Chapter 2
Practical Aspects of Cancer Chemotherapy

Drug Dosing

For the last 50 years most cytotoxics have been prescribed in relation to the patient's body surface area. The surface area is calculated from their height and weight, either by the use of nomograms or pre-programmed calculators or computers. The same principle is used for some, but not all, of the newer targeted therapies but, by contrast, hormonal treatments are almost always prescribed in standard doses that are the same for everybody.

The original rationale for prescribing cytotoxics on the basis of body surface area came from the realisation that there was only a narrow therapeutic window between unacceptable toxicity and efficacy for many of these agents: give too large a dose and the patient could well die from side-effects, give too small a dose and the drug would be ineffective against the cancer, and often the margin for error was small. So there was a need to individualise cytotoxic dosing. Many different factors may influence someone's response to a given dose of a drug, including their age, sex, their body size, any co-morbidities, liver and kidney function which might affect drug metabolism and excretion, and other drugs they are receiving. Measuring and assessing all these parameters for every patient is not generally practical and research in the late 1950s indicated that, for cytotoxics, adjusting the dose of drug according to the patient's surface area, was an

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acceptable surrogate in most instances. So the convention was established of prescribing cytotoxics on the basis of mg/m^2 surface area.

One cytotoxic that is the exception to this rule is carboplatin. The toxicity of carboplatin is closely related to its concentration in the blood over time, which in turn relates to its clearance by the kidney. The dose of carboplatin is therefore worked out by a formula, the Calvert formula, which takes account of a target blood/time level (the area under the curve, or AUC) and renal function (in terms of the glomerular filtration rate, GFR). The target AUC is usually either 5 or 7 mg/ml/min (depending on whether the patient has had previous treatment or not). The GFR may either be measured directly by the 51Cr-EDTA method or calculated by formulae such as those of Cockroft-Gault, Jellieff or Chatelet, based on measurements of serum creatinine. The Calvert formula is: $\text{dose} = \text{AUC} \times (\text{GFR} + 25)$.

Suggestions for Further Reading

Gurney H. Developing a new framework for dose calculation. J Clin Oncol. 2006;24:1489–90.

Kaestner SA, Sewell GJ. Chemotherapy dosing part I: scientific basis for current practice and use of body surface area. Clin Oncol. 2007;19:23–37.

Kaestner SA, Sewell GJ. Chemotherapy dosing part II: alternative approaches and future prospects. Clin Oncol. 2007;19:99–107.

Drug Delivery

Venous Lines

Historically, having a course of chemotherapy involved multiple venepunctures, both for all the blood tests that needed to be done and for giving the drugs themselves. This had disadvantages from a patient point of view – repeated

discomfort, needle phobia – and practically – the difficulty of finding 'a good vein'. Increasingly nowadays using a venous line offers an alternative. The line is a fine hollow silicone rubber catheter, which is inserted into a vein, and stays in place throughout the time of the chemotherapy. Two types of line are used: a central line, or a PICC (peripherally inserted central catheter) line. Central lines are also sometimes known by the names of the manufacturers of the lines, the two main ones being Hickman and Groshong.

The central line is inserted through the skin just below the collar bone. It is then tunneled for a distance subcutaneously before entering into the subclavian vein, and then threaded through this until its tip lies in the superior vena cava, just above the heart. The subcutaneous tunneling of the line helps reduce the risk of infection in the line. A PICC line is inserted through one of the large veins near the bend of the elbow, and threaded along this, through the subclavian vein and into the superior vena cava.

PICC lines are cheaper and simpler to insert than central lines but are usually only suitable for short term therapies over a maximum of 6–8 weeks, whereas central lines can stay in place for a year or more. Also many oncologists feel that drugs which are likely to cause irritation to the veins, such as anthracycline cytotoxics (doxorubicin and epidubicin), and fluorouracil, are not suitable for use with PICC lines.

Once in place, the line can be used for taking blood tests, and for giving all the drugs that would normally have to be injected into a vein, or given through a drip. Putting in the line is a simple procedure. Placing a PICC line can be done as an out-patient and does not need a general anaesthetic. The skin where the line is to be inserted is numbed with local anaesthetic, and threading the line through the veins is usually quite painless, so there shouldn't be much discomfort while this is being done. The insertion only takes a few minutes and is followed immediately by a chest x-ray immediately to check that the tip of the line is in the correct position. Putting in a central line is very similar, but sometimes this may be done with a short general anaesthetic rather than a local anaesthetic.

Table 2.1 Complications of central venous line insertion

Immediate – at the time of insertion	
Cardiac arrhythmia	13%[a]
Arterial puncture	2%
Tip in wrong position	2%
Pneumothorax	1%
Haemorrhage	1%
Late – following insertion	
Infection	4–40%
Thrombosis	
Symptomatic	5–40%
Asymptomatic	5–60%
Migration of catheter tip	5%
Fracture of catheter	3%

[a]%ages indicate the frequency of these complications, but their incidence varies widely in different series

Once the line is in place it is important that it doesn't get blocked. To prevent this it will have to be flushed through on a regular basis. Typical schedules for this are a weekly flush with 50 iu of heparin in 5 ml of 0.9% saline once weekly, or 500 iu heparin in 5 ml saline once monthly, or simply regular flushes with saline. This may be done by chemotherapy nurses or by the patients themselves.

Normally lines are relatively trouble-free. The most common problems that do occur are shown in Table 2.1. Of the immediate problems, which occur at the time of line insertion, the arrhythmias although the commonest are not usually clinically significant. The reported incidence of late complications varies enormously in different series. When thrombosis occurs it may be of one of three types:

- fibrin sheath formation around the catheter: this is only troublesome if it affects the tip of the catheter, leading to complete or partial obstruction

- intraluminal thrombosis which may either go undetected or may lead to blockage of the catheter
- blood vessel thrombosis: effectively a deep vein thrombosis in the vessel around the catheter.

Apart from possible catheter obstruction thrombosis may lead to pulmonary embolism which possibly complicates 5% of thrombotic episodes, or the phlebitis may result in venous distension and swelling of the ipsilateral arm, which may complicate up to 10% of thromboses.

Over the years improvements in catheter design and the use of low thrombotic materials in their manufacture have reduced the risk of thrombosis but it does remain a common problem and this has led to the suggestion that giving people with central venous lines prophylactic anticoagulant therapy may be beneficial. However, the evidence from clinical trials does not really support this and it is not usually recommended.

Removing lines is normally very simple. It is done in the out-patient clinic, with just a local anaesthetic to avoid any discomfort, and only takes a few minutes.

Suggestions for Further Reading

British Committee for Standards in Haematology. BCSH guidelines on the insertion and management of central venous access devices in adults. 2006. www.bcshguidelines.com.

Rosovsky RP, Kuter DJ. Intravenous access and catheter management. In: Chabner BA, Longo DL, editors. Cancer chemotherapy and biotherapy. 5th ed. Philadelphia: Lippincott, Williams and Wilkins; 2011. p. 746–58.

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Implantable Ports

Implantable ports (which are also known as portocaths) are a variation on venous lines. The line is placed in a similar way,

but instead of the end of it coming out on the skin, it ends in a subcutaneous port. This is a small soft plastic bubble, between about 2.5 and 4 cm across, which lies just under the surface of the skin. This means it is less obvious than a central or PICC line, and appears as just a small bump under the skin. It is usually placed near the top of the front of the chest.

Like central lines, implantable ports may be inserted either as an out-patient, using a local anaesthetic, or occasionally as a day-patient, if a general anaesthetic is used. They also need regular flushing to stop them becoming blocked.

Once in place implantable ports can be used just like the venous lines: for taking blood tests, or giving chemotherapy or blood transfusions or other intravenous fluids.

Infusion Pumps

When a chemotherapy drug is given into a vein it is usual to set up an intravenous infusion, with a bag of fluid, on a drip stand, which trickles through a tube into the vein. The drug may either be given as an injection into the tubing of the drip, or it may be mixed with the fluid in the bag and run in as an infusion.

Depending on the treatment that is being given, the infusion may last for anywhere from a few minutes to a few hours. But some chemotherapy treatments require the drugs to be given into a vein over a matter of days or even weeks. For these long infusions, a portable pump can be used, along with a venous line. The pump is a battery-driven device that holds a syringe, containing the chemotherapy drug. This is attached to the end of the venous line, and very slowly the pump squeezes a trickle of the drug into the vein. Once the infusion is complete, then the pump is easily disconnected.

Pumps vary in size, but are usually little bigger than a mobile phone. They can be worn in a special 'holster', meaning that they are easy to carry around, and not very obvious. This means that treatment can continue when the patient is at home, and there should be very little effect on there normal day-to-day activities while the infusion is in progress (Figs. 2.1 and 2.2).

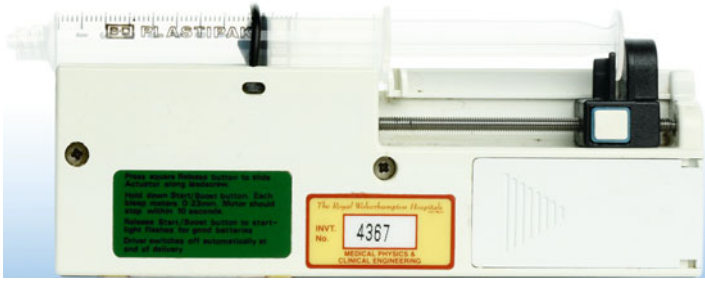

FIGURE 2.1 A battery-driven chemotherapy pump (Courtesy of Mr Simon Glazebrook, New Cross Hospital, Wolverhampton)

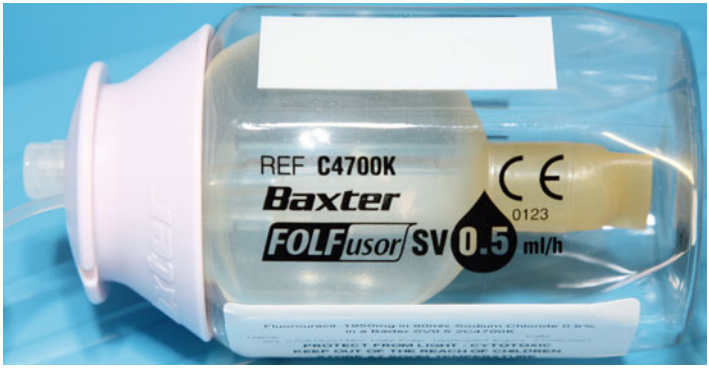

FIGURE 2.2 A disposable elastomeric infusion pump (Courtesy of Mr Simon Glazebrook, New Cross Hospital, Wolverhampton)

Epidural Chemotherapy

Very occasionally, most often with certain types of leukaemia, it may be necessary to give chemotherapy drugs via a lumbar puncture, into the space around the spinal cord, so that the drug can reach parts of the nervous system that it might not get to if it was given by an ordinary infusion into a vein. This type of treatment is called epidural chemotherapy. Unfortunately in

the UK there have been a number of fatal accidents in the past as a result of this technique, when either the wrong drug, or wrong doses of a cytotoxic, were given. Because of this there are now very strict regulations and protocols governing this particular type of treatment.

Side Effects of Cancer Chemotherapy

Most chemotherapy today is still based on the use of cytotoxic drugs; hormonal treatment is important in breast and prostate cancer, and the newer targeted therapies are gaining an increasing role in cancer treatment. These different groups of drugs have very different patterns of toxicity. Because of the frequency and potential severity of their side effects the potential adverse reactions to cytotoxics will be considered in some detail in this section. In discussing these it is important to remember that patients often react differently to the same treatment. Two people can have identical chemotherapy, for the same type of cancer, and be of similar age, with a similar level of fitness, one may experience virtually no problems, whilst the other might suffer considerable side effects, and their treatment may be quite challenging.

Common Side Effects of Cytotoxic Treatment

Cytotoxic drugs interfere directly with the process of mitosis. They have no ability to distinguish between cancer cells and normal cells, and so inhibit cell division in both populations. This accounts for many of their side effects. This means that the use of cytotoxic treatment is the art of differential poisoning: killing the cancer without killing the patient. Unfortunately it is easy to get this balance wrong and people still regularly die from the side effects of cytotoxic chemotherapy. Being aware of what those side effects are, and being vigilant to detect their development as early as possible, is therefore a priority for all clinicians involved with this form of treatment.

There are many different cytotoxic drugs, and many different combinations of these drugs are used in cancer treatment. This means that the potential side effects vary considerably depending on the drugs, and the doses that are used. Having said this, there are some side effects that occur much more often than others. These include bone marrow suppression, nausea and vomiting, tiredness, alopecia, oral mucositis, and reduced fertility. A much less common but very important problem is the risk of second cancers.

Marrow Suppression

Normally the effect of a dose of chemotherapy on the bone marrow cells is temporary. The changes come on a few days after treatment, reaching a peak at about 10–14 days, and then recovering over the next week or so.

The production of white blood cells is the process most sensitive to cytotoxic inhibition; changes to the red cells and platelets generally occur more slowly, and are only likely to show up after several courses of chemotherapy (and very often are not affected at all, throughout the entire treatment). Typically, the white cell count begins to fall about 5–7 days after a dose of cytotoxics, and will reach its lowest level about 2 weeks after the treatment. The count then recovers, and will be more or less back to normal by the end of the third week. This means that there is an increased risk of infection while having chemotherapy. The combination of an infection with neutropenia is termed febrile neutropenia (in more severe cases the term neutropenic sepsis is used).

Febrile neutropenia is defined as an oral temperature >38.5°C, or two consecutive readings of >38.0°C 2 h apart and an absolute neutrophil count $<0.5 \times 10^9$/l, or expected to fall below $<0.5 \times 10^9$/l.

This is a common and potentially serious complication and carries an overall mortality of about 5% although in some haematological cancers this figure can rise to about 10%.

Some chemotherapy regimens are more likely than others to cause profound neutropenia (see Table 2.2). A number of

Table 2.2 Chemotherapy regimens associated with a greater than 20% risk of febrile neutropenia

Acronym	Drugs	Indication
AT	Doxorubicin, docetaxel	Breast cancer
CAV	Cyclophosphamide, doxorubicin, vincristine	Lung cancer
DHAP	Dexamethasone, cisplatin, cytarabine	Non-Hodgkin lymphoma
Doc	Docetaxel	Breast cancer
ESHAP	Etoposide, methylprednisolone, cisplatin, cytarabine	Non-Hodgkin lymphoma
TAC	Docetaxel, doxorubicin, cyclophosphamide	Breast cancer
Topo	Topotecan	Lung cancer
VAPEC-B	Vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin	Non-Hodgkin lymphoma
VelP	Vinblastine, ifosfamide, cisplatin	Germ cell (testicular cancer)

other factors have been identified which increase the risk of febrile neutropenia and these are listed in Table 2.3.

Everyone undergoing cytotoxic chemotherapy should be alerted to the risk of febrile neutropenia. They should be warned that if, at any time during treatment, they get a temperature of more than 38°C, or if they develop symptoms suggesting an infection – like shivering, a sore throat, or a cough and shortness of breath, or cystitis, or if they simply suddenly feel unwell – then they should let the hospital know immediately, so that they can attend for assessment.

Neutropenic sepsis is considered a medical emergency requiring admission to hospital. Subsequent management depends on whether the individual is thought to be at low risk or high risk of developing further complications. The Multinational Association

Table 2.3 Patient-related factors increasing the risk of febrile neutropenia

Pre-existing neutropenia due to disease infiltration of bone marrow or other aetiology
Age >65 years
Advanced disease stage
Presence of a central venous line
Poor performance status
Previous episodes of febrile neutropenia whilst receiving earlier chemotherapy of a similar or less dose intensity
Extensive prior chemotherapy
Previous irradiation to large volume of bone marrow
Poor nutritional status
Active infections
Increased risk of infections due to skin or gut damage
Serious co-morbidities

for Supportive Care (MASCC) index is a widely used scoring system for classifying patients as high or low risk (Table 2.4). In both instances initial management will involve antibiotic therapy which will usually be given intravenously although for some people in the low risk category oral therapy may well be possible. Each department will have its own protocol specifying which antibiotics should be used. For people in the high risk category additional measures may be needed depending on the apparent site of infection and whether or not there are complications such as dehydration, hypotension and renal failure.

For those in the low risk group the mortality is about 1% and this has led to the suggestion that selected patients might be managed on an out-patient basis but this approach remains the exception and hospital admission is the norm, although an early discharge following resolution of fever and symptomatic stabilization is often possible.

Wherever possible once someone has recovered from an episode of neutropenic sepsis the aim will be for them to

Table 2.4 The MASCC scoring system

Characteristic	Score
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or lymphoma with no previous fungal infection	4
No dehydration	3
Out-patient at onset of fever	3
Age <60 years	2

Scores equal to or greater than 21 are at low risk of complications

continue their planned chemotherapy with no dose reduction. For some people this may involve the use of prophylactic antibiotics prior to and during subsequent cycles of treatment, for others the use of granulocyte colony stimulating factors (GCSF) may be considered. Once again the guidelines for using GCSF vary from country to country (in part influenced by cost considerations), and from department to department, but Table 2.5 gives a typical set of criteria in the UK.

The incidence of anaemia during chemotherapy, defined by a haemoglobin (Hb) level of <10 g/dl, is difficult to quantify, with estimates ranging from 20% to 60% of patients being affected. Clearly when the Hb level does fall below 10 g/dl symptoms will usually be fairly obvious, and treatment can be given. In the last few years, however, a number of studies have shown that patients can experience fatigue and other symptoms, when their Hb level falls to between 10 and 12 g/dl during their treatment. This a level that many clinicians would not usually consider as significantly anaemic but treatment to bring their Hb to above the 12 g/dl level has been shown to greatly improve their quality of life.

Table 2.5 Typical UK indications for the use of GCSF in patients receiving cytotoxic chemotherapy

GCSF may be used as either primary prophylaxis, to prevent the development of severe neutropenia, or secondary prophylaxis, to prevent recurrence of neutropenia with subsequent courses of treatment after an initial episode of neutropenic sepsis.

1. Primary Prophylaxis.

Primary prophylaxis may be considered in the following circumstances:

(i) Patients receiving radical or adjuvant chemotherapy who are at ≥40% risk of developing neutropenic fever

(ii) Hospitalised patients receiving radical or adjuvant chemotherapy who are at ≥20% risk of developing neutropenic fever while an inpatient.

(iii) Patients aged >65 receiving radical or adjuvant chemotherapy who are at ≥20% risk of developing neutropenic fever

(iv) Patients aged >50 with significant pulmonary or cardiovascular comorbidity receiving radical or adjuvant chemotherapy who are at ≥20% risk of developing neutropenic fever

(v) Patients aged with leukaemia or lymphoma receiving radical chemotherapy who are at ≥20% risk of developing neutropenic fever

The risk is assessed on the basis of the patient's age, tumour type, performance status, comorbidities and the likely myelotoxicity of the chosen drug regimen (see Table 2.2).

2. Secondary prophylaxis.

The use of GCSF should be considered in patients receiving curative chemotherapy for cancers where maintenance of dose intensity may improve survival. However the optimum scheduling of GCSF is not defined.

The choice of treatment for chemotherapy-induced anaemia rests between blood transfusion or the use of erythropoietic agents such as epoetin alfa (Eprex), epoetin beta (NeroRecormon) or darbepoetin alfa (Aranesp). These are all related to the hormone erythropoietin, which is produced in the kidneys and stimulates red blood cell production.

Although costly these agents were quite widely used in the past. However, more recently results from a number of studies have raised questions over the safety of these agents, suggesting they could lead to an increase in cancer growth and might cause thromboembolic complications. These concerns have led NICE in the UK to recommend that they are only used for women undergoing chemotherapy for ovarian cancer with platinum-based drugs who develop anaemia or people with severe treatment-related anaemia who are unable to have blood transfusions. The current US guidelines are slightly different, recommending that these agents should not be given to people undergoing curative chemotherapy.

Suggestions for Further Reading

De Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO clinical practice guidelines. Ann Oncol. 2010; 21 Suppl 5:v252–6.

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Nausea and Vomiting

Many cytotoxic treatments result in nausea and vomiting. The nausea comes on a few hours after the drugs are given. It is usually at its worst during the first 2 days after the chemotherapy, and then settles quite quickly over another day or two. The chance of experiencing sickness, and the severity of that sickness, vary enormously with different drugs, and the commonly used agents may be classified into those at high risk of emesis (where >90% of patients are likely to be affected), moderate risk (30–90%), low risk (10–30%), and minimal risk (<10%) (see Table 2.6).

Table 2.6 The emetic potential of anti-cancer drugs

Minimal risk
Bevacizumab
Bleomycin
Busulfan
Cetuximab
Chlorambucil
Gefitinib
Imatinib
Fludarabine
Rituximab
Vinblastine
Vincristine
Vinorelbine
Low risk
Bortezomib
Cabazetaxel
Capecitabine
Cytarabine <1,000 mg/m^2
Docetaxel
Etoposide
Fluorouracil
Gemcitabine
Methotrexate
Mitomycin
Mitoxantrone
Paclitaxel
Panitumumab

(continued)

Table 2.6 (continued)

Pemetrexed
Temsirolimus
Topotecan
Trastuzumab
Moderate risk
Azacitidine
Alemtuzumab
Bendamustine
Carboplatin
Clofarabine
Cyclophosphamide <1,500 mg/m^2
Cytarabine >1,000 mg/m^2
Daunorubicin[a]
Doxorubicin[a]
Epirubicin[a]
Idarubicin[a]
Ifosfamide
Irinotecan
Oxaliplatin
Procarbazine
Temozolamide
High risk
Carmustine
Cisplatin
Cyclophosphamide >1,500 mg/m^2
Dacarbazine
Dactinomycin
Nitrogen mustard

[a]These anthracyclines are high emetic risk if combined with cyclophosphamide

There is also evidence that some people are more vulnerable to chemotherapy-induced nausea and vomiting than others: women are more at risk than men, especially if they have experienced emesis during pregnancy; younger people are more at risk than older people; and a history of motion sickness means problems are more likely. A key point in managing cytotoxic emesis is to prevent it happening in the first place, so anti-emetic treatment is usually given as prophylaxis, rather than waiting for symptoms to develop. Although huge improvements have been made in the control of emesis over the last 20 years nausea can still be more difficult to prevent than vomiting.

For many years control of emesis relied on dopamine antagonists like metoclopramide (Maxolon) or domperidone (Motilium). Prevention and treatment of cytotoxic-induced emesis then improved dramatically in the 1990s with the introduction of the 5HT3 receptor antagonists, ondansetron (Zofran) and granisetron (Kytril). These were followed by the second generation drug palonosetron (Aloxi), which is the only 5HT3 receptor antagonist effective in preventing delayed emesis: sickness that comes on a day or two after chemotherapy and which is a troublesome feature of cisplatin and a number of highly emetogenic chemotherapy regimens. 5HT3 receptors, which are stimulated by serotonin (5-hydroxytryptamine) form part of both the central and peripheral pathways for the stimulation of nausea and vomiting. The effectiveness of all these drugs can be further increased by giving the steroid, dexamethasone, which is also an effective anti-emetic in its own right, at the same time.

A further development has been the introduction the neurokinin-1 (NK_1) inhibitors. These work in a different way to other anti-sickness drugs by inhibiting NK_1 receptors in the brain. These receptors are key to triggering the vomiting reflex and are stimulated by a neurotransmitter called substance P. The first NK_1 inhibitor in clinical use was aprepitant (Emend) which was followed by fosaprepitant (Emend for injection in the USA, Ivemend in Europe). The NK_1 inhibitors are especially good at preventing delayed emesis.

The protocol for anti-emetic therapy can be tailored to the risk of symptoms developing. So for minimal risk drugs treatment may not be necessary but if problems do occur then

Table 2.7 Advice for patients to reduce their risk of nausea

Avoid greasy, fatty or very spicy foods.
Ginger can help to ease sickness; so try nibbling a ginger biscuit or drinking ginger ale or ginger beer.
Avoid big meals, eat little and often with light bites and snacks
If you feel sick first thing in the morning, keep a couple of dry biscuits by your bed and try to eat one before you get up.
Make sure you have plenty of fresh air; keep a window open if you can, especially when cooking.
If cooking smells upset you, try to get someone else to prepare your meals, or opt for cold food, with salads and sandwiches.
Sea-bands may be helpful. These are bands that you strap on round your wrists. They are fitted with a button that gently presses on the skin over an acupressure point on the inner surface of the wrist. You can buy these sea-bands at any chemist.

metoclopramide or domperidone, starting immediately prior to chemotherapy and given tds for 4 days, should suffice. For low risk therapy a single dose of 8 mg dexamethasone 30–60 min before drug administration is recommended. For moderate risk drugs a combination of dexamethasone and a 5HT3 antagonist should be given whereas for high risk chemotherapy a three drug regimen is recommended with dexamethasone, a 5HT3 antagonist and an NK_1 inhibitor. These schedules will prevent sickness altogether, or keep it to a very low, and tolerable, level for the great majority of people.

Although 5HT3 antagonists are very effective at preventing and relieving sickness, some people do find they get side effects from them. The most common of these are constipation and headache. These can usually be relieved with a simple laxative like Senokot, or a simple painkiller like paracetemol. The NK_1 inhibitors can also cause side effects including hiccups, indigestion, diarrhea, constipation, loss of appetite and tiredness.

In addition to these pharmacological measures there are also things that patients can do themselves to help reduce the risk of nausea during chemotherapy. These are summarised in Table 2.7.

Suggestions for Further Reading

Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guidelines update. J Clin Oncol. 2011;29:4189–98.

Hesketh P. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358:2482–94.

Tiredness or Fatigue

Profound tiredness, or fatigue, is a very common problem during chemotherapy. It is thought that four out of five people will experience fatigue on some days during their treatment, and for about one in three it will be present most of the time. Not only is there often a complete lack of energy, but the tiredness can also interfere with other things – like memory, sleeping, and sex life. It may also lead to symptoms like breathlessness and loss of appetite. The tiredness usually comes on during the first week or two of treatment, and often gets more apparent as the course of treatment continues. Once the chemotherapy is over, the sense of fatigue slowly reduces, but it can take anywhere from a month or two to more than a year before it completely disappears. Studies suggest that even a year after treatment has finished, about one in five people will still regularly have days when they feel fatigued. Generally speaking, the older the patient, the longer it takes to recover their stamina. Tiredness is also more likely if someone is having, or has recently had, other treatments, like surgery or radiotherapy.

Although it is something that affects the majority of people, doctors have been slow to realize how important this tiredness is, and have concentrated on more obvious side effects like sickness and the risk of infection. This means there has been relatively little research into the causes and treatment of chemotherapy-related fatigue. Chemotherapy itself undoubtedly does cause fatigue, but frequently there can be other factors that might make the feeling worse. These include anaemia, the presence of an infection, being clinically depressed, or being in pain. All these are things that can often

readily be corrected. So if someone does complain of feeling very tired, then it is important to make sure none of these other factors are present.

Anaemia can usually be rapidly reversed by a simple blood transfusion, which can often be given as an out-patient. Even very mild levels of anaemia, with an Hb of 12 g/l or less, which would not normally be troublesome, can lead to severe tiredness in people who are having chemotherapy, and correcting this can make a big difference to how they feel. Similarly, giving antibiotics, or antifungal drugs, for an infection, or analgesics to relieve pain, or prescribing antidepressants for people who are clinically depressed, can ease their feeling of tiredness quite dramatically.

Some recent research has looked at giving the psychostimulant methylphenidate, Ritalin (used to treat attention-deficit-hyperactivity-disorder, ADHD) to people with cancer-related fatigue. These were randomised controlled trials comparing Ritalin with a placebo. Although there was some improvement among the people taking Ritalin there was also an improvement for those on the placebo. Whether this was simply a 'placebo-effect' or whether it was because, since they were in a trial, people were getting more support, in the form of additional consultations, tests, and telephone interviews from specialist nurses was uncertain. At the moment these results are not strong enough to recommend Ritalin routinely but the benefit in the placebo group suggests that just identifying the problem of chemotherapy-related fatigue and taking it seriously can have a positive effect.

An important thing to remember is to reassure people that tiredness is a very common feature of chemotherapy, and it does not mean that their cancer is coming back, or getting worse, nor does it mean that things are going wrong with their treatment.

Suggestions for Further Reading

Bruera E, Yennurajalingam S. Challenge of managing cancer-related fatigue. J Clin Oncol. 2010;28:3671–2.

Hofman M, Ryan JL, Colmar D, et al. Cancer-related fatigue: the scale of the problem. Oncologist. 2007;12 Suppl 1):4–7. This supplement includes a number of interesting papers on cancer-related fatigue.

Minton O, Richardson A, Sharpe M, et al. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Nat Cancer Inst. 2008;100:1556–66.

Mild Cognitive Impairment: Chemobrain

Whilst tiredness is a well-recognised and universally accepted side-effect of cytotoxic chemotherapy the risk of mild cognitive impairment as a result of treatment is more controversial. Although there is growing evidence for the phenomenon many oncologists remain sceptical about the existence of the problem. However, a number of studies, mostly looking at women treated for breast cancer, have reported people experiencing problems such as memory loss, difficulty in concentrating, difficulty in learning, reduced ability to multi-task and general mental 'fogginess'. These changes may appear acutely or at a later date. At the present time there are many unanswered questions about this possible toxicity: the incidence of the problem, the timing of onset, whether it is related to specific drugs and how it should be managed all remain unclear but the oncological community is increasingly accepting that the condition does exist and research is underway to try and define it more clearly.

Suggestions for Further Reading

Argyriou AA, Assimakopoulas K, Iconomou G, et al. Either called 'chemo-brain' or 'chemo-fog' the long-term chemotherapy induced cognitive decline in cancer survivors is real. J Pain Symptom Manage. 2011;41:126–39.

Wefel JC, Saleeba AK, Buzdar AV, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010;116:3348–56.

Hair Loss

For many people, the idea of having chemotherapy means that you must lose your hair. Alopecia is a major problem with cytotoxic treatment but not with most other types of

cancer chemotherapy. The risk of hair loss is linked directly to which cytotoxic drugs are given, with some hair loss is almost inevitable, with others it is virtually unknown (see Table 2.8). Both the incidence of hair loss and its impact on people's quality of life has frequently been underestimated by health professionals.

When hair loss occurs, it usually develops about 3–4 weeks after starting treatment. Frequently, once it starts, it can progress very rapidly, with almost complete hair loss within a day or two; with other types of treatment, it may be more a case of gradual thinning of the hair over several months. Scalp hair is the most sensitive to the effects of chemotherapy, because it grows more rapidly than hair on other parts of the body. But sometimes the drugs will cause loss of eyebrows, eyelashes, under-arm hair, and pubic hair as well. As well as warning patients about the risk of hair loss it is vital to remember to reassure them that, however much hair is lost, it will always grow back again (except occasionally in those undergoing high dose chemotherapy with a bone marrow or stem cell transplant). Normally the hair begins to reappear a month or so after the end of chemotherapy, and is back completely within 3–6 months (sometimes it even starts to grow while people are still having the drugs). Often, however, it comes back with a different colour and appearance – a grey/black, 'pepper and salt' colouring, with quite a thick texture, and a slightly curly or wavy look is very common, although these changes may be transient.

If treatment does involve drugs that carry a high risk of alopecia, the one thing that can sometimes be done to try to prevent, or reduce, this is scalp cooling. There are various types of scalp cooling, but the general principle is to chill the scalp, usually by wearing a special padded hat that contains a gel. The hat is stored in a freezer and is then strapped firmly on the patient's head about half an hour before they are due to have their drugs. It has been suggested that wetting the hair before applying the cap may increase its effectiveness but this is uncertain. They then continue to wear the hat for about half an hour after the drugs have been given. The underlying principle is that by keeping the scalp very cold the

Table 2.8 Cytotoxics and hair loss

Drugs which carry a high risk of total alopecia, or cosmetically significant hair loss	
Cyclophosphamide	Etoposide
Dactinomycin	Ifosfamide
Daunorubicin	Irinotecan
Docetaxel	Paclitaxel
Doxorubicin	Temozolamide
Epirubicin	Vindesine
Drugs which sometimes cause noticeable hair loss, or thinning of the hair	
Amsacrine	Lomustine
Bleomycin	Melphalan
Busulfan	Pemetrexed
Cytarabine	Pentostatin
Fludarabine	Topotecan
Fluorouracil	Vinblastine
Gemcitabine	Vincristine
Hydroxyurea	Vinorelbine
Idarubicin	
Drugs which rarely, or never cause hair loss	
Capecitabine	Mitomycin
Carboplatin	Mitoxantrone
Carmustine	Oxaliplatin
Chlorambucil	Procarbazine
Cisplatin	Raltitrexed
Cladribine	Tegafur
Dacarbazine	Thiotepa
Mercaptopurine	Thioguanine
Methotrexate	Treosulfan

blood vessels in the scalp contract, so the blood supply to the hair follicles is reduced and they will be less affected by the circulating cytotoxics. Scalp cooling doesn't always work. For many people it will prevent or greatly reduce the amount of hair loss, but for others it has very little effect. One group of patients in whom it is often ineffective are those who have disturbed liver function, due to liver secondaries or other causes, which delays metabolism of many cytotoxic drugs, and hence maintains their concentration in the blood after the scalp cooling is complete. Some people find scalp cooling uncomfortable. The hat is very cold, and can often cause headaches and occasionally dizziness and light-headedness, so it does not suit everyone (Fig. 2.3).

There have been concerns about the use of cold caps increasing the risk of scalp metastases but there is no clear evidence for this from clinical studies. However, the use of scalp cooling is generally considered contraindicated in people with haematological cancers and malignant melanoma because of this uncertainty.

For those people who do develop alopecia the most obvious way of coping is having a wig. Most chemotherapy departments have a specially trained member of staff who can discuss the available options with and arrange a wig that meets the individual's colour and style. Alternatives to wigs include headscarves and bandanas, which allow some people to turn their hair loss into a fashion statement!

Patients often ask if there is anything that they can do to reduce the risk of hair loss, and Table 2.9 gives some useful tips.

Suggestions for Further Reading

Breed WPM, ven den Hurk CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss. Expert Rev Dermatol. 2011;6:109–25.

Hesketh PJ, Batchelor D, Golant M. Chemotherapy-induced alopecia: psychosocial impact and therapeutic approaches. Support Care Cancer. 2004;12:543–9.

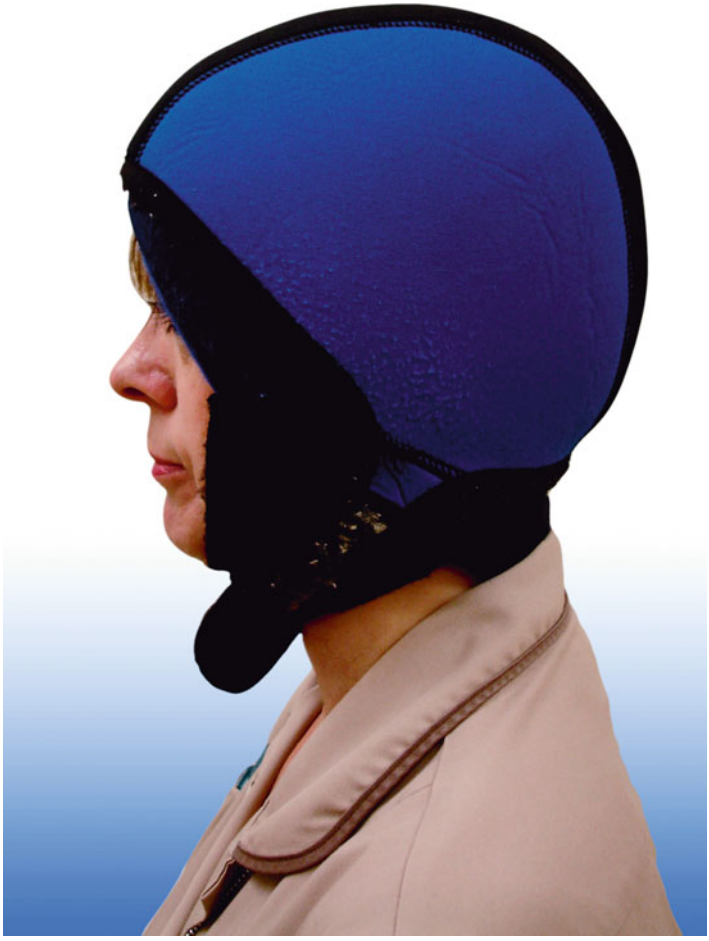

FIGURE 2.3 A typical 'cold cap' used for scalp cooling to prevent chemotherapy-induced hair loss (Courtesy of the author)

Oral Mucositis

Having a sore mouth during chemotherapy is quite common as a result of inflammation of the lining of the mouth. The chances of getting a sore mouth do vary depending on the

Table 2.9 Advice for patients to reduce their risk of alopecia

Avoid using heated products like curling tongs or heated rollers.
Try to wash your hair less often. The fewer times you wash your hair the better (but obviously you will have to find your own balance between reducing the frequency of washes and what you feel comfortable with).
Avoid shampoos and conditioners with lots of chemicals: try using a baby shampoo.
Avoid hair dyes and colourants, unless they are completely organic (plant-based), with no added chemicals.
Avoid perms.
If you have very long hair, then having it cut to a shorter style may help.

treatment; some drugs, or combinations of drugs, are more likely to cause mucositis than others (see Table 2.10). This oral mucositis usually comes on a few days after the drugs have been given and settles within about a week. The soreness can vary considerably in its severity. Often it is no more than a slight discomfort, but sometimes it can be very distressing, with the development of mucosal ulceration. Because the patient is often neutropenic as well, the soreness may be aggravated by the development of fungal infections in the mouth, most commonly oral monilia, which shows up as small whitish patches on the mucosa and the surface of the tongue. These infections are also common in people who are having steroids as part of their treatment. When mouth soreness develops it can also affect the sense of taste, so people often complain that things taste different, or that they cannot taste things so well whilst they are having their chemotherapy.

If a particular regimen is likely to cause mucositis then sucking crushed ice for 15–30 min before the cytotoxics are given, and continuing until about half an hour after the drugs have been administered, can sometimes prevent mouth soreness. One drug that is particularly associated with oral mucositis is methotrexate. The risk is usually dose-dependant and if higher doses of the drug are being used then this giving an iv dose of folinic acid (leucovorin) at the same time as the

Table 2.10 Cytotoxic drugs which commonly cause oral mucositis

Capecitabine	Hydroxyurea
Carboplatin	Lomustine
Chlorambucil	Melphalan
Cisplatin	Mercaptopurine
Cyclophosphamide	Methotrexate
Dacarbazine	Mitomycin
Dactinomycin,	Paclitaxel
Daunorubicin	Raltitrexed
Doxorubicin	Vinblastine
Etoposide	Vincristine
Fluorouracil	

methotrexate, and following this with a course of leucovorin tablets for a day or two can often prevent the problem (see page 28). If mucositis does develop after methotrexate administration, and folinic acid has not been given, then giving the tablets for a few days will often help. If someone does complain of a sore mouth after their chemotherapy then it is always important to check for the presence of oral monilia as this can readily be resolved with a course of an antifungal drug like nystatin, or amphotericin, for a few days. Oral soreness can also be eased by using a painkilling mouthwash such as Difflam Oral. Some people find using a full-strength mouthwash stings, and diluting it with an equal amount of warm water may help. An alternative is to suggest patients make their own mouthwash using soluble aspirin, dissolving a couple of tablets in a glass of warm water and using this to rinse their mouth well three or four times a day. If mouth ulcers develop, then there is a wide range of gels, pastes and sprays that may help these include Bonjela gel, Biora gel, Medijel, Rinstead contact pastilles.

More general advice for avoiding or easing oral mucositis includes ensuring that patients maintain good oral hygiene (see Table 2.11) and changing their diet to avoid foods and

Table 2.11 Advice for patients to reduce their risk of oral soreness

Have a routine check-up with your dentist before you start treatment, to make sure there are no obvious tooth or gum problems that need to be dealt with before your chemotherapy.
Maintain good oral hygiene; this means cleaning your teeth at least twice a day. Using a normal toothbrush can be uncomfortable, so using a soft toothbrush, or a child's brush, might help.
You may find that your usual toothpaste makes your mouth and gums sore, and changing to a brand for 'sensitive teeth', like Sensodyne Original or Macleans Sensitive, might help.
Mouthwashes can also be useful, and you can try these if you find that brushing your teeth is really painful. There are preparations you can get from your chemist or supermarket that help to prevent infection, these include chlorhexidine, Corsodyl, and thymol.
For simply keeping your mouth clean you can make your own mouthwash with a teaspoonful of baking powder (sodium bicarbonate) dissolved in a glass of warm water, and use this to rinse out your mouth thoroughly morning and night.
Keeping your mouth moist with regular fluids. You should be drinking at least 2 l of fluid every day during your treatment, but supplementing this with regular sips of water or other soft drinks can help (fizzy water, or fizzy drinks, tend to be better than still fluids).
Try to avoid, or reduce, smoking, alcohol and caffeine (in tea and coffee) all of which tend to make your mouth dry and can make soreness worse

drinks that may make their mouth sore if the mucosa is sensitive: these include very hot and spicy foods, vinegar, salt, neat spirits (whisky, brandy, gin, etc.) and acid drinks like grapefruit juice and some types of orange juice.

Suggestions for Further Reading

Mitchell EP. Gastrointestinal toxicity of antineoplastic agents. Semin Oncol. 2006;33:106–20.

Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer. 2007;109:820–31.

Reduced Fertility

As with other side effects, the risk of any effect on fertility is related to which drugs are used, and the doses given, and the length of time the treatment goes on for. Some cytotoxic treatments carry a very high risk of infertility, whereas with others there is almost no risk. The drugs that are most frequently associated with infertility are the alkylating agents. So if fertility is an issue then choosing regimens that either avoid these drugs completely, or keep their doses to a minimum, whilst maintaining anti-cancer efficacy, should be the objective. For example, in Hodgkin lymphoma, where young people are frequently affected, the original MOPP regimen, containing the potent alkylating agent nitrogen mustard leading to almost universal sterility, has largely been supplanted by ABVD, where the risk of infertility appears to be minimal.

For men, cytotoxics can have a direct effect on spermatogenesis, with a reduction in the sperm count becoming apparent within 3 weeks of starting treatment. This risk relates almost entirely to which drugs are used (see Table 2.12). But in some types of cancer, in particular cancer of the testicle, a reduced level of fertility, with a lower than normal sperm count, may actually be part of the man's condition, even before they begin any treatment.

For women, cytotoxics may cause destruction of the ovarian follicles, resulting in failure of ovulation, amenorrhoea, and sterility. The drugs may also lead to a reduction in ovarian hormone production, leading to menopausal symptoms. The risk of loss of ovarian activity with cytotoxic treatment increases the closer a woman is to the natural menopause. Sometimes, especially in younger women, cytotoxic treatment leads only to a temporary loss of ovarian activity, so the periods stop during treatment, and for anywhere from 3 to 18 months afterwards, but then can start again. The risk of permanent ovarian suppression is confined to the alkylating agents, and is largely dose dependant. Other drugs may cause a temporary interruption in ovarian function.

For men, if there is a chance that treatment will affect their fertility, they should always be offered the chance of

Table 2.12 Chemotherapy and male fertility

Drugs likely to cause permanent or prolonged azoospermia	
Busulfan	Ifosfamide
Carmustine	Lomustine
Chlorambucil	Melphalan
Cisplatin	Nitrogen mustard
Cyclophosphamide	Procarbazine
Dactinomycin	
Drugs which may cause some temporary reduction in sperm count when used alone, but can have an additive effect on fertility in combination regimens	
Amsacrine	Fluorouracil
Bleomycin	Fludarabine
Carboplatin	Mercaptopurine
Cytaribine	Methotrexate
Dacarbazine	Mitoxantrone
Daunorubicin	Thioguanine
Doxorubicin	Thiotepa
Epirubicin	Vinblastine
Etoposide	Vincristine
Drugs with an unknown effect on spermatogenesis	
Docetaxel	Oxaliplatin
Irinotecan	Paclitaxel
Monoclonal antibodies	Small molecule TK inhibitors

sperm banking before beginning therapy. Freezing the sample does further reduce the quality of the sperm, but once they are frozen they can be kept indefinitely without any further deterioration and this does offer some hope of fathering future children. For women, the options are more

limited. Freezing and storage of embryos that can be thawed and reimplanted into the womb after treatment is possible, but delaying treatment long enough for this to be arranged will not usually be possible. Even with this technique the chances of a successful pregnancy are probably still only about one in five. An operation to take away eggs (oocytes) from the ovary and have these frozen, or taking away pieces of ovarian tissue for storage (that could be replaced after treatment to try and make the ovaries work again), are both possible, but are really experimental approaches that are still being developed, with, at the moment, very little chance of success. Another option is egg donation, where, after the treatment is over, the patient's womb could be implanted with eggs donated by another woman. This has resulted in successful pregnancies for some women after their ovaries have failed as a result of chemotherapy.

There are two other points to mention. Firstly, because of the unpredictability of the effects of cytotoxics on fertility, it would be wrong to think that having treatment acts as a reliable form of contraception. So if patients are practising birth control, they should be advised continue this while they having their chemotherapy.

Secondly, people can be reassured that studies have shown that if fertility is reduced, but returns after chemotherapy, or if it was unaffected by treatment, the drugs that they have had will not lead to any increase in the chances of birth defects in children that they may father, or give birth to, in the future.

Suggestions for Further Reading

Banks E, Reeves G. Pregnancy in women with a history of breast cancer. Br Med J. 2007;334:166–67.

Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917–31.

Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360:902–11.

Second Cancers

A number of cytotoxic drugs have been linked to the development of second malignancies, most commonly leading to acute myeloid leukaemia (AML). This problem was first identified following treatment with alkylating agents, in particular the nitrogen mustards. The risk varies with different agents (melphalan being some ten times more potent a carcinogen than cyclophosphamide) and increases with the overall dose of the drug given. Typically the leukaemia is appears some 5–9 years after treatment and is proceeded by the development of a myelodysplastic syndrome. Early estimates suggested that the likelihood of developing AML after alkylating agent therapy was about 1.5% at 10 years, but with greater awareness of the hazard this figure has probably now reduced.

The assumption is that it is the direct effect of alkylating agents on DNA that leads to their leukemic potential and so other cytotoxics which interact directly with the DNA chain might be expected to pose similar risks. An increased incidence of AML has been identified following therapy with platinum compounds, and the topoisomerase inhibitors (etoposide and the anthracyclines: epirubicin, doxorubicin and mitoxantrone). Isolated cases have also been reported after taxane-based chemotherapy. Among these drugs the risk appears to be highest with mitoxantrone with up to 4% of patients being affected, with the others there is less than a 1% chance of AML developing. Once again the risk appears to be related to dose-intensity, but unlike the AML linked to alkylating agents the onset is earlier, at 2–4 years post-treatment and not associated with an initial myelodysplastic phase.

Suggestions for Further Reading

Le Deley M-C, Suzan F, Cutuli B, et al. Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol. 2007;25:292–300.

Praga C, Jonas B, Bliss J, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol. 2005;23:4179–91.
Travis LB. The epidemiology of second primary cancers. Cancer Epidemiol Biomarkers. 2006;15:2020–6.

Specific Side Effects of Cytotoxic Treatment

There are a number of side effects of chemotherapy which, although important, and occasionally serious, are limited to just a handful of the more commonly used cytotoxic drugs.

Peripheral Neuropathy

The peripheral neuropathy caused by cytotoxic drugs is mainly sensory. The first symptom is tingling, or pins and needles, in the fingers or toes. This gradually spreads to the rest of the hands and feet, and, if nothing is done, will go on to affect the remainder of the limbs. As the condition progresses, numbness of the affected areas will develop, and this leads to some loss of co-ordination, making fine movements like undoing buttons, typing, or tying shoelaces, more difficult. Loss of reflexes in the ankle and wrist are relatively early physical signs but weakness of the arms and legs is a very uncommon, late, occurrence.

Peripheral neuropathy is a recognized complication of treatment with three groups of chemotherapy drugs: the Vinca alkaloids (which include vincristine, vinblastine, vindesine and vinorelbine), the platinum compounds (cisplatin, carboplatin, and oxaliplatin), and the taxanes (paclitaxel and docetaxel). Of the vinca alkaloids vincristine is the drug most likely to cause neuropathy, and it may also affect the autonomic nervous system leading to constipation and, very occasionally, intestinal obstruction. As well as causing a typical peripheral neuropathy, oxaliplatin is also linked to a specific syndrome where intense, often painful, tingling sensations occur in the fingers and toes a few hours after the drug is

given, lasting from a few hours to a few days, the symptoms often being made worse by exposure to cold: up to 90% of people receiving oxaliplatin experience this problem.

Usually the peripheral neuropathy is dose related, and comes on gradually, after two or three doses of the drugs, sometimes appearing only after treatment is complete. Numerous drugs have been used to try and prevent the neurotoxicity developing, but the results have been mixed and no one agent has been sufficiently successful to enter routine practice. If early signs of neuropathy appear then reducing the dose of the offending drug, or stopping it completely will usually help ease the problem, but sometimes this is an unacceptable compromise of the treatment. The neuropathy resulting from both vinca alkaloids and taxanes is generally reversible, although it may take months after treatment is over to disappear completely. With platinum compounds the picture is more mixed with the changes sometimes being permanent, although usually with low to moderate doses of the drugs there will be a recovery eventually.

Suggestions for Further Reading

Hausher FH, Schilsky RL, Berghonr EJ, Liberman F. Diagnosis, management and evaluation of chemotherapy-induced peripheral neuropathy. Semin Oncol. 2006;33:15–49.

Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. J Peripher Nerv Syst. 2008;13:27–46.

Cardiotoxicity

A number of cytotoxics carry the risk of cardiac damage, including the anthracyclines, fluorouracil and vinca alkaloids. Cardiotoxicity is also a side effect of the monoclonal antibody trastuzumab (see page 98).

Doxorubicin is the anthracycline most likely to cause cardiac toxicity. Transient arrhythmias may occur in the first few hours after administration of the drug. These are most likely in people with previously abnormal ECGs. The arrhythmias

usually do not require treatment, and are not a contraindication to further doses of the drug. Very rarely more serious, life-threatening, ventricular arrhythmias have been reported. The more significant risk with the drug is chronic cardiomyopathy. This is dose-related. Early studies suggested that less than 1% of people who received a cumulative dose of <550 mg/m^2 were affected, with the incidence increasing to more than 30% with cumulative doses between 550 and 1,150 mg/m^2. With greater awareness of this problem, and better means of monitoring it, particularly the measurement of left ventricular ejection fraction (LVEF), it is now clear that the incidence may be higher and cardiac damage can occur even at relatively low doses. For these reasons many clinicians have reduced the maximum cumulative dose of the drug to 450–500 mg/m^2. The cardiomyopathy leads to congestive cardiac failure, which may not appear until some months, or even years, after the last dose of the drug. The heart failure can often be difficult to treat and carries quite a high mortality. Apart from dose, other predisposing factors include age over 70, pre-existing heart disease, and a past history of radiotherapy to the mediastinum. Most dose-schedules for doxorubicin give total doses below the 500 mg/m^2 level. For those people with risk factors that might leads to problems at lower levels monitoring of their LVEF is advisable; a pre-treatment value of 45% or a fall to this level during treatment, would usually mean that the drug is contra-indicated or should be stopped. Epirubicin has the potential to cause similar cardiac problems to doxorubicin, but the cumulative dose at which these are seen is significantly higher, at between 900 and 1,000 mg/m^2. Chronic cardiomyopathy may occur with other anthracyclines, and once again is dose-related: with daunorubicin 1.5% of people will develop cardiomyopathy at a cumulative dose below 500 mg/m^2, whereas between 500–100 mg/m^2 the figure rises to 12%, and for mitoxantrone the suggested maximum cumulative dose is 160 mg/m^2.

A number of suggestions have been made to reduce doxorubicin toxicity. There is limited evidence that the risk of cardiac damage is reduced if the drug is given by prolonged

intravenous infusion, or on a once weekly basis at lower doses. Also a number of agents have been investigated as cardioprotective agents during doxorubicin therapy, the most widely evaluated being dexrazoxane, but their value remains to be established. The liposomal formulation of doxorubicin does not permeate the blood vessels of the myocardium, and is associated with only minimal cardiotoxicity.

A further problem with doxorubicin is that when given in combination with paclitaxel there is a high risk of cardiotoxicity. Studies have now shown that this relates to the scheduling of the drugs, as the paclitaxel infusion delays doxorubicin clearance and prolongs its plasma half-life. The risk of cardiac damage can be minimised by giving doxorubicin first, with a delay of at least 30 min before the paclitaxel infusion, and limiting the cumulative dose of doxorubicin during treatment to 360 mg/m^2. By contrast, combining doxorubicin with docetaxel is not associated with an increased risk of cardiac damage, nor is there any increased risk if either taxane is given with epirubicin.

Both fluorouracil and capecitabine may cause cardiotoxicity. The signs of this range from asymptomatic ECG changes to angina pectoris and myocardial infarction, which may be fatal. The mechanism for these changes remains uncertain, although coronary vasospasm has been suggested. With fluorouracil they are most likely to occur within 72 h of the first dose of the drug, and are commoner with higher doses given by continuous infusion. When symptoms occur about half the patients experience angina, about 25% infarction, 15% arrhythmias, and the remainder either acute pulmonary oedema, pericarditis or cardiac arrest. The development of cardiotoxicity means that the drug should be stopped, in trials where patients have been rechallenged with fluorouracil after signs of cardiac problems there have been significant numbers of cardiac deaths.

Suggestions for Further Reading

Kristeleit R, O'Brien M. Cardiotoxicity from cytotoxics in the 21st century. Br J Cardiol. 2009;16:60–2.

Ng R, Better N, Green MD. Anti-cancer agents and cardiotoxicity. Semin Oncol. 2006;33:2–14.
Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. Cancer Treat Rev. 2010;37:300–11.

Renal Damage

Cisplatin is the cytotoxic drug most closely associated with nephrotoxicity. The degree of injury to the kidneys is dose-dependant, and cumulative, single doses below 50 mg/m^2 seldom causing problems. Higher doses lead to renal tubular injury which in turn may lead to electrolyte imbalance, especially low sodium and/or magnesium levels in the blood, as well as reduced creatinine clearance levels and ultimately renal failure. These changes persist for months, and often years, after treatment is over; for example, it has been estimated that 4 years after chemotherapy with cisplatin men treated for testicular cancer have, on average, a 15% reduction in their creatinine clearance.

As well as dose-limitation cisplatin nephrotoxicity can also be reduced by using a forced diuresis, with large volumes of intravenous normal saline before and after administration of the drug. This dilutes the concentration of cisplatin in the renal tubules and speeds its transit through the kidneys. Originally the schedules for the saline infusions lasted anywhere from 24 to 36 h, necessitating that treatment be given on an in-patient basis, but these have been modified over time and it is now often possible to give the treatment on a day-patient basis. A number of chemicals have been evaluated as possible agents to reduce the renal toxicity of cisplatin, the most widely tested being amifostine, but none of these has proved sufficiently successful to enter routine practice.

Carboplatin was developed as an analogue of cisplatin specifically to find a less nephrotoxic alternative. Carboplatin does cause less damage to the kidneys, only causing problems when given at high doses, but it does carry a greater risk of myelosuppression than cisplatin. To minimize the risk of renal damage carboplatin dosing is directly related to renal function (see page 46).

Table 2.13 Cytotoxic hepatotoxicity

Hepatotoxicity	Recognised side effect	Isolated reports
Hepatocellular toxicity	Cytarabine[a]	Chlorambucil
	Mercaptopurine	Gemcitabine
		Pentastatin
		Raltitrexed
Veno-occlusive disease	Busulfan[a]	Dacarbazine
	Carmustine[a]	Gemcitabine
	Cyclophosphamide	Mercaptopurine
	Cytarabine	Tioguanine
	Mitomycin	
Chronic fibrosis	Methotrexate	

[a]Following high-dose therapy

Other cytotoxics that have been linked to renal damage include mitomycin, methotrexate, and ifosfamide. Problems usually only occur with either prolonged cumulative administration, or higher than normal individual doses.

Suggestion for Further Reading

de Jonge MJA, Verweij J. Renal toxicities of chemotherapy. Semin Oncol. 2006;33:68–73.

Hepatotoxicity

Three types of liver damage have been linked to cytotoxic drugs: hepatocellular dysfunction, veno-occlusive disease and chronic fibrosis.

Hepatocellular dysfunction is characterised by an increase in the blood level of liver enzymes and bilirubin. It has most often been reported with high dose cytarabine therapy and mercaptopurine but it may occur occasionally as a result of a number of other drugs (see Table 2.13).

Veno-occlusive disease leads to blockage of small blood vessels in the liver which in turn causes hepatomegaly, ascites and oedema, and may progress to be fatal. It has been reported after high-dose therapy with a number of alkylating agents and also in isolated instances with a number of other cytotoxics.

Hepatic fibrosis is a complication of long-term low dose methotrexate administration. The drug is usually only given in this way in the treatment of a number of non-malignant conditions, such as rheumatoid arthritis.

Suggestion for Further Reading

Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. Semin Oncol. 2006;33:50–67.

Pulmonary Toxicity

Bleomycin is the cytotoxic most widely associated with lung damage, leading to chronic pulmonary fibrosis. Some estimates suggest as many as 1 in 10 people receiving the drug may be affected. Typically the changes appear 1–6 months after treatment. The pulmonary toxicity is dose-related and usually only appears when more than 400,000–500,000 units of the drug have been given (bleomycin dose-labelling varies in different parts of the world, and outside Europe this equates to 400–500 units). Other factors predisposing to drug-induced pulmonary fibrosis include older age, poor renal function (delaying excretion of the drug, allowing it to concentrate in the lungs), and radiotherapy to the chest. Much less commonly bleomycin may cause an early onset interstitial pneumonitis, which may also lead to long-term fibrosis in some cases; this is not dose-related and is similar to a hypersensitivity reaction.

Mitomycin can cause a range of pulmonary toxicities ranging from transient bronchospasm, which resolves spontaneously a few hours after the drug has been given, to acute

interstitial pneumonitis, to chronic pneumonitis and pulmonary fibrosis. Other drugs where lung toxicity, predominantly pulmonary fibrosis, has occasionally been reported include busulphan (the first cytotoxic to be linked to lung damage), methotrexate, cyclophosphamide, the taxanes and the vinca alkaloids.

Suggestion for Further Reading

Meadors M, Floyd J, Perry MC. Pulmonary toxicity of chemotherapy. Semin Oncol. 2006;33:98–105.

Skin Damage

Cytotoxic drugs may affect the skin in a number of ways but the two most important are extravasation (leakage of the drug outside the vein at the injection site) and hand-foot syndrome.

When cytotoxic drugs are given through a drip into a peripheral vein, even when the drug is given carefully, by trained skilled nurses, small amounts of the drug may occasionally leak outside the vein, into the surrounding soft tissues. It has been estimated that some degree of extravasation may occur in up to 5% of patients undergoing intravenous chemotherapy. With many drugs, extravasation is not a problem, and, at most, will only cause some slight brief discomfort. With a few drugs, however, any leakage into the tissues around the vein can cause quite severe inflammation, with redness, swelling and soreness. This comes on almost immediately after the extravasation has occurred, and, depending on the drug and the amount that has leaked into the tissues, may take days, or even weeks, to resolve. Occasionally long-term induration or even skin necrosis can result. The drugs most likely to cause irritation and skin damage when they leak are the anthracyclines doxorubicin and epirubicin, the Vinca alkaloids vincristine, vinblastine, vindesine and vinorelbine and the taxane paclitaxel.

If extravasation occurs then the tube through which the drug is being infused should be disconnected, but the needle

into the vein should remain in place. A syringe can then be connected to the needle and used to draw back any remaining drug. If the extravasation involves anthracyclines then ice packs should then be placed on the surrounding skin, and the arm kept elevated. For leakage of Vinca alkaloids or paclitaxel a warm compress should be applied. In addition specific antidotes have been recommended. For anthracycline extravasation topical application of dimethyl sulfoxide may help and more recently intravenous infusions of desrasoxane (Savene), started within 6 h of the leakage, have also been shown to be of value. Desresoxane helps prevent free radical formation which is an important component of anthracycline-related extravasation tissue necrosis. There is also some evidence that dimethyl sulphoxide (DMSO) may be beneficial, as well as being a free-radical scavenger this chemical increases tissue permeability which might help diffuse the extravasated drug. For Vinca alkaloid and paclitaxel leakage immediate local subcutaneous injection of hyaluronidase is beneficial. Hyaluronidase causes the release of fluid into the extracellular space which helps to dilute the extravasated drug. Using an anti-inflammatory, or antihistamine cream on the affected area for a week or so afterwards can also help. Very occasionally if chronic painful skin damage results hyperbaric oxygen therapy, or surgery, with removal of the affected soft tissues and skin grafting, may be necessary (Table 2.14).

In recent years cytotoxic extravasation has featured increasingly in legal claims by patients. So if it does occur it should not only be treated meticulously, but also all aspects of the incident should be carefully documented.

A completely different type of skin damage which can occur with a number of cytotoxic drugs including fluorouracil, capecitabine, irinotecan, the taxanes and cytarabine is hand-foot syndrome (also known as palmar-plantar erythrodysesthesia, or acral erythema). In hand-foot syndrome the skin on the palms of the hands and soles of the feet becomes red and sore, and may actually begin to blister and peel. Sometimes the pain from this can be so severe that narcotic analgesics are needed to control it. It usually only comes on gradually,

Table 2.14 Management of cytotoxic extravasation

Drug	Non-pharmacological	Pharmacological
Anthracyclines	Cold compress immediately for 20 min, then qds for 3 days	Desresoxane iv infusion within 6 h, repeat on days 2 and 3 DMSO sc at extravasation site 3–4 times daily for 7–14 days Topical antihistamine or steroid
Vinca alkaloids, Taxanes	Warm compress immediately for 20 min, then qds for 3 days	Hyaluronidase sc at six sites around the area of extravasation Topical antihistamine or steroid

with higher doses of the drugs, and adjusting the dose will often ease the problem. Sometimes taking tablets of Vitamin B6 (pyridoxine) at a dose of 200 mg daily will give some symptomatic relief.

Suggestions for Further Reading

Cassagnol M, McBride A. Management of chemotherapy extravasations. US Pharm. 2009;3 (9 Oncol Suppl):3–11.

Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. Semin Oncol. 2006;33:139–43.

Schulmeister L. Preventing and managing vesicant chemotherapy extravasations. J Support Oncol. 2010;8:212–15.

Ototoxicity

Cisplatin damages the outer hair cells in the organ of Corti in the inner ear. This injury can lead to symptoms ranging from reversible tinnitus to irreversible hearing loss and vestibular toxicity. The risk of ototoxicity is dose and schedule dependant,

being uncommon with doses of <60 mg/m^2/cycle. A number of drugs have been tried as agents to protect against cisplatin-induced ototoxicity, but none has so far proved successful. As a result dose-reduction is the only way of preventing severe, irreversible hearing loss.

Suggestion for Further Reading

Rademaker-Lakhai JM, Crul M, Zuur L, et al. Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol 2006;24:918–24.

Bladder Toxicity

The alkylating agents, ifosfamide and cyclophosphamide, when they are metabolized produce a number of chemicals which are excreted in the urine. A number of these are urotoxic, and can cause irritation to the urothelium, leading to haemorrhagic cystitis. This is usually only a problem with cyclophosphamide when the drug is given at high doses, but with ifosfamide it is a risk at standard doses of the drug. The main urotoxic chemical which is produced is acrolein and this can be neutralized by mercapto-ethanesulfonate (MESNA). MESNA is routinely given as an intravenous infusion at the same time as ifosfamide, and it binds with acrolein, and other metabolites, to form stable non-urotoxic compounds which are rapidly excreted. MESNA does not have any anticancer action in its own right, nor does it reduce the effectiveness of the alkylating agents.

Diarrhoea and Constipation

Diarrhoea is most likely to occur following the administration of either fluorouracil, capecitabine or irinotecan. Depending on the dose and schedule used this can be severe or even life-threatening, and patients should always be made aware of this risk. For mild to moderate diarrhoea (the passage of 4–6 stools daily) dietary advice combined with regular doses of loperamide and a good fluid intake to avoid dehydration, should suffice. If

Table 2.15 Factors complicating diarrhoea

Severe abdominal cramping
Grade II or greater nausea or vomiting
Reduced performance status
Fever
Sepsis
Neutropenia
Obvious rectal bleeding
Dehydration

the mild to moderate diarrhoea is accompanied by any complicating factors (see Table 2.15), or if the diarrhoea is more severe, with the passage of seven or more stools daily, then more aggressive management is indicated. This would normally involve admitting the patient for intravenous hydration, and subcutaneous or intravenous injections of the somatostatin analogue, octreotide, titrating the dose as necessary to bring the situation under control. Prophylactic antibiotics may also often be indicated.

Constipation is most commonly seen with vincristine therapy, and usually appears 3–4 days after the drug is given. It is due to the effects of vincristine on the autonomic nerves, and may often be accompanied by signs of peripheral neuropathy. It is more likely in elderly patients or those on higher doses of the drug. Usually it will respond to mild laxatives and stool softeners, but occasionally it can progress to a paralytic ileus. This will usually resolve with conservative management over 7–10 days.

Suggestions for Further Reading

Gibson R, Stringer A. Chemotherapy-induced diarrhea. Curr Opinion Supp Pall Care. 2009;3:31–5.

Gibson RJ, Keefe DMK. Cancer chemotherapy-induced diarrhea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006;14:890–900.

Table 2.16 Cytotoxic drugs likely to cause hypersensitivity reactions

Drug	Incidence of reactions
Bleomycin	1%
Carboplatin	5%
Docetaxel	20% (4% severe)
Doxorubicin (liposomal)	10%
Etoposide iv	2%
Oxaliplatin	20% (3% severe)
Paclitaxel	40% (2% severe)
Cabazitaxel	<10%

Hypersensitivity Reactions

These are most likely to be seen with the taxanes (see Table 2.16). The reaction is apparent within moments of starting the infusion and may include blood pressure changes (hypotension or hypertension), breathlessness, severe anxiety, flushing, a diffuse erythema, angioedema, itching and chest pain. The reaction is caused by sensitivity to solutes necessary to get the active drugs into solution rather than by the drugs themselves. The risk of reactions can be reduced by premedication. For paclitaxel and cabazitaxel this involves giving the steroid dexamethasone, together with an antihistamine and an H2 antagonist, for docetaxel usually only dexamethasone is given. Giving dexamethasone prior to docetaxel administration also reduces the risk of another complication of the drug: fluid retention, which can lead to oedema, pleural or pericardial effusions or ascites. If a reaction does occur then the infusion should be stopped immediately, and changed to intravenous saline, intravenous hydrocortisone and antihistamine should be given, and oxygen administered. In severe cases adrenalin may be necessary. The symptoms will usually rapidly subside, and often the infusion can be restarted after 30 min without further problems.

Liposomal doxorubicin causes similar immediate reactions in about 10% of patients, although the episodes are

usually less severe. They only occur with first infusions. For those patients who give a history of allergies premedication with a steroid and an antihistamine may be a wise precaution.

In contrast to the taxane hypersensitivity reactions those seen with oxaliplatin and carboplatin tend to occur only after a number of courses of the drug have been given, typically 6–8 cycles. A number of desensitization protocols have been reported which may prevent further reactions, but often the development of hypersensitivity necessitates stopping the drug completely.

Acute hypersensitivity reactions have been reported with many other cytotoxics but they only rarely occur.

Suggestions for Further Reading

de Lemos M. Acute reactions to chemotherapy agents. J Oncol Pharm Pract. 2006;12:127–9.

Markman M. Managing taxane toxicities. Support Care Cancer. 2003;11:144–7.

Weiss RB. Miscellaneous toxicities. In: DeVita VT, Hellman S, Rossenberg SA, editors. Cancer: principles and practice of oncology. 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 2602–14.

Tumour Lysis Syndrome

This is usually only seen with bulky, highly chemosensitive tumours, or in leukaemias with high blast counts. When cytotoxics are first given in the treatment of these cancers they may cause massive tumour necrosis which can lead to acute biochemical disturbances including hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. These can lead to acidosis and acute renal failure. Patients whose serum uric acid level or lactic dehydrogenase level (LDH) is raised prior to treatment, or those with poor renal function, are particularly at risk. The key to management of this complication is prevention. Patients who are deemed to be at risk

would usually be given oral allopurinol, to reduce their uric acid levels, prior to starting chemotherapy and continue this throughout their treatment. This, combined with ensuring a good fluid intake will usually be sufficient prophylaxis. If the syndrome does develop then giving allopurinol, if it has not already been given, intravenous hydration and urinary alkalinisation are the first line management. If allopurinol has already been given then rasburicase may be used as an alternative. This is a recombinant form of the enzyme urate oxidase, which converts poorly soluble uric acid to water-soluble metabolites. In severe cases with it may be necessary to consider renal dialysis.

Suggestion for Further Reading

Howard SC, Jones DP, Pui C-H. The tumor lysis syndrome. N Engl J Med. 2011;364:1844–54.

Side Effects of Hormonal Therapies

Menopausal Symptoms

Generally hormone therapies cause fewer, and less serious, side-effects than chemotherapy. Many women being treated for breast cancer have virtually no problems at all from their hormonal treatment. Having said this, for a small minority of women the therapy can be very upsetting. The most common problems are unpleasant menopausal side-effects. These include hot-flushes, drenching sweats, vaginal dryness and soreness, mood swings, and irritability, loss of concentration and difficulty in remembering things. These are most likely to occur with tamoxifen, or goserilin. In younger women taking tamoxifen about one third will find their periods stop (if this happens it is still possible for the woman to become pregnant and she should continue contraception), one third will find they become irregular, and one third will see no difference, but all may get menopausal symptoms, as may some women

who are postmenopausal and are given the drug. Recognising and sympathetically managing this problem is important as research has shown that up to 50% of women with breast cancer stop taking their hormonal within 2 years of starting, although they should take it for a minimum of 5 years. A variety of things can be done to try and ease these symptoms, and because this is a very common and significant problem, often underestimated by health professionals, these will be described in more detail.

If the symptoms are due to tamoxifen then changing the way the drug is taken might make a difference: either altering the time of day that it is taken, or breaking the tablet in two and taking half in the morning and half at night. Tamoxifen is made by a number of different manufacturers, and although all their products contain the same active drug some women find that changing from one brand of tamoxifen to another does make a difference to their symptoms. If none of these help, then for women who are past their menopause, a change from tamoxifen to an aromatase inhibitor, like anastrazole, letrozole, or exemestane, might well help, and will not affect the efficacy of treatment.

Sometimes simple lifestyle changes make things easier. Regular exercise, losing weight, and avoiding certain foods, particularly spicy foods, and certain drinks, particularly alcohol, may help to reduce the problem. Complementary therapies may also make a difference. There are a number of preparations available from pharmacists and health food shops which contain plant oestrogens (phyto oestrogens), the active ingredients include red clover, soy, genistein and black cohosh. There has been anxiety that because these compounds are a form of oestrogen, they might increase the risk of breast cancer recurrence but there is no evidence that this is the case. Vitamin E supplements have also been shown to help in some studies. Evening primrose oil, and ginseng are other popular remedies, and many women feel they reduce the number and severity of hot flushes and sweats, although scientific evidence for this is scarce. Studies have shown, however, that both acupuncture and relaxation therapies can benefit some women.

Sometimes prescription drugs may improve the situation. Hormone replacement therapy (HRT) is the most obvious

choice but its role is controversial. Certainly it is often very effective at relieving the symptoms, but its safety is in question. At least one large clinical trial showing that women who use HRT after a diagnosis of breast cancer have an increased risk of recurrence, but this risk only seems to affect women over 50. So up to that age HRT may be given but thereafter, unless symptoms are very severe and all else has failed, then HRT is not to be recommended.

There are a number of other prescription medicines that can be considered as alternatives to oestrogen-based HRT, but none is as effective. A point of interest is that in all the placebo-controlled clinical trials evaluating these drugs the placebos have eased symptoms in as many as 1 in 3 women. The options include:

- Progestins: these may help reduce hot flushes. Some concerns have been raised about their use in women with a history of breast cancer although there is no clinical evidence of an increased risk of recurrence as a result of these drugs being given.
- Tibolone: this drug has weak oestrogenic, progestogenic and androgenic effects and has been shown helpful in reducing hot flushes, improving vaginal dryness and may be better than HRT in improving sexual function. However, because of its oestrogenic properties it is not usually recommended for women with a history of breast cancer.
- Gabapentin: this comes closest to HRT in easing hot flushes, helping in about 50% of women. It is not contraindicated for women with a history of breast cancer but can causes side effects of drowsiness or dizziness in about 1 in 5 people, although these tend to ease after the first week of treatment.
- SSRIs and SNRIs: selective serotonin reuptake inhibitors or serotonin noradrenalin reuptake inhibitors which are normally used to treat depression can often be effective in easing hot flushes. The mechanism for their action is not clear but they are widely used. Side effects may include headache, nausea, dry mouth, anxiety/agitation, sleep disturbance or sexual dysfunction but they tend to be mild

and short-lived. Drugs used include fluoxetine, citalopram, paroxetine, sertraline, mirtazapine, venlafixine and desvenlafixine. Although they are safe for women who have had breast cancer fluoxetine and paroxetine should be avoided by women who are taking tamoxifen as they can interfere with its action.

- Clonidine: this has mild to moderate activity in reducing hot flushes and is not contraindicated for women with a history of breast cancer but it often causes side effects of a dry mouth and sleep disturbance (insomnia or drowsiness). Although usually used to treat hypertension there is no evidence that it affects blood pressure in the doses used for relief of menopausal symptoms.
- Androgen therapy: low testosterone levels may contribute to loss of libido and sexual problems in some postmenopausal women and if tests confirm androgen deficiency then testosterone supplements may be helpful but will only be appropriate for a small minority of women.
- Topical oestrogen: there are a range of preparations for local administration of vaginal oestrogen including creams, pessaries, vaginal tablets and oestradiol-releasing vaginal rings. These are effective in relieving vaginal dryness. Only small quantities of oestrogen are absorbed into the bloodstream from these preparations and they have generally been considered safe for women with a history of breast cancer although some clinicians do have concerns over their use in this situation.

Suggestions for Further Reading

Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8769 early breast cancer patients. J Clin Oncol. 2010;28:4120–8.

Hickey M, Davis SR, Sturdee DW. Treatment of post-menopausal symptoms: what shall we do now? Lancet. 2005;366:409–21.

Morrow PK, Mattair DN, Hortobagyi GN. Hot flashes: review of pathophysiology and treatment modalities. Oncologist. 2011;16:1658–64.

Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: current options, challenges and future directions. Int J Womens Health. 2010;2:123–35.

Endometrial Cancer

Long-term tamoxifen therapy is associated with a small but definite risk of developing cancer of the womb. Approximately 1 in 500 women taking tamoxifen for more than 2 years will develop endometrial cancer. This is because tamoxifen affects different oestrogen receptors differently, inhibiting those in breast cancer cells, but stimulating those in the endometrium, leading to endometrial hyperplasia, and ultimately endometrial cancer. For this reason postmenopausal women who are taking tamoxifen should always be warned to report any vaginal bleeding so that this can rapidly be investigated to exclude the possibility of cancer. Happily most endometrial cancers related to tamoxifen therapy have been detected at any early stage, and the cure rate has been high.

Thrombo-Embolic Disease

Another consequence of the oestrogenic properties of tamoxifen is an increased risk of venous thrombosis. The risk is quite small with less than 1% of women taking tamoxifen getting deep vein thromboses. It is, however, advisable that women with a history of venous thrombosis should have an alternative therapy, such as an aromatase inhibitor, if possible.

Osteoporosis

The reduction in oestrogen level that occurs after the menopause mean that older women are prone to develop osteoporosis. Use of aromatase inhibitors increases this risk. Exemestane is a steroidal aromatase inhibitor, in contrast to anastrazole and letrozole, and it has been suggested that it might be less likely to lead to a loss of bone mineral density. Whilst this is probably true there is still an increased risk of

osteoporosis even with this drug. Osteoporosis increases the risk of bone fractures, and these appear to be about 50% more common in women on an aromatase inhibitor than those on tamoxifen (the adverse effect of aromatase inhibitors on bone mineral density is in contrast to tamoxifen, which has a mild oestrogenic action on the bones, and hence offers some protection against osteoporosis). Although there are no definite national guidelines in the UK it is generally recommended that women who are to receive aromatase inhibitors have a baseline bone densitometry, DXA, scan, of their hip and lumbar spine prior to starting treatment. Depending on the result of this they may simply need advice on lifestyle measures to reduce the risk of osteoporosis (such as stopping smoking, reducing alcohol consumption, taking regular exercise and eating a healthy diet), or be advised to take vitamin D and calcium supplements. For women at high risk then adding a bisphosphonate, such as alendronic acid or risedronate sodium, to their drug regimen may be indicated.

Suggestions for Further Reading

Lester J, Dodwell D, McLoskey E, Coleman R. The causes and treatment of bone loss associated with cancer of the breast. Cancer Treat Rev. 2005;31:115–42.

Shapiro CL. Aromatase inhibitors and bone loss: the risks in perspective. J Clin Oncol. 2005;23:4847–9.

Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol. 2010;28:967–75.

Hormonal Therapies for Prostate Cancer

The gonaderilin analogues, goserilin and leuprorelin usually have relatively few side effects. The most important of these is the risk of tumour flare in metastatic disease, when the drugs may initially cause a surge in androgen production during the first 2 weeks of their administration, before inhibiting

release of the male hormones. This can be avoided by giving an anti-androgen at the same time as the gonaderilin analogue. Other side effects which may occur include 'menopausal' hot flushes and sweats, loss of libido and impotence, and irreversible breast pain and swelling (gynaecomastia) in up to 70% of men. Tumour flare is not a risk with the newer pituitary inhibitor degarelix which causes an immediate reduction in testosterone levels.

The anti-androgens may also lead to gynaecomastia, breast pain and 'menopausal' hot flushes. Giving a low dose of radiotherapy to the nipple area before starting the drugs can often prevent the development of gynaecomastia, similarly giving tamoxifen may also prevent breast swelling and pain. Because they do not reduce circulating androgen levels the non-steroidal anti-androgens, bicalutamide and flutamide, do not usually reduce libido or cause problems with erectile function or osteoporosis, whereas these may happen with the steroidal preparation, cyproterone. In addition cyproterone carries the risk of hepatotoxicity. The other main systemic hormonal therapy for prostate cancer, stilboestrol, carries the risk of cardiovascular toxicity due to thromboembolic complications.

These are all relatively immediate and recognizable side-effects of androgen-deprivation therapy but there are longer-term more subtle but more serious potential problems. Continued androgen-deprivation leads to a reduction in bone mineral density and decreased insulin sensitivity along with raised cholesterol levels and an increase in body fat mass. These factors mean that those men undergoing long-term treatment have an increased risk of osteoporosis, bone fractures, diabetes and cardiac disease.

Suggestion for Further Reading

Taylor LG, Canfield SE, Xianglin LD. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer. 2009;115:2388–99.

Side Effects of Targeted Therapies

By definition, targeted therapies specifically attack cancer cells, with little or no effect on normal tissues – in direct contrast to cytotoxic drugs, which have similar actions on normal and malignant cells. Consequently targeted therapies generally have fewer, and less severe, side effects than cytotoxic drugs. These are summarised in Table 2.17, but a few features do merit further explanation

Trastuzumab and Cardiotoxicity

Numerous clinical studies have now shown that trastuzumab can cause cardiotoxicity. This takes one of two forms: subclinical, in which there is a reduction in the left ventricular ejection factor (LVEF) and clinical, with the development of cardiac failure. Overall subclinical toxicity occurs in about 10% of people and cardiac failure in about 2%. A number of factors which increase the risk of this side effect appearing have now been identified and are listed in Table 2.18.

This has led to guidelines being developed to minimise the risk of cardiac problems and those developed by NICE are typical, recommending that cardiac function should be assessed prior to treatment and trastuzumab should not be given to women who have an LVEF of 55% or less, or who have any of the following:

- a history of congestive cardiac failure
- high-risk uncontrolled arrhythmias
- angina requiring medication
- clinically significant cardiac valvular disease
- evidence of transmural infarction on electrocardiograph (ECG)
- poorly controlled hypertension.

The LVEF should then monitored every 3 months during treatment and if it drops by 10% or more from baseline or to below 50% then trastuzumab treatment should be stopped.

Table 2.17 Summary of side effects of targeted therapies

	Alemtuzumab	Bevacizumab	Bortezomib	Cetuximab	Dasatinib	Erlotinib	Gefitinib	Imatinib
Infusion reactions	+			+				
Fever/flu like symptoms			+					
Skin rash	+			+		+	+	+
Cardiotoxicity								+
Hypertension		+						
Hypotension	+		+					
Haemorrhage								
Thrombosis		+						
Nausea			+		+	+		+
Diarrhoea	+		+			+		+
Constipation	+							
Fatigue			+			+		+
Alopecia								

(continued)

Table 2.17 (continued)

	Alemtuzumab	Bevacizumab	Bortezomib	Cetuximab	Dasatinib	Erlotinib	Gefitinib	Imatinib
Neuropathy			+					
Muscle/joint pain	+		+		+			+
Headache			+					+
Myelosuppression			+		+			
Oedema					+			+
Pleural effusion					+			
G-I perforation		+						

	Lapatinib	Nilotinib	Rituximab	Sorafinib	Sunitinib	Thalidomide	Trastuzumab
Infusion reactions			+				+
Fever/flu-like symptoms			+			+	+
Skin rash	+	+		+			
Hand foot syndrome				+	+		
Pruritis	+			+			
Cardiotoxicity							+

Hypertension				+	+		
Hypotension			+				
Thrombosis						+	
Nausea	+	+	+	+			
Diarrhoea	+			+	+		+
Constipation				+		+	
Fatigue	+			+	+	+	
Sedation						+	
Cardiotoxicity				+			
Neuropathy						+	
Muscle/joint pain		+					+
Headache		+					+
Myelosuppression		+	+			+	+
Tumour pain			+	+			+
Raised bilirubin		+				+	

Table 2.18 Factors increasing the risk of trastuzumab cardiotoxicity

Definite factors
Concurrent taxane use
Concurrent anthracycline use
Past treatment with anthracyclines
Age over 60
LVEF <50% at prior to treatment
Possible factors
Past or present hypertension
Body mass index (BMI) >25

The mechanism of the side effect of trastuzumab has yet to be fully clarified but unlike the cardiotoxicity seen with anthracycline cytotoxics (page 78) it is not dose related and appears to be reversible once the drug is stopped.

Suggestions for Further Reading

Morris PG, Hudis CA. Trastuzumab-related cardiotoxicity following anthracycline-based adjuvant chemotherapy: how worried should we be? J Clin Oncol. 2010;28:3407–10.

NICE Technology Appraisal 107. Trastuzumab for the adjuvant treatment of early stage HER2-positive breast cancer. NICE 2006.

Infusion Reactions: Cytokine Release Syndrome

Infusion reactions are common with the monoclonal antibodies and most often appear as hypersensitivity reactions with symptoms such as chills, fever, and an urticarial rash. Occasionally a more serious reaction may develop: cytokine release syndrome. This is thought to be due to monoclonal antibodies stimulating white blood cells to release large amounts of cytokines with produce an acute systemic inflammatory reaction. The most prominent symptom is severe dyspnoea, often with bronchospasm. As with the hypersensitivity reactions chills, rigors,

urticaria and angioedema are also frequently present but in contrast to those reactions cytokine release syndrome usually appears 1–2 h after the infusion has commenced, rather than in the first few minutes of an infusion. Cytokine release syndrome is also often accompanied by signs of tumour lysis syndrome (see page 90), with hyperuricaemia and hypercalcaemia. Cytokine release syndrome is a potentially fatal complication of treatment and requires emergency treatment. It is most likely in patients with a high tumour burden and those with pre-existing lung disease. If possible alternative treatments should be used for these patients. Cytokine release syndrome has most often been reported with rituximab and alemtuzumab but may rarely occur with other anti-cancer monoclonal antibodies.

Targeted Therapies and Skin Toxicity

About 80% of patients given cetuximab, and a majority receiving erlotinib and gefitinib, will develop an acneiform skin rash within the first week or two of treatment, for some this will be quite severe. Although labelled acneiform the rash is not true acne and routine acne medications, such as benzoyl peroxide, should be avoided. It can appear as either a pustular eruption, or a pustulo/papular or follicular rash. There is no universally agreed treatment but routine measures include the use of mild soaps and skin moisturisers, with topical or systemic antibiotics if there is evidence of secondary infection (which is quite common). For more troublesome macular rashes topical steroids may help and for pustular rashes topical clindamycin may be beneficial. The rash usually fades spontaneously after a few weeks, leaving the skin dry and liable to crack. An unusual feature of these rashes is that people who suffer a more severe reaction are more likely to gain a therapeutic response.

Suggestion for Further Reading

Potthoff K, Hofheinz R, Hassel JC, et al. Interdisciplinary management of EGFR-inhibitor-induced skin reactions: a German expert opinion. Ann Oncol. 2011;22:524–35.