliation

When cure is no longer possible, palliation, i.e. relief of tumour symptoms and prolongation of life, is possible in many cancers in proportion to their chemo- and radio-sensitivity. There is on average a 2–18 months prolongation in median life expectancy with treatments for solid tumours and up to 5–8 years for some leukaemias and lymphomas, with those with the most responsive tumours experiencing the greatest benefit. The development of more effective chemotherapeutic drugs and better supportive care such as antiemetics has done much to reduce the side-effects of chemotherapy and to improve the cost/benefit ratio for the patient receiving palliative treatment. In addition, through early assessment during treatment, it is possible to stop if there is no evidence of benefit within 6–8 weeks

of starting, so as to minimize exposure to toxic and unsuccessful treatment.

### Measuring response to treatment

A measurable response to treatment can serve as a useful early surrogate marker when assessing whether to continue a given treatment for an individual patient.

Response to treatment can be subjective or objective. A *subjective response* is one perceived by the patient in terms of, for example, relief of pain and dyspnoea, or improvement in appetite, weight gain or energy. Such subjective response is a major aim of most palliative treatments. Quantitative measurements of these subjective symptoms form a part of the assessment of response to chemotherapy, especially in those situations where cure is not possible and where the aim of treatment is to provide prolongation of good-quality life. In these circumstances, measures of quality of life enable an estimate of the balance of benefit and side-effects to be made.

*Objective response* to treatment is measured either as a complete response, which is a complete disappearance of all detectable disease clinically and radiologically or partial response, which is conventionally defined as more than a 50% reduction in the size of the tumour. The terms used to evaluate the responses of tumours are given in Box 9.2. The term 'remission' is often used synonymously with 'response' which if complete means an absence of detectable disease without necessarily implying a cure of the cancer.

### Oncological emergencies

- Superior vena caval obstruction** can arise from any upper mediastinal mass but is most commonly associated with lung cancer and lymphoma. The patient presents with difficulty breathing and/or swallowing, with stridor, swollen, oedematous facies and venous congestion. *Treatment* is with immediate steroids, vascular stents, anticoagulation and mediastinal radiotherapy or chemotherapy. Some tumours, e.g. lymphomas and germ cell tumours, are so sensitive to chemotherapy that this is preferred to radiotherapy, as the masses are likely to be both large and associated with more disseminated disease elsewhere. An early decision is necessary on the patient's likely prognosis, as ventilatory support may be required until treatment has had time to relieve the obstruction.

#### **i** Box 9.2 Definitions of response

Complete response	Complete disappearance of all detectable disease
Partial response	More than 50% reduction in the product of the bidimensional diameters of the tumour
Stable disease	No change, or < 50% reduction and < 25% increase
Progressive disease	Increase in size of tumour by at least 25% at any site

- *Spinal cord compression* (p. 1250) needs to be rapidly diagnosed and urgent treatment arranged to salvage as much functional capacity as possible. Early neurological clinical features may be incomplete, more subjective than objective and gradual in onset. MR scanning is the investigation of choice. *Treatment* should begin with high-dose steroids followed by surgical decompression and radiotherapy to the affected vertebrae to achieve the best disease control and palliation.
- *Neutropenic sepsis* (p. 495).
- *Acute lysis syndrome*. This occurs if treatment produces a massive breakdown of tumour cells, leading to increased serum levels of urate, potassium and phosphate. Urate deposition in the renal tubules can cause renal failure (hyperuricaemic nephropathy) requiring dialysis. The xanthine oxidase inhibitor (allopurinol) is given before treatment is started. Intravenous rasburicase, a recombinant urate oxidase, is occasionally used for prophylaxis and treatment but is very expensive.
- *Acute hypercalcaemia* presents with vomiting, confusion, constipation and oliguria. Treatment is by resuscitation with intravenous fluids until a saline diuresis is established, followed by i.v. pamidronate (Emergency box 18.2).
- *Raised intracranial pressure* due to intracerebral metastases presents classically with headache, nausea and vomiting. However, for many there is a slower onset with non-specific symptoms such as drowsiness or mental deterioration. *Treatment* is by high-dose steroids and investigation by MRI as to whether surgery is appropriate or chemotherapy and radiotherapy are required.
- *Hyperviscosity* affects those with a very high haematocrit (> 50), white cell count (>  $100 \times 10^9/L$ ) or platelet cell count (>  $1000 \times 10^9/L$ ) from untreated acute leukaemia, or polycythaemia. *Treatment* is by leucopheresis and plasmapheresis followed by chemotherapy treatment for the underlying malignancy.

### Adjuvant therapy for solid tumours

This is defined as treatment given in the absence of macroscopic evidence of metastases, to patients at risk of recurrence from micrometastases, after treatment of the primary lesion has been given. 'Neoadjuvant' therapy is given before primary therapy, which may shrink the tumour size and treat any micrometastases as soon as possible.

Micrometastatic spread by lymphatic or haematological dissemination often occurs early in the development of the primary tumour, and can be demonstrated by molecular biological methods capable of detecting the small numbers (1 in  $10^6$ ) of circulating cells. Studies correlating prognosis with histological features of the primary cancer, e.g. differentiation or presence of early metastatic invasion of blood vessels or regional lymph nodes, have led to an increasing ability to predict which patients are at high risk of local or distant recurrence from micrometastatic disease.

Trials of treatment with local radiotherapy or endocrine, biological or chemotherapy treatments have shown a significant improvement in survival in common adult cancers such as breast, bowel, prostate, head and neck, cervical cancer, choriocarcinoma and gonadal germ cell cancers. Central to these studies has been the careful selection of patients according to defined risk criteria, and the reduction of treatment toxicity to reach a balanced risk/benefit ratio. Absolute improvements in survival of 5–10% and relative risk reductions in the order of 12–25% (dependent upon the pre-existing risk) have been achieved in common epithelial cancers such as bowel, breast and prostate, with greater absolute improvements of 25% in the more sensitive germ cell tumours.

While these improvements currently translate into many lives saved from common diseases at a public health level, the majority who receive such treatment do not benefit because they were already cured, or because the cancer is resistant to the treatment. Better tests in the future will identify those with the micrometastases who really need treatment. On an individual patient basis the decision on whether adjuvant treatment will be worthwhile must include consideration of other factors such as the patient's life expectancy, concurrent medical conditions, and lifestyle priorities.

### Treatment of malignancy in sanctuary sites

A 'sanctuary site' is the term used to indicate that metastatic disease has involved a site that is not accessible to conventional drug therapy. An example of this is leukaemic infiltration of the meninges in children with acute lymphoblastic leukaemia. Because of the blood-brain barrier, agents such as vincristine and prednisolone do not enter the subarachnoid space in sufficient quantity to eliminate all the leukaemic cells, and are therefore ineffective in preventing the development of meningeal infiltration. In order to treat these cells, intrathecal chemotherapy and/or cranial irradiation are required for patients at risk (p. 505).

## PRINCIPLES OF CHEMOTHERAPY

Chemotherapy employs systemically administered drugs that directly damage cellular DNA (and RNA). It kills cells by promoting apoptosis and sometimes frank necrosis. There is a narrow therapeutic window between effective treatment of the cancer and normal tissue toxicity, because the drugs are not cancer specific (unlike some of the biological agents), and the increased proliferation in cancers is not much greater than in normal tissues (see tumour growth and failure of apoptosis, p. 162). The dose and schedule of the chemotherapy is limited by the normal tissue tolerance, especially in those more proliferative tissues of the bone marrow and gastrointestinal tract mucosa. All tissues can be affected, however, depending

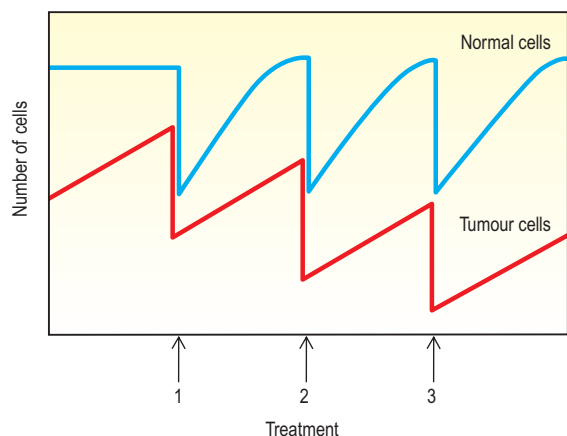
upon the pharmacokinetics of the drug and affinity for particular tissues (e.g. heavy metal compounds for kidneys and nerves).

The therapeutic effect on the cancer is achieved by a variety of mechanisms which seek to exploit differences between normal and transformed cells. While most of the drugs have been derived in the past by empirical testing of many different compounds, e.g. alkylating agents, the new molecular biology is leading to targeting of particular genetic defects in the cancer (see tyrosine kinase inhibitors for CML, p. 506).

Toxicity to normal tissue can be limited in some instances by supplying growth factors such as granulocyte colony-stimulating factor (G-CSF) or by the infusion of stem cell preparations to diminish myelotoxicity. The use of more specific biological agents with relatively weak pro-apoptotic effects in combination with the general cytotoxics will also improve the therapeutic ratio (see trastuzumab and breast cancer, p. 521).

Most tumours rapidly develop resistance to single agents given on their own. For this reason the principle of intermittent combination chemotherapy was developed. Several drugs are combined together, chosen on the basis of differing mechanisms of action and non-overlapping toxicities. These drugs are given over a period of a few days followed by a rest of a few weeks, during which time the normal tissues have the opportunity for regrowth. If the normal tissues are more proficient at DNA repair than the cancer cells, it may be possible to deplete the tumour while allowing the restoration of normal tissues between chemotherapy cycles (Fig. 9.3).

In many experimental tumours it has been shown that there is a log-linear relationship between drug dose and number of cancer cells killed and that the maximum effective dose is very close to the maximum tolerated dose at which dose-limiting toxicity is reached. With a chemosensitive tumour, relatively small increases in dose may have a large effect on tumour cell kill. It is therefore apparent that where cure is a realistic option the dose administered is critical and may need to be maintained



**Fig. 9.3** Effects of multiple courses of cytotoxic chemotherapy.

despite toxicity. In situations where cure is not a realistic possibility and palliation is the aim, a sufficient dose to exceed the therapeutic threshold, but not cause undue toxicity, is required as the short-term quality of life becomes a major consideration.

## Classification of cytotoxic drugs (Table 9.8)

### DNA damaging

#### Alkylating agents

Alkylating agents act by covalently binding alkyl groups, and their major effect is to cross-link DNA strands, interfering with DNA synthesis and causing strand breaks. Despite being among the earliest cytotoxic drugs developed, they maintain a central position in the treatment of cancer. Melphalan is one of the original nitrogen mustards and is used in multiple myeloma. Chlorambucil is used in Hodgkin's lymphoma and chronic lymphocytic leukaemia. Other common alkylating agents include cyclophosphamide and ifosfamide, as well as the nitrosoureas, carmustine (BCNU) lomustine (CCNU) and busulfan used in chronic myeloid leukaemia. Tetrazines also alkylate DNA; dacarbazine is used in malignant melanoma and temozolomide in malignant gliomas.

#### Platinum compounds

Cisplatin, carboplatin and oxaliplatin cause interstrand cross-links of DNA and are often regarded as non-classical alkylating agents. They have transformed the treatment of testicular cancer and have a major role against many other tumours, including lung, ovarian and head and neck cancer. Toxicity, as for other heavy metals, includes renal and peripheral nerve damage.

#### Antimetabolites

Antimetabolites are usually structural analogues of naturally occurring metabolites that interfere with normal synthesis of nucleic acids by falsely substituting purines and pyrimidines in metabolic pathways. Antimetabolites can be divided into:

**Table 9.8** Chemotherapy: some cytotoxic drugs

#### DNA damaging

Free radicals – alkylators, e.g. cyclophosphamide  
DNA cross-linking – platinum, e.g. cisplatin, carboplatin, oxaliplatin

#### Antimetabolites

Thymidine synthesis, e.g. 5-fluorouracil, methotrexate, cytarabine and mercaptopurine

#### DNA repair inhibitors

Topoisomerase inhibitors – epipodophyllotoxins, e.g. etoposide; camptothecins, e.g. irinotecan  
DNA intercalation – anthracyclines, e.g. doxorubicin

#### Antitubulin

Tubulin binding – alkaloids, e.g. vincristine, vinorelbine  
Taxanes – e.g. paclitaxel, docetaxel

## Malignant disease

- **Folic acid antagonist**, e.g. methotrexate. This is structurally very similar to folic acid and binds preferentially to dihydrofolate reductase, the enzyme responsible for the conversion of folic acid to folinic acid. It is used widely in the treatment of solid tumours and haematological malignancies. Folinic acid is often given to 'rescue' normal tissues from the effects of methotrexate.
- **Pyrimidine antagonists**. 5-Fluorouracil (5-FU) consists of a uracil molecule with a substituted fluorine atom. It acts by blocking the enzyme thymidylate synthase, which is essential for pyrimidine synthesis. 5-Fluorouracil has a major role in the treatment of solid tumours, particularly gastrointestinal cancers. Capecitabine is metabolized to 5-FU, and is useful in colorectal cancer. Tegafur with uracil is used with calcium folinate in metastatic colorectal cancer.
- **Arabinosides** inhibit DNA synthesis by inhibiting DNA polymerase. Cytosine arabinoside (cytarabine) is used almost exclusively in the treatment of acute myeloid leukaemia where it remains the backbone of therapy, while its analogue gemcitabine is proving useful in a number of solid cancers such as lung and ovary. Fludarabine is used in the treatment of B cell chronic lymphocytic leukaemia; it is also used in reduced intensity stem cell transplantation (p. 496) because of its immunosuppressive effect.
- **Purine antagonists**, e.g. 6-mercaptopurine and 6-thioguanine, which are both used almost exclusively in the treatment of acute leukaemia.

### DNA repair inhibitors

#### *Epipodophyllotoxins*

These are semisynthetic derivatives of podophyllotoxin, which is an extract from the mandrake plant. Etoposide is a drug used in a wide range of cancers and works by maintaining DNA strand breaks by acting on the enzyme topoisomerase II. Topoisomerase I inhibitors such as irinotecan and topotecan have also proved active against a variety of solid tumours. Both these enzymes allow unwinding and uncoiling of supercoiled DNA.

#### *Cytotoxic antibiotics*

These drugs such as doxorubicin and bleomycin act by intercalating adjoining nucleotide pairs on the same strand of DNA and by inhibiting DNA repair. They have a wide spectrum of activity in haematological and solid tumours. Doxorubicin is one of the most widely used of all cytotoxic drugs but has cumulative toxicity to the myocardium, while bleomycin has particular toxicity for the lungs. Pegylated liposomal doxorubicin is used as second-line treatment for advanced ovarian cancer with reduction of cardiotoxicity, but infusion reactions occur.

### Antitubulin agents

#### *Vinca alkaloids*

Drugs such as vincristine, vinblastine and vinorelbine act by binding to tubulin and inhibiting microtubule formation (see p. 158). They are used in the treatment of haematological and non-haematological cancers. They

are associated with neurotoxicity due to their anti-microtubule effect and must never be given intrathecally.

#### *Taxanes*

Paclitaxel is isolated from the bark of the western yew. Docetaxel is a semisynthetic taxane. They bind to tubulin dimers and prevent their assembly into microtubules. They are active drugs against many cancers such as ovarian, breast and lung cancer. Taxanes can cause neurotoxicity and hypersensitivity reactions and patients should be premedicated with steroids, H<sub>1</sub> and H<sub>2</sub> histamine antagonists prior to treatment.

## Side-effects of chemotherapy

Chemotherapy carries many potentially serious side-effects and should be used only by trained practitioners. The four most common side-effects are vomiting, hair loss, tiredness and myelosuppression (Table 9.9). Side-effects are much more directly dose related than anti-cancer effects and it has been the practice to give drugs at doses close to their maximum tolerated dose, although this is not always necessary to achieve their maximum anticancer effect. Common combination chemotherapeutic regimens are shown in Table 9.10.

### Nausea and vomiting

The severity of this common side-effect varies with the cytotoxic and it can be eliminated in 75% of patients by using modern antiemetics. Nausea and vomiting are particular problems with platinum analogues and with doxorubicin. A stepped policy with antiemetics such as metoclopramide and domperidone or 5-HT<sub>3</sub> serotonin antagonists (e.g. ondansetron, granisetron) combined with dexamethasone should be used to match the emetogenic potential of the chemotherapy. Aprepitant, a neurokinin receptor antagonist is helpful in preventing acute and delayed nausea and vomiting associated with cisplatin-based chemotherapy. It is used with dexamethasone and a 5-HT<sub>3</sub> antagonist.

**Table 9.9** Side-effects of chemotherapy

<b>Common</b>
Nausea and vomiting
Hair loss
Myelosuppression
Mucositis
Fatigue
<b>Drug-specific</b>
Cardiotoxicity, e.g. anthracyclines
Pulmonary toxicity, e.g. bleomycin
Neurotoxicity, e.g. cisplatin, vinca alkaloids, taxanes
Nephrotoxicity, e.g. cisplatin
Skin plantar-palmar dermatitis, e.g. 5-fluorouracil
Sterility, e.g. alkylating agents
Secondary malignancy, e.g. alkylating agents, epipodophyllotoxins

**Table 9.10** Some chemotherapy regimens

Hodgkin's lymphoma	ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
	BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone
Non-Hodgkin's lymphoma	CHOP	Cyclophosphamide, hydroxy-doxorubicin, vincristine, prednisolone
Breast	CMF	Cyclophosphamide, methotrexate, 5-fluorouracil
	AC	Doxorubicin, cyclophosphamide
	MM	Mitoxantrone, methotrexate
Lung	PE	Cisplatin, etoposide
	MIC	Mitomycin, ifosfamide, cisplatin
Stomach	ECF	Epirubicin, cisplatin, 5-fluorouracil

**Hair loss**

Many but not all cytotoxic drugs are capable of causing hair loss. Scalp cooling can sometimes be used to reduce hair loss but in general this side-effect can only be avoided by selection of drugs where this is possible. Hair always regrows on completion of chemotherapy.

**Bone marrow suppression and immunosuppression**

Suppression of the production of red blood cells, white blood cells and platelets occurs with most cytotoxic drugs and is a dose-related phenomenon. Severely myelosuppressive chemotherapy may be required if treatment is to be given with curative intent despite the potential for rare but fatal infection or bleeding. Anaemia and thrombocytopenia are managed by erythropoetin or red cell or platelet transfusions.

Neutropenic patients are at high risk of bacterial and fungal infection, often from enteric bowel flora. Those with a fever  $> 37^{\circ}\text{C}$  and less than  $0.5 \times 10^9$  neutrophils/L are managed by the immediate introduction of broad-spectrum antibiotics intravenously for the treatment of infection (Box 9.3). Initial empirical therapy should be reviewed following microbiological results. Haemopoietic growth factors and peripheral blood stem cells can reduce the duration of neutropenia significantly, benefiting patients at high risk of infectious complications.

**Mucositis**

This common side-effect of chemotherapy reflects the sensitivity of the mucosa to antimetabolic agents. It causes severe pain and problems with swallowing. Treatment is with antiseptic and anticandidal mouthwash and, if severe, fluid and antibiotic support, as the mouth is a

**Box 9.3** Febrile neutropenia treatment

Resuscitation with intravenous fluids to restore circulatory function, e.g. urine output, followed by cultures of blood, urine, sputum and stool and empirical antibiotics:

- Commonly used antibiotics should include activity against pseudomonas, e.g. ceftazidime or ticarcillin with gentamicin
- May require antibiotics against *Staph. aureus* especially with indwelling venous access lines, e.g. flucloxacillin or vancomycin.

If the patient deteriorates clinically and/or temperature still elevated after 48 hours, change antibiotics according to culture results or empirically increase Gram-negative and Gram-positive cover.

- Consider adding treatment for opportunistic infections if fever not responding to broad-spectrum antibiotics, e.g. amphotericin B liposomal amphotericin B or voriconazole (latter two are very expensive) or caspofungin – fungus high-dose co-trimoxazole – pneumocystis clarithromycin – mycoplasma.

portal for entry of enteric organisms. A recent study has shown a keratinocyte growth factor to be helpful (palifermin).

**Cardiotoxicity**

This is a rare side-effect of chemotherapy, usually associated with anthracyclines such as doxorubicin. It is dose-related and can largely be prevented by restricting the cumulative total dose of anthracyclines within the safe range (equivalent to  $450 \text{ mg/m}^2$  body surface area cumulative doxorubicin dose).

**Neurotoxicity**

This occurs predominantly with the plant alkaloids, vinca, taxanes and platinum analogues (but not carboplatin). It is dose-related and cumulative. Chemotherapy is usually stopped before the development of a significant polyneuropathy, which once established is only partially reversible. Vincristine must *never* be given intrathecally as the neurological damage is progressive and fatal.

**Nephrotoxicity**

Cisplatin (but not oxaliplatin or carboplatin), methotrexate and ifosfamide can potentially cause renal damage. This can usually be prevented by maintaining an adequate diuresis during treatment.

**Sterility**

Some anticancer drugs, particularly alkylating agents, may cause sterility, which may be irreversible. In males the storage of sperm prior to chemotherapy should be offered to the patient when chemotherapy is given with curative intent. In females it may be possible to collect oocytes to be fertilized in vitro and cryopreserved as embryos. Cryopreservation of ovarian tissue and retrieval

## Malignant disease

of viable oocytes for subsequent fertilization is still experimental.

### Secondary malignancies

Anticancer drugs have mutagenic potential and the development of secondary malignancies, predominantly acute leukaemia, is an uncommon but particularly unwelcome long-term side-effect in patients otherwise cured of their primary malignancies. The alkylating agents and epipodophyllotoxins are particularly implicated in this complication.

### Drug resistance

Drug resistance is one of the major obstacles to curing cancer with chemotherapy. Some tumours have an inherently low level of resistance to currently available treatment and are often cured. These include gonadal germ cell tumours, Hodgkin's lymphoma and childhood acute leukaemia. Solid tumours such as small-cell lung cancer initially appear to be chemosensitive, with the majority of patients responding, but most patients eventually relapse with resistant disease. In other tumours such as melanoma the disease is largely chemoresistant from the start.

Most resistance occurs as a result of genetic mutation and becomes more likely as the number of tumour cells increases. It has also been shown that anticancer drugs can themselves increase the rate of mutation to resistance. Resistance to cytotoxic drugs is often multiple and is then known as multidrug resistance (MDR), e.g. resistance to doxorubicin is often associated with resistance to vinca alkaloids and epipodophyllotoxins, and is mediated through increased expression of P-glycoprotein (a 170 kDa membrane phosphoglycoprotein), which mediates the efflux of cytotoxic drugs out of the cells. Many other mechanisms may also be involved in resistance to chemotherapy, such as the upregulation of anti-apoptotic proteins Bcl-2 and Bax.

### High-dose therapy

Most anticancer drugs have a sigmoid dose-response relationship which suggests that, up to a point, a higher dose of a cytotoxic drug will induce a greater response. However, increasing cytotoxic drug doses is often not possible, owing to toxicity. For many chemotherapeutic agents the toxicity which limits the dose is bone marrow failure, and infusion of stem cells is necessary to restore the lymphohaemopoietic system.

### Haemopoietic stem cell transplantation

Bone marrow and transplanted cells may be:

- autologous – from self or identical twin
- syngeneic – from identical twin
- allogeneic – from non-identical donor (matched or sometimes mismatched)
- from umbilical cord blood. This is increasingly being used for adult and childhood leukaemia.

It usually takes 2–3 weeks for engraftment to take and during this time patients need supportive care with nursing in isolated cubicles with air filtration.

### Principles of autologous stem cell transplantation

Autologous stem cells are used as rescue from myeloablative chemotherapy. Haemopoietic stem cells are collected from the patients' bone marrow, or more commonly by leucopheresis from peripheral blood following administration of the growth factor granulocyte colony-stimulating factor (G-CSF) prior to chemotherapy. They are stored by cryopreservation. These cells are then re-infused intravenously after an intensive, myeloablative chemotherapy regimen. This approach has been particularly effective in relapsed leukaemias, lymphomas and in myeloma. There is no risk of graft rejection or graft-versus-host disease (GVHD) but the graft-versus-tumour effect is lost (see below).

### Principles of allogeneic stem cell transplantation

Historically, the transplantation of donor haemopoietic cells has been combined with myeloablative chemotherapy ± radiotherapy. This has the dual effects of treating the malignancy as well as immunosuppression that allows the graft 'to take'. Anti-T cell antibodies are often given to reduce graft-versus-host disease and immune-related infection. It is thought that the engraftment of the donor immune system, with antitumour activity (graft versus tumour), is primarily responsible for the increased effectiveness of this approach. In general, ideal donors are fully matched at the major HLA antigens. Thus siblings are more likely to be found to be potential donors than unrelated volunteers. Some degree of HLA antigen mismatch may be tolerated in children, but is problematic in adults. Allogeneic transplantation has been successfully used in acute and chronic leukaemias, and myeloma.

*Complications* include 'graft-versus-host disease', an immune reaction of the donor cells against normal host organs, which can affect 30–50% of transplant recipients and is potentially fatal in some cases. Immunosuppression, both from conditioning therapy and from the immunosuppressive drugs (ciclosporin or tacrolimus) given to prevent graft-versus-host disease, results in a high incidence of opportunistic infections. All patients receive prophylactic antibacterial, antifungal and antiviral drugs but infections still occur. Mortality therefore from conventional allogeneic stem cell transplantation is a major problem, with 20–40% at risk of dying from the procedure, depending on the age and status of the recipient, and the degree of HLA compatibility of the donor (see also Immunotherapy, p. 498).

### Non-myeloablative allogeneic stem cell transplantation

In this procedure, also known as 'reduced intensity' transplantation, conditioning therapy is non-myeloablative

without radiation therapy but it is immunosuppressant. The principle is that the anticancer effect of the stem cell transplantation will still be present without the complications of conventional allogeneic stem cell transplantation. Mortality (mainly GVHD) is lower, and the technique is being used more widely, particularly in the elderly.

## PRINCIPLES OF ENDOCRINE THERAPY

Oestrogens are capable of stimulating the growth of breast and endometrial cancers, and androgens the growth of prostate cancer. Removal of these growth factors by manipulation of the hormonal environment may result in apoptosis and regression of the cancer. Endocrine therapy can be curative in a proportion of patients treated for micrometastatic disease in the adjuvant setting for breast and prostate cancer and provides a minimally toxic non-curative (palliative) treatment in advanced/metastatic disease. The presence of detectable cellular receptors for the hormone markedly increases the likelihood that the therapy will be effective. Figure 9.4 shows the binding of the hormone to the receptor.

### Oestrogens and progestogens

#### **Breast cancer** (see Table 9.21)

About one-third of patients have receptors for oestrogens and progesterones. Hormonal manipulation includes the use of tamoxifen, which blocks oestrogen receptors, and the reduction of endogenous oestrogen by oophorectomy or 'medical oophorectomy' via pituitary downregulation using a gonadotrophin-releasing hormone (GnRH) analogue such as goserelin.

Tamoxifen is used as an adjuvant therapy to surgery and in advanced metastatic breast disease (see p. 519).

Progestogens have a direct effect on breast tumour cells through progesterone receptors, as well as effects on

the pituitary/ovarian (premenopausal) and adrenal/pituitary axis (postmenopausal) and can be as effective as tamoxifen.

In postmenopausal women, androgens are synthesized by the adrenal glands and converted in subcutaneous fat to estrone by the enzyme aromatase. Aromatase inhibitors, for example anastrozole, letrozole and exemestane, reduce circulating oestrogen levels and oestrogen synthesis in tumour cells and have shown greater efficacy than tamoxifen in the treatment of metastatic breast cancer and equivalence in the adjuvant setting in the postmenopausal woman.

#### **Endometrial cancers**

Endometrial cancers have receptors for both oestrogens and progestogens. Approximately 20% of receptor-positive metastases will regress for a median 20 months with synthetic progestogens such as medroxyprogesterone acetate but paradoxically tamoxifen has little effect. Trials to date with adjuvant progestogens have not been successful in increasing survival.

#### **Androgens**

In advanced prostate cancer, androgen deprivation induces regression in 70% of cases for a median duration of 24 months. GnRH agonists, e.g. goserelin, and orchidectomy, are equally effective; however, androgen receptor blockers such as flutamide are less so. Combinations of goserelin and flutamide may be used in the initial phase of treatment to avoid a disease flare from the initial agonist action of GnRH analogues, but prolonged combination therapy has been no more effective than goserelin alone. In the adjuvant setting, the addition of androgen deprivation to prostatic radiotherapy or surgery has improved survival.

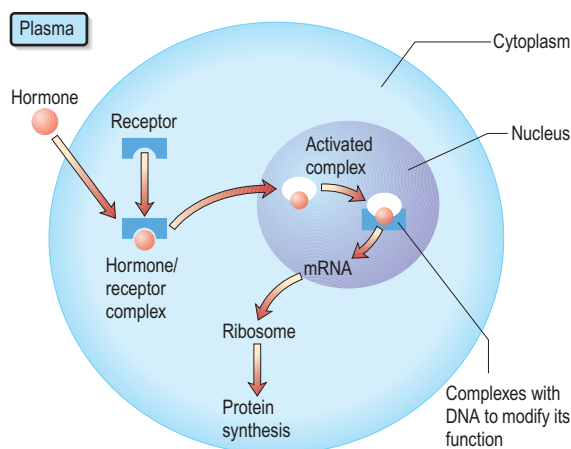
## PRINCIPLES OF BIOLOGICAL THERAPY

The group includes a range of protein molecules, from small peptide chemokines, larger cytokines, to complex antibody molecules, made available by genetic engineering.

#### **Interferons**

Interferons (p. 202) are naturally occurring cytokines that mediate the cellular immune response. They have many actions in treatment of malignant disease with both antiproliferative activity and stimulation of humoral and cell-mediated immune responses to the tumour that can result in an antitumour effect if the host effector mechanisms are present and fully competent.

Alpha-interferon (IFN- $\alpha$ ) has been used against several malignancies to treat established disease such as melanoma, renal cell carcinoma and chronic myeloid leukaemia. In the latter, it results in a reduction in the number of Philadelphia (Ph) chromosome-positive cells in at least 50% of patients, with total elimination in 10%.



**Fig. 9.4** Mechanism of the interaction between a steroid hormone and its receptor. This interaction modifies DNA activity and hence cell growth and replication.

## Malignant disease

It has been replaced by imatinib first-line treatment (p. 506). Interferon has also been used to maintain remission after cytotoxic treatment by suppressing microscopic residual disease, e.g. myeloma. In renal cell carcinoma alpha-interferon has a low (10–15%) but significant anticancer effect and prolongation of survival.

Treatment with IFN has side-effects (p. 371), most commonly flu-like symptoms which tend to diminish with time, and fatigue which generally does not and can be treatment limiting. IFN was given as a daily subcutaneous injection, but conjugation with polyethylene glycol (PEG interferon) has led to a reduction in frequency of injection and severity of side-effects.

### Interleukins

Originally described for their activity in modulating leucocyte activation, these cytokines have widespread activity in coordinating cellular activity in many organs. Interleukin-2, a recombinant protein, is used to activate T cell responses, often in conjunction with interferon-stimulated B cell activation. Antitumour activity has been observed in renal cell carcinoma and melanoma with responses in 10–20% of patients, occasionally for prolonged periods. Toxicity is common; acutely this includes the capillary leak syndrome with hypotension, whilst pulmonary oedema, autoimmune thyroiditis and vitiligo occur later.

### Haemopoietic growth factors

Erythropoietin for anaemia and granulocyte (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF) are used:

- to reduce the duration of neutropenia following chemotherapy
- with or without chemotherapy, to stimulate the proliferation of haemopoietic progenitor cells in the marrow so that they enter the circulation and can be collected from the peripheral blood to support high-dose chemotherapy treatment, particularly in myeloma (p. 518).

### Monoclonal antibodies (Table 9.11)

Monoclonal antibodies directed against tumour cell surface antigens are 'humanized' by being genetically engineered as a chimera comprising a human constant region with the murine heavy and light chains of the antigen-combining site, to reduce formation of blocking human anti-mouse antibodies when used in patients. Uses include:

- *In vitro*, in conjunction with complement, they are used to deplete autologous bone marrow of tumour cells in patients with leukaemia and lymphoma receiving high-dose treatment with autologous haemopoietic progenitor cell support.
- *In vitro* in immunoabsorption columns to select the CD34-positive (stem cell) fraction from peripheral blood progenitor cell or autologous bone marrow collections, to support high-dose treatment in haematological and other malignancies.

**Table 9.11 Biological therapies**

Drug	Function	Malignancy
Imatinib	Tyrosine kinase inhibitor	Stromal cell tumour Chronic myeloid leukaemia
Gefitinib	Tyrosine kinase inhibitor	Non-small-cell lung cancer
Cetuximab	Anti-EGF receptor	Colorectal cancer
Bevacizumab	Anti-VEGF	Colorectal cancer
Rituximab	Anti-CD20 on B cells	Lymphoma
Dallizumab	Anti-CD25	Leukaemia/lymphoma
Alemtuzumab	Anti-CD52	Chronic lymphocytic leukaemia
Trastuzumab	Anti-HER-2 protein	Breast cancer
Bortezomib	Proteasome inhibitor	Leukaemia Myeloma

- As direct treatment for B cell non-Hodgkin's lymphoma (e.g. Rituximab anti-CD20 surface antigen). Tumour cell lysis occurs by both complement- and antibody-dependent cellular cytotoxicity.
- As a *carrier molecule* to target toxins or radioisotopes to the tumour cells, e.g. anti-CD20 conjugated to radioactive iodine is being used as treatment for non-Hodgkin's lymphoma.
- As anti-growth factor agents added to chemotherapy, e.g. trastuzumab against the Her2/ Neu or c-erbB2 antigen, a member of the epidermal growth factor receptor family, to increase the apoptotic response to cytotoxics with improved survival in metastatic breast cancer or with bevacizumab in colorectal cancer.

### Immunotherapy

Activation of the immune system using bacille Calmette–Guérin (BCG) for bladder cancer or interleukin-2 for renal cancer induces responses in 60% and 10% of patients respectively. Certain antigens that are specific to cancer cells, such as sequences of tumour immunoglobulin from B cell lymphomas or melanoma antigens have been used as tumour vaccines. Antigen-presenting cells (dendritic cells) from the patient can be genetically engineered to present both antigen and cytokines such as interleukin-2 or granulocyte–macrophage colony-stimulating factor, and clinical responses have been observed. Another approach has used dendritic cells to further improve the vaccination strategy by engineering them to display the full range of HLA and B7 costimulatory molecules.

The use of non-myeloablative haemopoietic stem cell and donor lymphocyte infusions, while losing some of the specificity, has produced the strongest evidence for the efficacy of immunotherapy at the risk of the greatest toxicity.

### Gene therapy

Antisense oligonucleotides are short sequences of DNA bases which specifically inhibit complementary sequences of either DNA or RNA. As a result, they can be generated against genetic sequences which are specific for tumour

cells. Their clinical development has been hampered by poor uptake by tumour cells and rapid degradation by natural endonucleases. However, one antisense sequence directed against the *Bcl-2* oncogene has been shown to have an antitumour effect in patients with non-Hodgkin's lymphoma. Creation of reliable vectors for the transfection of tumour cells in vivo still forms a major barrier to the greater application of this modality.

### Intracellular signal inhibitors

The recognition that many cancer cells are transformed by the activity of the protein products of oncogenes has led to the search for peptides or other compounds which inhibit these proteins, or their intracellular signal pathways. An example is the tyrosine kinase inhibitor imatinib, which specifically inhibits the fusion oncoprotein BCR-ABL. This compound is an extremely effective treatment for chronic myeloid leukaemia, a disease characterized by the presence of the BCR-ABL fusion protein. Many other similar molecules, inhibiting enzymes involved in cell cycling or cytokine signalling, are in preclinical or early clinical development. Examples include farnesyl transferase inhibitors, which inhibit ras proteins, inhibitors of the platelet-derived growth factor receptor, and drugs which inhibit matrix metalloproteinases.

## PRINCIPLES OF RADIATION THERAPY

Radiation delivers energy to tissues, causing ionization and excitation of atoms and molecules. The biological effect is exerted through the generation of single- and double-strand DNA breaks, inducing apoptosis of cells as they progress through the cell cycle, and through the generation of short-lived free radicals, particularly from oxygen, which damage proteins and membranes.

The most commonly used form of radiotherapy is *external beam* or *teletherapy* from a linear accelerator source which provides X-rays, the energy of which is transmitted as photons. Cobalt-60 generators can also provide gamma rays and high-energy photons.

*Brachytherapy* is the use of radiation sources in close contact with the tissue to provide intense exposure over a short distance to a restricted volume.

*Systemic radionuclides*, e.g. iodine-131, or radioisotope-labelled monoclonal antibodies and hormones can be administered by intravenous or intracavitary routes to provide radiation targeted to particular tissue uptake via surface antigens or receptors.

The *radiation dose* is measured in grays (Gy), where 1 gray = 1 joule absorbed per kilogram of absorbing tissue and 1 centigray = 1 rad. The biological effect is dependent upon the dose rate, duration, volume irradiated, and the tissue sensitivity. Sensitivity to photon damage is greatest during the G<sub>2</sub>-M phase of the cell cycle and is also dependent upon the DNA repair capacity of the cell. Fractionation is the delivery of the radiation dose in increments separated by at least 4–6 hours to try to exploit any

advantage in DNA repair between normal and malignant cells. Radiation dose is thus described by three factors:

- total dose in cGy
- number of fractions
- time for completion.

Most treatments are delivered in 150–200 cGy fractions daily for 5 days per week, although a regimen of two fractions daily (hyperfractionation) had improved survival benefit in a lung cancer trial.

The radiation effect will also depend upon the intensity of the radiation source, measured as the linear energy transfer or frequency of ionizing events per unit of path, which is subject to the inverse square law as the energy diminishes with the distance from the source.

The generation of free radicals depends upon the degree of oxygenation/hypoxia in the target tissues. This can affect the biological effect by up to threefold and is the subject of continuing research for hypoxic cell sensitizers.

The depth of penetration of biological tissues by the photons depends upon the energy of the beam. Low-energy photons from an 85 kV source are suitable for superficial treatments, while high-energy 35 MeV sources produce a beam with deeper penetration, less scatter both at the initial skin boundary (skin sparing) and at the margins of the beam, and less absorption by bone. Superficial radiation may be also delivered by electron beams from a linear accelerator that has had the target electrode that generates the X-rays removed.

Radiotherapy treatment planning involves both detailed physics of the applied dose and knowledge of the biology of the cancer and whether the intention is to treat the tumour site alone, or include the likely loco-regional patterns of spread. Normal tissue tolerance will determine the extent of the side-effects, and a balanced decision is made according to the curative or palliative intent of the treatment and the likely early or late side-effects.

The cancers for which radiotherapy is usually employed as primary curative when the tumour is anatomically localized are listed in Table 9.12 along with those in which radiotherapy has curative potential when used in addition to surgery (adjuvant radiotherapy). Palliative treatments are frequently used to provide relief of symptoms to improve quality if not duration of survival (Box 9.4).

### Side-effects of radiotherapy

Radiotherapy side-effects may occur early within days to weeks of treatment when they are usually self-limiting but associated with general systemic disturbance (Table 9.13). The side-effects will depend upon tissue sensitivity, fraction size and treatment volume and are managed with supportive measures until normal tissue repair occurs. The toxicity may also be enhanced by exposure to other radiation-sensitizing agents, especially some cytotoxics, e.g. bleomycin, actinomycin, anthracyclines, cisplatin and 5-fluorouracil.

## Malignant disease

**Table 9.12** Curative radiotherapy treatment**Primary modality**

Retina  
CNS  
Skin  
Oropharynx and larynx  
Cervix and vagina  
Prostate  
Lymphoma

**Adjuvant to primary surgery**

Lung  
Breast  
Uterus  
Bladder  
Rectum  
Testis-seminoma  
Sarcoma

**Box 9.4** Palliative benefits of radiotherapy

- Pain relief, e.g. bone metastases
- Reduction of headache and vomiting in raised intracranial pressure from CNS metastases
- Relief of obstruction of bronchus, oesophagus, ureter, and lymphatics
- Preservation of skeletal integrity from metastases in weight-bearing bones
- Reversal of neurological impairment from spinal cord or optic nerve compression by metastases

Later side-effects occur from months to years later, unrelated to the severity of the acute effects because of their different mechanism. Late effects reflect both the loss of slowly proliferating cells and a local endarteritis which produces ischaemia and proliferative fibrosis.

Growth may be arrested if bony epiphyses are not yet fused and are irradiated, leading to distorted skeletal growth in later life.

Secondary malignancies following radiotherapy typically appear 10–20 years after the cure of the primary cancer. Haematological malignancies tend to occur sooner than solid tumours from the irradiated tissues. The latter are very dependent upon the status of the tissue at the time of treatment, e.g. the pubertal breast is up to 300 times more sensitive to malignant transformation than the breast tissues of a woman in her thirties. Patients who smoke are more liable to develop lung cancer. Treatment of these secondary cancers can be successful providing there is normal bone marrow to reconstitute the haemopoietic system or the whole tissue at risk (e.g. thyroid after mantle radiotherapy for lymphoma) can be resected.

**FURTHER READING**

Gregor A (2000) How to improve effects of radiation and control its toxicity. *Annals of Oncology* **11** (Suppl. 3): 231–234.

**Table 9.13** Side-effects of radiotherapy**Acute side-effects**

Anorexia, nausea, malaise  
Mucositis, oesophagitis, diarrhoea  
Alopecia  
Myelosuppression

**Late side-effects**

Skin	Ischaemia, ulceration
Bone	Necrosis, fracture, sarcoma
Mouth	Xerostomia, sialitis, ulceration
Bowel	Stenosis, fistula, diarrhoea
Bladder	Cystitis
Vagina	Dyspareunia, stenosis
Lung	Fibrosis
Heart	Pericardial fibrosis, cardiomyopathy
CNS	Myelopathy
Gonads	Infertility, menopause
Second malignancies,	e.g. Leukaemia Cancer, e.g. thyroid

**HAEMATOLOGICAL MALIGNANCIES**

The leukaemias, the lymphomas and multiple myeloma are an interrelated spectrum of malignancies of the myeloid and lymphoid systems. They are uncommon but not rare, the lymphomas alone being the seventh commonest cancer in the UK. The aetiology of these diseases is unknown, although viruses, irradiation, cytotoxic poisons and immune suppression have been implicated in a small proportion of cases (p. 501). The pathogenesis involves at least one or usually more molecular abnormalities, and non-random chromosomal abnormalities have been detected in several leukaemias and lymphomas. Classification has become increasingly complex, with the universally applied WHO scheme demanding morphological, cytogenetic and sometimes molecular criteria to be fulfilled. Treatment options are multiple. Patients need to be supported through treatment involving prolonged myelosuppression and immunosuppression. These are potentially life-threatening but can also be curative. This has given rise to the need for highly skilled staff and specialist facilities, and patients should be referred to these centres for treatment.

Large multicentre Phase III trials have validated single centre data and show that curative therapy can be delivered in the community.

In the management of these diseases it is critical that patients are appraised of the natural history, its potential modification by treatment and the risks of both severe morbidity and mortality. It must be made clear from the outset whether a curative or palliative strategy is most appropriate and why. If cure is to be pursued, the patient must be appraised of the approximate probability of success and its potential price. The possibility of failure needs to be addressed at the outset and not at the last minute.

## THE LEUKAEMIAS

These are relatively rare diseases with an incidence of about 10 per 100 000 per year. They are classified as being acute (short natural history) or chronic (long natural history), and of myeloid or lymphoid origin. More than half of the leukaemias present acutely (ALL, AML) with the remainder being chronic types (CLL, CML). The type of leukaemia varies with age; acute lymphoblastic leukaemia (ALL) is mainly seen in childhood and chronic lymphocytic leukaemia is a disease of the elderly. The myelodysplastic syndromes are considered pre-leukaemia and are discussed on page 453. Leukaemia can be diagnosed by examination of a stained slide of peripheral blood and bone marrow, with immune phenotyping, cytogenetics and molecular genetics being essential for complete subclassification and prognostication.

### General classification

The characteristics of leukaemic cells can be assessed by light microscopy, expression of cytosolic enzymes and expression of surface antigens. These will reflect the lineage and degree of maturity of the leukaemic clone. Thus, leukaemia can be divided on the basis of the speed of evolution of the disease into acute or chronic. Each of these is then further subdivided into myeloid or lymphoid, according to the cell type involved.

- acute myeloid leukaemia (AML)
- acute lymphoblastic leukaemia (ALL)
- chronic myeloid leukaemia (CML)
- chronic lymphocytic leukaemia (CLL).

### Aetiology

This is unknown but several factors have been associated:

- **Radiation.** This can induce genetic damage to haemopoietic precursors and ALL, AML and CML have been seen in increased incidences in survivors of Hiroshima and Nagasaki and in patients treated with ionizing radiation.
- **Chemical and drugs.** Exposure to benzene used in industry, may lead to marrow damage. AML occurs after treatment with alkylating agents, e.g. melphalan.
- **Genetic.** The incidence of leukaemia is increased in identical twins and in syndromes of somatic cell chromosomal aneuploidy, e.g. Down's syndrome, Klinefelter's syndrome.
- **Viruses.** Leukaemias are associated with human T cell lymphotropic virus type 1 (HTLV-1), which is found particularly in Japan and the Caribbean.

### Genetic abnormalities in leukaemia

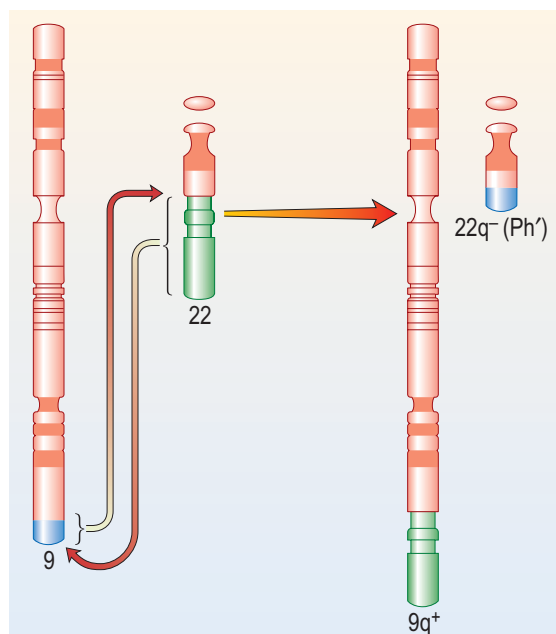
Leukaemic cells often have a somatically acquired cytogenetic abnormality, which may be of prognostic, as well as diagnostic, importance.

These genetic alterations change the normal cell regulating process by interfering with the control of normal proliferation, blocking differentiation, maintaining an unlimited capacity for self-renewal and lastly, promoting resistance to death signals, i.e. decreased apoptosis.

The first non-random chromosomal abnormality to be described was the Philadelphia (Ph) chromosome, which is associated with chronic myeloid leukaemia (CML) in 97% of cases. The Ph chromosome is also found in ALL, the incidence in the latter illness increasing with age. The translocation is shown schematically in Figure 9.5. The Ph chromosome is an abnormal chromosome 22, resulting from a reciprocal translocation between part of the long arm of chromosome 22 and chromosome 9. The resulting karyotype is described as t(9;22)(q34;q11). The molecular consequences of the translocation are that part of the Abelson proto-oncogene (*c-ABL*) normally present on chromosome 9 is translocated to chromosome 22, where it comes into juxtaposition with a region of chromosome 22 named the 'breakpoint cluster region' (BCR). The translocation creates a hybrid transcription unit consisting of the 5' end of the *BCR* gene and the *c-ABL* proto-oncogene.

The new 'fusion' gene *BCR-ABL* is capable of being expressed as a chimeric messenger RNA which has been identified in cells from patients with CML. When translated, this produces a fusion protein that has tyrosine kinase activity and enhanced phosphorylating activity compared with the normal protein, resulting in altered cell growth, stromal attachment and apoptosis. The breakpoint differs in CML and Ph-positive ALL, leading to the production of two different tyrosine kinase proteins with molecular weights of 210 kDa and 190 kDa respectively. It is unclear whether the presence of *BCR-ABL* is sufficient for the development of the disease. It has recently been shown that normal subjects can carry low levels of the *BCR-ABL* fusion gene in their blood without developing leukaemia.

Almost all patients with acute promyelocytic leukaemia (APML), a subtype of acute myelogenous leukaemia,



**Fig. 9.5** The Philadelphia chromosome (Ph). The long arm (q) of chromosome 22 has been shortened by the reciprocal translocation with chromosome 9.

## Malignant disease

have the t(15;17) reciprocal translocation, which occurs at the q25 band on chromosome 15 and the q22 band on chromosome 17. The breakpoint on chromosome 17 occurs in the gene encoding the retinoic acid receptor, fusing it with part of the *PML* gene. This is to some extent the explanation for the responsiveness of patients with APLM to all-*trans*-retinoic acid (ATRA, see p. 504). Other genetic and cytogenetic abnormalities are often seen in leukaemic cells (see Table 9.14).

### Cell surface markers

These can be used to classify acute leukaemias. Immature myeloid cells have cell surface markers, e.g. CD13, CD14, CD33, CD34, which can be identified using monoclonal antibodies. The majority of patients with ALL (60%), for example, show the common ALL antigen (CALLA – CD10).

### ACUTE LEUKAEMIAS

The acute leukaemias are predominantly diseases of adulthood, increasing in incidence with advancing age. Acute myeloid (myeloblastic, myelogenous) leukaemia (AML) has a median age at presentation of 65 years and may arise 'de novo' or against a background of myelodysplasia, either of unknown aetiology or related to cytotoxic chemotherapy. Acute lymphoid (lymphoblastic) leukaemia (ALL) has a substantially lower median age at presentation and in addition is the commonest malignancy in childhood. The WHO classification is shown in Table 9.14.

### Clinical features

The majority of patients with acute leukaemia, regardless of subtype present with symptoms arising from:

- anaemia – shortness of breath on effort; excessive tiredness, weakness
- leucopenia – recurrent infections
- thrombocytopenia – bleeding and bruising (particularly acute promyelocytic leukaemia)
- marrow infiltration – bone pain.

Examination may be unremarkable, but features include:

- pallor
- fever (due to infection, not the disease itself)
- petechiae, purpura, bruises, fundal haemorrhage (particularly acute promyelocytic leukaemia)
- lymphadenopathy, hepatosplenomegaly (more notable in lymphoblastic leukaemia)
- violaceous skin lesions (acute myelomonocytic leukaemia)
- testicular enlargement (acute lymphoblastic leukaemia)
- cranial nerve palsies occasionally found (acute lymphoblastic leukaemia).

### Investigations

**Confirmation of diagnosis** (Fig. 9.6)

- **Blood count.** Hb low, WBC raised usually (sometimes low), platelets low.

**Table 9.14 WHO classification of acute leukaemia**

#### (a) Acute myeloid leukaemia

##### **AML with recurrent genetic abnormalities**

AML with t(8;21)(q22;q22), (AML1/ETO)  
 AML with abnormal bone marrow eosinophils and inv(16)(p13;q22) or t(16;16)(p13;q22), (CBFβ/MYH1 1)  
 Acute promyelocytic leukaemia with t(15;17)(q22;q12), PML/RAR-alpha and variants  
 AML with 11q23 (MLL) abnormalities

##### **AML with multilineage dysplasia**

Following MDS or MDS/MDP  
 Without antecedent MDS or MDS/MDP, but with dysplasia in at least 50% of cells in two or more myeloid lineages

##### **AML and myelodysplastic syndromes, therapy related**

Alkylating agent/radiation-related type  
 Topoisomerase II inhibitor-related type  
 Other

##### **AML, not otherwise categorized\***

AML, minimally differentiated  
 AML without maturation  
 AML with maturation  
 Acute myelomonocytic leukaemia  
 Acute monoblastic/acute monocytic leukaemia  
 Acute erythroid leukaemia (erythroid/myeloid and pure erythroleukaemia variants)  
 Acute megakaryoblastic leukaemia  
 Acute basophilic leukaemia  
 Acute panmyelosis with myelofibrosis  
 Myeloid sarcoma

#### (b) Acute lymphoid leukaemia

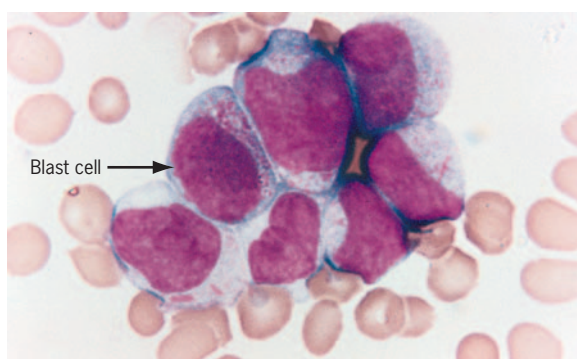
Precursor B cell acute lymphoblastic leukaemia  
 t(9;22)(q34;q11); BCR/ABC fusion gene  
 t(4;11)(q21;q23); MLL-AF4 fusion gene  
 t(1;19)(q23;p13.3); E2A/PBX1 fusion gene  
 t(12;21)(p13;q22); TEL/AML1  
 Precursor T cell acute lymphoblastic leukaemia  
 Burkitt-cell leukaemia

\* The entities included in this group are defined almost identically to the corresponding entity in the French-American-British (FAB) classification

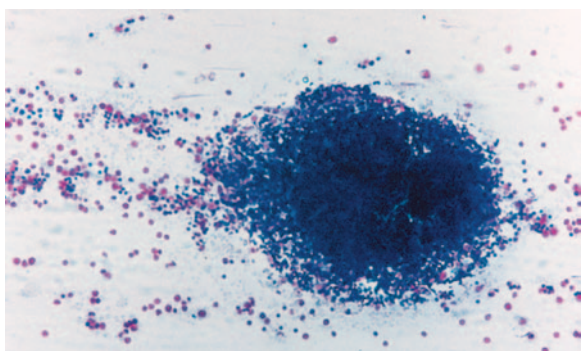
MDS, myelodysplastic syndromes; MPD, myeloproliferative diseases

Modified from Jaffe ES, Harris NL, Stein H, Vardiman JW (eds) (2001) *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press, with permission

- **Blood film.** Blast cells almost invariably seen, (Fig. 9.6a), lineage identified morphologically, confirmed with immunophenotyping.
- **Bone marrow aspirate.** Increased cellularity, reduced erythropoiesis, reduced megakaryocytes, sometimes trilineage dysplasia. Blast cells > 20% (often approaching 100%) (Fig. 9.6b). Lineage confirmation by immunophenotyping (FISH), cytogenetic and molecular genetics.
- **Chest X-ray.** Mediastinal widening often present in T lymphoblastic leukaemia.



(a)



(b)

**Fig. 9.6** (a) Peripheral blood film showing characteristic blast cells. The arrow points to the abnormal blast cell. (b) Bone marrow aspirate showing particle with increased cellularity. Courtesy of Dr Manzoor Mangi.

#### For planning therapy

- Biochemistry, serum urate, renal and liver biochemistry.
- Cardiac function; ECG and direct tests of left ventricular function, e.g. echocardiogram or MUGA scan (p. 756).

#### Principles of management

Untreated acute leukaemia is invariably fatal, most often within months, though with judicious palliative care it may be extended to perhaps a year. Treatment with curative intent may be successful, or may fail, either because the leukaemia cannot be eradicated or because the patient cannot sustain the therapy, death occurring as early as if treatment had not been initiated.

At initial presentation, acute leukaemias range from being probably curable (most favourable risk – childhood acute lymphoblastic leukaemia) through possibly curable (de novo low-risk AML) to probably incurable (AML with adverse cytogenetic features in the elderly, secondary AML, recurrent acute leukaemia). Since curative treatment even for ‘low-risk’ acute leukaemia carries considerable morbidity and potential mortality and that for ‘high-risk’ acute leukaemia even more, it is essential that the ‘risk/benefit’ ratio is clearly understood by physician and patient alike.

In AML, patients with t(15;17) t(8;17) or inv(16) (or its variant t16;16), i.e. low risk, do not benefit from allogeneic

stem cell transplantation during their first complete remission because the risks outweigh benefits. Patients with adverse factors (high risk) – (5/del5q), -7, abnormal 3q, t(9;22) or a complex karyotype – should have transplantation because they respond poorly to conventional chemotherapy. Other poor prognostic factors (high risk) include developing the disease over 60 years of age, leukaemia following myelodysplastic syndrome (MDS), relapsed disease, secondary leukaemia and extramedullary disease.

#### Palliative therapy

The patient must understand that the decision to manage palliatively does not mean ‘no therapy’, or abandonment, but rather the recognition of a different goal from prolongation of life, though this may also be achieved to some degree. Every attempt should be made to ensure that the patients are at home as much as possible, whilst making available the full range of supportive care. Palliation may well include both chemotherapy and irradiation in addition to blood product support. ‘Moral’ support is invaluable.

#### Curative therapy

The decision to treat with curative intent, particularly if successful, implies severe disruption of normality for the patient and family for at least 6 months and often up to a year, and, regardless of success, life is never quite the same again. In the short term, it may demand transfer to another hospital, as acute leukaemia should only be treated in units seeing at least 10 such cases per year. It is highly likely to involve admission to hospital for up to a month in the first instance, with further, partly predictable, subsequent admissions of several days’ to weeks’ duration, requiring discussions and decisions about work or education.

The decision to treat with curative intent implies that cure is possible, and that the chance of cure justifies the risks of the therapy. It does not imply that cure is guaranteed or even expected. The failure rate may be high, and the patient must know that he or she will be told if cure becomes an unrealistic goal. Treating with curative intent may well involve rapid decisions about resuscitation with transfer to the intensive care unit, the possibility of which is discussed in advance.

#### Active therapy

##### Supportive care

This forms the basis of treatment whether for cure or palliation:

- Avoidance of symptoms of anaemia (haemoglobin > 10 g/dL) – repeated transfusion of packed red cells (sometimes irradiation of cells is required).
- Prevention or control of bleeding (platelet count <  $10^9$ /L in the uninfected, and  $20 \times 10^9$ /L in the infected patient).
- Treatment of infection:
  - (a) *Prophylactically*. Education of patients, relatives and staff about hand washing and isolation facilities. The use of selected antibiotics and antifungals.

## Malignant disease

(b) *Therapeutically.* Management of fever with protocol/algorithm of antibiotic and antifungal combinations.

- Control of hyperuricaemia with hydration, prophylactic allopurinol and very occasionally rasburicase (p. 492).

### Specific treatment

The initial requirement of therapy is to return the peripheral blood and bone marrow to normal (complete remission; CR) with 'induction chemotherapy' tailored to the particular leukaemia and the individual patient's risk factors. Since this treatment is not leukaemia specific but also impairs normal bone marrow function, it leads to a major risk of life-threatening infection, which increases the risk of early death in the short term. Since infection is the major problem, it is necessary to conduct the early therapy in hospital, the patient sleeping in a single room with en-suite lavatory and washing facilities ('some' isolation).

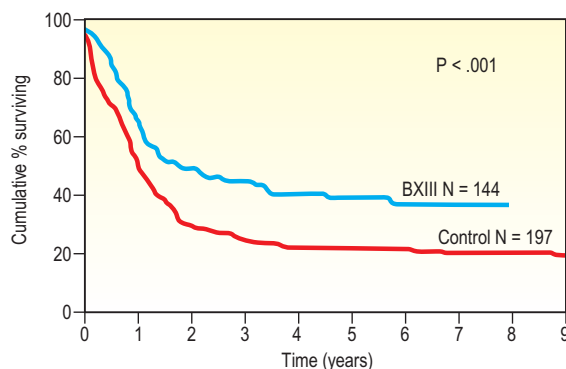
Successful remission induction is always followed by further treatment (consolidation), the details being determined by the type of leukaemia and the patient's risk factors (and the patient's tolerance of treatment). Recurrence is almost invariable if 'consolidation' therapy is not given. This reflects the lack of sensitivity of the definition of 'complete remission', which has until very recently been solely morphological. Cytogenetics and molecular genetic techniques can identify residual leukaemic cells not detected morphologically, and they are highly predictive of recurrence. Recommendations have recently been made to modify the definition of remission to reflect this. Failure to achieve morphological CR with two cycles of therapy carries almost as bad a prognosis as the leukaemia untreated. If CR can be achieved, e.g. by new experimental approaches, cure may still be possible with stem cell transplantation (p. 496).

### Acute myeloid leukaemia (AML; excluding APML, p. 504)

Treatment with curative intent is undertaken in the majority of adults below the age of 60 years, provided there is no significant co-morbidity. Risk of failure is based on the cytogenetic pattern (p. 503). Those at 'low risk' are treated with moderately intensive combination chemotherapy always including an anthracycline antibiotic such as daunorubicin and cytosine arabinoside (cytarabine) and consolidation with a minimum of four cycles of treatment given at 3- to 4-week intervals. Those at 'high risk' may only be treated with curative intent if an HLA-identified sibling is available for stem cell transplantation.

Those at 'intermediate risk' are a heterogeneous group but when possible they should be given consolidating chemotherapy to induce remission followed by sibling matched allogeneic transplantation, despite its attendant risks.

The initial treatment of the older patient is much more contentious. Intuitively, biological age should determine the management of the individual patient. Unfortunately



**Fig. 9.7** Acute myeloid leukaemia: overall survival with or without myeloablative therapy. BXIII = treatment group. (from Rohatiner AZS et al. (2000) *Annals of Oncology* 11: 1007–1015 with permission).

'high risk AML' is commoner with increasing age, but is only curable with allogeneic transplantation, and the toxicity of this treatment increases dramatically with age.

Complete remission will be achieved in about three-quarters of patients under the age of 60, failure being due to either resistant leukaemia or death due to infection or (rarely) bleeding. It may be expected that approximately 50% of those entering complete remission will be cured. (i.e. approximately 30% overall) (Fig. 9.7). The management of recurrence is undertaken on an individual basis, since the overall prognosis is very poor despite the fact that second remissions may be achieved. Long survival following recurrence is rarely achieved without allogeneic transplantation. Experimental therapy should be considered.

### Acute promyelocytic leukaemia (APML)

This is an uncommon variant of AML characterized by the translocation  $t(15;17)$  (p. 501). There is an almost invariable coagulopathy, which was a major cause of death. The empirical discovery that all-*trans*-retinoic acid (ATRA) causes differentiation of promyelocytes and rapid reversal of the bleeding tendency was a major breakthrough. It is now conventional to treat APML with ATRA combined with chemotherapy and to follow successful remission induction with maintenance ATRA. Allogeneic transplantation may be necessary either if the leukaemia is not eliminated at the molecular level, or following a second remission after recurrence. Arsenic trioxide, which induces apoptosis via activation of the caspase cascade (p. 162) is also effective.

Complete remission and molecular remission occur in at least 80% of younger adults with APML (it is uncommon in the elderly). At least 60% will expect to be cured. In contrast to the other subtypes of AML, the prognosis after recurrence is quite favourable with prolonged second remissions being possible with further blocks of ATRA and chemotherapy even if allogeneic transplant is not performed, though it is the treatment of choice.

### Acute lymphoblastic leukaemia (ALL)

The overall strategy for the treatment of ALL differs in detail from that for AML (Fig. 9.8). Remission induction is undertaken with combination chemotherapy including vincristine, prednisolone, asparaginase (crisantaspase) and usually an anthracycline antibiotic, e.g. doxorubicin. Once remission is achieved, the details of consolidation will be determined by the anticipated risk of failure.

Allogeneic transplantation is only recommended for those at highest risk, i.e. those with t(9;22) since this is otherwise incurable with conventional therapy. It is unclear yet what the role of imatinib (see below) will be in this setting. Patients with certain subtypes receive maintenance therapy for 2 years.

The other major difference between therapy for ALL and AML is the need for central nervous system directed therapy. Prophylaxis should be given with intrathecal chemotherapy under platelet cover if necessary, as soon as blasts are cleared from the blood. Depending upon risk this may be continued for up to 2 years, and complemented by high doses of systemic cytosine arabinoside (cytarabine) or methotrexate. Cranial irradiation previously given to all patients is reserved for those at very high risk and those who are symptomatic (Fig. 9.8).

#### Prognosis

The prognosis of ALL in childhood is now excellent: complete remission is achieved in almost all, with up to 80% being alive without recurrence at 5 years. Failure occurs most frequently in those with high blast count and t(9;22) translocation.

The situation is far less satisfactory for adults, the prognosis getting worse with advancing years. Comorbidity and t(9;22) translocation increases in frequency with age. Overall the complete remission rate is 70–80%, failure being due partly to resistant leukaemia and partly

to failure of supportive care. Failure to achieve complete remission with first-line therapy carries a very poor prognosis. If CR can be achieved with new therapies, it should be consolidated with sibling or possibly even unrelated donor transplantation despite the high risk of graft-versus-host disease. Thirty to 40% of patients continue in durable first remissions, resulting in approximately 25–30% overall patient cure.

As with AML, most recurrences occur within the first 3 years and the outcome is extremely poor. Second remissions, though usually achieved, are rarely durable except following allogeneic transplantation. Isolated extramedullary recurrences, however, may be cured.

### CHRONIC LEUKAEMIAS

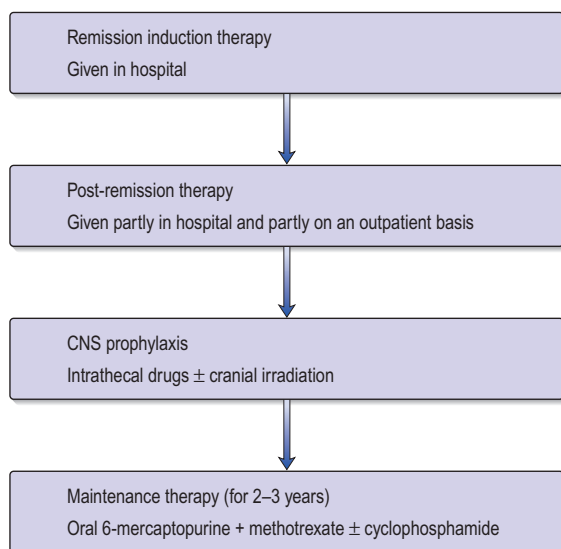
#### Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia (CML) accounts for about 14% of all leukaemias, is almost exclusively a disease of adults with the peak of presentation being at 40–60 years and is characterized by the presence of the Philadelphia chromosome (Fig. 9.9). Unlike the acute leukaemias which are either rapidly reversed or rapidly fatal, CML has a more slowly progressive course which if not initially cured will be followed eventually by blast crisis (90% myeloid, 20% lymphoid) or myelofibrosis and death after 3–4 years.

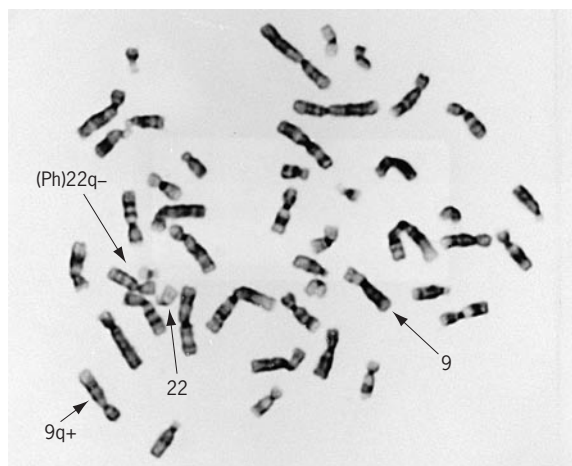
#### Clinical features

CML usually presents in the chronic phase and some patients have no symptoms. Symptoms include:

- shortness of breath due to anaemia
- abdominal discomfort due to splenomegaly
- weight loss
- fever, sweats, NOT due to infection



**Fig. 9.8** Treatment regimen for acute lymphoblastic leukaemia.



**Fig. 9.9** Philadelphia chromosome. This is formed by a reciprocal translocation of part of the long arm (q) of chromosome 22 to chromosome 9. It is seen in 90–95% of patients with chronic myeloid leukaemia. The karyotype is expressed as 46XX, (9;22)(q34;q11).

## Malignant disease

- headache (occasionally) due to hyperleucocytosis
- bruising, bleeding (uncommon).

### Signs

- Pallor
- Splenomegaly, often massive
- Lymphadenopathy, at times of blast crisis
- Retinal haemorrhage due to leucostasis.

### Investigations

- **Blood count.** Hb low or normal, WBC raised, platelets low, normal or raised.
- **Blood film.** Neutrophilia with the whole spectrum of myeloid precursors including occasional blasts.
- **Bone marrow aspirate.** Increased cellularity, increased myeloid precursors. Cytogenetics reveals t(9;22) translocation (the Philadelphia chromosome) (Fig. 9.9)
- **Fluorescein-in-situ hybridization (FISH),** reverse transcriptase polymerase chain reaction (RT-PCR) or microarray expression may be needed to demonstrate the cytogenetic/molecular abnormality.
- **LAP is usually reduced.**

### Management

*Imatinib*, a tyrosine kinase inhibitor that specifically blocks the enzymatic action of the BCR-ABL fusion protein is first-line treatment for the chronic phase. It has replaced alpha-interferon. Imatinib produces a complete haematological response in over 95% of patient, and 70–80% of these have no detectable BCR-ABL transcripts in the blood. Event-free, and overall, survival appear to be better than for other treatments. Imatinib can be continued indefinitely.

In the acute phase (blast transformation) most patients have only a short-lived response to imatinib, and other treatments (see below) will be necessary.

Side-effects of imatinib, which usually are well tolerated, include nausea, headaches, rashes and cytopenia. Resistance to imatinib as a single agent has developed and further clinical studies are necessary.

### Stem cell transplantation (SCT)

Allogeneic haemopoietic stem cell transplantation can cure approximately 70% of chronic phase CML patients but with a risk of complications and death due to graft-versus-host disease (GVHD) and opportunistic infections.

Factors making complications more likely include:

- increasing age
- SCT in acute phase
- degree of histocompatibility between donor and recipient.

Graft-versus-leukaemia effect plays a role in the increased survival following SCT so that reduced-intensity transplantation is being more frequently used.

The exact role of SCT in the imatinib era is unclear but failure to respond to that agent is an indication. Monitoring of patients following either SCT or imatinib is by measuring BCR-ABL transcripts using the reverse transcriptase PCR.

## Chronic lymphocytic leukaemia (CLL)

This is the commonest leukaemia, occurring predominantly in later life and increasing in frequency with advancing years. It is almost invariably B lymphocytic in origin. In many patients it is a chance finding with no symptoms, while others present with the features of marrow failure or immunosuppression. The median survival may be 10 years, and may be found to correlate with various presentation features (Table 9.15). It is becoming increasingly recognized that cytogenetic and molecular abnormalities carry prognostic significance (see below).

### Clinical features

Common symptoms are:

- recurrent infection because of (functional) leucopenia and immune failure (reduced immunoglobulins)
- anaemia due to haemolysis or marrow infiltration
- painless lymphadenopathy
- splenic discomfort.

The commonest findings on examination are:

- anaemia
- fever (due to infection)
- generalized lymphadenopathy
- hepatosplenomegaly, sometimes massive.

However, none of these may be present.

### Investigations

- **Blood count.** Hb normal or low; WBC raised, and may be very high; platelets normal or low.
- **Blood film.** Lymphocytes increased above  $5 \times 10^9/L$ .
- **Bone marrow.** Reflects peripheral blood, often very heavily infiltrated with lymphocytes.
- **Immunophenotyping** shows mainly CD19/20 + CD5<sup>+</sup> B cells. They may weakly express surface immunoglobulin.
- **Cytogenetics** can help assess prognosis. Abnormalities include deletions at trisomy 12 (40%) 13q14 (60%), long arms of 6, 11 and 13 and abnormalities in the *p53* gene. There are mutations of IgVH (on B cells) which help in assessing prognosis. IgVH is difficult to measure. However, intracellular ZAP-70 (zeta-associated protein) which correlates closely with the IgVH mutated status can be measured by flow cytometry in a general laboratory.
- **Coombs' test.** May be positive if there is haemolysis.
- **Immunoglobulins.** Low or normal.

### Management

In CLL, the major consideration is when to treat. Treatment depends on the 'stage' (Table 9.15) of the disease, although the cytogenetic markers are being increasingly used. In particular, low levels of ZAP-70 indicate a good prognosis with no treatment necessary. Conversely unmutated IgVH (high levels of ZAP-70) indicate a poor prognosis.

Early-stage disease is usually managed expectantly, advanced-stage disease is always treated immediately

**Table 9.15** The Rai and Binet staging systems for chronic lymphocytic leukaemia\*

System and stage	Risk	Manifestations	Percent of patients	Median survival	Recommended treatment
<b>Rai staging system</b>					
0	Low	Lymphocytosis	31	> 10	Watch and wait
I	Intermediate	Lymphadenopathy	35	9	Treat only with progression <sup>†</sup>
II	Intermediate	Splenomegaly, lymphadenopathy, or both	26	7	Treat only with progression <sup>†</sup>
III	High	Anaemia, organomegaly,	6	5	Treatment indicated in most cases
IV	High	One or more of the following: anaemia, thrombocytopenia and organomegaly	2	5	Treatment indicated in most cases
<b>Binet staging system</b>					
A	Low	Lymphocytosis, < 3 lymphoid areas enlarged <sup>‡</sup>	63§	> 10	Watch and wait
B	Intermediate	≥ 3 Lymphoid areas enlarged <sup>‡</sup>	30	7	Treatment indicated in most cases
C	High	Anaemia, thrombocytopenia or both	7	5	Treatment indicated in most cases
* Lymphocytosis is present in all stages of the disease					
<sup>†</sup> Progression is defined by weight loss, fatigue, fever, massive organomegaly and a rapidly increasing lymphocyte count					
<sup>‡</sup> Enlarged lymphoid areas may include the cervical, axillary and inguinal lymph nodes; the spleen or liver may be enlarged					
<sup>§</sup> Stage A includes all patients with Rai stage 0 disease, two-thirds of patients with Rai stage I disease and one-third of those with Rai stage II					
From Dighiero G, Binet JL (2000) <i>New England Journal of Medicine</i> 343: 1800					

and the approach to the intermediate stage is variable. The absolute indication for treatments are:

- anaemia (especially due to haemolysis)
- recurrent infection
- splenic discomfort
- progressive disease manifest by doubling of the lymphocyte count in 6 months.

#### General/supportive treatment

*Anaemia* due to haemolysis is treated with steroids. If it is refractory or recurrent, or if splenic discomfort is a problem, a splenectomy is performed. Anaemia due to marrow infiltration is treated with chemotherapy and, when necessary, blood transfusion. Erythropoietin (p. 422) may avoid the need for transfusions, particularly in patients receiving chemotherapy.

*Infection* is treated with antibiotics, with prophylactic therapy being given during periods of chemotherapy. Immunoglobulin replacement may be helpful.

Allopurinol is given to prevent hyperuricaemia.

#### Specific treatment

Chlorambucil, given in modest doses, usually reduces the blood count and decreases lymphadenopathy and splenomegaly, and successfully palliates the disease. The bone marrow rarely returns to normal. Treatment is usually limited to a few months' duration and then withheld until progression.

Since the introduction of the purine analogues, fludarabine alone or in combination with cyclophosphamide or mitoxantrone (with or without steroids), treatment has had a much greater impact on the bone

marrow and can induce complete or molecular complete remission. More recently, the addition of rituximab (relatively ineffective alone) in combination therapy has been reported to result in a dramatic improvement in the response rate. Myeloblastic chemotherapy with autologous stem cell rescue and allogeneic stem cell transplantation with myeloablative or non-myeloablative condition regimens are currently undergoing trials.

#### Outcome

Survival correlates closely with cytogenetic findings and Rai or Binet stage at any time. The median survival from diagnosis is very variable with normal life expectancy in some groups and rapid progression in others. Poor prognostic factors include a high Rai and Binet stage, a short lymphocyte doubling time (< 12 months), diffuse bone marrow infiltration, cytogenetic abnormalities involving *p53* dysfunction, *Ilq23*, trisomy 12 and CD38/ZAP-70 positivity, male gender and developing the disease over 60 years of age. Intervention, when indicated, usually causes improvement in symptoms and in the blood count. The effect on survival is unclear. More aggressive treatments, particularly combinations of cytotoxic chemotherapy with antibody therapy, result in better quality remission of longer duration. These improvements may translate into a survival advantage, to accompany the improvement in quality of life afforded by good supportive care.

#### Hairy cell leukaemia (HCL)

HCL is a clonal proliferation of abnormal B (or very rarely T) cells which, as in CLL, accumulate in the bone marrow

## Malignant disease

and spleen. It is a rare disease, median age at presentation is 52 years old and the male to female ratio is 4 : 1. The bizarre name relates to the appearance of the cells on a blood film and in the bone marrow – they have an irregular outline owing to the presence of filament-like cytoplasmic projections. They show a strong acid phosphatase reaction that is resistant to tartaric acid. The cells express many cellular differentiation markers including CD19, 20 and 103 but not CD21 or 5.

**Clinical features** include anaemia, fever and weight loss. Splenomegaly occurs in 80%, lymphadenopathy is uncommon. Anaemia, neutropenia, thrombocytopenia and low monocyte counts are found.

### Treatment

The purine analogues 2-chloroadenosine acetate (2-CDA) (cladribine) and pentostatin have specific activity in this condition; complete remission is achieved in 90% with just one cycle of treatment. The remissions sometimes last for several years and patients can be retreated. Rituximab is used in cases who do not respond to the above drugs.

### Prolymphocytic leukaemia

Prolymphocytic leukaemia is another rare disorder, often mistaken for CLL. It may be of B or of T cell lineage. It is characterized by bone marrow failure (anaemia, neutropenia and thrombocytopenia) and – as in HCL –

splenomegaly. Treatment generally comprises chlorambucil as for CLL, although splenectomy may be indicated and fludarabine can be useful.

## THE LYMPHOMAS

The lymphomas are commoner than the leukaemias and are increasing in incidence for reasons which are unclear. They arise as the result of abnormal proliferation of the lymphoid system, and hence occur at any site where lymphoid tissue is found. Most commonly they are manifest by the development of lymphadenopathy at single or multiple sites, although primary extranodal presentations account for up to 20% of non-Hodgkin's lymphoma. The prognosis is determined by the specific subtype of lymphoma and the anatomical extent of disease and its bulk, the clinical course ranging from months to years.

The guiding principles of management are broadly the same as for the leukaemias. The precise diagnosis is established, appropriate further investigation is conducted to allow a management plan to be formulated, both for the short and long term, and the situation is clearly explained to the patient.

Lymphomas are currently classified on the basis of histological appearance into:

- Hodgkin's lymphoma
- non-Hodgkin's lymphoma.

The distinction between lymphoid leukaemia and lymphoma is not always clear.

### HODGKIN'S LYMPHOMA (HL)

This is a rare disease involving primarily the lymph nodes. The incidence in the UK is approximately 2.5/100 000 with a male to female ratio of 1.3 : 1. Its peak incidence is in the third decade. The incidence is stable.

#### Aetiology

There is epidemiological evidence linking previous infective mononucleosis with HL and up to 40% of patients with HL have increased EBV antibody titres at the time of diagnosis and several years prior to the clinical development of HL. EBV DNA has been demonstrated in tissue from patients with HL. These data suggest a role for EBV in pathogenesis. Other viruses have not been detected. Other environmental and occupational exposure to pathogens have been postulated.

#### Pathology

The hallmark of HL is the Reed–Sternberg cell (Fig. 9.10) which is usually derived from germinal centre B cells or, rarely, peripheral T cells. CD30 and CD25 are almost always expressed in the majority of cases of classical HL.

The WHO classification of HL is shown in Table 9.16. Classical HL can be divided into:

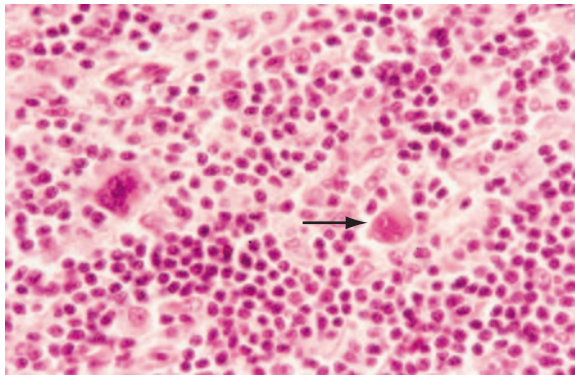
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**Table 9.16** Pathological classification of Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis HL
Lymphocyte-rich HL
Mixed cellularity HL
Lymphocyte-depleted HL

From Harris NL et al. (1999) *Journal of Clinical Oncology* 17: 3835–3849



**Fig. 9.10** Histological appearance of Hodgkin's lymphoma. There is a background rich in benign small lymphocytes and histiocytes together with scattered mononuclear Hodgkin's cells and a classical malignant binucleate Reed-Sternberg cell (arrow) to the right of centre. Courtesy of Dr AJ Norton.

- **Nodular sclerosing HL** (70% of cases) where many fibrotic bands are present. This type is typically seen in young females, involving particularly lymph nodes in the mediastinum and neck.
- **Lymphocyte-rich HL** appears in 5% and is characterized by an infiltrate of many small lymphocytes and Reed-Sternberg cells. It often occurs in peripheral lymph nodes. It is often an indolent disease.
- **Mixed cellularity HL**. Approximately 25% of cases have mixed cellularity with lymphocytes, eosinophils, neutrophils and histiocytes. Reed-Sternberg cells are present but no fibrotic bands. It is more common in men and is associated with B symptoms.
- **Lymphocyte-depleted HL** is rare and there is lack of cellular infiltrate with numerous Reed-Sternberg cells. It is seen in HL associated with HIV.

In addition to classical HL, *nodular lymphocyte-predominant HL* (5% of cases) contains malignant L and H cells (lymphocytic and/or histiocytic Reed-Sternberg cell variants, also called 'popcorn' cells) which are positive for CD20, CD45, BCL6, CD79a without expressing CD15 or CD30.

### Pathogenesis

This remains unclear but several factors have been identified in classical HL:

**B cells.** There is a lack of expression of surface immunoglobulin (or BCR) in the Hodgkin and Reed-Sternberg cell. This may be due to destructive mutations or non-functional rearrangements in the immunoglobulin genes, and/or a lack of immunoglobulin-specific transcription factors.

**Resistance to apoptosis.** The malignant lymphoma cell may have acquired a Fas-resistant phenotype that prevents its death in the germinal centre. Destruction mutations have been found in the Fas gene inactivating the Fas pathway.

**Development of non-regulatory growth signals.** It has been suggested that the transforming Reed-Sternberg cell may acquire self-sufficiency in growth signals and develop non-regulated, permanent transcription activity by NFκB. Mutations have been reported in the  $\text{I}\kappa\text{B}\alpha$  gene

**Environmental.** A delayed exposure to ubiquitous infections in childhood may suggest that HL is a late infection with a common virus. See EBV above.

**Genetic factors.** Monozygotic twins have a 100 times greater risk of concordantly developing HL. No increase has been seen in dizygotic twins.

It is clear that several pathways may lead to HL but the central issue must be that lymphocytes of the B-cell lineage not expressing immunoglobulins somehow escape apoptosis.

### Clinical features

- Lymph node enlargement, most often of the cervical nodes (other causes are shown in Table 9.17); these are usually painless and with a rubbery consistency.
- Enlargement of the spleen/liver.
- 'B' symptoms: fever, (25%) drenching night sweats, weight loss of > 10% bodyweight (see Table 9.18).
- Other constitutional symptoms, such as pruritus, fatigue, anorexia and, occasionally, alcohol-induced pain at the site of enlarged lymph nodes.
- Symptoms due to involvement of other organs (e.g. lung – cough and breathlessness).

### Investigations

- **Blood count** may be normal, or there can be a normochromic, normocytic anaemia. Lymphopenia and occasionally eosinophilia are present.
- **Erythrocyte sedimentation rate (ESR)** is usually raised and is an indicator of disease activity.
- **Liver biochemistry** is often abnormal, with or without liver involvement.
- **Serum lactate dehydrogenase**; raised level is adverse prognostic factor.
- **Uric acid** is normal or raised.
- **Chest X-ray** may show mediastinal widening, with or without lung involvement.
- **CT scans** show involvement of intrathoracic nodes in 70% of cases. Abdominal or pelvic lymph nodes are also found. It is the investigation of choice for staging

**Table 9.17** Differential diagnosis of cervical lymph node enlargement

<b>Infections</b>	<b>Primary lymph node malignancies</b>
<b>Acute</b>	
Pyogenic infections	Hodgkin's lymphoma
Infective mononucleosis	Non-Hodgkin's lymphoma
Toxoplasmosis	Chronic lymphocytic leukaemia
Cytomegalovirus infection	Acute lymphoblastic leukaemia
Infected eczema	
Cat scratch fever	
Acute childhood exanthema	
<b>Chronic</b>	<b>Secondary malignancies</b>
Tuberculosis	Nasopharyngeal
Syphilis	Thyroid
Sarcoidosis	Laryngeal
HIV infection	Lung
	Breast
	Stomach
<b>Connective tissue disorders</b>	<b>Miscellaneous</b>
Rheumatoid arthritis	Kawasaki's syndrome
<b>Drug reactions</b>	
Phenytoin	

(Table 9.18), although PET scanning is increasingly being used.

- **Bone marrow aspirate and trephine biopsy** are seldom done but show involvement in patients with advanced disease. This is unusual at initial presentation.
- **Lymph node biopsy** is required for a definitive diagnosis (Fig. 9.10).

A typical chest X-ray and CT scan in one patient are shown in Figure 9.11.

### Management

Treatment is almost always recommended and undertaken with curative intent and considerable expectation of success (Figs 9.12 and 9.13). Expectant management may be reasonable in some cases of lymphocyte-predominant Hodgkin's lymphoma, although the rationale for this must be made clear to the patient and there needs to be close early surveillance.

Specific treatment is based otherwise on the anatomical distribution of disease, its 'bulk' and the presence or absence of 'B' symptoms. ('stage': Table 9.18).

#### 'Early stage' (I<sup>A</sup>, II<sup>A</sup> no bulk)

The treatment of choice now is brief chemotherapy followed by involved field irradiation. Extended field megavoltage irradiation was used with 70% of patients being cured, and probably half of those in whom it failed were 'salvageable' with combination chemotherapy. Large field irradiation has come under recent criticism because of a significantly increased incidence of breast cancer in young women, lung cancer in smokers and cardiac disease following supradiaphragmatic 'mantle' field irradiation. 'Moderate' chemotherapy ABVD (Table 9.10), 2–4 cycles (i.e. non sterilizing and low secondary cancer risk) followed by involved field irradiation (20–30 Gy) has become

**Table 9.18** Cotswolds modification of Ann Arbor staging classification

Stage	Description
Stage I	Involvement of a single lymph-node region or lymphoid structure (e.g. spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site
Stage II	Involvement of two or more lymph-node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph-node region(s) on the same side of the diaphragm (II <sub>E</sub> ). The number of anatomic regions involved should be indicated by a subscript (e.g. II <sub>3</sub> )
Stage III	Involvement of lymph-node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (IIIS) or by localized involvement of only one extranodal organ site (IIIE) or both (IIISE)
III1	With or without involvement of splenic, hilar, coeliac, or portal nodes
III2	With involvement of para-aortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph-node involvement

#### Designations applicable to any disease state

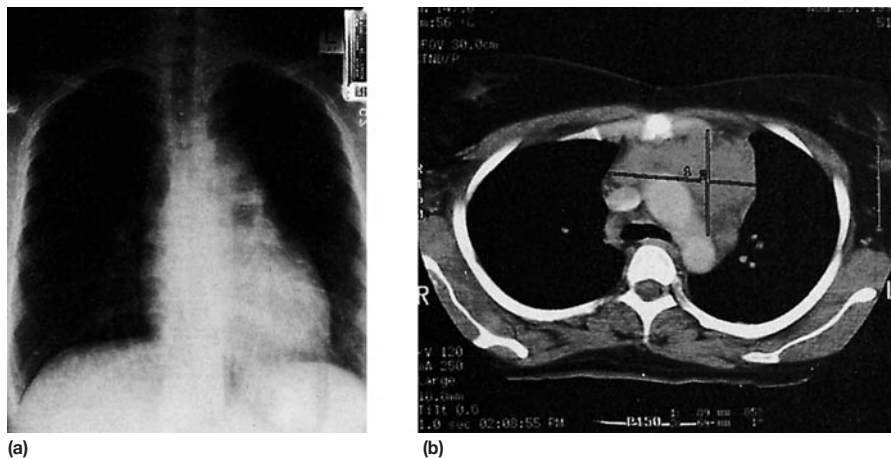
A	No symptoms
B	Fever (temperature > 38°C), drenching night sweats, unexplained loss of more than 10% of body weight within the previous 6 months
X	Bulky disease (a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension greater than 10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

From Diehl V et al. (2004) Hodgkin's lymphoma – diagnosis and treatment. Reprinted with permission from Elsevier (*Lancet Oncology* 5: 19–26).

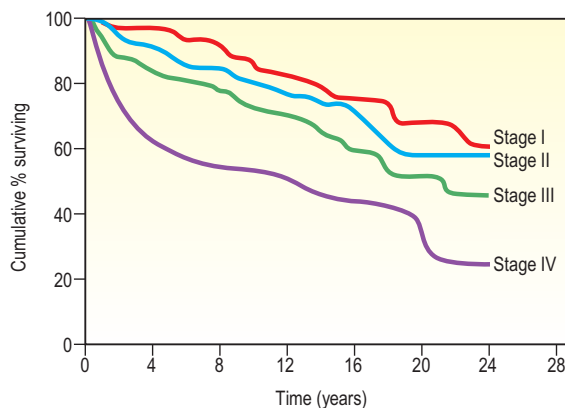
standard care. Current trials are evaluating the role of PET scanning to see if patients who become 'PET' negative can be spared irradiation altogether.

#### Advanced disease

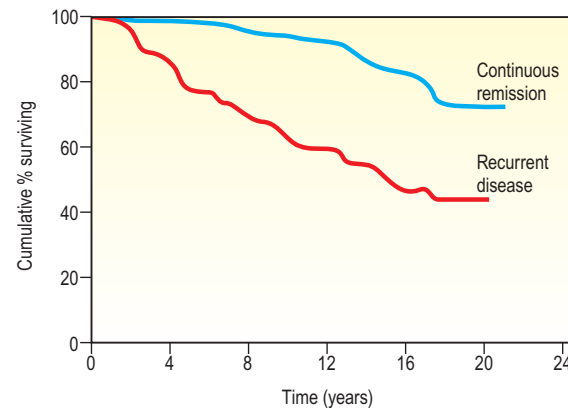
This is also curable for a significant proportion of patients, the median survival exceeding 5 years. Cyclical combination chemotherapy with or without irradiation to sites of 'bulk' disease is the treatment of choice for all these patients. The 'gold standard' combination is ABVD (Table 9.10) given to a total of 6–8 cycles each month, the blood count permitting. All patients with mediastinal bulk receive irradiation whether or not the CT scan returns to normal. It may well be that in the future PET scanning, as for those with early disease, may reduce the need for irradiation. This approach will be curative for approximately 50–60% of those with advanced disease, the major potential toxicity in the short term being



**Fig. 9.11** (a) Chest X-ray of a large mediastinal mass that is due to Hodgkin's lymphoma. (b) CT scan of the same patient. The mass is indicated here by crossed lines.



**Fig. 9.12** Survival in Hodgkin's lymphoma related to Ann Arbor stage at presentation.



**Fig. 9.13** Survival of patients with Hodgkin's lymphoma. From Oza AM et al. (1993) Patterns of survival in patients with Hodgkin's disease: long follow-up in a single centre. From Oza AM et al. (1993) *Annals of Oncology* 4: 385-392, with permission.

myelosuppression with a mortality of ~ 1%. In the long term the risks are to the heart and lungs. Infertility and second malignancy are much less common than following the previous gold standard therapy MOPP (or MVPP). The 15-year survival of this group of patients is approximately 65%.

Twenty-five per cent of patients fail to achieve remission of advanced Hodgkin's lymphoma with the initial ABVD chemotherapy. 'Intensification' of treatment by increasing the number of drugs, alternating combinations, or hybrids may have reduced this proportion in resistant patients. Recently two schedules, one given cyclically with many drugs, some in high doses, and the other as a continuous 12-week programme of chemotherapy (both complemented with significant amounts of irradiation) have been reported to reduce the failure rate substantially in the short term. Confirmation of these results with longer follow-up is awaited. Clearly, the development of a prognostic index to identify these resistant patients prospectively would be a major step forward, although the highest-risk group is very small. The alternative to the strategy of overtreating some for

the benefit of the few, is to undertreat the few to the advantage of the many, and then 'salvage' the failures. Limited success with myeloablative chemotherapy with haemopoietic stem cell rescue has been reported in those with 'refractory disease'.

Recurrent Hodgkin's lymphoma, certainly after 'conventional'-dose chemotherapy is potentially very serious though not necessarily fatal. The median survival from the first recurrence is more than 10 years; it may be influenced by the duration of first remission: it may not be so good if failure occurs after more intensive initial therapy. Second, and third remissions are achieved more often than not with 'appropriate' re-induction chemotherapy. It is conventional to consolidate remission in this group when possible, with high-dose therapy and peripheral blood cell progenitor rescue (PBPCR). Registry data suggest that this may be curative in up to 50%, although follow-up does not extend beyond 15 years.

Experimental approaches for recurrent and refractory disease include new cytotoxic drugs, monoclonal antibodies and reduced-intensity allogeneic transplantation.

**FURTHER READING**

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- Thomas RK et al. (2004) Hodgkin's lymphoma – molecular biology of Hodgkin and Reed–Sternberg cells. *Lancet Oncology* 5: 11–18.

**NON-HODGKIN'S LYMPHOMA (NHL)**

These are malignant tumours of the lymphoid system classified separately from Hodgkin's lymphoma. Most (70%) are of B cell origin although T cell tumours are increasingly being recognized.

The incidence of these tumours is approximately 15/100 000 per year in developed countries, an incidence which has increased over the last 20–30 years. There is a slight male predominance. The median age of presentation is 55–75 years.

**Aetiology**

The cause is unknown. There is wide geographical variation which probably reflects different environmental factors. NHL is associated with the EBV virus (Burkitt's lymphoma) and the human T cell lymphotropic virus which is prevalent in Japan, Africa, South America and the Caribbean. Herpesvirus 8 is associated with primary effusion lymphomas and Castleman's disease; there is an increase in lymphoma in patients with AIDS. *Helicobacter pylori* is an aetiological factor in gastric MALT lymphoma.

Lymphomas also occur in congenital immunodeficiency, post-transplantation and in autosomal family cancer syndromes (Table 9.3). Other causes, e.g. occupation, dietary and exposure to chemicals, have been linked to the increasing incidence but the evidence is unconfirmed.

**Pathogenesis**

There is a malignant clonal expansion of lymphocytes which might occur at a different stage of lymphocyte development. In general, neoplasms of non-dividing mature lymphocytes are indolent whereas those of proliferating cells (e.g. lymphoblasts, immunoblasts) are much more aggressive. This malignant transformation is usually due to errors in gene rearrangements which occur during the class switch, or gene recombinations for immunoglobulins and T cell receptors. Thus, many of the

errors occur within immunoglobulin loci or T cell receptor loci. For example, an abnormal gene translocation may lead to the activation of a proto-oncogene next to a promoter sequence for the immunoglobulin heavy chains (Ig-H).

**Cytogenetic features** (Table 9.19)

Burkitt's lymphoma was the first tumour in which a cytogenetic change was shown to involve the translocation of a specific gene. The most frequent change is a translocation between chromosomes 8 and 14 in which the *myc* oncogene moves from chromosome 8 to a position near the constant region of the immunoglobulin heavy chain gene on chromosome 14, resulting in upregulation of *myc*. Similar rearrangements involving the light chain loci are seen in the alternative Burkitt's lymphoma translocations between chromosome 8 and either chromosome 2 or 22. Other somatic cytogenetic abnormalities associated with human lymphoma are the t(14;18) in follicular lymphoma, involving upregulation of the *Bcl-2* gene, or the upregulation of *Bcl-1* (also called cyclin D1) as a result of t(11;14) in mantle cell lymphoma.

**Immunophenotypes**

All NHL B cells express CD20 and surface immunoglobulin. Individual lymphomas vary in their expression, e.g. follicular lymphomas express CD10, mantle cell CD43, while the diffuse large B cell lymphoma expresses both CD10 and CD43. They can be used in the classification. T cell lymphomas do not express CD20 but variably express CD3, 4, 8 and 30.

**Classification**

The WHO classification (2001) which is based on the Revised European American Lymphoma (REAL) system is shown in Table 9.20. Previous classifications have divided lymphomas into indolent (or low grade) and aggressive (or high grade), and the WHO classification has been modified to include aggressive or highly aggressive lymphomas.

**Clinical features**

- *Peripheral lymphadenopathy.* Most patients present with painless, superficial lymph node enlargement.
- *Systemic symptoms (B symptoms).* Fever, sweats, anorexia and weight loss.
- *Extranodal presentation.* This is more common than in HL and may involve the gastrointestinal tract, lung,

**Table 9.19** Chromosome translocations in non-Hodgkin's lymphoma

Type	Translocation	Genes	Function
Follicular	t(14;18)	<i>Bcl-2/IgH</i>	Suppresses apoptosis
Lymphoplasmacytic	t(9;14)	<i>PAX5</i>	Transcription factor
Mantle cell	t(11;14)	<i>Bcl-1</i> (cyclin D1)	Cell cycle regulator
Diffuse large B cell	t(3;4)	<i>Bcl-6</i>	Cell cycle regulator
Burkitt's	t(8;14) t(2;8)	<i>c-myc</i> and Ig	Transcription factor
Anaplastic	t(2;5)	<i>NPM1/ALK</i>	Tyrosine kinase
MALT	t(11;18)	<i>BIRC3/MALT1</i> fusion protein	Suppresses apoptosis

MALT, mucosal associated lymphoid tissue

**Table 9.20 Modified WHO classification of lymphoid neoplasms other than ALL (2001)**

<b>B cell lymphomas</b>	
Precursor B cell lymphoma	Precursor B lymphoblastic lymphoma/leukaemia ( <i>highly aggressive</i> )
Mature B cell lymphoma	Chronic lymphocytic leukaemia/small lymphocytic lymphoma Lymphoplasmacytic lymphoma Splenic marginal zone lymphoma Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) Nodal marginal zone B cell lymphoma Follicular lymphoma ( <i>aggressive</i> ) Mantle cell lymphoma Diffuse large B cell lymphoma ( <i>aggressive</i> ) Mediastinal (thymic) large B cell lymphoma Intravascular large B cell lymphoma Primary effusion lymphoma Burkitt's lymphoma/leukaemia ( <i>highly aggressive</i> )

<b>T/NK cell lymphomas</b>	
Precursor T cell lymphoma	Precursor T cell lymphoblastic leukaemia/lymphoma ( <i>highly aggressive</i> ) Blastic NK cell lymphoma
Mature T/NK cell lymphoma	Adult T cell leukaemia/lymphoma ( <i>very aggressive</i> ) Extranodal NK/T cell lymphoma, nasal type Enteropathy-type T cell lymphoma Hepatosplenic T cell lymphoma Subcutaneous panniculitis-like T cell lymphoma Mycosis fungoides Sézary syndrome Primary cutaneous anaplastic large cell lymphoma Peripheral T cell lymphoma, unspecified ( <i>aggressive</i> ) Angioimmunoblastic T cell lymphoma Anaplastic large cell lymphoma ( <i>aggressive</i> )

NK, natural killer

Modified from Jaffe ES, Harris NL, Stein H, Vardiman JW (eds) (2001) *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press

brain, testes, thyroid and skin. Abdominal involvement may reveal hepatosplenomegaly. Skin involvement (T cell lymphomas) presents as mycosis fungoides (p. 1352) and Sézary syndrome (p. 1353).

- Oropharyngeal involvement occurs rarely.
- HIV predisposes to NHL.

### Investigations

- **Full blood count.** Normochromic, normocytic anaemia, an elevated white cell count or neutropenia and thrombocytopenia are suggestive of bone marrow infiltration.
- **ESR** may be elevated.
- **Urea and electrolytes.** Patients may have renal impairment as a consequence of ureteric obstruction secondary to intra-abdominal or pelvic lymph node enlargement.
- **Serum uric acid level** may be raised.
- **Liver biochemistry.** This may be abnormal if there is hepatic involvement.
- **Serum lactate dehydrogenase and  $\beta_2$ -microglobulin** are prognostic indicators.
- **Serum immunoglobulins** – decreased levels may occur with paraproteinaemia.
- **Chest X-ray, CT scans** of chest, abdomen and pelvis. **PET and gallium scans** help in staging.
- **Bone marrow aspirate** and trephine biopsy are always performed.
- **Lymph node biopsy** (or Trucut needle biopsy, often under radiological guidance, in the case of surgically inaccessible nodes). Immunophenotyping and cytogenetic/molecular analysis (DNA micro-array analysis), to distinguish type of NHL.

### Follicular lymphoma

These comprise 20% of all B cell lymphomas. Most patients with follicular lymphoma present feeling well but with painless lymphadenopathy. Investigation usually reveals multiple sites of disease: involvement of the bone marrow is common. Managed conservatively it is a remitting and recurring disease with a clinical course running over a median of 10 (1–20 years) years during which there will be about three 'episodes' of relapse. Death occurs because of resistant disease, transformation to diffuse large B cell lymphoma (LBCL) or the effects of therapy.

The 'well' patient should be managed with no specific therapy until progression is documented. Repeat biopsy should be performed at this time in case there has been histological transformation to LBCL as this has specific implications for therapy.

The indications for the initiation of therapy are:

- **Stage I presentation (10–15%).** This is treated with 'involved' field irradiation, which almost invariably induces 'complete remission'. The median time to progression is 10–15 years. Some patients may be cured. There is no evidence that mortality is affected by treatment, but the therapy has a low morbidity and mortality.
- **Advanced disease** with:
  - constitutional 'B' symptoms
  - 'organ impairment', i.e. bone marrow failure
  - 'bulky' disease, i.e. lymph node mass > 10 cm
  - progressive disease after expectant management, documented if necessary on two scans 3 months apart

## Malignant disease

- histological transformation.
- *Philosophy of patient and physician.*

A specific follicular lymphoma international prognostic index (FLIPI) has been formulated, defining 'low', 'intermediate' and 'high' risk groups. This may provide a more objective basis for the decision to begin therapy, and with what.

A recent study showed that survival can be predicted by the different genes expressed on accompanying T cells and dendritic cells (not tumour cells) identified by DNA micro-array analysis of tumour tissue.

### Treatment options

Standard initial treatment in the UK is with an alkylating agent, e.g. chlorambucil, or a combination containing an alkylating agent, e.g. COP (cyclophosphamide, vincristine and prednisolone), given usually over 3–6 months. The overall response rate is high (~80%), but the proportion of complete remissions is low. It may be possible to push those patients for whom the first treatment fails into remission with a second therapy. Progression is the rule after a median of 2–3 years: there is no evidence of cure. Provided transformation has not occurred, further remissions (an average of three) can be achieved with the same or other single agents or combination of drugs. The remission becomes significantly shorter after the third, and death supervenes. Quality of life, except during treatment (and often during treatment), is normal until the disease becomes refractory.

Thus, managed conventionally, follicular lymphoma is a paradigm for the 'indolent' but incurable malignancy. Whilst this overall approach is acceptable for the elderly it is manifestly unsatisfactory for the younger patient.

### Other therapies

- Aggressive combination chemotherapy gives high complete remission rates and molecular remission.
- High-dose chemotherapy with PBPCR. Open Phase II trials, comparing outcome with historical controls and now Phase III trials suggest an advantage over conventional therapy in first or second remission (molecular remission also occurs).
- Antibody therapy. The monoclonal antibody rituximab induces remission (partial) in 30–70% of patients, almost without toxicity. Molecular remissions are observed. Complications include the cytokine release syndrome, with fever, vomiting and allergic reactions (angio-oedema, bronchospasm and dyspnoea).
- Rituximab/chemotherapy combination. These have now been reported to improve the complete remission rate (with disappearance of Bcl-2 positive cells from the bone marrow in 100% of patients), freedom from progression and event-free survival, even though there is (as yet) no effect on overall survival. This may become the standard therapy for CD20 positive lymphoma.
- Antibody-targeted irradiation. This short-term therapy using anti-CD20 to deliver either  $^{131}\text{I}$  or  $^{90}\text{Y}$  yields 'durable' complete remission.

In addition, two major additional biological therapies are under evaluation:

- vaccine therapy
- reduced intensity allogeneic transplantation.

The median survival of follicular lymphoma appears to have been extended from 5 years to 10 years following the introduction of alkylating agent chemotherapy. There are grounds for optimism that the new approaches outlined above will improve it further or even result in cure. The challenge, beyond giving the best current advice to the patient today is to devise the initial strategy which will convert follicular lymphoma from a treatable to a curable disease. If the strategy brings greater potential toxicity, the risks have to be weighed carefully against *potential* long-term benefits. The same strategy will not be right for all patients.

### Lymphoplasmacytic lymphoma

This is an uncommon B cell lymphoma often presenting with heavy bone marrow infiltration, and is almost the only lymphoma to be diagnosed on bone marrow biopsy alone. There is frequently splenomegaly and anaemia, and in some an associated paraprotein IgM with associated immune paresis (Waldenström's macroglobulinaemia; WM) occurs. Patients in this group are usually older and commonly present with the symptoms of bone marrow failure or hyperviscosity. It may be a chance diagnosis.

Management may be expectant, the indications for treatment being:

- symptomatic anaemia
- recurrent infection
- symptoms of hyperviscosity, e.g. headache, visual disturbance
- progression.

Treatment is supportive in the first instance. Transfusion and/or erythropoietin is given for the anaemia, particularly if chemotherapy is being given. Plasmapheresis is an excellent means of controlling the paraproteinaemia both in the short and longer term.

Chlorambucil is the conventional treatment, the 'response criteria' for WM being different from those of the rest of the lymphomas. The paraprotein will be reduced by 50% (response) in 50–70% of cases in the short term. Progression is the rule and as with follicular lymphoma there may be further response. The purine analogue fludarabine is also 'effective'.

It is not clear how much the use of chemotherapy has actually influenced overall survival, and quality of life is poorly recorded. The median survival is several years.

A heightened awareness of this relatively uncommon but symptomatic lymphoma has led to more enthusiastic exploration of the new therapies being tested on the other B cell lymphomas (see above).

### Mantle cell lymphoma

This is an uncommon lymphoma (6% of non-Hodgkin's

lymphoma) with a median survival of 3–4 years. It occurs predominantly in the elderly and is almost always widely disseminated at presentation, with lymphadenopathy and frequent involvement of the bone marrow and gastrointestinal tract. Treatment is often compromised by co-morbidity.

Combination chemotherapy is the most usual first-line therapy, if possible: the response rate may be above 50% but the complete remission rate is low. The addition of rituximab has been reported to improve this. Intensifying chemotherapy appears to improve the results, but recurrence is almost invariable. New approaches are greatly needed.

### Large B cell lymphoma (DLBCL)

This is the commonest lymphoma and is almost invariably fatal without therapy within months, and was previously classified as aggressive or high-grade lymphoma. Now > 50% of young patients are cured. The only indications for a palliative approach at the initial presentation are extreme co-morbidity and the will of the patient. Expectant management is inappropriate. Patients present with rapidly progressive lymphadenopathy and progressive infiltration of many organs, e.g. spinal cord, gastrointestinal tract.

#### Treatment

Treatment decisions are based on the stage and may be tailored by the International Prognostic Index (Box 9.5).

In the absence of relevant co-morbidity all patients should receive cyclical combination chemo-immunotherapy, the gold standard being cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone and rituximab (CHOP + R). Sixty to seventy percent of those with early stage disease (I, II<sub>A</sub> without bulk) may expect to be cured either with 6 cycles or 3 cycles followed by involved field irradiation. Those with more extensive disease conventionally receive 6–8 cycles. There has been a suggestion that decreasing the interval between cycles may be feasible (with growth factor support), and this may improve the results. There are conflicting reports about the advantages of increasing the intensity of initial treatment for those perceived to be at 'high risk'. There is also controversy about the indications for central nervous system prophylaxis and which form it should take.

For those with advanced disease the cure fraction, which was about 30%, has been increased with the incorporation of rituximab as standard therapy, by 15%.

#### **i** Box 9.5 Prognostic factors in non-Hodgkin's lymphoma

##### Adverse factors:

- Age > 60 years
- Stage III or IV, i.e. advanced disease
- High serum lactate dehydrogenase level
- Performance status (ECOG 2 or more)
- More than one extranodal site involved

ECOG, Eastern Cooperative Oncology Group

Progression during therapy or failure of the initial treatment to achieve complete remission has a very poor prognosis. Second-line therapy e.g. platinum or gemcitabine should be initiated with a view, if possible, to high-dose therapy and PBPCR if further response is achieved. This is not usually possible and long-term success is rare. Proper consideration should be given to palliation or experimental therapy. In contrast, recurrence after a disease-free interval is potentially still curable. The complete remission rate after a second treatment is 40–50%: it is conventional to consolidate such remissions with high-dose therapy which will cure perhaps half (i.e. 25% 'cure' overall of the selected younger patients in whom curative therapy is attempted).

### Burkitt's lymphoma

This is an uncommon lymphoma in the western world. It is endemic to Africa in the mosquito belt: there is a close association with the Epstein–Barr virus and it is a disease with a very high proliferative index which is very rapidly fatal without therapy.

The clinical presentation worldwide is usually that of lymphadenopathy, often with an abdominal mass and frequently with bone marrow infiltration (and 'leukaemia'). Central nervous system involvement is common, up to 30% having meningitis at the time of presentation. In Africa, by far the two commonest presentations are the abdominal mass or a large tumour involving the jaw (Fig. 9.14); the bone marrow and central nervous system are also frequently involved.

#### Treatment

Treatment, whilst undoubtedly toxic with both morbidity and mortality, is much less dangerous than the disease. It relieves symptoms and is potentially curative in a high proportion of cases.

*Supportive care* is with hydration and prevention of hyperuricaemia with allopurinol associated with rapid tumour lysis. Rasburicase is a major advance.



**Fig. 9.14** A child with Burkitt's lymphoma.

## Malignant disease

### Drug therapy

The management of the newly diagnosed case in Europe is straightforward but in Africa it may be very difficult.

Cyclical combination chemotherapy, incorporating at least high doses of cyclophosphamide and methotrexate as well as vincristine and doxorubicin, is followed by further cycles including high-dose cytarabine depending on the extent of disease at presentation. Up to six cycles must be given at about monthly intervals. While both the high-dose systemic methotrexate and cytarabine cross the blood–brain barrier in tumoricidal doses, many prefer to supplement them with intrathecal chemotherapy also. The role of cranial irradiation is unclear. In Africa, treatment can be difficult to coordinate but is based on the same principles.

This treatment will be tolerated quite well by the majority of patients, who tend to be young. The reported complete remission rate is very high, 70–90% depending on age (and excluding those with concurrent HIV infection), with very few recurrences occurring after 1 year. Hence 60–70% may be cured. Demonstrating improvements on this will be difficult but rituximab may have a role.

The management of progression despite treatment is difficult and rarely successful. Remission induction with alternative therapy, possibly including cisplatin, is the first line of attack. If achieved, it is consolidated with high-dose therapy or allogeneic transplantation.

### T Cell lymphomas

These are much less common than the B cell counterparts. In the main, the overall treatment strategies are the same, but success is much more limited.

### Primary extranodal lymphoma

The WHO classification does not distinguish between primarily nodal or extranodal at the time of presentation if the histological picture is the same.

### Primary cerebral lymphoma

This is a very aggressive disease with survival untreated measured in months. It is particularly dangerous within the setting of HIV infection. Irradiation plus corticosteroids has, until recently, been the treatment of first choice. It is rarely curative, and may be associated with severe cerebral toxicity when given in high enough doses to eliminate lymphoma, particularly in the elderly. Even following irradiation, the median time to progression is less than a year. Subsequent management is palliative.

Recent data suggest that a very aggressive approach, involving sequential very high doses of methotrexate followed by cytarabine may obviate the need for irradiation and be curative in a proportion of cases. Followed by irradiation this treatment may eliminate lymphoma in an even higher proportion of cases, but the potential central nervous system toxicity is considered by most to be unacceptable.

### Primary gastric lymphoma

In a high proportion of cases, particularly in Northern Italy, lymphoma is associated with *Helicobacter pylori* infection (p. 283). Biopsy of the gastric lesion usually shows lymphoma ('low-grade' B cell pathologically, of extranodal marginal zone type) and *H. pylori* is usually detected. Treatment to eradicate *H. pylori* is with antibiotics (and a proton pump inhibitor) for 2 weeks. Symptomatic relief is usually rapid. Provided there is no evidence of disease outside the stomach, further treatment is not given but surveillance endoscopy is performed, first at 3 months then 6-monthly. Partial or complete remission is the rule, but may take many months to achieve. Treatment of progression (always confirmed by biopsy) is with more antibiotics initially. Both irradiation and alkylating agent therapy are effective. Rituximab is being investigated. There is no role for surgery in the management of gastric lymphoma.

### Primary cutaneous lymphoma (see p. 1352)

This is much commoner than generally perceived. It must be carefully distinguished from cutaneous infiltration with lymphocytes in a patient with nodal disease. It is usually of T cell origin (Sézary syndrome, mycosis fungoides). It is often multifocal and responds well to local therapy even when it appears histologically aggressive. Survival may be very long without chemotherapy, and in many cases treatment may only serve to disrupt the quality of life.

#### FURTHER READING

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## MYELOMA

Myeloma is a malignant disease of the plasma cells of bone marrow, accounting for 1% of all malignant disease. There is a clonal expansion of abnormal, proliferating plasma cells producing a monoclonal paraprotein, mainly IgG (55%) or IgA (20%) and rarely IgD. The paraproteinaemia may be associated with excretion of light chains in the urine (Bence Jones protein), which are either kappa or lambda. In approximately 20% there is no paraproteinaemia, only light chains in the urine.

### Clinicopathological features

Myeloma is a disease of the elderly, the median age at presentation being over 60 years. It is rare under 40 years of age. The annual incidence is 4 per 100 000 and it is commoner in males and in black Africans but less common in Asians. There is:

- **Bone destruction**, often causing fractures of long bones or vertebral collapse (which can cause spinal cord compression) and hypercalcaemia
- **Bone marrow infiltration** with plasma cells, resulting in anaemia, neutropenia, thrombocytopenia, together with production of the paraprotein which may (rarely) result in symptoms of hyperviscosity
- **Renal impairment** (p. 637) owing to a combination of factors – deposition of light chains in the renal tubules, hypercalcaemia, hyperuricaemia, use of NSAIDs and (rarely) in patients who have had the disease for some time, deposition of amyloid.

In addition there is a reduction in the normal immunoglobulin levels (immune paresis), contributing to the tendency for patients with myeloma to have recurrent infections, particularly of the respiratory tract.

### Cytogenetics

Abnormalities of chromosomes were found in only 50% of patients with old techniques. However, with fluorescent in situ hybridization and microarray techniques abnormalities are found in most. Abnormalities of chromosome 13 and hypodiploidy have been shown to be associated with poor survival, as have t(4;14), t(14;16) and p53 deletions.

### Bone metastases

There is dysregulation of bone remodelling which leads to the typical lytic lesions, e.g. spine, skull. In myeloma there is increased osteoclastic activity with no increased osteoblast formation of bone. Bisphosphonates that inhibit osteoclast activity are useful in myeloma but surprisingly there is no increase in bone deposition (see below).

Adhesion of stromal cells to myeloma cells stimulates the production of RANKL, IL-6, and also VEGF (which plays a role in angiogenesis). RANKL also stimulates osteoclast formation and the lytic lesions (see Fig. 9.1). Myeloma cells also produce dickkopf-1 (DKK1) which *inhibits* osteoblast activity and therefore production of new bone. This occurs because DKK1 binds to the Wnt co-receptor, lipoprotein receptor-related protein 5 (LRP5), inhibiting Wnt signalling and osteoblast differentiation.

### Symptoms

- Bone pain – most commonly backache owing to vertebral involvement (60%)
- Symptoms of anaemia
- Recurrent infections
- Symptoms of renal failure (20–30%)
- Symptoms of hypercalcaemia
- Rarely, symptoms of hyperviscosity and bleeding due to thrombocytopenia.

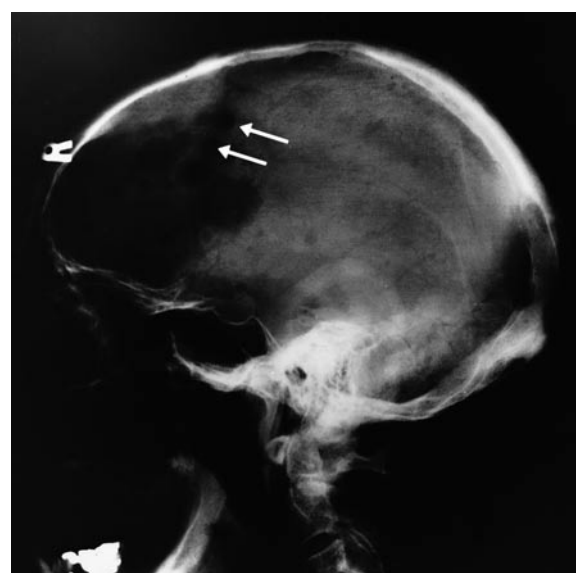
Patients can be asymptomatic, the diagnosis being suspected by 'routine' abnormal blood tests. Life-threatening complications are shown in Box 9.6.

### Box 9.6 Life-threatening complications of myeloma

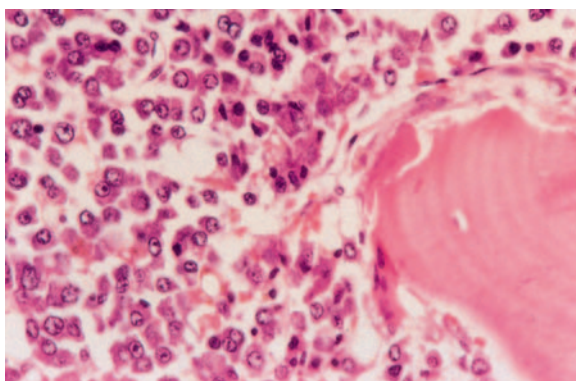
- Renal impairment – often a consequence of hypercalcaemia – requires urgent attention and patients may need to be considered for long-term peritoneal or haemodialysis.
- Hypercalcaemia should be treated by rehydration and use of bisphosphonates such as pamidronate.
- Spinal cord compression due to myeloma is treated with dexamethasone, followed by radiotherapy to the lesion delineated by a magnetic resonance imaging (MRI) scan.
- Hyperviscosity due to high circulating levels of paraprotein may be corrected by plasmapheresis.

### Investigations

- **Full blood count.** Hb is normal or low. WCC is normal or low. The platelet count is normal or low.
- **ESR.** This is almost always high.
- **C-reactive protein** is always raised.
- **Blood film.** There may be rouleaux formation as a consequence of the paraprotein.
- **Urea and electrolytes.** There may be evidence of renal failure (see above)
- **Serum  $\beta_2$ -microglobulin** > 2.5 mg/L } useful in
- **Serum lactate dehydrogenase (LDH)** } prognosis.
- **Serum calcium** is normal or raised.
- **Serum alkaline phosphatase** is usually normal.
- **Total protein** is normal or raised.
- **Serum albumin** is normal or low.
- **Serum protein electrophoresis or immunofixation** characteristically shows a monoclonal band.
- **Uric acid** is normal or raised.
- **Skeletal survey.** This may show characteristic lytic lesions, most easily seen in the skull (Fig. 9.15). CT,



**Fig. 9.15** Myeloma affecting the skull. Note the rounded lytic translucencies produced by infiltration of the skull with myeloma cells.



**Fig. 9.16 Multiple myeloma.** Histology shows replacement of the medullary cavity by abnormal plasma cells with some binucleate forms. A residual bony trabeculum is present towards the right. Courtesy of Dr AJ Norton.

MRI and PET are used in plasmacytomas (bone lesions without plasma cells in the blood).

- **DXA scanning** is valuable for follow-up of treatment.
- **24-hour urine immunofixation** is used for assessment of light-chain excretion.
- **Bone marrow aspirate** or trephine shows characteristic infiltration by plasma cells (Fig. 9.16). Amyloid may be found.

### Diagnosis

Two out of three diagnostic features should be present:

- paraproteinaemia or Bence Jones protein
- radiological evidence of lytic bone lesions
- an increase in bone marrow plasma cells.

An international prognostic index which would help in staging the disease is being developed; the Durie–Salmon criteria are no longer used.

**Monoclonal gammopathy of unknown significance (MGUS).** MGUS describes an isolated finding of a monoclonal paraprotein in the serum, usually in the elderly; 20–30% go on to develop multiple myeloma.

### Treatment

With good supportive care and chemotherapy with autologous or allogeneic stem cell transplantation, median survival is now 5 years with some patients surviving to 10 years. Young patients receiving more intensive therapy may live longer.

#### Supportive therapy

- Anaemia should be corrected; blood transfusion may be required. Erythropoietin often helps.
- Infection should be treated promptly with antibiotics. Give yearly flu vaccinations.
- Bone pain can be helped most quickly by radiotherapy. NSAIDs are also useful (beware of use in renal involvement).
- Pathological fractures may also be prevented by prompt orthopaedic surgery (kyphoplasty) with pinning of lytic bone lesions seen on the skeletal survey.

#### Specific therapy

Conventional treatment, incorporating first-class supportive care including long-term bisphosphonates, e.g. zoledronate or clodronate, which inhibit osteoclast activity, reduces progression of bone disease. Initial chemotherapy with melphalan and prednisolone has a response rate of approximately 50%. Complete remission is never attained and all patients will relapse without further treatment. High-dose melphalan therapy and peripheral blood stem cell rescue (autotransplantation) has undoubtedly improved the duration of remission and overall survival of younger patients, even if cure has not been attained. ‘Reduced-intensity’ allogeneic stem cell transplants are also used, with a reduction of mortality over normal-intensity allogeneic transplants, but still with graft-versus-myeloma effect.

‘New’ approaches are showing considerable promise and may lead to greater improvements:

- **Thalidomide.** This anti-angiogenesis agent has been shown, outside the context of pregnancy, to reduce the paraprotein in heavily pretreated patients with myeloma. Phase III trials in combination with chemotherapy are in progress and new analogues are becoming available.
- **Bortezomab.** This proteasome inhibitor has now been licensed in the USA on the basis of single agent data. As with thalidomide, Phase II trials with chemotherapy have been most encouraging and Phase III trials are underway.

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## COMMON SOLID TUMOUR TREATMENT

Common solid cancer mortality is listed in Table 9.1; the improvements over the past 10 years have come from advances in the prevention, diagnosis, and treatment. The presentation, diagnosis, and natural history of the common cancers are described in the relevant organ system chapters. In this section the systemic therapy of the common cancers is described, and in addition the treatment of germ cell tumours illustrates what can be achieved when chemotherapy resistance is overcome. The decision to treat and the aim of that treatment whether for palliation or cure, require knowledge of the disease, prognostic factors, the patient’s performance status, and the potential efficacy of treatment. Management should be carried out by multi-disciplinary teams, usually led by an oncologist.

### Lung cancer (p. 947)

#### Prognostic factors

Presentation, diagnosis and surgery are discussed on p. 948.

Lung cancer histology is divided into two main types; small-cell (neuroendocrine) lung cancers (SCLC) and non-small-cell lung cancers (NSCLC). In addition, tumour stage and patient performance status are used in selecting treatment and predicting response and prognosis. While overall 5-year survival has remained approximately 15%, treatment is beginning to have an impact in selected groups and the multidisciplinary team can greatly aid in the appropriate application of treatment and the avoidance of nihilism.

### Non-small-cell lung cancer

#### Prognostic factors

The staging is classified according to the TNM system (Table 9.5), by which the disease can be divided into local, locally advanced, and advanced stages with 5-year survival varying from 55–67%, to 23–40%, to 1–3% respectively. The addition of CT and PET scanning has increased the accuracy of staging and improved the selection of patients for surgery and adjuvant therapy.

#### Treatment

In *operable disease* stages T1N0 to T3N2 (stage I to IIIa) adjuvant radiotherapy and chemotherapy are still of uncertain benefit, although recently the international adjuvant lung cancer trial showed that cisplatin-based combination chemotherapy produced an improvement in 5-year survival of 4% from 40.4% to 44.5%. Uracil and tegafur given for 2 years after complete resection can improve survival in stage I adenocarcinoma.

For *unresectable disease*, the combination of concurrent cisplatin with radiotherapy when compared with radiotherapy alone has increased the resection rate and 3-year survival from 11% to 23% at the expense of greater oesophageal toxicity.

In *advanced disease* cisplatin or carboplatin in combination with one other drug such as paclitaxel or gemcitabine for 12 weeks produces a symptomatic improvement in 40%, and increases median survival from 6 to 10 months compared with best supportive care, with 10–20% alive at 1 year.

### Small-cell lung cancer

#### Prognostic factors

The staging of small-cell lung cancer is divided into limited and extensive disease according to whether or not it is confined to a single anatomical area or radiation field.

#### Treatment

*Limited disease* is present in approximately 30% of patients and is best treated with concurrent chemo- and radiotherapy using a combination of cisplatin and etoposide or irinotecan, which increases the survival at 5 years from 15% to 25% compared with radiotherapy alone. A similar degree of improvement can also be achieved with hyperfractionated radiotherapy. Prophylactic whole-brain radiation to prevent cerebral metastases can reduce symptomatic CNS disease and improve overall survival by 5%.

*Extensive disease* can be palliated with the combination of carboplatin and etoposide or irinotecan, which when compared with best supportive care can increase median survival from 6 months to 9–13 months and 2-year survival to 20%.

### Breast cancer

Breast cancer is the most common cancer in women who do not smoke. The screening programme in the UK, with mammography every 3 years in women aged 50–64 and improvements in multimodality treatment have improved overall survival and rates of cure, while breast-conserving surgery has greatly ameliorated the psychosexual impact of the disease.

#### Symptoms and signs

Most women present with a painless increasing mass which may also be associated with nipple discharge, skin tethering, ulceration and, in inflammatory cancers, oedema and erythema. In developing countries, 80% present with advanced disease.

#### Investigations

The triple assessment of any symptomatic breast mass by palpation, radiology (mammography, ultrasound and MRI scan) and fine-needle aspiration cytology is the most reliable way to differentiate breast cancer from the 15 times more common benign breast masses. Assessment should be carried out in a dedicated one-stop clinic able to provide the appropriate support and referral accordingly. Staging is both surgical with respect to tumour size and axillary lymph node status and, in advanced disease, by investigation of common sites of metastasis by chest X-ray, bone and liver scan. At present, only 20% of patients are diagnosed with no evidence of microscopic nodal metastases.

#### Prognostic factors

The size of the primary tumour, the histological subtype (most are infiltrating ductal carcinoma), histological grade/differentiation, oestrogen and progesterone receptor status, patient age and menopausal status are all significant independent predictors of risk of recurrence. Expression of *c-erbB2* is linked to the above and a predictor of treatment response.

#### Early breast cancer

The prognosis (10-year survival) can be predicted from the independent prognostic factors in Box 9.7. Survival

#### Box 9.7 Poor prognostic factors for breast cancer

- Young age
- Premenopausal
- Large tumour size
- High tumour grade
- Oestrogen and progesterone receptor negative
- Positive nodes

will vary from 90% for small (< 1 cm) low-grade node-negative tumours to 20% for large high-grade tumours with more than three axillary nodes involved and no adjuvant therapy.

### Local treatment

Surgery with wide local excision and breast conservation, or mastectomy with or without reconstruction, is dictated by the location and extent of the breast mass, and patient preferences. Surgery of the axilla may require full dissection or sentinel lymph node guided sampling in order to gain local control and provide prognostic information to guide adjuvant treatment if there are clinically involved nodes. The greater the amount of axillary surgery the more the risk of post-operative lymphoedema. Radiotherapy is given to the conserved breast after wide local excision to reduce local recurrence, and after mastectomy if there are risk factors such as proximity to surgical margins or lymph node metastases, to complete the local control measures. Adjuvant radiotherapy reduces the risk of local recurrence by 25% and improves 10-year survival by 3%. Recent data suggest that women over 70 years with oestrogen receptor positive cancers up to 2 cm may be offered surgery and tamoxifen alone without radiotherapy, without compromising outcome.

### Adjuvant systemic treatment

Tamoxifen (p. 497) adjuvant therapy immediately following surgery for oestrogen and/or progesterone receptor-positive disease has reduced the 10-year relative risk of women dying from breast cancer by about 25% and the absolute 10-year death rate by 12%. A meta-analysis of all randomized trials of adjuvant therapy in breast cancer has shown that for *premenopausal women* with axillary lymph node metastases or other high-risk features (Box 9.7), adjuvant chemotherapy with CMF (cyclophosphamide, 5-fluorouracil plus methotrexate) or more effective regimens with epirubicin, or ataxane (Epi-CMF or FEC) for 6 months, reduces the absolute 10-year death rate by about 10% and the relative risk of death by 20%. Ovarian ablation is equally effective as CMF chemotherapy. The effects of tamoxifen and chemotherapy are additive and most effective given serially, not concurrently.

For *postmenopausal women* with oestrogen and/or progesterone receptor-positive disease, adjuvant tamoxifen or aromatase inhibitors given for 5 years reduces the risk of death from breast cancer by a similar 25%. Aromatase inhibitors avoid the adverse effects of tamoxifen on the uterus and venous thromboembolism but add risks of osteoporosis. Menopausal status does not affect the relative efficacy of tamoxifen or chemotherapy; however, since the risk of recurrence is lower after the menopause, the absolute improvement in survival is less. Toxicity may also be higher in this age group so that treatment decisions may need to be more individualized in discussion between the patient and her doctors. The combined effect of radiotherapy, chemotherapy and tamoxifen or aromatase inhibitor halves the risk of dying of breast cancer for appropriately selected patients.

### Advanced breast cancer

Patients with established metastatic disease may require endocrine therapy, chemotherapy or radiotherapy. The treatment is not curative but may be of great palliative benefit and consistent often with many years of good-quality life. Little additional benefit has been gained by adding endocrine and chemotherapy together, although the addition of anti-HER2 (antibodies) to chemotherapy has produced a modest survival advantage. In general, therefore, the serial use of intermittent courses of the different hormonal and chemotherapies seems most consistent with maintaining a good quality of life for as long as possible.

### Endocrine therapy (p. 497)

Women who have high levels of oestrogen receptors and progesterone receptors in their tumour have a greater chance of responding to endocrine treatments. In addition, certain clinical features can predict the likelihood of responding to hormonal manipulations (Box 9.8).

Endocrine therapy is usually tried first in those patients who have characteristics suggesting they are likely to respond and who do not have immediately life-threatening disease. Remission lasts on average 2 years and is consistent with an excellent quality of life. When relapse occurs, further treatment with alternative agents may produce another remission. A range of hormonal manipulations is available (Table 9.21).

### Chemotherapy (p. 492)

Chemotherapy is considered for patients who are unlikely to respond to hormonal treatment or who fail to respond to endocrine therapy or who require a rapid response if at risk of, for example, liver or respiratory failure. If chosen carefully, chemotherapy can provide

#### **i** Box 9.8 Clinical features that increase the likelihood of response to endocrine treatment for metastatic disease

- Oestrogen or progesterone receptor positive (60% vs 10% response in oestrogen receptor (ER) negative disease)
- Long interval (more than 2 years) from initial surgery to time of relapse

**Table 9.21** Endocrine therapy of metastatic breast cancer

#### For premenopausal patients

- (a) Suppression of ovarian function by means of oophorectomy, radiation-induced ovarian ablation or a GnRH analogue, e.g. goserelin
- (b) Oestrogen receptor antagonist, tamoxifen, fulvestrant
- (c) Progesterone

#### For postmenopausal patients

- (a) Oestrogen receptor antagonists, tamoxifen, fulvestrant
- (b) Progesterone
- (c) Aromatase inhibitors (e.g. anastrozole, letrozole and exemestane)

good-quality palliation and prolongation of life. The most common regimens used include:

- CMF (cyclophosphamide, methotrexate, 5-fluorouracil)
- MM (mitoxantrone (mitozantrone) and methotrexate)
- doxorubicin and cyclophosphamide
- paclitaxel or docetaxel used as single agents or in combination with an anthracycline or capecitabine
- vinorelbine
- capecitabine.

There is very little difference in efficacy between the different regimens for metastatic disease, with response rates varying from 40% to 60% for median duration of 8 months. More recently, the addition of trastuzumab (p. 498) monoclonal antibody to the cytotoxic drugs has significantly improved survival for those women whose tumour over-expresses the *c-erbB2/Her2* oncogene. The addition of capecitabine to docetaxel or trastuzumab, has also improved survival in metastatic breast cancer. The regimens do differ in toxicity with MM being one of the least toxic. The multiple regimens provide the possibility of avoiding drug resistance over several episodes of treatment interspersed with treatment-free periods so that the disease can be palliated, often for several years.

### Gastrointestinal cancer

Presentation, diagnosis and local treatments are described in Chapter 6.

#### Oesophageal cancer

Histology, stage, age and performance status are critical to treatment decisions, which should be made by a multi-disciplinary team in designated units. The prognosis for the majority of symptomatic patients is poor, 50% have distant metastases at the time of diagnosis and the majority of the remainder will have loco-regional spread into mediastinal structures.

#### Treatment

Neoadjuvant therapy for potentially resectable squamous carcinomas with cisplatin, 5-fluorouracil and concurrent radiotherapy achieves complete remission in 20–40% with 25–35% of patients alive 5-years after surgery. There is an increased perioperative mortality. Postoperative chemotherapy for adenocarcinomas has failed to improve overall survival.

Locally advanced or metastatic disease can be palliated with 5-fluorouracil chemotherapy in approximately 30%, increasing to 45–55% with the addition of oxaliplatin or irinotecan for a median duration of 6–8 months.

#### Gastric cancer

Presentation and diagnosis are described on page 288.

#### Prognostic factors

The histological grade and staging with respect to the presence of serosal involvement (T3) and nodal involvement (N1–2) are the main factors in prognosis. For the

majority of patients with node-positive disease the 5-year survival is only 20% following surgery alone.

#### Treatment

A recent study of combined chemo-radiotherapy with cisplatin and 5-fluorouracil compared with surgery alone showed significantly increased median survival from 28 to 35 months and 3-year survival from 41% to 50%. This was achieved mainly through improvement in loco-regional control but is suitable only for good performance status patients.

Advanced disease may be palliated with chemotherapy such as epirubicin, cisplatin, and infusional 5-fluorouracil in 40–50% of patients for a median of 8–10 months but is suitable only for the younger fitter patient.

#### Colorectal cancer

Presentation and diagnosis are described on page 329.

The site of the disease, above or below the pelvic peritoneal reflection, and TNM stage are the main prognostic factors (see Table 6.17).

#### Treatment

Local therapy is discussed on page 330.

Adjuvant chemotherapy with 5-fluorouracil and folinic acid for rectal and colonic adenocarcinoma significantly increases 5-year survival for node-positive disease stage III (Dukes' C) by 5% from 40% to 45%. A further 6% improvement in a recent trial was achieved by the addition of oxaliplatin, and trials are examining the addition of monoclonal antibody to the EGF receptor (cetuximab) or VEGF (bevacizumab).

Advanced colorectal cancer is successfully palliated with little toxicity by 5-fluorouracil and folinic acid regimens in approximately 30% of patients for a median of 12–14 months. The addition of irinotecan or oxaliplatin increases the proportion who benefit to 55% but with increased toxicity. The monoclonal antibody bevacizumab (and possibly cetuximab) increases the response rate to chemotherapy and in one trial the median survival from 14 to 21 months.

### Epithelial ovarian cancer

Epithelial ovarian cancer comprises 80% of all ovarian cancers, the remainder being of germ cell or stromal origin.

#### Symptoms and signs

Ovarian cancer typically causes few specific symptoms, sometimes there is a sensation of a pelvic mass, which may become (acutely) painful, often there is only vague abdominal distension and epigastric discomfort.

#### Investigation

Pelvic examination should be complemented by a transvaginal ultrasound and serum CA125. Magnetic resonance imaging is the definitive imaging technique for the pelvis.

## Malignant disease

### Prognostic factors

Histological subtype, grade/differentiation stage, and extent of residual disease following surgery are all significant independent prognostic factors for survival.

### Treatment

Surgery (with total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy) has a major role in the treatment of ovarian cancer. For patients in whom the disease is confined to the ovary, the surgery can be curative in 80–90% if the histology is well to moderately differentiated. For patients with poorly differentiated or more advanced disease, with spread throughout the peritoneal cavity, surgery still has a major role in staging the patient and improving survival when it is possible to debulk optimally to <1 cm residual. Primary chemotherapy and delayed surgery is an alternative approach currently under investigation.

Drugs used to treat ovarian cancer are cisplatin and its analogue carboplatin, which is associated with fewer side-effects. Response is achieved in approximately two-thirds of patients. Paclitaxel has been shown to improve the survival of many patients when added to a platinum-based treatment.

Adjuvant treatment with carboplatin and paclitaxel for stage I high-risk disease increases the absolute 5-year survival by 9% from 70% to 79%. In advanced disease 75% of patients will respond to combination chemotherapy and the median survival is approximately 3 years. Up to 30% of those with metastatic disease may be alive after 5 years, although this falls to 5–10% if the cancer is not able to be debulked at operation or has spread outside the peritoneal cavity.

## Prostate cancer

### Early prostate cancer

Presentation and diagnosis are described on page 685.

### Prognostic factors

The histological appearances are graded and accorded a Gleason Score which together with the height of the serum PSA plus accurate staging of the local extent of disease with pelvic MRI and transrectal ultrasound can identify prognostic groups. This allows the selection of patients with good prognosis who may reasonably choose to be kept under surveillance with no active treatment and, like 75% of men over the age of 80, die with, but not because of, their prostate cancer.

### Treatment

Curative surgery (radical prostatectomy) and either external beam radiotherapy or brachytherapy can achieve equivalent survival rates but differ in the spectrum of unwanted side-effects with respect to incontinence and sexual dysfunction. In appropriately selected series of patients a 5-year survival of 85% can be achieved. Discussion between patient and clinician is vital before treatment is started.

Adjuvant androgen deprivation treatment such as monthly depot goserelin has not improved the survival from surgery but when given before and during radiotherapy can improve the overall survival at 3 years from 62% to 78%.

## Advanced prostate cancer

### Treatment

Metastatic prostate cancer with either local or skeletal spread is rapidly and effectively palliated in 70% of patients by androgen deprivation. The median duration of response is 2 years and, on the development of hormone resistance, mitoxantrone or docetaxel possibly with estramustine, chemotherapy can be guided by PSA response to provide some further months' palliation when compared with best supportive care. Radiotherapy provides a very effective palliation of painful skeletal metastases and can be delivered systemically by intravenous bone-seeking strontium-labelled bisphosphonate for patients with multiple affected sites.

## Testicular and ovarian germ cell tumours

Germ cell tumours are the most common cancers in men aged 15–35 years but comprise only 1–2% of all cancers. They are much less common in women. There are two main histological types, seminoma (dysgerminoma in women) and teratoma. Teratomas may comprise varying proportions of mature and immature elements. Germ cell tumours may rarely occur in extragonadal sites in the midline from pituitary, mediastinum or retroperitoneum but should be treated in a similar manner.

### Symptoms and signs

Most men present with a testicular mass which is often painful, some with symptoms of metastases to the para-aortic lymph nodes with back pain. In women the mass presents with vague pelvic symptoms but at a younger age than the more common epithelial ovarian cancers.

### Investigations

Ultrasound scanning of the testicle or ovary is required, with assay of serum tumour markers,  $\alpha$ -fetoprotein (AFP) and  $\beta$ -human chorionic gonadotrophin ( $\beta$ -HCG), and lactic dehydrogenase (LDH), followed by CT or MRI scan for distant metastases. Surgery for men is by the inguinal approach to avoid spillage of highly metastatic tumour in the scrotum. Surgery for diagnosis and staging should be conservative in women with preservation of fertility because of the efficacy of chemotherapy.

### Treatment

#### Seminomas

Seminomas are the least common of these tumours and are very radiosensitive and chemosensitive. Seminomas are associated with a raised serum LDH but only rarely a mildly raised HCG and never a raised AFP. Stage I disease limited to the gonad is associated with a 30% risk

of recurrence with surgery alone. Adjuvant therapy with either chemo- or radiotherapy leads to greater than 95% cure in early-stage disease but chemotherapy with single-agent cisplatin or carboplatin does not have the long-term risks of secondary malignancy associated with radiotherapy. Combination chemotherapy (e.g. cisplatin, etoposide and bleomycin) will cure 90% of those with metastatic disease.

### Teratomas

The risk of relapse with stage I disease varies from 5% to 40% depending upon the histological differentiation and extent of local invasion. Adjuvant chemotherapy for those at moderate to high risk (e.g. cisplatin, etoposide and bleomycin) leads to a 95% cure rate. Metastatic disease commonly involves para-aortic lymph nodes and lungs but may spread rapidly, especially if there are trophoblastic (HCG-producing) elements present. HCG can be associated with gynaecomastia and can be tested for in any young male with a urinary pregnancy test to enable rapid institution of potentially life-saving treatment. About 80% of teratomas will express either HCG or AFP and almost all metastatic disease will be associated with an elevation of the less-specific serum marker lactate dehydrogenase (LDH). Chemotherapy cure for metastatic teratoma varies from over 90% for those with small-volume to 40% for those with large-volume metastases and associated rises of AFP > 10 000 and  $\beta$ -HCG > 100 000 IU/L.

Although approximately 20% of men will be infertile due to azoospermia at the time of diagnosis, the majority of the remainder will retain their fertility after chemotherapy and be able to father normal children. Similarly, most women retain their fertility, although less is known about the association with infertility at presentation owing to the much lower frequency of germ cell tumours in women.

### Cancer with unknown primary

Patients presenting with symptoms of their metastases without a clinically obvious primary after investigation represent a common clinical problem and comprise 5–10% of patients in a specialist oncological centre. As a result of several systematic studies, some with post-mortem follow-up, the following guidance should aid the choice of appropriate investigation and treatment.

#### Diagnosis

Diagnosis requires histology first and foremost, as it will lead to the identification of several distinct groups.

1. *Squamous cancers* – mostly presenting in the lymph nodes of the cervical region, 80% will be associated with an occult head and neck primary, the remainder arising from the lung. Inguinal nodes point usually to a primary of the genital tract or anal canal. Treatment with radiotherapy and chemotherapy may have curative potential.
2. *Poorly differentiated or anaplastic cancers* – this group will contain the majority of the curable cancers such as

#### **i** Box 9.9 Adenocarcinoma with unknown primary: primary sites with major treatment benefits

- Breast, e.g. isolated axillary lymphadenopathy
- Ovary, e.g. peritoneal carcinomatosis
- Prostate, e.g. pelvic lymphadenopathy

high-grade lymphomas and germ cell tumours identifiable by their immunocytochemistry and tumour markers. Treatment and prognosis is as outlined in the respective primary sites.

3. *Adenocarcinomas* form the majority, and their investigation should be guided by the desire to identify the most treatable options and the knowledge that the largest proportion will have arisen from the lung or pancreas, with relatively poor treatment prospects (Box 9.9). Investigations should therefore comprise a chest X-ray and abdominal CT scan with, in men, serum PSA and rectal ultrasound to identify prostate cancers, and in women, mammography to identify occult breast cancer, and pelvic CT or MRI to identify ovarian cancer. Tumour markers for other solid cancers, although highly sensitive, are too non-specific to be useful as diagnostic aids in this situation.

Further investigation may require MRI for breast and ovarian masses, PET for head and neck, lung and possibly other primaries, and radioisotope scans for thyroid and carcinoid tumours.

For good prognosis patients wishing to have palliative chemotherapy, investigations such as endoscopy to identify lung, colon or stomach primaries are indicated to guide the choice of chemotherapy agents.

#### Prognosis

The histological type and extent of the disease, and performance status of the patient are the key factors. Most large series report an overall median survival of 12 weeks but considerably better survival amongst the special subgroups below.

Patients presenting with isolated nodal metastases do have a significantly better prognosis than the majority with visceral and/or bone metastases and may warrant more extensive investigation.

#### Treatment

In women, an isolated axillary lymph node metastasis should be treated as for lymph-node-positive breast cancer. Malignant ascites in women should have a trial of chemotherapy as for epithelial ovarian cancer. The prognosis for those responding to the therapeutic trial is similar to the disease of known primary origin. For men, the occasional occult prostatic cancer found from a raised serum PSA offers some palliative treatment prospects. An increasing choice of chemotherapy agents for gastrointestinal cancers has potential to improve the palliation of patients with liver metastases. If after all efforts, no primary has been identified, palliative chemotherapy treatment can achieve responses in 20–40% in highly selected series, with

median survivals of 9–10 months and 5–10% surviving to 5 years.

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## PALLIATIVE MEDICINE AND SYMPTOM CONTROL

Palliative care may be defined as the active, total care of patients whose disease is no longer responsive to curative treatment. The goal of this care is to achieve the best possible quality of life for patients and their families by controlling physical symptoms as well as recognizing psychological, social and spiritual problems. Death is accepted as a normal process, which should neither be hastened nor postponed and the need to provide a support system for the family in bereavement is also recognized.

Many symptoms suffered in incurable illness have a complex aetiology in which the physical component may be overlaid by psychosocial issues. For such patients considerable input from a multidisciplinary team of specialist palliative care professionals may be needed to resolve the symptoms. There is good evidence that integration of palliative care and antitumour management early in the course of disease will reduce long-term distress and difficulty in symptom management. This view moves away from the traditional concentration on the provision of palliative care at the end of life.

The most appropriate first step in providing care in complex situations is often to deal with physical symptoms.

### Pain

The symptom most feared by cancer patients is pain, although only two-thirds suffer significant pain throughout the course of their disease. Those patients who suffer pain may present with several pains of differing aetiology, with cancer being directly responsible for about 70%. Pain may be related to associated problems such as rapid weight loss or pressure sores, or may have a separate, non-malignant cause, such as arthritis. The principles of pain relief are careful assessment and diagnosis of the cause of pain, use of analgesics according to the analgesic ladder, and regular review of the effectiveness of the prescribed drugs (Fig. 9.17).

#### The analgesic ladder

The cancer pain relief programme of the World Health Organization groups drugs into three main classes:

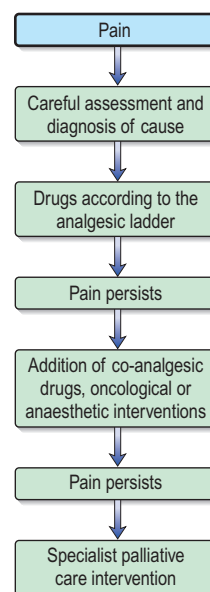


Fig. 9.17 Management of cancer pain.

1. non-opioid drugs, such as paracetamol or aspirin and other non-steroidal anti-inflammatory medications
2. weak opioid drugs, such as codeine, dextro-propoxyphene and combinations of codeine with paracetamol
3. strong opioid drugs, such as morphine and diamorphine.

The analgesic ladder states that, if optimal use of a drug from the non-opioid class (e.g. 1000 mg of paracetamol 6-hourly) does not result in satisfactory pain relief, the prescription should be increased up one step to a weak opioid. If the equivalent of codeine 60 mg 4-hourly is not sufficient to control pain, the patient will require a strong opioid. Adjuvant, co-analgesic drugs may be added to each step of the ladder.

#### Strong opioid drugs

*Morphine* is the drug of choice and in most circumstances should be given regularly by mouth. The dose can be tailored to the individual patient's needs by the addition of 'as required' doses; morphine has no ceiling analgesic effect. A suitable starting dose of morphine is 10 mg 4-hourly, or 5 mg if the patient is elderly or frail. Patients with renal failure will have impaired excretion of morphine metabolites; they should receive a single dose of morphine and be carefully observed for the return of pain in order to determine the approximate rate of excretion of the metabolites.

If a 10 mg dose of morphine relieves the pain but the relief does not last for 4 hours, a 50% increase in the dose should be made (i.e. 10, 15, 20, 30, 45, 60, 90, 120, 180 mg) until satisfactory pain control is achieved.

When the patient's 24-hour morphine requirement has been established, the prescription may be converted to a

*controlled-release preparation.* There are both 12-hour and 24-hour release preparations available. The appropriate dose may be calculated by simple addition. For example:

20 mg morphine elixir 4-hourly  
 = 120 mg morphine per day  
 = 60 mg twice-daily of a 12-hour preparation  
 or 120 mg daily of a 24-hour preparation.

If the patient is unable to take oral medication because of nausea or vomiting, gastrointestinal obstruction or altering levels of consciousness, the opioid should be given rectally or parentally. For cancer patients who need long-term analgesia, continuous subcutaneous infusion is the preferred route. Diamorphine is used in this situation because of its greater solubility. By subcutaneous or intramuscular injection, diamorphine is approximately twice as potent as morphine orally. Hence the conversion from oral morphine may be calculated as follows:

30 mg oral morphine 4-hourly  
 = 180 mg morphine per day  
 = 90 mg diamorphine subcutaneously over 24 hours.

**Side-effects.** *Constipation* caused by analgesic drugs is almost universal. The prescription of a stimulant laxative such as dantron 1–3 capsules at night should be mandatory at the same time as morphine is started. No tolerance develops to this side-effect and laxative medication must be continued as long as analgesics are prescribed.

*Nausea or vomiting* may occur in 30–60% of patients first started on morphine. However, for those who have worked up the analgesic ladder and who have no other cause for vomiting, the prescription of an 'as required' centrally acting antiemetic is usually sufficient. Tolerance will develop to this side-effect, usually within 4–5 days.

*Confusion, nightmares and hallucinations* occur in a small percentage of patients. Tolerance to these side-effects does not develop and a change of opiate drug is usually required.

### **Pain not responsive to opioids**

Not all cancer pains are relieved by opioids. In some situations the addition of co-analgesic drugs will result in improved pain control. An increasing number of different classes of drugs have been used in this setting. Some of the most common include the following.

Non-steroidal anti-inflammatory drugs used in addition to a weak or strong opioid for bone pain. Published studies have most frequently used naproxen (500 mg twice-daily) but there is no clear evidence of any one drug being superior in effect. It may be that idiosyncratic side-effects require a trial of a different NSAID.

Pains of nerve destruction called dysaesthetic or deafferentation pain are generally only marginally improved by strong opiates. Several classes of drug, including steroids, have been found to be helpful in reducing the symptoms. In cases of constant burning

dysaesthesia, the tricyclic antidepressants are helpful. Amitriptyline 10 mg at night increasing incrementally to 75–100 mg is usually sufficient (compare with the doses required for mood elevation) and the response, if achieved, can be expected in about a week. Anticonvulsant drugs are useful in the management of lancinating, neuropathic pains. Carbamazepine starting at a dose of 100 mg twice-daily is most commonly used, but sodium valproate 300 mg twice-daily may cause fewer adverse side-effects. Gabapentin and pregabalin are of benefit in some forms of neuropathic pain.

In addition to drugs, many other techniques such as radiotherapy, anaesthetic and neurosurgical intervention are employed for the treatment of specific pains.

Regular review of the patient is necessary to achieve optimal pain control. Pain is a complex experience unique to each individual and its perception is modulated by the psychosocial and spiritual situation of the patient. If pain is proving difficult to control, it will be necessary to pay further attention to these other significant factors.

### **Gastrointestinal symptoms**

Anorexia, malaise and weakness are among the most frequently troublesome symptoms in advanced cancer. Endogenously produced cytokines (e.g. tumour necrosis factor and interleukins) are mediators of the anorexia/cachexia syndrome. There is at present no specific therapy, but the approach to treatment depends on adequate management of associated symptoms. Care should be given to addressing the psychological distress caused by a change in body image, with attention to nutrition including dietary advice and the judicious use of steroids.

Nausea and vomiting occur in up to two-thirds of cancer patients in the last 6 weeks of life. The approach to treatment should be similar to that required for pain, involving careful assessment and diagnosis of the cause. It may, however, be more difficult to reach a diagnosis and a somewhat empirical approach to treatment is often adopted. In order to ensure adequate absorption of the antiemetic, parenteral administration, preferably by the subcutaneous route, may be helpful for the first 24–48 hours.

Antiemetics are classified according to their affinities for neurotransmitter receptor sites. A gastrokinetic dopamine antagonist such as metoclopramide 10 mg every 6–8 hours would be helpful in vomiting related to upper gastrointestinal tract stasis or to liver metastases. Metoclopramide should be avoided in cases of intestinal obstruction as it increases peristalsis in the upper bowel. Centrally acting antiemetics such as the phenothiazines, e.g. prochlorperazine 10 mg 8-hourly, cyclizine 50 mg 8-hourly, or the dopamine antagonist butyrophenone, haloperidol 1.5 mg 8-hourly are the drugs of choice in vomiting caused by drugs or metabolic disturbance. As with the prescription of analgesics, antiemetics will be most effective if prescribed on a regular rather than 'as-required' basis.

### Bowel obstruction

Bowel obstruction may present acutely or in a more chronic manner and the cause is often multifactorial.

A small number of patients may benefit from surgical intervention, so consideration must be given to this modality of treatment in every case. Most patients will not be suitable for surgery and can be managed medically. The active medical management of malignant bowel obstruction includes:

- the relief of intestinal colic using an antispasmodic such as hyoscine butylbromide 60–80 mg daily; loperamide is sometimes helpful
- treating continuous pain with adequate analgesia such as diamorphine
- treating vomiting if nausea is a problem with a centrally acting antiemetic such as cyclizine 150 mg daily or haloperidol 5–10 mg daily.

It will be necessary to administer all of these medicines parenterally and the subcutaneous route is most appropriate.

Evidence suggests that the use of corticosteroids or the somatostatin analogue octreotide may shorten the length of episodes of obstruction. Octreotide also reduces the volume of fluids secreted into the bowel, thus reducing the volume of nasogastric aspirate or vomit.

Patients may be allowed to drink and eat low-residue diets which are mostly absorbed in the proximal gastrointestinal tract. It is usually possible, with adequate mouth care, to prevent a sensation of thirst, and routine parenteral fluids are not required. A few patients with intractable vomiting due to a high intestinal block may benefit from continuous nasogastric aspiration or gastrostomy drainage.

### Respiratory symptoms

Respiratory symptoms, in particular breathlessness, cause great distress to patients and their carers. Management is based on an accurate diagnosis of the cause and active treatment of all potentially reversible situations. Infections should be treated, pleural and pericardial effusions drained and symptomatic anaemic patients transfused. Radiotherapy, cytotoxic agents and local laser therapy or stent insertions may relieve specific areas of bronchial tree obstruction. The place of oxygen in managing breathlessness is not clear, but it may be helpful in patients with correctable hypoxia.

The sensation of breathlessness and a cycle of respiratory panic may be partially relieved by the prescription of regular benzodiazepines. Regular doses of short-acting opioids 5–20 mg 4-hourly are also helpful, as they are postulated to have a local as well as a central effect. Nebulization of a morphine solution may reduce the sensation of breathlessness in a proportion of patients.

Persistent unproductive cough is a very troublesome symptom. Opiates, codeine, methadone or morphine elixir are helpful as antitussive agents. Antitumour therapy

may be required to alleviate pressure on a large airway. Nebulized local anaesthetic may also be helpful in the prevention of cough.

### Other physical symptoms

Patients with cancer may develop a large number of physical symptoms. These may be related directly to the presence of the tumour (e.g. vaginal blood loss from a cervix carcinoma) or to the treatment received (e.g. lymphoedema of the arm following breast surgery and radiotherapy). Management of these symptoms will be specific and may require the intervention of other specialists.

Patients may also develop symptoms as a reflection of their debility, such as pressure sores, urinary incontinence, jaundice or recurrent infections. These symptoms may be managed according to the overall expectations and requirements of the patient and their family. These situations of multiple symptomatology in frail patients put considerable demands on the expertise and creativity of clinicians as they present a great challenge for the maintenance of the best possible quality of life.

### Psychological symptoms

Effective communication with all patients and their families is a fundamental tenet of clinical practice but is particularly necessary in the stressful situations which surround fatal disease. Basic communication skills include allowing time for the patient to talk, using language which is appropriate to the circumstances, being prepared to repeat information, and being aware that both the patient and the family may receive bad news by blocking or denying it. Remember that it is not always necessary to have an answer or a solution to every problem that is presented, but that considerable support may be given by sympathetic listening.

Care of cancer patients should be designed to allow them to spend as much time as possible in their own homes. Effective liaison between the cancer centre, the palliative care team and the primary healthcare team is essential to ensure total care. You must avoid misinterpretation of any information that may be given regarding treatment and prognosis.

Approximately 60% of cancer patients will die in general hospital wards under the care of the physician or surgeon who first diagnosed their tumour, although many are transferred to hospice care. Every clinician should develop some basic skills in symptom control and the ability to recognize those patients who require more specialist intervention. Caring for this group of patients demands detailed attention to alleviating physical symptoms and the establishment of a secure environment for the patient and family to obtain information and support.

The practice of specialist palliative medicine has traditionally been confined to patients with cancer, although most services cover HIV and AIDS and some of the rapidly fatal neurological diseases. These are all conditions in which the clinical situation is changing

rapidly and where difficult symptoms exist. There are undoubtedly patients with non-malignant disease such as end-stage renal or cardiac failure who benefit from a similar multidisciplinary approach to their care. Expansion

of specialist palliative medicine into non-malignant situations is being actively pursued. The patient-orientated principles of palliative medicine can, however, be usefully applied throughout all medical practice.

#### FURTHER READING

Hardy J (2000) Sedation in terminally ill patients. *Lancet* **356**: 1866–1867.

Morrison RS, Meier DE (2004) Palliative care. *New England Journal of Medicine* **350**: 2582–2590.

#### SIGNIFICANT WEBSITES

<http://www.cancerbacup.org.uk>

UK patient organization

<http://www.cancerresearchuk.org/>

UK charity (formed from merged Imperial Cancer Research Fund and Cancer Research Campaign).

<http://www.cancer.org>

US cancer organisation

<http://www.palliativemedjournal.com>

Journal of Palliative Medicine

